Curtin School of Population Health

A Longitudinal Linked Cohort Study Evaluating Early Childhood Health Outcomes Following Exposure to Seasonal Influenza Vaccine during Pregnancy

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This thesis is presented for the degree of
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Author’s Declaration

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains work that has been published in a peer-reviewed journal and detailed contributions and signed statements from all co-authors are presented in **Appendix A**.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the Australian Code for the Responsible Conduct of Research and the National Statement on Ethical Conduct in Human Research. The research study received human research ethics approval from the Department of Health Western Australia Human Research Ethics Committee (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217-0808).

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Table of Contents

Abstract

Background and objectives

Maternal influenza vaccination is highly recommended to pregnant women to provide protection from severe influenza illness for both the mother and their infants in their first six months of life. Extensive research has been conducted and has established the safety of maternal influenza vaccination in regard to health outcomes at birth, however, few studies have evaluated the impact of *in utero* exposure to influenza vaccine, particularly seasonal influenza vaccine, on health outcomes beyond infancy and into early childhood. This body of research aimed to evaluate several safety outcomes associated with seasonal influenza vaccination during pregnancy, including infectious, allergic, autoimmune, neurodevelopmental and morbidity outcomes, and mortality, among children aged < 5 years in Western Australia (WA).

Methods

A systematic review was conducted to synthesise the literature on the association between maternal influenza vaccination and early childhood health outcomes. A longitudinal, population-based mother-child cohort was established using a series of probabilistic record linkages of administrative health datasets using probabilistic linkage. Birth, perinatal, maternal and health information were derived from Birth Registrations and the Midwives Notification System. Exposure (or vaccination) information was derived from the WA Antenatal Vaccination Database. Outcome information was derived from the WA Notifiable Infectious Diseases Database, the Hospital Morbidity Data Collection, the Emergency Department Data Collection, and Death Registrations. Cox regression models, weighted by the inverse-probability of treatment (vaccination), were used to compare the risk of several early childhood health outcomes between children of vaccinated and unvaccinated mothers.

Results

The systematic review indicated that nine studies evaluated the association between maternal influenza vaccination and infectious, atopic, autoimmune, and neurodevelopmental outcomes, and all-cause morbidity and mortality. No association was identified between maternal influenza vaccination and adverse health outcomes in childhood. Seasonal influenza vaccination during pregnancy had a protective association against laboratory-confirmed influenza and hospitalisation for influenza and acute respiratory infections among infants aged <6 months (adjusted hazard ratio [aHR]: 0.32; 95% confidence interval [CI]: 0.12-0.84) and had a slight adverse association with laboratory-confirmed influenza among children aged 6 months to <2 years of mothers that were vaccinated during the first trimester (aHR: 2.28; 95% CI: 1.41-3.69). Children of mothers vaccinated during the third trimester were less likely to be diagnosed with asthma (aHR: 0.68; 95% CI: 0.48-0.96) and anaphylaxis (aHR: 0.62; 95% CI: 0.43-0.91), and children of mothers vaccinated during the first trimester were less likely to be diagnosed with a seizure disorder (aHR: 0.73; 95% CI: 0.54-0.99).

Conclusion

These results show that prior to this thesis, little evidence existed examining *in utero* exposure to seasonal influenza vaccine. Results from the series of cohort analyses mostly support the safety of seasonal influenza vaccination during pregnancy and suggest there are potential health benefits associated with seasonal influenza vaccine administered in the first and third trimester in regards to seizure disorders, asthma and anaphylaxis, respectively, among children aged <5 years. Although we identified a potential transient risk of laboratory-confirmed influenza among children aged 6 months to <2 years of mothers who were vaccinated during the first trimester, additional research is required to confirm this finding. This potential risk is likely to be outweighed by the benefits of seasonal influenza vaccination during pregnancy. The findings of this body of research support the safety of seasonal influenza vaccination during pregnancy and the continued implementation of existing vaccine programs and policies promoting the provision of seasonal influenza vaccines to pregnant women. Data on the safety and potential benefits of seasonal influenza vaccination during pregnancy could be used by prenatal care providers to promote maternal vaccination to prospective parents and pregnant women.

Acknowledgements

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I am indebted to both my parents, Christopher and Kim, for their unconditional love and support throughout my life. I am forever grateful for how you have raised, nurtured, and motivated me to become the man I am today. Also special thanks to my two brothers, Jordan and Justin, my aunt, Lynda, and my extended family for always showing their support and offering words of encouragement. Thank you also to Elle for the countless cups of coffee and for your support. I feel blessed to have you in my life, not only as a friend, but as a true sister. Finally, I am thankful to my partner, Samuel Cockayne, who has been by my side for the entirety of my PhD journey, offering his love, encouragement and support which were essential to me in completing this PhD.

Thank you!

Statement of Contribution

This thesis is presented in a hybrid format and has been completed during my period of candidature for the degree of Doctor of Philosophy (Public Health) at the Curtin School of Population Health, Curtin University. The thesis summarises my own original work, including peer-reviewed publications and additional unpublished work, except where otherwise stated. This thesis contains no material which has been submitted or accepted for the award of any other degree or diploma at any university or institution. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where otherwise cited, referenced or acknowledged.

This thesis includes five original papers published in or prepared for submission to peer-reviewed journals. The ideas, development and writing up of all papers in this thesis were the principal responsibility of myself, the candidate.

The inclusion of co-authors reflects the strong collaboration between researchers and acknowledges the input into team-based research. In Chapters Five through Nine, I contributed to the following publications:

Thesis Chapter	Publication title	Publication status	Nature and extent of candidate's contribution
Five	Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review	Published in *Pediatrics*	Led the development and registration of the original protocol, performed data collection and analysis, and led the writing of the manuscript.
Six	Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood	Published in *Vaccine*	Performed data management and analysis, and led the writing of the manuscript.
Seven	Prenatal influenza vaccination and	Formally accepted for	Performed data management and

	allergic and autoimmune diseases in childhood: A longitudinal, population-based linked cohort study	publication in *PLoS Medicine*	analysis, and led the writing of the manuscript.
Eight	Association between maternal influenza vaccination and neurodevelopmental disorders in childhood: A longitudinal, population-based cohort study	In preparation for submission to *Archives of Childhood Diseases*	Performed data management and analysis, and led the writing of the manuscript.
Nine	Maternal influenza vaccination and child mortality: longitudinal, population-based cohort study	In preparation for submission to *Vaccine*	Performed data management and analysis, and led the writing of the manuscript.

I have renumbered sections of published manuscripts and additional unpublished work to provide a consistent presentation with the thesis. The published versions of these co-authored are provided in **Appendix B and Appendix D**.

Signature: 

Date: 10/02/2022

List of Tables

List of Figures

List of Abbreviations

AEFI	Adverse events following immunisation
aHR	Adjusted hazard ratio
aIRR	Adjusted incidence rate ratio
ALRI	Acute lower respiratory infection
aOR	Adjusted odds ratio
ARI	Acute respiratory infection
aRR	Adjusted rate ratio
ASD	Autism spectrum disorder
aVE	Adjusted vaccine effectiveness
BMI	Body mass index
CI	Confidence interval
ED	Emergency department
EDDC	Emergency Department Data Collection
GIHSN	Global Influenza Hospital Surveillance Network
HMDC	Hospital Morbidity Data Collection
HCP	Healthcare provider
HR	Unadjusted hazard ratio
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICU	Intensive care unit
IIV	Inactivated influenza vaccine
IPTW	Inverse-probability treatment weight(ing)
IQR	Interquartile range
IRR	Unadjusted incidence rate ratio
LCI	Laboratory-confirmed influenza
MNS	Midwives Notification System
NHMRC	National Health Medical Research Council
NIP	National Immunisation Program

NOS	Newcastle-Ottawa Scale
OR	Unadjusted odds ratio
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Unadjusted rate ratio
SEIFA	Socioeconomic Indexes for Areas
UK	United Kingdom
US	United States
WA	Western Australia(n)
WAAVD	Western Australia Antenatal Vaccination Database
WADLB	Western Australian Data Linkage Branch
WANIDD	Western Australia Notifiable Infectious Diseases Database
WHO	World Health Organization

Conference Presentations and Awards

Conference presentations

- Foo D, Sarna M, Pereira G, Moore HC, Fell DB, and Regan AK. Paediatric health outcomes following antenatal influenza vaccination: A Systematic Review. 2019 5th International Neonatal & Maternal Immunization Symposium, Vancouver, British Columbia, Canada, September 2019 (Poster).
- Foo D, Sarna M, Pereira G, Moore H, and Regan A. Longitudinal, population-based cohort study of influenza and other acute respiratory infections following antenatal influenza vaccination. 2021 17th National Immunisation Conference (Virtual), Perth, Western Australia, Australia, June 2021 (Long Oral Presentation).

Awards

- Wesfarmers Centre of Vaccines and Infectious Diseases Top-up Higher Degree of Research Scholarship (2019-2021)

Alice Klein (2022). Flu vaccines during pregnancy protect babies for 6 months after birth [Internet]. *New Scientist*. Available from: https://www.newscientist.com/article/2304697-flu-vaccines-during-pregnancy-protect-babies-for-6-months-after-birth/?utm_medium=social&utm_campaign=echobox&utm_source=Twitter#Echobox=1642179651.

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Flu vaccines during pregnancy protect babies for 6 months after birth

Evidence shows that getting a flu jab during pregnancy provides substantial protection to young babies, but uptake in many countries is still concerningly low

HEALTH 14 January 2022

By Alice Klein

Pregnant women can pass on antibodies to their babies
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Babies are two-thirds less likely to get the flu in their first six months of life if their mother had a flu vaccine while they were pregnant, a large Australian study shows.

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Chapter One: Introduction

1.1 Overview

Globally, influenza causes serious morbidity and mortality contributing to an estimated 39 million cases of influenza and nearly 60,000 deaths each year.[1] Pregnant women and young children, particularly newborn infants, have an increased risk of influenza infection and serious complications associated with influenza infection.[2-6] Although seasonal influenza vaccines are available free of charge to young children aged between 6 months and 5 years in Australia,[7] there are no current influenza vaccines licensed for use for infants aged less than six months. Over the past decade, maternal influenza vaccination has been a public health strategy to prevent influenza infection in pregnant women and newborn infants under six months of age via passive immunity.[8, 9] In Australia, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommends influenza vaccination to all pregnant women, regardless of gestational age.[10]

The effectiveness of maternal influenza vaccination has been well-researched and several systematic reviews and meta-analyses have consistently demonstrated the health benefits in preventing influenza infection in both pregnant women and their infants under six months of age. While extensive research has evaluated the safety of maternal influenza vaccination in regards to health outcomes at birth and during the perinatal period, fewer studies have evaluated its potential impact on early childhood health outcomes. The proposed body of research will evaluate the paediatric impacts of maternal influenza vaccination in young children <5 years of age. By linking information from multiple administrative datasets in Western Australia (WA), I examined multiple health outcomes, including infectious, allergic, autoimmune, neurodevelopmental, and mortality outcomes, in children <5 years of age whose mothers were vaccinated during pregnancy. It was envisaged that findings from this body of work would inform recommendations for current influenza vaccinations programs in Australia and worldwide.

1.2 Outline of chapters

This thesis has eleven chapters and is a combination of published manuscripts, manuscripts under review and chapters formatted for publication.

This chapter (Chapter One) provides an overview of the thesis structure. Chapter Two provides a review of the current literature summarising maternal influenza vaccination and highlights gaps in the area. Chapter Three and Four outline the research aims and objectives and the methodology used to address each research objective, respectively. Chapters Five through Nine will describe the study results by research objective and are formatted as manuscripts. At the time of thesis submission, Chapters Five and Six were published in peer-reviewed journals. Finally, Chapter Ten will provide an overview of the study findings, a discussion of the implications for public health practice, and recommendations for future research.

1.3 Motivation for this research

Despite recommendations for maternal influenza vaccination by national and international health agencies, including the RANZCOG and the World Health Organization (WHO),[10, 11] and several studies demonstrating the safety and effectiveness of maternal vaccination, vaccine uptake among pregnant women is sub-optimal.[12] Multiple determinants and barriers of vaccine acceptance and hesitancy among pregnant women have been identified,[13, 14] including concerns around the safety of the vaccine for themselves and for their child[15] and lack of advocacy by healthcare providers (HCP), particularly prenatal care providers.[16-20] Therefore, it is important to communicate the evidence around the effectiveness and safety of maternal influenza vaccination to pregnant women to improve vaccine uptake.

While previous population-based studies have addressed the safety of maternal influenza vaccination in regards to birth and perinatal outcomes, fewer studies have explored the longer-term impacts of maternal influenza vaccination in young children. My motivation for this thesis was to summarise the current research and literature in the areas of maternal influenza vaccination, identify the scientific gaps in knowledge in this area, and address these gaps.

Chapter Two: Review of the Literature

2.1 Preamble

This chapter provides a literature review of the background information relevant to the topics presented in the following chapters (Chapters Six through Nine). This review covers the subject areas relevant to my thesis including influenza and the epidemiology of influenza, maternal vaccination, maternal vaccine programs and policies, maternal antibodies, immunity, effectiveness and safety of maternal influenza vaccination, and the gaps in knowledge in maternal influenza vaccination. For the purpose of this thesis, children of mothers that received an influenza vaccine during pregnancy were considered 'maternally vaccinated' and children of mothers that did not receive an influenza vaccine during pregnancy were considered 'maternally unvaccinated'.

2.2 Influenza

2.2.1 Influenza virus

Respiratory infections, including influenza, are considered to be one of the leading causes of death among infants aged less than six months worldwide.[21, 22] The majority of these infections occur in low- and middle-income countries. Influenza is caused by the influenza virus, an RNA virus that can be classified into three antigenic sub-types, including influenza: A, B, and C.[23] Only influenza A and B sub-types cause major respiratory infection in humans, resulting in seasonal epidemics, and can lead to severe illness and death at any age.[24]

2.2.2 Epidemiology

Globally, influenza infects approximately 5-10% of adults and 20-30% of children in seasonal epidemics per annum and is known to cause serious morbidity and mortality,[11, 23] leading to an estimated 39.1 million influenza infections and 58.2 thousand deaths each year.[1] Pregnant women and young children, particularly newborn infants, have an elevated risk of serious complications due to influenza illness.[2-6] Influenza A and B sub-types are known to cause seasonal outbreaks during the winter months of the northern and southern hemisphere, and influenza A is known to cause the majority of seasonal epidemics and pandemics.[23]

In Australia, laboratory-confirmed influenza (LCI) is a notifiable disease. Laboratory confirmation of influenza includes one of the following: i) detection of influenza virus by nucleic acid testing; ii) isolation of influenza virus by culture; iii)

detection of influenza virus antigen by antigen assay, or iii) clear seroconversion or a four-fold increase in antibody titre to influenza virus.[25] In WA, cases that meet these criteria are reported to the WA Department of Health by health care providers and all pathology testing laboratories and case information is stored in the WA Notifiable Infectious Diseases Database (WANIDD).[26] In Australia, influenza virus circulation typically peaks between June and August. The northern region of Australia often experiences two influenza seasons; the main influenza season during the tropical dry season (June-August) coinciding with the southern temperate winter season and a smaller influenza season during the tropical wet season (November-April) coinciding with the southern temperate summer and autumn seasons.[27] In Australia, Aboriginal and/or Torres Strait Islander (hereafter respectfully referred to as Aboriginal) people have historically had a significantly higher risk of morbidity and mortality, including influenza infection, compared to their non-Aboriginal counterparts, and are predisposed to severe health complications. Between 2012 and 2016, there were 28,329-100,583 LCI notifications and 48-150 LCI-associated deaths reported to the Department of Health in Australia each year, of which approximately 35-40% and 75-84% were among Aboriginal people, respectively. The rate of LCI was 265-584 per 100,000 among Aboriginal people compared to 163-480 per 100,000 among non-Aboriginal people.[28-32] A large-scale epidemiological study recently estimated that influenza-associated excess respiratory mortality rate was 2.6 per 100,000 in Australia with the excess annual respiratory hospitalisation rate at 57.4 per 100,000.[33] Significant annual variation was also noted.

2.2.2.1 Influenza infection in pregnant women

During pregnancy, a number of immunological changes occur whereby the pregnant woman's immune system adapts to tolerate the fetus. As a consequence, the pregnant woman becomes immunocompromised and has increased susceptibility to severe viral infection.[3] In pregnant women, suppression of cell-mediated immunity leads to an impaired ability to clear viral infections.[34-36] Pregnancy and pregnancy-associated hormones, including estradiol, estriol, progesterone, and glucocorticoids, have an anti-inflammatory effect and the inhibition of inflammatory responses of the immune system reduce the activity of inflammatory macrophages, natural killer cells, and helper T cell type 1 cells.[37, 38] Since infections such as influenza are mitigated by such

inflammatory responses and a prompt inflammatory response is necessary for the initial control and clearance of the pathogen, an attenuated inflammatory response can increase the severity of influenza infection.[37, 38] In addition to immunologic and hormonal changes, a number of cardiopulmonary changes occur during pregnancy, including increased heart rate, stroke volume and oxygen consumption, and decreased lung capacity which may increase the risk of hypoxia, and contribute to increased risk of severe influenza illness among pregnant women.[3, 35, 39]

The Global Influenza Hospital Surveillance Network (GIHSN) is an international public and private collaboration that aims to improve understanding of influenza epidemiology and to determine the burden of severe influenza disease. Since 2012, the GIHSN has conducted annual prospective, active-surveillance, hospital-based epidemiological studies during influenza seasons and has consistently shown that influenza can cause adverse outcomes among high-risk groups, including pregnant women.[40-45] Although the rate of infection is comparable between pregnant and non-pregnant women of similar age, pregnant women are more likely to experience serious medical complications following influenza infection compared to their non-pregnant counterparts.[4, 6] Compared to non-pregnant women, these studies reported that pregnant women were 2.1-3.8 times more likely to be hospitalised for influenza during influenza seasons.[40-45] Similarly, a meta-analysis of 33 datasets reported a higher odds of influenza-associated hospitalisation among pregnant women (adjusted odds ratio [aOR]: 6.80; 95% CI: 6.02-7.68) compared to non-pregnant women.[4] Interestingly, this study also observed a lower odds of intensive care unit (ICU) admission among pregnant women (aOR: 0.57; 95% CI: 0.49-0.69). There was no significant difference in the odds of influenza-associated mortality between pregnant and non-pregnant women.

A systematic review[46] of nine articles reported the incidence rates of LCI using serology (n = 3) and LCI-associated outcomes, including LCI-associated hospitalisation (n = 4), LCI-associated ICU admission (n = 4), and LCI-associated mortality (n = 4) which were highly variable in pregnant women (**Table 2-1**). Most studies originated from high-income countries (n = 8) and one study originated from an upper-middle income country (n = 1). Of the included studies, there was high methodological and statistical heterogeneity (I^2: 93.1% > 75%) in regards to

study design, outcome ascertainment and study duration, and therefore a meta-analysis could not be performed.

Table 2-1. Previous research measuring the incidence of laboratory-confirmed influenza and laboratory-confirmed influenza-associated outcomes.

Outcome	Unadjusted incidence rates (per 10,000 pregnancies)
LCI using serology (n = 3)	483-1,097
LCI-associated hospitalisation (n = 4)	0.04-7.7
LCI-associated ICU admission (n = 4)	0.01-6.8
LCI-associated mortality (n = 4)	0.003-0.69

Influenza infection during pregnancy (or maternal influenza infection) is known to cause serious health complications to the infant as well as the mother. Multiple systematic reviews have identified several studies reporting that maternal influenza infection is associated with a higher risk of preterm birth,[47] low birthweight (<2,500 g),[48] low APGAR score,[48] congenital anomalies,[49] stillbirth,[48, 50] and fetal death.[47] A meta-analysis of 22 studies by Luteijn et al. [49] found that infants born from mothers following influenza infection during the first trimester were more likely to have any congenital anomaly (unadjusted odds ratio [OR]: 2.00; 95% 1.62-2.48), neural tube defects (OR: 3.33; 95% CI: 2.05-5.40), hydrocephaly (OR: 5.74; 95% CI: 1.10-30.0), congenital heart defects (OR: 1.56; 95% CI: 1.13-2.14), orofacial clefts (OR: 1.96; 95% CI: 1.33-2.91), digestive system defects (OR: 1.71; 95% CI: 1.09-2.69), and limb reduction defects (OR: 2.03; 95% CI: 1.27-3.27).[49] Another meta-analysis of 10 studies by He et al.[48] reported that offspring of mothers that were exposed to influenza A during pregnancy had a higher risk of stillbirth (RR: 2.36; 95% CI: 1.05-5.31), having a low birthweight (RR: 1.71; 95% CI: 1.03-2.84), and having a low 5-minute APGAR (RR: 1.39; 95% CI: 1.08-1.79).[48] A recent meta-analysis of 17 studies by Wang et al.[50] found that offspring of mothers following maternal influenza infection had a higher risk of stillbirth (RR: 3.62; 95% CI: 1.60-8.20) but not preterm birth (RR: 1.17; 95% CI: 0.95-1.45), small-for-gestational age (RR: 1.10; 95% CI: 0.98-1.24), low birthweight (RR: 1.88; 95% CI: 0.46-7.66), and fetal death (RR: 0.93; 95% CI: 0.73-1.18).

2.2.2.2 Influenza infection in young children

Poehling et al.[51] has postulated that the burden of influenza infection in young children is an under-recognised problem. Influenza contributes considerably to the burden of hospitalisation and mortality among young children.[52] Li et al[53] reported on the global incidence of influenza infection, influenza-associated acute lower respiratory infection (ALRI), influenza-associated ALRI hospital admission, and influenza-associated very severe ALRI hospital admission and was estimated to be 109.5 million, 10.1 million, 0.9 million, and 0.1 million, respectively, among children aged 0 to <5 years between 1995 and 2018. Among children aged 1 to <5 years, the global incidence of influenza infection, influenza-associated ALRI hospital admission, and influenza-associated very severe ALRI hospital admission was estimated to be 74.4 million, 0.5 million, and 0.05 million.[53] A global systematic analysis study by Lafond et al[54] estimated that 870,000 hospitalisations due to influenza occur each year among children aged <5 years, and another global systematic analysis by Troeger et al[22] reported that 8,360 influenza-associated respiratory deaths occur each year among children aged <5 years.

Young infants are particularly vulnerable and highly susceptible to influenza infection due to their under-developed immune systems.[55] A meta-analysis study by Nair et al[52] used data from studies published between January 1995 and October 2010, and grey literature, identified from a systematic review, to estimate the global burden of seasonal influenza among young children. In 2008, the global incidence of influenza infection among infants aged <1 year was 15.2 million. Between 1995 and 2018, the global incidence of influenza-associated ALRI hospital admission and influenza-associated very severe ALRI hospital admission was particularly high among infants aged 0 to <6 months (200,000 and 185,000, respectively) and infants aged 6 to <1 year (21,000 and 25,000, respectively).[53] Another study using surveillance data between 2003-2012 by Lafond et al[54] reported similar estimates of influenza-associated hospitalisation among infants aged 0 to <6 months (228,000) and infants aged 6 to <1 year (146,000).[54]

2.3 Influenza vaccination

Vaccines have prevented more deaths than any other medical intervention.[56, 57] Influenza vaccines have been used to prevent influenza infection for over six decades.[23] In Australia, currently licensed influenza vaccines include inactivated influenza vaccines (IIV), either: i) split virion or ii) subunit vaccines prepared from purified, inactivated influenza virus that was cultivated in embryonated hens' eggs.[58] Annually, the composition of influenza vaccines is determined by the Australian Influenza Vaccine Committee based on the influenza strains predicted to circulate in the upcoming influenza season and approved by the Therapeutic Goods Administration. Since the late 1970s,[58] trivalent influenza vaccines have been used containing three strains of influenza virus, two influenza A sub-types (i.e., A/H1N1, A/H3N2) and one influenza B lineage, and in 2014, quadrivalent influenza vaccines were introduced which contained one additional influenza B lineage.[59-62] In Australia, the National Immunisation Program (NIP) has provided influenza vaccines free of charge to eligible recipients including children aged 6 months to <5 years, older adults aged ≥65 years, Aboriginal people aged ≥6 months, pregnant women, and individuals aged ≥6 months with a medical condition predisposing them to severe influenza infection and influenza-associated complications.[7]

2.3.1 Maternal vaccination programs

2.3.1.1 Global maternal influenza vaccination programs

In 2006, the Global Action Plan for Influenza Vaccines was initiated by the WHO with the primary goal of increasing the global use of seasonal IIV.[63] The 2012 Vaccine Against Influenza WHO position paper affirms that influenza induces significant morbidity globally and that countries should contemplate the implementation of influenza vaccination programs as national capacities and available resources permit.[11, 64] High-risk groups prioritised for influenza vaccination include those at particular risk of severe influenza infection and influenza-associated complications, namely pregnant women, children aged <5 years, older adults aged ≥65 years and people with underlying medical conditions, as well as HCPs due to their increased risk of occupational exposure to the influenza virus.[11, 64] While these special risk groups are the primary target

of influenza vaccines, the WHO recommends that pregnant women should have the highest priority for seasonal influenza vaccination programs. [11, 64]

A global review of national influenza immunisation policies was conducted on 194 WHO Member States in 2017, of which 117 (60%) countries reported having a national influenza immunisation policy, and 116 (99%) countries had vaccination programs targeting risk groups.[65] This compared to 115 (59%) countries having a national influenza immunisation policy and 81 (42%) countries that had vaccination programs specifically targeting pregnant women in 2014.[66] Over the past decade, vaccine programs targeting pregnant women have been introduced to prevent severe influenza disease in women and their infants. Since 2006, the countries targeting pregnant women for influenza vaccine increased from 15 countries to 81 countries (including Australia) in 2014.[66]

2.3.1.2 Maternal influenza vaccination programs in Australia

Seasonal IIVs have been funded for pregnant women under the NIP since January 2010. The distribution of NIP-funded seasonal influenza vaccines typically commences in April of each year, preceding the beginning of seasonal influenza activity.[67] Pregnant women typically receive their free seasonal influenza vaccine at general practices and public hospital-based prenatal clinics.[68] Since March 2012, midwives and nurses have been authorised to administer seasonal influenza vaccines to pregnant women seeking prenatal care from any WA public metropolitan and regional health facility.[69]

2.4 Maternal influenza vaccination

Following administration of seasonal IIV, generally >80% of adults and children vaccinated with seasonal IIV attain a sufficient seroprotective level of pathogen-specific antibodies or antibody titre to protect against infection.[70-72] This seroprotective level of antibodies has also been observed among pregnant women.[73-76] The immunisation of pregnant women has long been a public health strategy to protect both mother and their infants from influenza infection in the first six months of life via passive immunity. [8, 9]

2.4.1 Passive immunity

Passive immunity to protect against influenza infection is granted to the infant by maternal antibodies, predominantly IgG, delivered via placental transfer. In the

absence of these maternally-acquired antibodies and since there are no current influenza vaccines licensed for use for infants aged less than six months, protection of infants from influenza infection is reliant on the infant's naturally-acquired immunity. Several studies have reported high cord blood haemagglutination-inhibition antibody titres following maternal influenza vaccination suggesting that seasonal IIV protects newborns against influenza via passively maternally-acquired antibodies.[77, 78] In addition to antibodies delivered to the fetus via placental transfer, maternal antibodies, predominantly IgA, are also delivered through the ingestion of colostrum and breastmilk by the newborn providing mucosal immunity through the neutralisation and prevention of adherence of toxins and virulence factors in the respiratory and gastrointestinal tract.[79-82] Larger amounts of disease-specific antibodies have been found in the breastmilk of mothers up to 6 months after birth following maternal vaccination.[82-84]

The amount of maternal antibodies transferred to neonates via placental transfer and breast milk depends on the timing of vaccination during pregnancy, the placental function, and the concentration of maternal antibodies in pregnant women.[85, 86] Maternal antibody concentrations in pregnant women are dependent on the vaccination status of the women and/or the time since last vaccination or infection. For the moment, there is still some debate in regard to the optimal timing of influenza vaccination during pregnancy, although one systematic review and meta-analysis has reported that vaccination later in pregnancy resulted in higher influenza-specific maternal antibody levels at birth, and therefore greater antibody transfer to the newborn.[85] Vaccination earlier in pregnancy would provide protection against influenza infection for a larger proportion of the pregnancy. The benefit of early vaccination during pregnancy is the increased probability of protection for the mother throughout the entire pregnancy, and ultimately reducing the risk of complications to the fetus due to maternal influenza infection. It has been suggested that the higher the concentration of serum maternal antibodies, the greater the transfer of maternal antibodies to the fetus.[87]I Infants of vaccinated mothers are protected by maternal antibodies in early life and infants with higher levels of maternal antibodies at birth have a longer persistence of protective antibodies until the infant's active vaccination. Once

these antibodies wane approximately 2-4 months after birth,[88] this leaves a temporary window of susceptibility to influenza infection.

2.4.2 Vaccine uptake among pregnant women

Despite recommendations for influenza vaccination for pregnant women by national and international health agencies such as the RANZCOG and the WHO,[10, 11] vaccination remains low among pregnant women.[12] Historically, despite significant evidence supporting the effectiveness and safety of influenza vaccines, pregnant women have been reported to have the lowest vaccine uptake among high-risk groups recommended for influenza vaccination.[39] Since the 2009 H1N1 influenza pandemic, although influenza vaccine uptake among pregnant women increased over time, estimates of seasonal influenza vaccine uptake remain sub-optimal and well below the recommended target of 80% in high-income countries.[12] Between 2010 and 2018, approximately 40-60% of pregnant women in Australia were vaccinated against influenza.[68, 89-92] Similar estimates of influenza vaccine uptake have been reported in other high-income countries with similar recommendations including the United States (US),[93-98] Canada,[99, 100] and the United Kingdom (UK).[101, 102]

2.4.3 Factors influencing vaccine uptake

Several studies, including systematic reviews and meta-analyses, have explored the potential factors influencing seasonal influenza vaccination during pregnancy and have identified several determinants and barriers of vaccine acceptance and hesitancy among HCPs, prospective parents, and pregnant women.[13, 14]

One of the most cited barriers of vaccine uptake of the seasonal influenza vaccine among pregnant women is concerns around the safety of the vaccine for themselves and for their child. A meta-analysis of 75 studies found that women who perceived vaccines to be unsafe were 78% less likely to have received the seasonal influenza vaccine.[15] Conversely, studies have identified several factors that increase the likelihood of seasonal influenza vaccination among pregnant women. Among pregnant women that believed that they were susceptible to seasonal influenza and pregnant women that believed that seasonal influenza could be harmful to their pregnancy or their infant, there was a two-fold and four-fold increase in the odds of seasonal influenza vaccination, respectively. This study also reported that pregnant women that perceived the vaccine to be

effective, that the vaccine would benefit themselves, and that the vaccine would benefit their infant were seven-times, three-times and two-times more likely to have received a seasonal influenza vaccine during pregnancy, respectively.[15] Other barriers of seasonal influenza vaccine uptake among pregnant women have been cited such as objections to drugs during pregnancy and lack of understanding of the burden and severity of influenza,[13, 17, 19, 39, 103] however, fewer studies have identified these barriers and there is inconclusive evidence behind the association between these barriers and seasonal influenza vaccination among pregnant women.

Several reviews have concurred that recommendations from a HCP for vaccination is the most important factor influencing pregnant women's decision making regarding vaccination.[16-20] A meta-analysis reported a twelve-fold increase in the odds of acceptance of the seasonal influenza vaccine among pregnant women that received an HCP recommendation, compared to pregnant women that received no recommendation.[15] In 2018, although 81.1% of US women received a HCP recommendation or an offer for seasonal influenza vaccination during pregnancy, 50.9% of pregnant women remained unvaccinated.[104] A 2018 WA survey reported that 74% of women were recommended and 61% of women received the seasonal influenza vaccine during pregnancy, respectively. Compared to pregnant women that received no seasonal influenza vaccine recommendation, pregnant women that received a seasonal influenza vaccine recommendation were 4.47 times more likely to have received the seasonal influenza vaccination during pregnancy. In addition, 53.6% of unvaccinated women would have accepted the seasonal influenza vaccine if a HCP recommended it.[68] Another WA study reported that 69.4% and 72.2% of pregnant women would have accepted the seasonal influenza vaccine if a general practitioner or an obstetrician had recommended it, respectively.[91]

Since March 2012, midwives and nurses have been authorised to administer seasonal influenza vaccines to pregnant women seeking prenatal care from any WA public metropolitan and regional health facility.[69] In 2014, 65.7% of WA women reported that they would have accepted the seasonal influenza vaccination if a midwife had recommended it.[91] Given midwives have frequent contact with pregnant women and have a positive influence on vaccine

acceptance among pregnant women, midwives have a key role in recommending and providing seasonal influenza vaccines to pregnant women.[105]

Despite the positive influence of HCP recommendations of seasonal influenza vaccination during pregnancy, a recent global review has shown that HCPs, including general practitioners, obstetricians and gynaecologists, midwives, and nurses, are reluctant to recommend vaccines to pregnant women due to various reasons,[39, 106] including perceptions of effectiveness, safety and utility of vaccines which were the most frequently reported barriers, irrespective of geographic and sociodemographic context.[106] Among higher-income countries, financial barriers were frequently reported to influence HCP recommendations. Among low- to middle-income countries, policy-related barriers, vaccine acceptability and supply barriers were frequently reported.[106] It is apparent that HCPs have a key role in counselling pregnant women about the effectiveness and safety of seasonal influenza vaccines for themselves and for their infants, and advocating for the benefits of passive immunity granted to their newborns via maternal immunisation.[39]

Although knowledge and perceptions of influenza vaccination are known to affect vaccine acceptance among pregnant women, a recent multi-directional, meta-analysis of 36 studies identified multiple sociodemographic and health-related characteristics that influence seasonal influenza vaccine uptake among pregnant women.[14] This study reported that women were more likely to be vaccinated against seasonal influenza if they received an influenza vaccine during a previous pregnancy, received prenatal care, were nulliparous, were a non-smoker, were in an older age group, were employed, were married, and lived in a rural area. Women that had one or more chronic diseases were more likely to have received a seasonal influenza vaccine during pregnancy, particularly, women with asthma. Conversely, women with a cardiovascular disease were less likely to be vaccinated during pregnancy. There was no association between seasonal influenza vaccine uptake and educational attainment, income levels, socioeconomic status, alcohol consumption during pregnancy, and seasonal influenza uptake.[14] Knowledge of these barriers, determinants, and sociodemographic and health-related characteristics among pregnant women may be useful in designing more effective public health interventions to improve vaccine uptake among this important high-risk group (**Figure 2-1**).

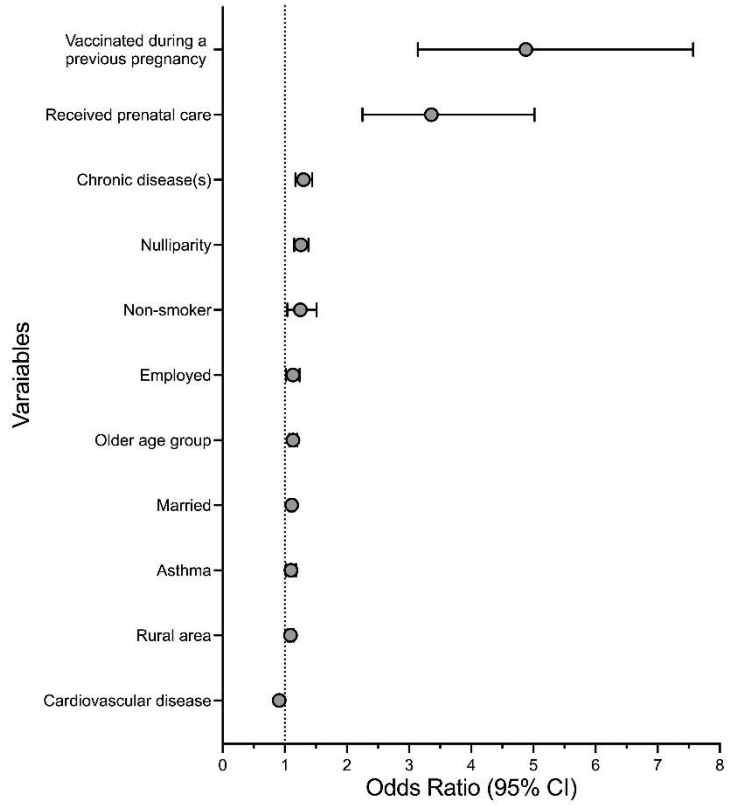


Figure 2-1. The association between sociodemographic and health-related characteristics and seasonal influenza vaccination among pregnant women.
Note: Effect estimates drawn from a systematic review and meta-analysis.[14]

2.4.4 Vaccine efficacy and effectiveness of maternal influenza vaccination

Efficacy is defined as the capacity of a vaccine to prevent illness and its complications under ideal circumstances such as a clinical trial. Effectiveness is defined as the capacity of a vaccine to prevent influenza and its complications under typical circumstances of health care practice such as in observational studies.[107] Several clinical trials and observational studies have demonstrated the efficacy and effectiveness of influenza vaccination during pregnancy in preventing influenza infection in both mothers and their infants. However, most studies have evaluated the efficacy and effectiveness of pandemic vaccines and fewer studies have focused on seasonal vaccines.

2.4.4.1 Vaccine efficacy and effectiveness in pregnant women

There is strong evidence supporting the efficacy and effectiveness of seasonal influenza vaccination to prevent influenza infection in pregnant women. A meta-analysis of 19 studies from 11 countries evaluated the efficacy and/or effectiveness of both the pandemic and seasonal influenza vaccine in protecting

against LCI, influenza-like illness, and respiratory illness.[107] This study reported that pandemic influenza vaccination during pregnancy was associated with a 70% lower risk and 85% lower risk of LCI and influenza-like illness among pregnant women, respectively.[107] Pooled estimates from three randomised controlled trials (RCTs) and two case-control studies found that women that received a seasonal influenza vaccine during pregnancy had a 53% lower risk and 63% lower odds of LCI. No association was observed for influenza-like illness and respiratory illness.[107] A more recent pooled analysis study of three RCTs in Nepal, Mali and South Africa reported pooled estimates of vaccine efficacy of seasonal influenza vaccination against laboratory-confirmed influenza.[88] This study reported that seasonal influenza vaccination during pregnancy was highly efficacious against LCI during the entire study period (pooled efficacy: 50%; 95% CI: 32-63%; p <0.001), during pregnancy (pooled efficacy: 42; 95% CI: 12-61%; p = 0.01), and after pregnancy (pooled efficacy: 60%; 95% CI: 36-75%; p <0.001).[88]

2.4.4.2 Vaccine efficacy and effectiveness in infants

Maternal influenza vaccination has been recommended as a means to protect infants against influenza and influenza-associated complications during their first six months of life. A meta-analysis of four RCTs and three observational studies found that seasonal influenza vaccination during pregnancy was associated with a 42% and 72% reduction of LCI and LCI-associated hospitalisation among infants aged <6 months.[108] Studies have also shown that seasonal influenza vaccination during pregnancy is protective against other non-influenza outcomes. A pooled analysis of data from three RCTs found that seasonal influenza vaccination during pregnancy was highly efficacious against LCI among infants aged <6 months (efficacy: 35%; 95% CI: 19-47%).[88] Another pooled analysis study of the same RCTs reported a 20% lower incidence of severe pneumonia among infants aged <6 months of mothers that received a seasonal influenza vaccine during pregnancy.[109] A more recent study from Spain using 2017/18 and 2018/19 influenza season data reported that seasonal influenza vaccination during pregnancy was 61% effective in preventing hospitalisation due to severe LCI among infants aged <6 months.[110]

2.4.5 Safety of maternal influenza vaccination

2.4.5.1 Pregnant women

A number of RCTs and observational studies have evaluated the acute safety of maternal influenza vaccination also known as adverse events following immunisation (AEFI).[111] RCTs have shown that women receiving a seasonal influenza vaccine during pregnancy reported experiencing common minor adverse events, including malaise (42%), injection site reactions (24-77%), weakness/tiredness (24-36%), headache (21-35%), nausea (18%), myalgia (11-21%), joint pain (11-20%), and rigors (3-5%).[112, 113] While severe AEFI are not common, less than 6% of women have reported experiencing fever[112, 113] and severe injection site reactions[112] following vaccination. A recent Australian study using active surveillance of adverse events following routine influenza vaccination, found that 4.9% of women that received the influenza vaccine only reported experiencing an AEFI, and 7.4% of women that received both the influenza and pertussis vaccine reported experiencing a AEFI.[114] A prospective cohort study concluded that there was no significant difference in the rate of AEFI reports among pregnant women compared to non-pregnant women.[115]

In 2014, Naleway et al.[116] reviewed the existing literature of the safety of maternal influenza vaccination in regard to obstetric outcomes, including hypertensive disorders, gestational diabetes, and chorioamnionitis, and also reported on findings from two cohort studies involving the Vaccine Safety Datalink[117] and the Pregnancy and Influenza Project[118] cohort. One large, retrospective matched cohort study found a 11-12% reduction of gestational diabetes among women vaccinated with seasonal influenza vaccine during pregnancy compared to unvaccinated women.[119] Of the 10 studies, no other associations were reported; and this review reported consistent findings with other published studies of no increased risk of obstetric outcomes following maternal influenza vaccination. Few studies have evaluated the association between maternal influenza vaccination and mortality in pregnant women. A pooled analysis of two RCTs involving 5,809 pregnant women in Nepal, Mali and South Africa found no association between seasonal influenza vaccination and maternal all-cause mortality.[120]

2.4.5.2 Fetuses and newborns

Extensive research has been done to evaluate the impact of maternal influenza vaccination on health at birth. Several systematic reviews and meta-analyses have identified studies reporting on the safety of maternal influenza vaccination, showing no increased risk of preterm birth,[47, 121-126] low birthweight,[121-123, 125] small-for-gestational age at birth,[47, 122-125] stillbirths,[121, 122, 124, 127] spontaneous abortion,[124, 127, 128] congenital anomalies,[121-123, 128] ICU admission,[121] low APGAR score,[121] and fetal death. [47, 123, 126, 128] Multiple meta-analyses that evaluated the association between maternal influenza vaccination and multiple birth and fetal outcomes found decreased risks of preterm birth,[121, 123] very preterm birth,[121] low birthweight,[123] stillbirth,[124, 127] and fetal death.[123] However, many reviews have noted high levels of clinical, methodological, and/or statistical heterogeneity between studies and potential bias in the reviewed studies, and therefore these findings should be interpreted cautiously.[121, 124-126, 128, 129]

2.5 Gaps in knowledge

2.5.1 Effect of maternal antibodies on early childhood health

Although it is evident that maternal influenza vaccination is the best strategy to protect both mothers and their infants from influenza infection and the complications of influenza, there are potential unintended consequences of maternal immunisation that should be considered. The main biological mechanism responsible for the protection of infants from influenza infection is through maternal antibodies that are transferred to the fetus via transplacental transfer before birth and breastfeeding after birth.[130] High concentrations of vaccine-induced maternal antibodies have been shown to interfere with the infant's humoral immune response by inhibiting the generation of antibodies following routine childhood vaccination, and ultimately lowering the antibody titre.[131] Studies have highlighted concerns of the potential of maternal antibodies in blunting or dampening the infant's immune responses to primary vaccination.[80, 130] This phenomenon is known as immune interference or immunological blunting which has been shown to occur with multiple maternal vaccines, including measles, pertussis, and influenza.[80, 132] However, this inhibitory effect is mostly temporary and mainly affects the infant's humoral immune response to primary vaccination, with minimal effect after a booster dose.[132] Whether high

concentrations of maternal antibodies affect the cellular immune response in infants is yet to be confirmed.[55, 133] Furthermore, the clinical consequences, if any, of immunological blunting could vary depending on the disease and the vaccine.[134]

In conclusion, maternal influenza vaccination is effective in protecting younger infants from influenza infection in the first six months of life when they are more susceptible to severe infection, but there may be a potential inhibitory effect of maternally acquired antibodies which may increase the risk of infection among older infants. The risk of hospitalisation and death is much lower for older infants, therefore, this may be an acceptable trade-off.[135]

2.5.2 Effect of maternal influenza infection on early childhood health

The Developmental Origins of Health and Diseases hypothesis postulates that the prenatal period is a critical period of fetal development and is susceptible to exposure to adverse agents, particularly *in utero*, which can lead to long-term negative impacts on the health trajectory of the offspring (i.e., developmental programming).[136] It has been posited that *in utero* exposure to infection can impact the development of the neurologic system, and ultimately increasing susceptibility to adverse health outcomes later in life. Although the placenta functions as a physiologic and immunologic barrier and viruses rarely cross the placental barrier,[137] the developing fetus is still susceptible to physiological changes in the mother, such as fever and inflammation, which trigger immune responses to the infection in the mother.[137-139] The release of pro-inflammatory cytokines induced by viral infection (e.g., measles, rubella, varicella, polio, and herpes) during pregnancy has been shown to the impair critical brain development in offspring which may be responsible for the development of neurodevelopmental disorders,[137, 140] including schizophrenia, autism spectrum disorder (ASD), bipolar disorder and depression, and cerebral palsy.[136, 138, 139, 141, 142]

While multiple systematic reviews and meta-analyses have investigated the association between maternal influenza infection and health outcomes at birth and during the perinatal period, health outcomes beyond infant period have yet to be comprehensively reviewed. Of the studies evaluating the association between maternal influenza infection and early childhood health outcomes,

several studies have examined multiple neurodevelopmental disorders, particularly schizophrenia[143-157] and ASD.[158-162] Most studies originated from high-income countries in North America and Europe, and reported findings from seasonal epidemics.

Several studies have examined the association between maternal influenza infection and schizophrenia. A Danish register-based study, using a time-matched case-control design, reported an eight-fold increase in the incidence of schizophrenia among children aged >15 years of mothers that were hospitalised due to influenza.[144] This is consistent with two other studies that observed an increased odds and risk of schizophrenia among offspring of mothers that were exposed to influenza during the fifth month of pregnancy[146] and 5 months before delivering,[154] respectively. Another WA ecological study reported a significant increased risk of schizophrenia among female offspring of mothers that were exposed to influenza in the second trimester during the 1951 influenza epidemic only.[151] Conversely, this study also observed a decreased risk of schizophrenia among offspring, particularly males, of mothers that were exposed to influenza in the first trimester during the 1959 influenza epidemic only.[151] While these studies reported some significant associations, other studies have reported no association between maternal influenza infection and schizophrenia.[143, 145, 147-149, 151-153] A meta-analysis of 3 studies[163-165] reported no association between maternal influenza infection and ASD.[162] This is consistent with other epidemiological studies.[158-161]

Fewer studies have explored other neurodevelopmental outcomes and results have been mixed. Some studies have suggested that maternal influenza infection may be associated with an increased risk of bipolar disorder,[152, 166-168] psychosis and psychosis-like experiences,[169, 170] depression and depressive disorders,[152] attention deficit hyperactivity disorder,[171] and intellectual disability.[151, 172] Other studies examining the same outcomes have reported no associations.[143, 154, 168, 170, 173] No associations have been observed between maternal influenza infection and anorexia nervosa[174] and dementia.[175]

Many of the studies evaluating the association between maternal influenza infection and neurodevelopmental outcomes were conducted over a decade or more ago, and therefore the methodology and statistical techniques may be out-

dated and of lower quality compared to more recent studies. While there were mixed results with regard to the association between maternal influenza infection and neurodevelopmental outcomes, it is evident that additional studies using larger sample sizes and follow-up durations, and more up to date methodology and statistical techniques, are required to investigate this relationship further.

2.5.3 Effect of maternal influenza vaccination on early childhood health

In comparison to birth outcomes, relatively few studies have evaluated the longer-term health outcomes beyond the infant period and into early childhood. Of these studies, most studies have evaluated the long-term impact of pandemic influenza vaccines; few studies have focused on seasonal influenza vaccines specifically.

2.5.3.1 Maternal pandemic influenza vaccination and early childhood health

Following the expedited licensing of the pandemic A/H1N1 influenza vaccine, multiple studies have examined the association between pandemic influenza vaccination during pregnancy and multiple early childhood health outcomes. In Denmark, Bischoff et al[176] conducted a nested RCT and reported no difference in the incidence of all-cause infections between infants aged <1 year of vaccinated and unvaccinated mothers.[176] Another Dutch study, using a retrospective cohort design, observed no difference in the incidence of infection-related primary care contact between infants of vaccinated and unvaccinated mothers. In Canada, a large, retrospective cohort study conducted by Fell et al[177] assessed the incidence of influenza and influenza and pneumonia combined during multiple influenza time periods. During the post-2010-2011 period, the incidence of influenza and pneumonia combined was higher among infants aged <1 year of vaccinated mothers compared to infants of unvaccinated mothers. There were no other significant differences in the incidence of influenza and pneumonia combined in any other influenza time period nor for influenza only.[177]

Hviid et al[178] conducted a large, retrospective cohort study in Denmark which compared children aged <5 years of unvaccinated mothers with children of mothers vaccinated during the first trimester and children of mothers vaccinated during the second or third trimester. This study observed an increased risk of all-cause infections among children of mothers vaccinated during the first trimester and an increased risk of sepsis and Sjögren syndrome among children of mothers

vaccinated during the second or third trimester. Conversely, Hviid et al[178] reported a decreased risk of upper respiratory infections and gastrointestinal infections among children of mothers vaccinated during the second or third trimester. After accounting for multiple comparisons, the association between maternal influenza vaccination and the abovementioned outcomes were no longer significant. This study also found a decreased risk of 1-year, 3-year and 5-year all-cause hospitalisation among children of mothers vaccinated during the second or third trimester. This study observed no association between maternal influenza vaccination and multiple other infectious, allergic, autoimmune, neurological, and behavioural outcomes.

Another large, Canadian retrospective cohort study, conducted by Walsh et al,[179] found a small, increased risk of asthma and a lower incidence of gastrointestinal infections among children aged <5 years of vaccinated mothers compared to children of unvaccinated mothers. However, after accounting for multiple comparisons, these associations were no longer significant. Walsh et al[179] reported no other associations between maternal influenza vaccination and multiple other infectious, sensory, and non-specific morbidity outcomes, neoplasms and all-cause mortality. A large, Swedish prospective cohort study, using record linkage of national registry data, found no association between maternal influenza vaccination and all-cause mortality among children aged <6.4 years. Furthermore, no associations were observed when considering the trimester of vaccination and siblings as controls.[180]

2.5.3.2 Maternal seasonal influenza vaccination and early childhood health

Few studies have evaluated the early childhood health outcomes following seasonal influenza vaccination during pregnancy. A US matched case-control study assessed the effectiveness of seasonal IIV in preventing LCI-associated hospitalisation among infants aged <6 months (n = 247) and infants aged 6 months to <1 year (n = 58) that were born between October 2000 and April 2009.[181] There were 33 (13.4%) and 3 (5.2%) infants aged <6 months and aged 6 months to <1 year, respectively, of vaccinated mothers. While this study found that seasonal influenza vaccination during pregnancy was effective in preventing LCI-associated hospitalisation among infants aged <6 months (adjusted vaccine

effectiveness [aVE]: 91.5%; 95% CI: 61.7-98.1%) which is consistent with previous studies,[108] the study lacked statistical power to assess the vaccine effectiveness for infants aged 6 months to <1 year (unadjusted vaccine effectiveness [VE]: -41.4%; 95% CI: -2,257.3-91.5%).[181]

Another US study by van Santen et al,[182] using a retrospective cohort design, assessed the vaccine effectiveness of pneumococcal conjugate vaccine and pneumococcal conjugate vaccine and seasonal IIV combined among infants aged <1 year born between June 2002 and December 2009. This study included 9,807 infants, of which 2,416 (24.6%) and 7,391 (75.4%) were born from vaccinated and unvaccinated mothers, respectively. Infants of mothers that received pneumococcal conjugate vaccine and seasonal IIV combined had a higher absolute aVE (47.9%; 95% CI: 42.0-53.3%) against otitis media than for infants of mothers that received pneumococcal conjugate vaccine only (aVE: 37.6%; 95% CI: 23.1-49.4%), compared maternally unvaccinated infants. This was also observed for medically attended acute respiratory infections (aVE: 39.6%; 95% CI: 31.6-46.7% and aVE: 29.8%; 95% CI: 29.8%; 95% CI: 11.4-44.3%, respectively). Due to a small sample size, this study was unable to perform analyses for infants of mothers that received only seasonal IIV during pregnancy.

Zerbo et al[160] conducted a population-based cohort study which included 196,929 US children born between January 2000 and December 2010. This study prospectively followed 45,231 (23.0%) children of vaccinated mothers and 151,698 (77.0%) children of unvaccinated mothers for up to 15 years and found no difference in the risk of ASD between children of vaccinated and unvaccinated mothers. In trimester-specific analyses, there was a small, increased risk of autism spectrum disorder among children of mothers vaccinated during the first trimester (aHR: 1.20; 95% CI: 1.04-1.39). However, after accounting for multiple comparisons, this association was no longer significant. No associations were observed for maternal influenza vaccination during the second and third trimester.

2.5.4 Summary of gaps in knowledge

A review of the literature indicates that the effectiveness and safety of maternal influenza vaccination has been researched for several decades. Previous

research indicates that maternal influenza vaccination provides significant health benefits to both mothers and infants aged <6 months, and the most effective public health intervention to protect both these groups from influenza and the serious complications associated with influenza.[88, 107-110] While extensive research has consistently shown the safety of maternal influenza vaccination in regards to health outcomes at birth and during the perinatal period, fewer studies have evaluated the longer-term safety of maternal influenza vaccination, particularly the seasonal influenza vaccine, among children aged 6 months and above. The summary of current gaps in knowledge in the area of maternal influenza vaccination and early childhood health can be found in **Table 2-2**. This body of research will address several of these research gaps.

Table 2-2. Summary of current gaps in knowledge in the area of maternal influenza vaccination and early childhood health.

Effect of maternal influenza vaccination on early childhood health	
Gap 1	**Follow-up period:** Few studies have evaluated health outcomes among children beyond one year of age. Studies with longer follow-up durations are necessary to more effectively estimate the association between maternal influenza vaccination and outcomes that are typically diagnosed later in life (e.g., ASD).
Gap 2	**Consistent outcome measures:** More studies are needed that examine similarly defined outcomes ascertained in the same way to allow for comparisons between studies and for prospective meta-analyses.
Gap 3	**Influenza vaccine type:** More research is needed to evaluate early childhood health outcomes following seasonal influenza vaccination during pregnancy.
Gap 4	**Alternative approaches to bias control:** More studies are required that use causal inference techniques such as inverse-probability treatment weights, propensity score matching, and negative control analyses to control for biases and confounding.

Gap 5	**Geographic location:** The majority of studies examining the association between maternal influenza vaccination and early childhood health outcomes have originated from high-income countries in North America and Europe; more research is needed in other geographic locations. To date, no known published studies have evaluated the long-term health impacts of maternal influenza vaccination in countries in other continents (i.e., South America, Asia, Africa, Australia) and in low- and middle-income countries.
Gap 6	**Different stages of antibody transfer:** More studies are needed that stratify by preterm birth status to consider different stages of antibody transfer during pregnancy.

2.6 Chapter summary

Although most of the existing literature supports the continuation of current maternal vaccination programs, more population-based research is needed to evaluate paediatric impacts of seasonal influenza vaccination during pregnancy in young children <5 years of age. Through the use of record linkage of multiple administrative datasets in Western Australia, have the unique opportunity to conduct longitudinal cohort studies of maternal influenza vaccination at a population-level. Chapter Three will describe the research aims and objectives of the proposed study and Chapter Four will describe the methodology used to address these aims and objectives.

Chapter Three: Research Aims and Objectives

3.1 Research aim

This body of research will address several research gaps presented in **Table 2-2**. The proposed research will establish a population-based mother-child paired cohort in WA and using longitudinal linked data will estimate the association between seasonal influenza vaccination during pregnancy on multiple health outcomes among children <5 years of age. Findings from this body of work may be used to inform recommendations for current influenza vaccination programs in Australia and worldwide.

The overall aim of this body of research is to address the key gaps in knowledge of the potential health impacts of maternal influenza vaccination, particularly seasonal influenza vaccines, on early childhood health outcomes.

3.2 Research objectives

The current research involved the use of Western Australian, population-based mother-child paired cohort data derived from longitudinal linked retrospective data sources from several state-wide and national administrative datasets to address the following research aims and objectives:

Aim 1: To synthesise the current evidence on the association of maternal influenza vaccination and early childhood health outcomes in the first five years of life.

- **Objective 1.1:** To systematically search, compile, synthesise and critically review the current evidence on the association between maternal influenza vaccination and early childhood health outcomes (Chapter Five).

Aim 2: To measure the association between exposure to seasonal influenza vaccination during pregnancy and health outcomes in children up to five years of age. Specifically, the objective of this research is to estimate the association between exposure to seasonal influenza vaccination during pregnancy and:

- **Objective 2.1:** Laboratory-confirmed influenza and hospitalisation for influenza and other acute respiratory infections during childhood (Chapter Six).
- **Objective 2.2:** Allergic/atopic and autoimmune diseases during childhood (Chapter Seven).
- **Objective 2.3:** Neurodevelopmental disorders during childhood (Chapter Eight).
- **Objective 2.4:** All-cause child mortality (Chapter Nine).

Chapter Four: Methodology

4.1 Preamble

This chapter provides an overview of the methods used for this research, including information on the study population and setting, study design, and datasets used to address the research aims and objectives (Chapter Three). Chapters Six through Nine provide a detailed description of the analytical approach used for each specific outcome(s).

4.2 Study setting

WA covers the western third of Australia with a land size of 2.5 million square kilometres and a resident population of approximately 2.6 million people.[183, 184] There are approximately 33,000 births in WA each year, of which approximately 5% of the population is of Aboriginal ethnicity.[184] Influenza virus circulation tends to peak during the southern hemisphere winter months (June-August), with less distinct seasonality in the northern areas of the state.[27] Seasonal influenza vaccines are typically available in the beginning of April of each year and are disbursed throughout the year.[185] In Australia, seasonal IIV during pregnancy has been recommended by the Australian Technical Advisory Group on Immunisation since March 2000 and funded under the NIP since January 2010.[58, 186]

4.3 Study design, cohort, and population

This thesis work is based on a systematic review, followed by a series of population-based linkages to create the final study cohort, which included all singleton, live-born children identified from Birth Registrations and their mothers. These mother-child pairs were probabilistically linked with other population-based administrative health datasets using best practice protocols through the WA Data Linkage Branch.[187] As guided by the research aims and objectives of this body of work (**Sections 3.1 and 3.2**), the key steps involved in this research can be found in **Figure 4-1**.

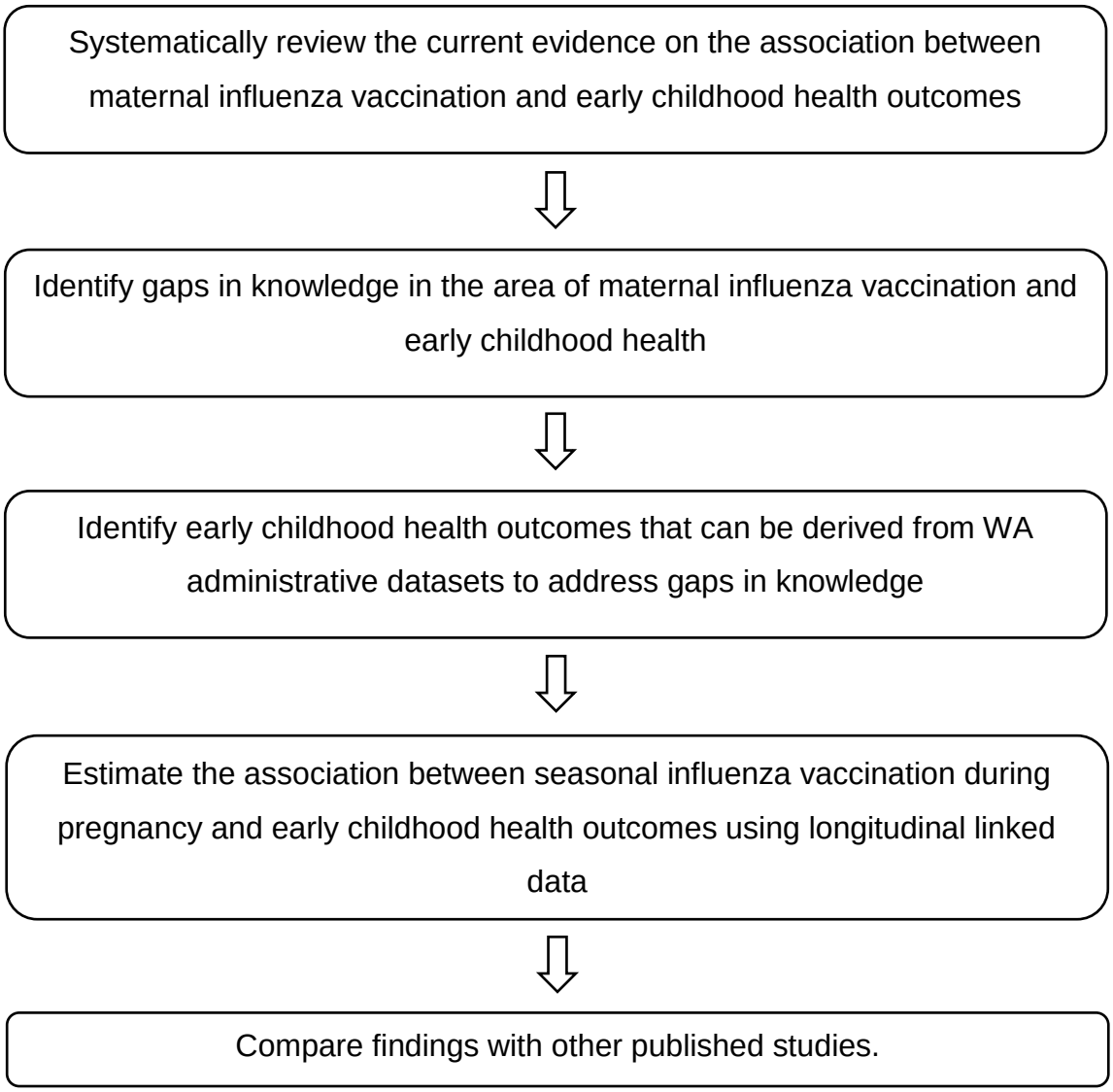


Figure 4-1. Flow diagram of steps involved in this research.

4.4 Record linkage in WA

Record linkage is the method of combining information of an individual, group, place or event from several sources. When an individual comes into contact with a particular service, such as being admitted to hospital, presenting to the emergency department (ED) or registering the birth or death of a child, a record of information is created and is documented in the relevant database or register. WA has a long history of success with record linkage research dating back to the 1970s.[188-190] In 1995, the WA Data Linkage System was formerly established as a collaboration between the WA Department of Health, Curtin University, the University of Western Australia and the Telethon Kids Institute and in 1997, the

WA Data Linkage Branch (WADLB; formerly named Data Linkage Unit) was established.[187]

The WADLB is responsible for creating and maintaining linkages within and between data sources, and grants access to linked data for ethically approved research, planning, evaluation and policy development projects.[191] Although WA lacks a population-wide, personal unique identifier (i.e., social security number) which is necessary for deterministic linkage, the WADLB uses probabilistic linkage processes to overcome this challenge. This method compares groups of records using complex non-unique identifiers or field matching algorithms.[192] These algorithms compare common fields, such as given name, surname, date of birth, and other relevant fields (dependent on the contents and context of the dataset),[193] and provides a similarity weighting index which is positively associated with the likelihood that two or more records belong to the same individual.[192] Clerical review is required to assess potential non-matched records;[192] this process has been shown to reduce the error rate of matching to less than 0.1%.[189]

Obtaining individual consent for population-level data is impractical, however, a waiver of consent can be approved by a properly constituted Human Research Ethics Committee in accordance with state and national privacy legislation. This allows the use of administrative data containing personal information for approved health research.[194] The WADLB implements the 'best practice protocol' which involves the 'separation principle' and de-identification to maintain confidentiality and protect privacy. This protocol involves: 1) the separation of personal demographic data, such as name, address and date of birth, from clinical or service information, such as health outcome data, 2) the linkage of records from different data sources, 3) the removal of personal identifiers (i.e., de-identification), and 4) the assignment of unique encrypted linkage keys to allow researchers to link individuals between different datasets. The record linkage process for the proposed body of research is illustrated in **Figure 4-2**.

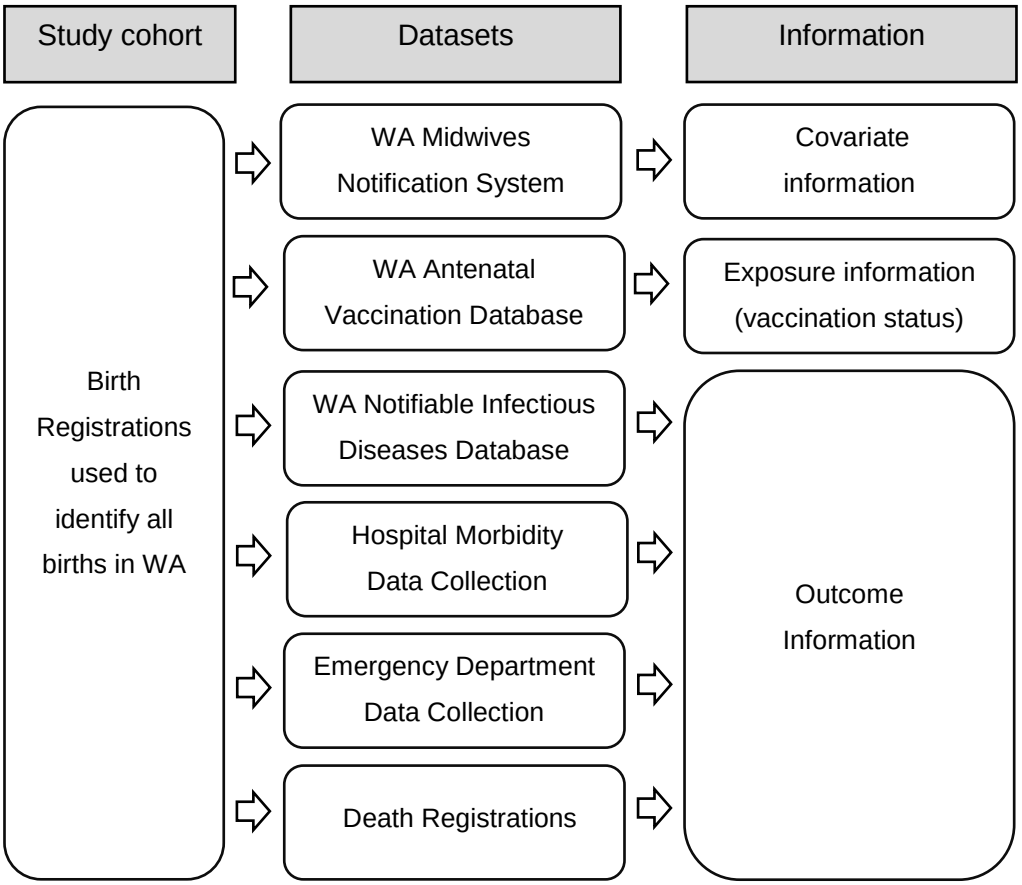


Figure 4-2. Flow diagram of record linkage process.

4.5 Description of datasets

4.5.1 Birth Registrations

The birth register is a state-wide register of all registered births in WA since 1974 and includes parental and infant information.[195] Under the *Births, Deaths and Marriages Act 1998*, births are obligated to be registered within 60 days of birth by the attending midwife, first attending medical professional, or the hospital.[196] Parental demographic information includes the age at the time of delivery, Aboriginal status, place of birth, and the year of arrival to Australia. Infant information includes the date of birth, sex, estimated gestational age, birthweight, and plurality.

4.5.2 Midwives Notification System

The Midwives Notification System (MNS) is a legally mandated, state-wide perinatal data collection and notification system, established in WA in 1975.[197]

This data collection routinely records data from birth notifications received from: a) public and private hospital maternity service midwives, b) public-funded and private practice midwives, c) and midwives, nurses and other medical practitioners that provided primary care to women who gave birth. This data collection includes all notified births of ≥20 weeks of gestation or birthweight ≥400 g (where gestational age is unknown) and includes maternal and infant information.

Maternal demographic and health information includes the age at the time of delivery, height, weight and body mass index, marital status, ethnicity, and diagnosed pre-existing medical conditions. Obstetric history information includes the number, outcome and mode of delivery of previous pregnancies (i.e., Caesarean section, vaginal delivery), estimated gestational age at the first prenatal care visit, smoking during pregnancy, diagnosed pregnancy complications, procedures/treatments, and as of July 2016, influenza and pertussis vaccination status during pregnancy. Labour and delivery details include onset of labour, induction, augmentation and analgesia use during labour, anaesthesia use during delivery, mode of delivery, plurality, and complications of labour and delivery. Infant information includes the date of birth (used to derive age in days), sex, ethnicity, estimated gestational age, and birthweight. Geocoding details include the mother's residential postcode, collector's district, and local government area.[197-199]

4.5.3 WA Antenatal Vaccination Database

The WA Antenatal Vaccination Database (WAAVD) is a state-wide database, managed by the WA Department of Health, summarising all vaccination records reported by health professionals administering vaccines, including seasonal IIV, to pregnant women since 1 April 2012. This database includes information on the date of vaccination, the vaccine brand and batch number, and the estimated gestation at the time of vaccination.[200] The database was retired following the introduction of routine antenatal immunisation data collection through the WA MNS in July 2016.[201] WAAVD vaccination records for seasonal IIV with dates of vaccinations between 1 April 2012 and 1 July 2016 were extracted.

4.5.4 WA Notifiable Infectious Diseases Database

The WA Notifiable Infectious Diseases Database (WANIDD) is a legally mandated database of notifiable infectious diseases, managed by the Communicable Disease Control Directorate, Public Health and Clinical Services Division, WA Department of Health. In Australia, LCI is a notifiable disease and WANIDD includes information on the date of specimen collection, notification, onset and optimal onset date, age at time of infection, laboratory method of confirmation (i.e., serology, antigen, nucleic acid amplification for influenza virus detection), virus type/sub-type, vaccination status and source of vaccination status.[202] WANIDD notification records for LCI with dates of specimen collection between 1 April 2012 and 2 July 2017 were extracted.

4.5.5 Hospital Morbidity Data Collection

The Hospital Morbidity Data Collection (HMDC) is a state-wide data collection summarising all episodes of care provided in the state's public and private hospitals, public and private psychiatric hospitals, and private day surgeries. The data collection includes information on the date of submission and separation, primary diagnosis code and up to 20 diagnosis codes (classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] codes), and inpatient procedures performed.[203]

4.5.6 Emergency Department Data Collection

The Emergency Department Data Collection (EDDC) is a state-wide data collection summarising emergency department presentations in WA's metropolitan public and private hospitals and includes information on patient demographics, admission and separation details, and diagnostic information (presenting symptom complaint and ICD-10-AM codes).[204]

4.5.7 Death Registrations

Death Registrations are recorded in a state-wide register of all registered deaths in WA since 1969. Under the *Births, Deaths and Marriages Act 1998*, deaths are obligated to be registered within 14 days of death. This register provides information on the age, sex, date and cause of death.[205] Information on the cause of death is provided by the medical practitioner or coroner.[206]

4.5.8 Time period of study datasets

The time period of availability of data from the following datasets can be found in **Table 4-1**.

Table 4-1. Time period of available data of datasets.

Dataset	Date range
Birth Registrations	1 January 2012 - 30 April 2018
Midwives Notification System	1 January 2012 - 31 December 2017
WA Antenatal Vaccination Database	1 April 2012 - 1 July 2016
WA Notifiable Infectious Diseases Database	1 January 2012 - 31 August 2017
Hospital Morbidity Data Collection	1 January 2012 - 30 June 2017
Emergency Department Data Collection	1 January 2012 - 30 June 2017
Death Registrations	1 January 2012 - 31 March 2018

4.6 Exposure measurement

Maternal influenza vaccination status (exposure of interest) was derived from the WAAVD for children born between 1 April 2012 and 1 July 2016. For the assessment of child mortality, where we had a longer follow-up period available due to more recent death registration data, we additionally derived vaccination status from the MNS for children born after 1 July 2016. Children of mothers who had a record of receipt of seasonal IIV during pregnancy were considered 'maternally vaccinated'. Children whose mothers had no such record were considered 'maternally unvaccinated.'

4.7 Outcome assessment

In this thesis, the primary outcomes of interest were:

a) respiratory infections, specifically laboratory-confirmed influenza, hospitalisation for influenza, and hospitalisation for acute respiratory infections (Chapter Six),

b) allergic/atopic and autoimmune outcomes, specifically hospitalisation or ED presentation for allergic/atopic and autoimmune disorders (Chapter Seven)

c) neurodevelopmental disorders (Chapter Eight), and

d) child mortality (Chapter Nine).

All outcomes were identified from WANIDD, the HMDC, the EDDC and death registration. Individual ICD-10-AM codes used to identify each of these outcomes of interest are described in the Appendices for each results chapter.

4.8 Statistical analysis

The studies included in this thesis all used the following statistical approach. Descriptive statistics were calculated to compare the demographic and health characteristics between children of vaccinated and unvaccinated mothers. The odds of maternal vaccination were estimated using univariate logistic regression models. The analyses either applied inverse-probability of treatment (maternal vaccination) weights (IPTW) to restrict the influence of baseline probability of vaccination (Chapters Six through Eight) or adjusted for prior identified confounders (Chapter Nine), and we also included all-cause injury and skin infections were included as negative control conditions to assess for possible residual bias. Cox proportional hazard regression models were used to estimate unadjusted and adjusted hazard ratios (HR and aHR, respectively) with 95% confidence intervals (CI) for each study outcome. A more comprehensive description of the statistical approach for each chapter of results, including post hoc sensitivity analyses, are provided in Chapters Six through Nine.

4.9 Ethical approval

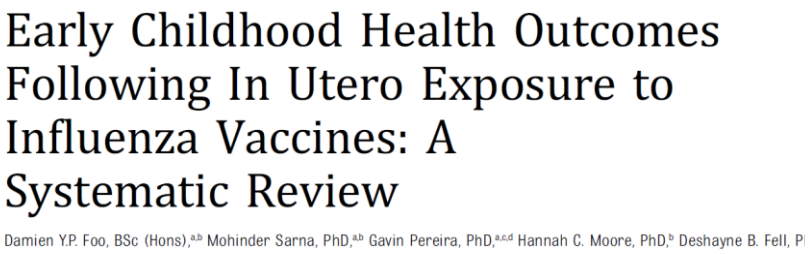
This study was part of a multi-jurisdictional study which aims to measure the effectiveness of maternal influenza and pertussis vaccination in Western Australia, Northern Territory and Queensland (Links2HealthierBubs: Influenza and pertussis vaccine effectiveness and safety in pregnancy) and was funded by the National Health and Medical Research Council (GNT1141510). As part of this study, ethical approval and a waiver of consent from the Department of Health WA Human Research Ethics Committee (RA#2016.56), the Curtin University Human Research Ethics Committee (RA#20217-0808), and the Western Australia Aboriginal Health Ethics Committee (#889) was obtained. A student research and confidentiality declaration by the WA Department of Health was signed by the PhD Candidate to ensure data is kept confidential.

Chapter Five: Systematic Review

5.1 Preamble

This chapter is based on a paper published in *Pediatrics*. The chapter which follows is a verbatim copy of the content from the published manuscript, except for minor modifications for readability. A copy of the published manuscript is available in **Appendix B**, and the online supplementary material is available in **Appendix C**.

Study One – Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review


Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review

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5.2 Abstract

Context: Vaccination during pregnancy is an effective strategy for preventing infant disease; however, little is known about early childhood health after maternal vaccination.

Objectives: To systematically review the literature on early childhood health associated with exposure to influenza vaccines *in utero*.

Data sources: We searched CINAHL Plus, Embase, Medline, Scopus, and Web of Science for relevant articles published from inception to July 24, 2019.

Study selection: We included studies published in English reporting original data with measurement of *in utero* exposure to influenza vaccines and health outcomes among children <5 years of age.

Data extraction: Two authors independently assessed eligibility and extracted data on study design, setting, population, vaccines, outcomes, and results.

Results: The search yielded 3,647 records, of which 9 studies met the inclusion criteria. Studies examined infectious, atopic, autoimmune, and neurodevelopmental outcomes, and all-cause morbidity and mortality. Authors of 2 studies reported an inverse association between pandemic influenza vaccination and upper respiratory tract infections, gastrointestinal infections, and all-cause hospitalisations; and authors of 2 studies reported modest increased association between several childhood disorders and pandemic or seasonal influenza vaccination, which, after adjusting for confounding and multiple comparisons, were not statistically significant.

Limitations: Given the small number of studies addressing similarly defined outcomes, meta-analyses were deemed not possible.

Conclusions: Results from the few studies in which researchers have examined outcomes in children older than 6 months of age did not identify an association between exposure to influenza vaccines *in utero* and adverse childhood health outcomes.

5.3 Introduction

Influenza is a major respiratory infection that can lead to severe illness and death at any age,[24] but high-risk populations such as pregnant women and infants <6 months of age have a greater risk of severe illness.[207, 208] No vaccines are currently licensed for infants in this age group.[11, 209, 210] Because maternal antibodies cross the placenta during pregnancy,[133] influenza vaccines administered to pregnant women are an effective means of protecting both mothers and their infants from influenza infection.[211-213] Given these benefits, the 2012 WHO position paper on influenza vaccines recommended pregnant women be considered the highest priority risk group for countries considering expansion of their seasonal influenza vaccination program.[11] Globally, >50% of countries have policies recommending influenza vaccines to pregnant women.[10, 11, 214-216]

Despite these widespread recommendations, vaccine uptake is poor in many countries,[91, 92, 95, 96, 99, 100, 102, 104] with concerns around vaccine safety cited as the most common reason for vaccine hesitancy.[103] These concerns stand in contrast to the substantial evidence supporting the safety of administration of IIVs during pregnancy on maternal, fetal, and early infant outcomes. The safety of influenza vaccination during pregnancy has been consistently highlighted in systematic reviews and meta-analyses.[124, 125, 127] These studies concluded that influenza vaccination during pregnancy was not associated with increased risk of congenital anomalies, stillbirth, preterm birth, fetal growth restriction, and/or low birth weight.[124, 125, 127, 217] Although a recent review assessed influenza and other respiratory outcomes in early childhood, no study has comprehensively assessed longer-term child health outcomes in association with *in utero* exposure to IIV.[218]

5.4 Methods

We conducted a systematic review of the literature related to IIV during pregnancy and childhood health outcomes, as guided by the minimum evidence-based set of items for reporting in systematic reviews outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[219] The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews (CRD42014014384) before commencing the review.

5.4.1 Data Sources and Search Strategy

We searched CINAHL Plus, Embase, Medline, Scopus, and Web of Science databases for peer-reviewed literature from inception to July 24, 2019, using a combination of medical subject headings and keywords related to prenatal influenza vaccination and early childhood health outcomes (**Supplementary Table C-1**). Our search included experimental and observational studies, including cross-sectional, case-control, and cohort studies. As recommended,[220, 221] we consulted with a medical librarian to develop our search strategy.

5.4.2 Study Selection

Eligible studies included those investigating any mother–child pair population, in which exposure to influenza vaccines *in utero* (pandemic or seasonal) was reported, an unexposed mother–child pair control group is present, and ≥1 health outcome in children aged 6 months to 5 years was investigated. We made the following exclusions: articles not published in peer-reviewed journals, articles published in languages other than English, studies not conducted in humans, reviews, editorials, commentaries, letters, case studies, and case series. First, two independent reviewers (D.Y.P.F. and M.S.) screened and reviewed the titles and abstracts of records retrieved during the search for inclusion criteria. Second, the reviewers screened and reviewed the full-text articles for eligibility in accordance with study inclusion and exclusion criteria. Studies deemed to meet the inclusion criteria by the two reviewers were included in the final review. A third reviewer (A.K.R.) resolved any conflicts between the two reviewers during each screening and review stage.

5.4.3 Data Extraction and Risk-of-Bias Assessment

We developed a standardised data collection form to extract information on study characteristics, including study design, geographic location, participant demographics, definition and ascertainment of exposure and outcomes (including type of influenza vaccine), effect sizes and CIs, and confounding variables. Two reviewers (D.Y.P.F. and M.S.) independently extracted information from each of the included articles.

For observational studies, we used the Newcastle–Ottawa scale (NOS) to assess risk of bias (**Tables 5-1 to 5-3**).[222] The NOS has a maximum score of 9, with a greater score indicating the lowest risk of bias. The scoring system is based on the following criteria: selection bias (maximum score: 4), comparability of study groups (maximum score: 2), and ascertainment of exposure for case-control studies or outcome for observational studies (maximum score: 3).[222] Observational studies were considered at low risk of bias if they scored ≥8 and moderate-high risk of bias if they scored <8.

For RCTs, we used the Cochrane risk-of-bias tool to assess risk of bias.[221] The Cochrane risk-of-bias tool addressed 5 major domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel and other potential threats to validity), detection bias (blinding of outcome assessment and other potential threats to validity), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting).[221] Consistent with the Cochrane risk-of-bias tool scoring, articles were classified as low risk of bias, some concerns of bias, or high risk of bias.[221] Two reviewers (D.Y.P.F. and M.S.) independently assessed the quality of case-control and cohort studies and RCTs using the NOS[223] and Cochrane risk-of-bias tool,[224] respectively. Any conflicts between the two reviewers during the quality assessment process were resolved by a third reviewer (A.K.R.).

5.4.4 Data Synthesis and Analysis

We developed a narrative description of the characteristics and results of included studies. Where possible, results were provided by trimester of vaccination and type of vaccine. To generate pooled effect estimates for each outcome, a random effects meta-analysis was planned *a priori*, dependent on whether a sufficient number of studies were retrieved using commonly defined end-points (n > 2).

Table 5-1. Results of Risk-of-Bias Assessment for Cohort Studies.

			Selection				Comparability[b]		Outcome	
Cohort studies[a]	**Overall quality score (Maximum score: 9/9)**	**Risk of bias[c]**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of cases**	**Outcome of interest was not present at the start of study**	**Comparability of the design and analysis for cohorts**	**Assessment of outcome**	**Sufficient follow-up duration**	**Adequacy of follow-up of cohorts**
van Santen *et al.* (2013)	6/9	High	—	★	★	★	★	★	★	—
Ludvigsson *et al.* (2015)	8/9	Low	★	★	★	★	★★	★	★	—
van der Maas *et al.* (2016)	7/9	High	—	★	—	★	★★	★	★	★
Fell *et al.* (2016)	8/9	Low	★	★	★	★	★★	★	★	—
Zerbo *et al.* (2017)	7/9	High	—	★	★	★	★★	★	★	—
Hviid *et al.* (2017)	8/9	Low	★	★	★	★	★★	★	★	—
Walsh *et al.* (2019)	8/9	Low	★	★	★	★	★★	★	★	—

[a] Cohort studies were assessed using the Newcastle–Ottawa scale. Each ★ represents whether an individual criterion is satisfied. Each — represents whether an individual criterion is not satisfied.

[b] Low risk of bias: overall risk of bias score ≥8; high risk of bias: overall risk of bias score <8.

[c] All criteria receives a maximum score of 1 ★ except for comparability of study groups where an additional ★ may be allocated for the control of additional important confounders.[222]

Table 5-2. Results of Risk-of-Bias Assessment for Case-Control Studies.

			Selection			Comparability[b]		Outcome		
Case-control studies[a]	**Overall quality score (Maximum score: 9/9)**	**Risk of bias[c]**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of cases**	**Outcome of interest was not present at the start of study**	**Comparability of the design and analysis for cohorts**	**Assessment of outcome**	**Sufficient follow-up duration**	**Adequacy of follow-up of cohorts**
Benowitz *et al.* (2010)	7/9	High	★	—	★	★	★	★	★	★

[a] Cohort studies were assessed using the Newcastle–Ottawa scale. Each ★ represents whether an individual criterion is satisfied. Each — represents whether an individual criterion is not satisfied.
[b] Low risk of bias: overall risk of bias score ≥8; high risk of bias: overall risk of bias score <8.
[c] All criteria receives a maximum score of 1 ★ except for comparability of study groups where an additional ★ may be allocated for the control of additional important confounders.[222]

Table 5-3. Results of Risk-of-Bias Assessment for RCTs.

		Selection bias		Performance bias	Attrition bias	Detection bias	Reporting bias
RCTs[a]	**Risk of bias[b]**	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel and other potential threats to validity**	**Incomplete outcome data**	**Blinding of outcome assessment and other potential threats to validity**	**Selective outcome reporting**
Bischoff *et al.* (2015)	High	Low	Low	Low	Low	High	High

[a] RCTs were assessed using the Cochrane risk-of-bias tool. Each risk of bias item receives a judgement on risk of bias.
[b] Risk of bias judgement given by algorithm.[224]

5.5 Results

5.5.1 Study Selection

We identified 3,647 records, of which 3,551 were excluded after initial title and abstract screening. We reviewed 96 full-text articles, of which 9 were deemed eligible for inclusion (**Figure 5-1**). Reasons for exclusions included no measurement of influenza vaccination during pregnancy (n = 4), no reported outcome measure of early childhood health (n = 33), not a comparative observational study or RCT (n = 44), or not published in English (n = 6).

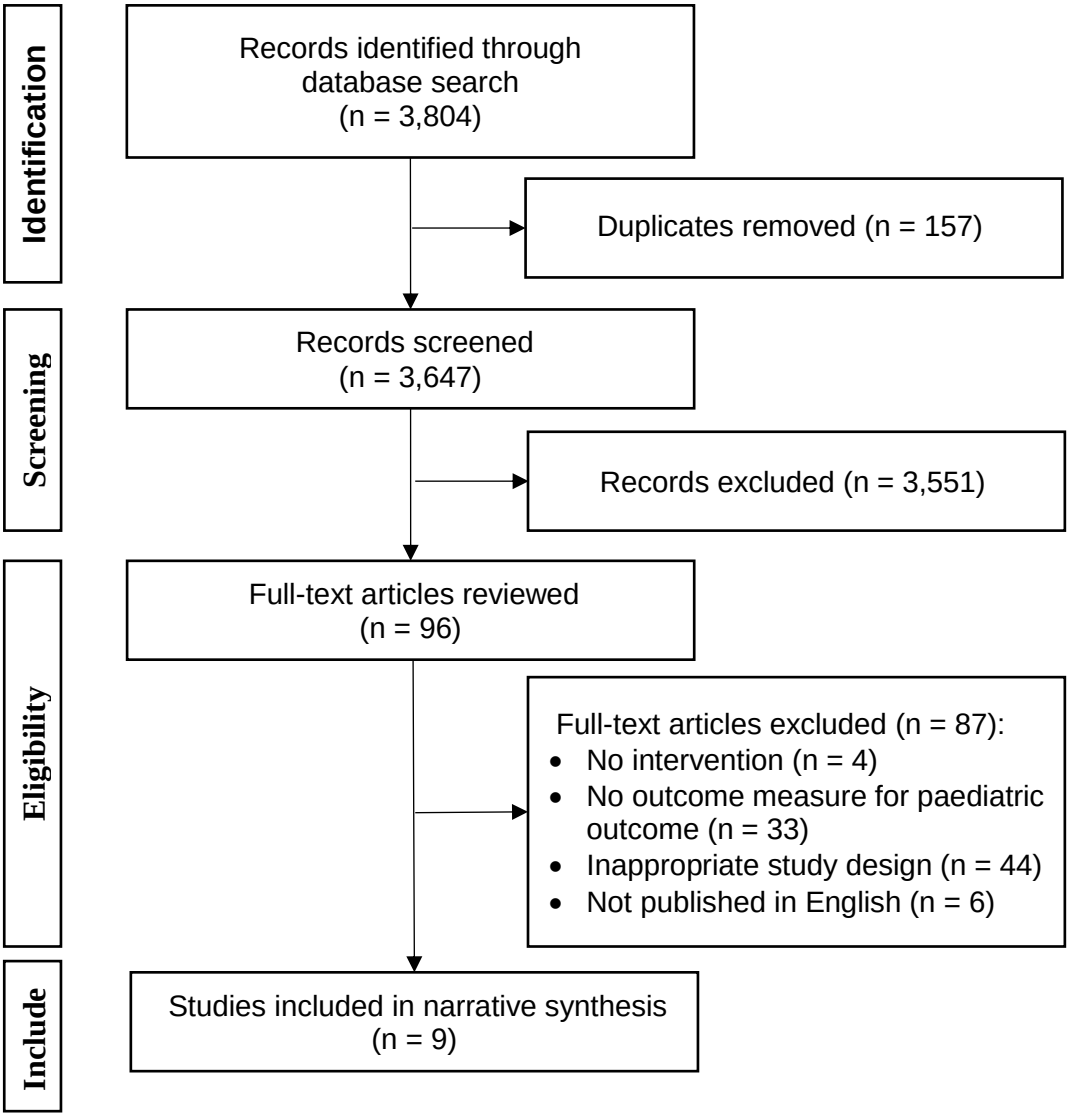

Figure 5-1. Flow diagram of study selection process for systematic review of the literature on early childhood health outcomes associated with in utero exposure to influenza vaccines.

5.5.2 Study Characteristics

Of the 9 included studies, methodology and study outcomes were highly diverse (**Table 5-4**). All of the studies originated from high-income countries in North America[160, 177, 179, 181, 182] (n = 5) or Europe[176, 180, 225, 226] (n = 4), and study periods ranged between 1980 and 2012. Estimates from the same population were reported in 2 articles.[160, 182] One study was an RCT,[176] 5 studies were retrospective cohort studies,[177-179, 182, 225] and 2 were prospective cohort studies[160, 180]; 1 study used a case-control design.[181] Record linkage was used in most studies to measure prenatal influenza vaccination and early childhood health outcomes (n = 7). Studies ranged in sample size from 306 to 275,500 mother–infant pairs. With the exception of 1 study in which children 6 to 12 months of age were specifically examined,[181] the follow-up period of included studies began at birth and ranged from 1 to 15 years of age.

5.5.3 Exposure Assessment

Researchers in 6 studies investigated pandemic[176-180] influenza vaccines, and researchers in 3 investigated seasonal[160, 181, 182] influenza vaccines (**Table 5-4**). Of the 6 studies on 2009 monovalent pandemic influenza A virus subtype H1N1 (A/H1N1) vaccines, researchers of 4 studies exclusively investigated adjuvanted vaccines (MF59-adjuvant: n = 2;[176, 225] AS03-adjuvant: n = 2[178, 180]). Vaccination status during pregnancy was ascertained by self-report (n = 1),[225] random allocation (n = 1),[176] written or electronic health records (n = 3),[160, 181, 182] and registry information (n = 4).[177-180]

5.5.4 Outcome Assessment

Outcomes included infectious (n = 7), atopic (n = 2), autoimmune (n = 2), and neurodevelopmental (n =3) conditions, neoplasms (n = 1), and all-cause morbidity (n = 2) and mortality (n = 2) (**Table 5-5**). Infections or infectious conditions included influenza, pneumonia, otitis media, sepsis, acute respiratory infections, gastrointestinal infections, viral infections, and all-cause infection-related primary care contact. Atopic conditions included asthma. Autoimmune conditions included coeliac disease, ulcerative colitis, Crohn disease, juvenile arthritis, Sjögren syndrome, vasculitis, reactive arthropathy, idiopathic

Table 5-4. Characteristics of Studies Included in a Systematic Review of the Literature on Early Childhood Health Outcomes Associated With In Utero Exposure to Influenza Vaccines.

Author(s) (year), country	Study design	Ascertainment of exposure	Type of vaccine	Study period	Age of follow-up	No. of participants		Trimester of exposure, n (%)			Ascertainment of outcome	Outcome(s)
						Exposure	Control	First	Second	Third		
Pandemic influenza vaccine												
Bischoff *et al.* (2015), Denmark	Nested randomised controlled trial	Random allocation	MF59-adjuvanted pandemic A/H1N1 influenza vaccine	2009 to 2010	0-1 year	51	332	Not specified			Parent-reported daily diary cards reviewed by research doctor	Infections (common cold, pharyngitis, otitis, pneumonia, fever and gastrointestinal infection)
Ludvigsson *et al.* (2015), Sweden	Prospective cohort	Register	AS03-adjuvanted pandemic A/H1N1 influenza vaccine	October 2, 2009 to November 26, 2010	0-6.4 years	41,183	234,317	Not specified			Death Register	Mortality
van der Maas *et al.* (2016), Netherlands	Retrospective cohort	Self-report	MF59-adjuvanted pandemic A/H1N1 influenza vaccine	November, 2009 to December 2009	0-1 year	1,357	669	-	1,357 (100) across the second and third trimester		Register and medical records	Infection-related primary care contact (fever, symptoms of infection of ≥1 organ system or prescriptions for infectious symptoms)
Fell *et al.* (2016), Canada	Retrospective cohort	Register	Pandemic A/H1N1 influenza vaccine[a]	November 2, 2009 to October 31, 2010	0-1 year	36,044	81,302	Not specified			Medical records	Influenza; combination of pneumonia and influenza
Hviid *et al.* (2017), Denmark	Retrospective cohort	Register	AS03-adjuvanted pandemic A/H1N1 influenza vaccine	November 2, 2009 to March 31, 2010	0-5 years	6,311	55,048	349 (5.5)	5,962 (94.5) across the second and third trimester		Register and medical records	Hospitalisations; infectious diseases; autoimmune diseases; neurological diseases; behavioural disorders
Walsh *et al.* (2019), Canada	Retrospective cohort	Register	Pandemic A/H1N1	November 2, 2009 to	0-5 years	31,295	72,954	Not specified			Medical records	Infectious diseases; atopic diseases; neoplasms; sensory

			influenza vaccine[a]	October 31, 2010								disorders; urgent and inpatient health services use; complex chronic conditions; mortality
Seasonal influenza vaccine												
Benowitz *et al.* (2010), United States of America	Matched case-control	Medical records	Inactivated influenza vaccine	October 1, 2000 to April 30, 2009	0-1 year	113[b]	193	-	8 (22.2)	28 (77.8)	Direct fluorescent antibody test	Laboratory-confirmed influenza
van Santen *et al.* (2013), United States of America	Retrospective cohort	Medical records	Trivalent inactivated influenza vaccine	June 2, 2002 to December 31, 2009	0-1 year	2,416	7,391	Not specified			Medical records	Acute otitis media; medically attended acute respiratory infections
Zerbo *et al.* (2017), United States of America	Prospective cohort	Medical records	Inactivated influenza vaccine[c]	2000 to 2010	0-15 years	45,231	151,698	13,477 (29.8)	17,475 (38.6)	16,095 (35.6)	Medical records	Autism spectrum disorder

[a] Study did not distinguish between unadjuvanted pandemic influenza vaccine (targeted at pregnant women) and AS03-adjuvanted pandemic influenza vaccine (targeted at the general population).
[b] Number of case participants (infants hospitalised for laboratory-confirmed influenza).
[c] Study included the 2009 A/H1N1 pandemic year; investigators did not distinguish between the seasonal trivalent influenza vaccine from the pandemic monovalent vaccine during this period of time.

thrombocytopenic purpura, type-1 diabetes, Bell palsy, and Guillain-Barré syndrome. acute respiratory infections, gastrointestinal infections, viral infections, and all-cause infection-related primary care contact. Atopic conditions included asthma. Autoimmune conditions included coeliac disease, ulcerative colitis, Crohn disease, juvenile arthritis, Sjögren syndrome, vasculitis, reactive arthropathy, idiopathic thrombocytopenic purpura, type-1 diabetes, Bell palsy, and Guillain-Barré syndrome.

Neurodevelopmental conditions included epilepsy, autism spectrum disorder, intellectual disability, and sensory disorders. All-cause morbidity outcomes included 1-year all-cause hospitalisation, 3-year all-cause hospitalisation, 5-year all-cause hospitalisation, urgent and inpatient health services used, and paediatric complex chronic conditions. International Classification of Diseases clinical diagnosis codes were used in the majority of studies (n = 5) to identify outcomes.

Given the small number of studies in which similarly defined outcomes were addressed, meta-analyses were deemed not possible.

5.5.5 Confounder Assessment

Among the 9 included studies, several maternal and child characteristics were included as potential confounders (**Supplementary Table C-2**). Maternal characteristics included maternal age (n = 6), ethnicity (n = 2), place of birth (n = 3), place of residence (n = 3), socioeconomic status and income (n = 4), education (n = 3), BMI (n = 2), parity (n = 5), medical comorbidities (n = 5), pregnancy complications (n = 3), multiple gestations and/or births (n = 3), smoking during pregnancy (n = 4), season of conception (n = 2), and gestational age (n = 2). Child characteristics mostly included sex (n = 4). Other characteristics, such as marital status, calendar year of conception, use of antenatal care, medication use, the child's ethnicity, and other birth outcomes, were less commonly controlled for as confounders (n = 1) (**Supplementary Table C-2**). One study accounted for the potential influence of childhood influenza immunisation by censoring at age at influenza vaccination.[182]

5.5.6 Infectious Conditions

In the 2 studies in which researchers examined influenza infection, infection status was ascertained either by a positive result by direct fluorescent antibody test (for LCI)[181] or by using primary or secondary diagnostic codes for (1) influenza alone or (2) influenza and pneumonia.[177] Outcome measures were expressed as VE (calculated as [1 – OR comparing the odds of infection in exposed versus unexposed] × 100%) or crude incidence rates for influenza infection among children exposed to IIV *in utero* versus unexposed. Benowitz et al[181] assessed LCI and did not identify an association between IIV exposure *in utero* and VE in infants aged ≥6 months (VE: 241.4%; 95% CI: -2257.4-91.5%) (**Table 5-5**). However, as noted by Benowitz et al,[181] because of the small sample size of infants aged ≥6 months, there was low statistical power to assess VE. In a study that followed infants ≤1 year of age, Fell et al[177] observed incidence rates of influenza that did not differ between children exposed to IIV *in utero* compared with unexposed children for each influenza time period examined, including the 2009 A/H1N1 pandemic season (IRR: 0.61; 95% CI: 0.32-1.17) and the post-2009 A/H1N1 pandemic period (adjusted incidence rate ratio [aIRR]: 1.05; 95% CI: 0.81-1.37). Incidence rates for influenza and pneumonia were significantly higher among infants exposed to IIV *in utero* compared with unexposed infants in the post-2009 A/H1N1 pandemic period (aIRR: 1.17; 95% CI: 1.05-1.31). However, incidence rates for influenza and pneumonia did not differ significantly during the 2009 A/H1N1 pandemic season (aIRR: 1.04; 95% CI: 0.84-1.29) (**Table 5-5**).

Researchers of two studies assessed infection-related primary care contact (fever, symptoms of infection of ≥1 organ system, or prescriptions for infectious symptoms) by examining medical records given by primary care providers[225] and infections (common cold, pharyngitis, otitis, pneumonia, and gastrointestinal infection) or fever by parent-reported daily diary cards reviewed by a research doctor.[176] Neither van der Maas et al[225] (aIRR: 1.07; 95% CI: 0.91-1.28) nor Bischoff et al[176] (aIRR: 0.99; 95% CI: 0.84-1.18) found a difference in incidence of infections between children of vaccinated and unvaccinated mothers in their studies (**Table 5-5**).

Studies in which upper respiratory tract infections, lower respiratory tract infections, and all-cause infections were examined found a statistically significant reduction in risk of upper respiratory tract infections (adjusted rate ratio [aRR]: 0.92; 95% CI: 0.85-0.99)[178] and all-cause infections (aRR: 1.71; 95% CI: 1.08-2.44)[178] but not lower respiratory tract infections (**Table 5-5**).[178, 179] Hviid et al[178] observed an inverse association with upper respiratory tract infections and all-cause infections in children whose mothers were vaccinated with pandemic influenza vaccine in the second or third trimester and in the first trimester, respectively. However, after adjusting for multiplicity using a Bonferroni correction, these associations were no longer significant. Data from one of 2 studies[179, 182] that investigated otitis media in infants ≤1 year of age reported a lower absolute adjusted VE (calculated as 1 – the ratio of the incidence of otitis media in exposed versus unexposed children) for children whose mothers received a pneumococcal conjugate vaccine while pregnant (37.6%; 95% CI: 23.1-49.4) than children whose mothers received a pneumococcal conjugate vaccine and trivalent IIV while pregnant (47.9%; 95% CI: 42.0-53.3), as compared with the children whose mothers received no vaccines during pregnancy.[182] The second study, by Walsh et al,[179] followed offspring ≤5 years of age and found no difference in incidence rates between children exposed to IIV *in utero* and unexposed children (aIRR: 1.03; 95% CI: 1.00-1.06). Walsh et al[179] and Hviid et al[178] each observed a statistically significant reduction in the risk of gastrointestinal infections (aIRR: 0.94; 95% CI: 0.91-0.98 and aRR: 0.84; 95% CI: 0.74-0.94, respectively). Hviid et al[178] observed this association in children whose mothers were vaccinated in either the second or third trimester but not in the first trimester. Second or third trimester prenatal influenza vaccination was also associated with a significant increase in risk of sepsis (aRR: 1.96; 95% CI: 1.26-3.05).[178] However, after taking multiple comparisons into account using Bonferroni-corrected CIs, associations for gastrointestinal infections and sepsis were not significant and could have been due to chance (**Table 5-5**).[178, 179]

Table 5-5. Adjusted Effect Estimates of Early Childhood Health Outcomes Associated With In Utero Exposure to Influenza Vaccine, by Pandemic and Seasonal Influenza Vaccines.

Author(s) (year)	Outcome assessed	Effect estimate for vaccination at any time during pregnancy	Effect estimate by trimester		
			First trimester	Second trimester	Third trimester
Pandemic influenza vaccine					
Bischoff *et al.* (2015)	All infections (common cold; pharyngitis; otitis; pneumonia; fever; gastrointestinal infection)	aIRR: 0.99 (0.84-1.18)			
Ludvigsson *et al.* (2015)	Mortality	aHR: 0.97 (0.69-1.36) vs. sibling control: aHR: 0.78 (0.52-1.19)[a]	aHR: 0.86 (0.51-1.47) vs. sibling control: aHR: 0.47 (0.22-1.01)[a]	aHR: 1.10 (0.69-1.76) vs. sibling control: aHR: 1.44 (0.74-2.78)[a]	aHR: 0.93 (0.54-1.60) vs. sibling control: aHR: 0.65 (0.30-1.39)[a]
van der Maas *et al.* (2016)	Infection-related primary care contact	aIRR: 1.07 (0.91-1.28)			
Fell *et al.* (2016)	Influenza, by season				
	2009 A/H1N1 pandemic season	IRR: 0.61 (0.32-1.17)			
	Post 2009 A/H1N1 pandemic period	aIRR: 1.05 (0.81-1.37)			
	Pre-2010-2011 period	aIRR: 1.08 (0.80-1.44)			
	2010-2011 period	aIRR: 0.88 (0.76-1.02)			
	Post-2010-2011 period	aIRR: 0.72 (0.50-1.04)			
	Pre-2011-2012 period				
	Influenza and pneumonia, by season				
	2009 A/H1N1 pandemic season	aIRR: 1.04 (0.84-1.29)			
	Post 2009 A/H1N1 pandemic period	aIRR: **1.17 (1.05-1.31)**			
	Pre-2010-2011 period	aIRR: 1.07 (0.93-1.25)			

	2010-2011 period	aIRR: 0.99 (0.92-1.07)		
	Post-2010-2011 period	aIRR: 1.00 (0.85-1.17)		
	Pre-2011-2012 period	aIRR: 0.81 (0.38-1.70)		
Hviid *et al.* (2017)	1-year hospitalisation		aHR: 1.10 (0.89-1.37); aRR: 1.15 (0.90-1.48)	aHR: **0.94 (0.89-0.99)**; aRR: **0.93 (0.87-0.99)**
	3-year hospitalisation		aHR: 1.15 (0.97-1.37); aRR: 1.21 (0.98-1.50)	aHR: **0.95 (0.90-0.99)**; aRR: **0.96 (0.90-1.01)**
	5-year hospitalisation		aHR: 1.13 (0.96-1.32); aRR: 1.17 (0.94-1.45)	aHR: **0.95 (0.91-0.99)**; aRR: **0.93 (0.87-0.99)**
	Upper respiratory tract infections		aRR: 1.08 (0.80-1.46)	aRR: **0.92 (0.85-0.99)**; aRR: 0.92 (0.81-1.03)[b]
	Lower respiratory tract infections		aRR: 0.90 (0.63-1.28)	aRR: 0.92 (0.84-1.00)
	Gastrointestinal infections		aRR:1.03 (0.68-1.55)	aRR: **0.84 (0.74-0.94)**; aRR: 0.84 (0.70-1.00)[b]
	Meningitis			aRR: 1.17 (0.61-2.24)
	Sepsis			aRR: **1.96 (1.26-3.05)**; aRR: 1.96 (0.98-3.91)[b]
	Viral infections		aRR: 1.20 (0.82-1.73)	aRR: 0.91 (0.82-1.00)
	Other infections		aRR: **1.71 (1.08-2.73)**; aRR: 1.71 (0.83-3.56)[b]	aRR: 0.92 (0.81-1.05)
	Asthma		aRR: 1.50 (0.99-2.29)	aRR: 1.02 (0.89-1.16)
	Coeliac disease			aRR: 0.81 (0.31-2.12)
	Crohn disease			aRR: 1.24 (0.31-11.90)
	Ulcerative colitis			aRR: 2.48 (0.41-14.82)
	Juvenile arthritis			aRR: 0.60 (0.23-1.54)
	Sjögren's syndrome		aRR: 1.15 (0.24-5.53)	aRR: **1.59 (1.04-2.44)**; aRR: 1.59 (0.82-3.11)[b]
	Vasculitis			
	Reactive arthropathy		aRR: 0.80 (0.09-6.88)	aRR: 1.40 (0.96-2.05)
	Idiopathic thrombocytopenic purpura			aRR: 0.68 (0.15-3.05)

	Idiopathic urticaria			aRR: 1.03 (0.38-2.78)
	Type-1 diabetes			aRR: 0.80 (0.23-2.77)
	Bell's palsy			aRR: 1.24 (0.34-4.57)
	Epilepsy		aRR: 1.01 (0.21-4.74)	aRR: 0.86 (0.58-1.27)
	Guillain-Barré syndrome			
	Autism spectrum disorder			aRR: 1.22 (0.79-1.86)
	Intellectual disability			aRR: 0.66 (0.28-1.56)
Walsh *et al.* (2019)	Upper respiratory tract infections	aIRR: 1.01 (0.98-1.03)		
	Lower respiratory tract infections	aIRR: 0.99 (0.95-1.03)		
	Gastrointestinal infections	aIRR: **0.94 (0.91-0.98)**; aIRR: 0.94 (0.88-1.00)[b]		
	Otitis media	aIRR: 1.03 (1.00-1.06)		
	All infections	aIRR: 1.01 (0.98-1.03)		
	Asthma	aHR: **1.05 (1.02-1.09)**; aHR: 1.05 (1.00-1.11)[b]		
	Neoplasms	aHR: 1.12 (0.79-1.59)		
	Sensory disorders	aHR: 0.94 (0.67-1.33)		
	Urgent and inpatient health services used	aIRR: 0.99 (0.98-1.01)		
	Paediatric complex chronic conditions	aHR: 0.98 (0.80-1.20)		
	5-year mortality	aHR: 0.83 (0.64-1.08)		
Seasonal influenza vaccine				
Benowitz *et al.* (2010)	Laboratory-confirmed influenza	VE: -41.4% (-2257.4-91.5%)		
van Santen *et al.* (2013)	Acute otitis media	aVE: 47.9% (42.0-53.3%)		
	Medically attended acute respiratory infections	aVE: 39.6% (31.6-46.7%)		

Zerbo *et al.* (2017)	Autism spectrum disorder	aHR: 1.10 (1.00-1.21)	aHR: **1.20 (1.04-1.39)**	aHR: 1.03 (0.90-1.19)	aHR: 1.03 (0.90-1.20)

Abbreviations: aIRR, adjusted incidence rate ratio; aHR, adjusted hazard ratio; aRR, adjusted rate ratio; VE, vaccine effectiveness; aVE, adjusted vaccine effectiveness.
[a] Overall estimates are compared to unexposed children; an additional comparison to unexposed siblings also provided; [b] Adjusted for multiplicity using Bonferroni correction.

5.5.7 Atopic, Autoimmune, and Neurodevelopmental Conditions

In the 2 studies in which asthma was examined, asthma status was identified from a regional asthma database[179] or by using primary or secondary ICD diagnostic codes.[178, 179] Walsh et al[179] reported a small, but significant, increase in asthma among children exposed to IIV *in utero* compared with unexposed children (aHR: 1.05; 95% CI: 1.02-1.09) (**Table 5-5**). However, results were no longer statistically significant after adjusting for multiplicity using Bonferroni correction (aHR: 1.05; 95% CI: 1.00-1.11).[179] Hviid et al[178] reported no significant difference in asthma for first trimester vaccination (aRR: 1.50; 95% CI: 0.99-2.29) or second or third trimester vaccination (aRR: 1.02; 95% CI: 0.89-1.16).

Estimates on rates of autism spectrum disorder were provided in 2 studies, of which 1 group evaluated pandemic influenza vaccine[179] and the other evaluated seasonal influenza vaccine.[160] For both studies, autism spectrum disorder was identified using ICD diagnostic codes. Zerbo et al[160] reported a slightly elevated risk of autism spectrum disorder after prenatal influenza vaccination in the first trimester (aHR: 1.20; 95% CI: 1.04-1.39) but not in the second or third trimester (**Table 5-5**). However, this association was no longer significant after adjusting for multiplicity using a Bonferroni correction (P = .1). Hviid et al[178] found no significant association between IIV exposure *in utero* and autism spectrum disorder. Additionally, Hviid et al[178] observed an increase of risk in Sjögren syndrome, only after prenatal influenza vaccination in the second or third trimester (aRR: 1.59; 95% CI: 1.04-2.44) but not in the first trimester. After adjusting for multiplicity using a Bonferroni correction, this association for Sjögren syndrome was no longer significant (aRR: 1.59; 95% CI: 0.82-3.11). Across all studies, there were no other significant associations between prenatal influenza vaccination and coeliac disease,[178] Crohn disease,[178] ulcerative colitis,[178] juvenile arthritis,[178] vasculitis,[178] reactive arthropathy,[178] idiopathic thrombocytopenic purpura,[178] idiopathic urticaria,[178] type-1 diabetes,[178] Bell palsy,[178] epilepsy,[178] Guillain-Barré syndrome,[178] intellectual disability,[178] neoplasms,[179] and sensory disorders[179] (**Table 5-5**).

5.5.8 All-Cause and Non-specific Childhood Morbidity

All-cause childhood morbidity outcomes included all-cause hospitalisations and urgent care services; researchers in 1 study examined a non-specific outcome,

including a complex of paediatric chronic conditions.[179] Walsh et al[179] found no significant associations between IIV exposure *in utero* and urgent and inpatient health services used[179] or the non-specific complex of chronic conditions (**Table 5-5**).[179] Hviid et al[178] observed a statistically significant reduction in the risk of 1-year all-cause hospitalisation (aHR: 0.94; 95% CI: 0.89-0.99), 3-year all-cause hospitalisation (aHR: 0.95; 95% CI: 0.90-0.99), and 5-year all-cause hospitalisation (aHR: 0.95; 95% CI: 0.91-0.99) in children whose mothers were vaccinated in the second or third trimester.

5.5.9 Paediatric mortality

Paediatric mortality was defined as death occurring from birth through 5 years of age[179] or from 7 days to 4.6 years of age.[180] No significant associations were identified in the 2 studies that examined mortality as an outcome. Although Walsh et al[179] reported a reduced association between pandemic influenza vaccine given during pregnancy and paediatric mortality (aHR: 0.83; 95% CI: 0.64-1.08), this result was not statistically significant (**Table 5-5**). Similarly, Ludvigsson et al[180] reported no significant association between pandemic influenza vaccine during pregnancy and paediatric mortality overall (aHR: 0.97; 95% CI: 0.69-1.36) or by trimester of vaccination (first trimester: aHR: 0.86; 95% CI: 0.51-1.47; second trimester: aHR: 1.10; 95% CI: 0.69-1.76; third trimester: aHR: 0.93; 95% CI: 0.54-1.60). Secondary analyses, using unvaccinated siblings as controls, also revealed no significant associations (overall: aHR: 0.78; 95% CI: 0.52-1.19; first trimester: aHR: 0.47; 95% CI: 0.22-1.01; second trimester: aHR: 1.44; 95% CI: 0.74-2.78; third trimester: aHR; 0.65; 95% CI: 0.30-1.39).[180]

5.5.10 Risk of Bias

For observational studies, risk of bias scores ranged from 6 to 8 on the NOS, of which 4 studies were deemed to be at low risk of bias,[177-180] and 4 studies were deemed to be at moderate-high risk of bias (**Tables 5-1 to 5-3**).[160, 181, 182, 225] Common causes of potential bias included inadequate representativeness of the exposed cohort (n =3)[160, 182, 225] and inadequately described follow-up of exposed and nonexposed cohorts (n = 6). The 1 RCT included was deemed to be at high risk of bias because of the lack of blinding of outcome assessment (detection bias) and inadequate ascertainment of outcomes (reporting bias).[176]

5.6 Discussion

Although there has been increasing interest in the potential impacts of IIV exposure *in utero* on later child health, we identified relatively few studies in which health outcomes through the age of 5 years have been evaluated. In this systematic review, we summarised results from 9 studies including information on over 750,000 children, 163,924 of whom were exposed to IIV *in utero*. Researchers in 2 studies suggested lower risk of upper respiratory tract infection, all-cause infections, all-cause hospitalisation, and gastrointestinal infection associated with pandemic IIV exposure *in utero*. While the data from some studies suggested a potential increase in the risk of asthma, sepsis, and Sjögren syndrome after exposure to pandemic IIV *in utero* and an increased risk of autism spectrum disorder after exposure to seasonal IIV *in utero*, after adjusting for multiple comparisons using Bonferroni-corrected CIs, these associations were no longer statistically significant.

Narrative synthesis of these few studies indicates there is limited evidence evaluating health outcomes through the age of 5 years after exposure to IIV *in utero*, particularly for seasonal IIVs. Existing studies assessed a range of outcomes and the majority examined exposure to pandemic influenza vaccines. Only 3 studies on seasonal influenza vaccines in children were identified, and these were prone to bias; additional high-quality studies are warranted. Furthermore, given seasonal IIV is recommended in all trimesters of pregnancy and fetal development varies by gestational age, outcomes should be assessed according to gestational age at vaccination. Only 3 studies assessed outcomes by trimester of vaccination, of which 1 study combined second and third trimesters. The number of vaccinated individuals, particularly in the first trimester, was small and consequently limited the statistical power to detect differences between the children in the exposed and unexposed group. Differences in study quality, exposure ascertainment, vaccine type (ie, pandemic or seasonal, adjuvanted or nonadjuvanted, monovalent or trivalent), and study outcomes and outcome ascertainment, made it difficult to compare results across studies and precluded statistical pooling of results. These differences may have also influenced the reliability of findings. For example, diagnoses recorded in medical records and not using a validated standardised clinical assessment could lead to potential outcome misclassification.

Importantly, while the potential confounding influence of maternal age, parity, and pre-existing medical conditions was accounted for in most studies, the study by van Santen et al[182] was the only one that factored for receipt of childhood immunisations as a potential confounding variable by censoring children after receiving their own influenza vaccine.[182] No study factored for receipt of other recommended childhood vaccines. Given that receipt of vaccines during pregnancy may be predictive of childhood vaccination as well as other health behaviours,[227] it is possible that residual bias in the observational studies identified may have influenced findings, especially the observed protective associations. Future studies should aim to account for childhood immunisation status as a potential confounding variable.

Finally, there was little geographic variation in the geographic location of studies identified. All included studies were conducted in high-income countries in North America or Europe, and thus these findings may not generalise to children in low and middle-income countries, whose population demographics and risk profiles differ markedly. Research on the safety of influenza vaccination during pregnancy from low and middle-income countries would be useful for guiding future vaccine policies and programs in these settings.

5.7 Conclusion

Maternal influenza vaccination is a growing public health tool for improving the health of mothers and their infants. Despite long-standing recommendations, maternal influenza immunisation policies were not widely adopted until the 2009 influenza A/H1N1 pandemic, and, as identified as part of this review, the long-term health impacts of *in utero* exposure of influenza vaccines in children >6 months of age are under-investigated. We identified relatively few studies in which early childhood health outcomes were evaluated in children aged >6 months of age in children of vaccinated and unvaccinated mothers, and the same outcomes were rarely measured in the few existing studies. This made formal meta-analyses impractical. Although our review indicates that exposure to IIV *in utero* is not associated with adverse health outcomes in childhood, additional epidemiological studies of early childhood health outcomes after maternal influenza vaccination are still needed to address this gap. Future well-controlled research in which seasonal IIV administered in different trimesters and in different

settings is considered is required to provide a stronger evidence-base for the long-term safety of maternal influenza vaccination. Notwithstanding the need for additional research in this area, the results of the studies to date have not revealed any adverse effect of maternal influenza vaccination on childhood health outcomes during the first 5 years. These findings are reassuring and can help support health care providers and pregnant women in making decisions about influenza vaccination during pregnancy.

Chapter Six: Laboratory-confirmed influenza and acute respiratory infections

6.1 Preamble

This chapter is based on a paper published in *Vaccine*. The chapter which follows is a verbatim copy of the content from the published manuscript, except for minor modifications for readability. A copy of the published manuscript is available in **Appendix D**, and the online supplementary material is available in **Appendix E**.

Study Two – Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood

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Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood

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6.2 Abstract

Background: Influenza vaccination is recommended to protect mothers and their infants from influenza infection. Few studies have evaluated the health impacts of *in utero* exposure to influenza vaccine among children more than six months of age.

Methods: We used probabilistically linked administrative health records to establish a mother–child cohort to evaluate the risk of influenza and acute respiratory infections associated with maternal influenza vaccination. Outcomes were laboratory-confirmed influenza (LCI) and hospitalisation for influenza or acute respiratory infection (ARI). Adjusted hazard ratios accounted for child's Aboriginal status and were weighted by the inverse-probability of treatment.

Results: 14,396 (11.5%) children were born to vaccinated mothers. Infants aged <6 months of vaccinated mothers had lower risk of LCI (aHR: 0.32; 95% CI: 0.12, 0.84), influenza-associated hospitalisation (aHR: 0.39; 95% CI: 0.16, 0.94) and ARI-associated hospitalisation (aHR: 0.85; 95% CI: 0.77, 0.94) compared to maternally unvaccinated infants. With the exception of an increased risk of LCI among children aged 6 months to <2 years old following first trimester vaccination (aHR: 2.28; 95% CI: 1.41, 3.69), there were no other differences in the risk of LCI, influenza-associated hospitalisation or ARI-associated hospitalisation among children aged >6 months.

Conclusion: Study results show that maternal influenza vaccination is effective in preventing influenza in the first six months and had no impact on respiratory infections after two years of age.

6.3 Introduction

Influenza causes serious morbidity and mortality through seasonal epidemics each year, particularly in children under the age of five years.[11, 24] Although the best preventative tool for influenza is seasonal influenza vaccination,[228] there are currently no influenza vaccines licensed for use for infants aged <6 months.[11] Since maternal antibodies cross the placenta during pregnancy,[229] prenatal administration of seasonal IIV is recommended for pregnant women in many countries, including Australia, at any stage of pregnancy to protect both mothers and their newborns from influenza illness during their first few months of life.[11, 58]

Several studies have found that maternal influenza vaccination is effective in reducing the risk of LCI illness and ARIs in young infants.[108, 230] A systematic review and meta-analysis of four randomised controlled trials and five observational studies reported a lower risk of LCI infection by 48% and lower risk of LCI-associated hospitalisations by 72% among children aged less than six months following maternal influenza vaccination.[108] However, few studies have evaluated the risk of LCI infection beyond six months of age among offspring of vaccinated mothers.[231] Maternally-acquired antibodies have been known to ‘‘blunt” or dampen primary immune responses to infection or vaccination.[134, 232] Although seven studies identified no difference in the risk of acute respiratory infections through five years of age,[231] no study has evaluated the risk of LCI after 12 months of age.[231]

The aim of the present study was to measure the association between *in utero* exposure to seasonal IIV and the occurrence of ARIs, including LCI, from birth to five years of age.

6.4 Methods

6.4.1 Study setting

WA has a resident population of approximately 2.6 million people,[233] with approximately 33,000 births in WA each year.[184] In Australia, seasonal IIV during pregnancy has been recommended by the Australian Technical Advisory Group on Immunisation since March 2000 and funded under the NIP since January 2010.[58, 186] Influenza virus circulation tends to peak during the winter months (June-August), with less distinct seasonality in the northern areas of the state; seasonal influenza vaccines are typically available in April of each year.[185]

6.4.2 Study design, population, and data sources

We conducted a retrospective, population-based cohort study. The cohort included all singleton, live-born children identified from birth registrations between 1 April 2012 and 1 July 2016 and their mothers (**Figure 6-1**). These mother-infant pairs were probabilistically linked with other population-based administrative health datasets using best practice protocols through the WA Data Linkage Branch,[188] including the Midwives Notification System (MNS),[198] WA Antenatal Vaccination Database (WAAVD),[200] WA Notifiable Infectious Diseases Database (WANIDD),[202] Hospital Morbidity Data Collection (HMDC),[203] and death registrations. This study and a waiver of consent was approved by the WA Department of Health (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217–0808).

The MNS is a legally mandated perinatal data collection of all births ≥20 weeks gestation or birthweight of ≥400 g (where gestational age is unknown). The MNS includes maternal demographics and health information, obstetric history, date of delivery, gestational age, and birthweight. The WAAVD is a state-wide database, managed by the WA Department of Health, and includes the date of vaccination, vaccine brand and batch number, and the estimated gestation at which vaccinations were administered as reported by their healthcare provider.

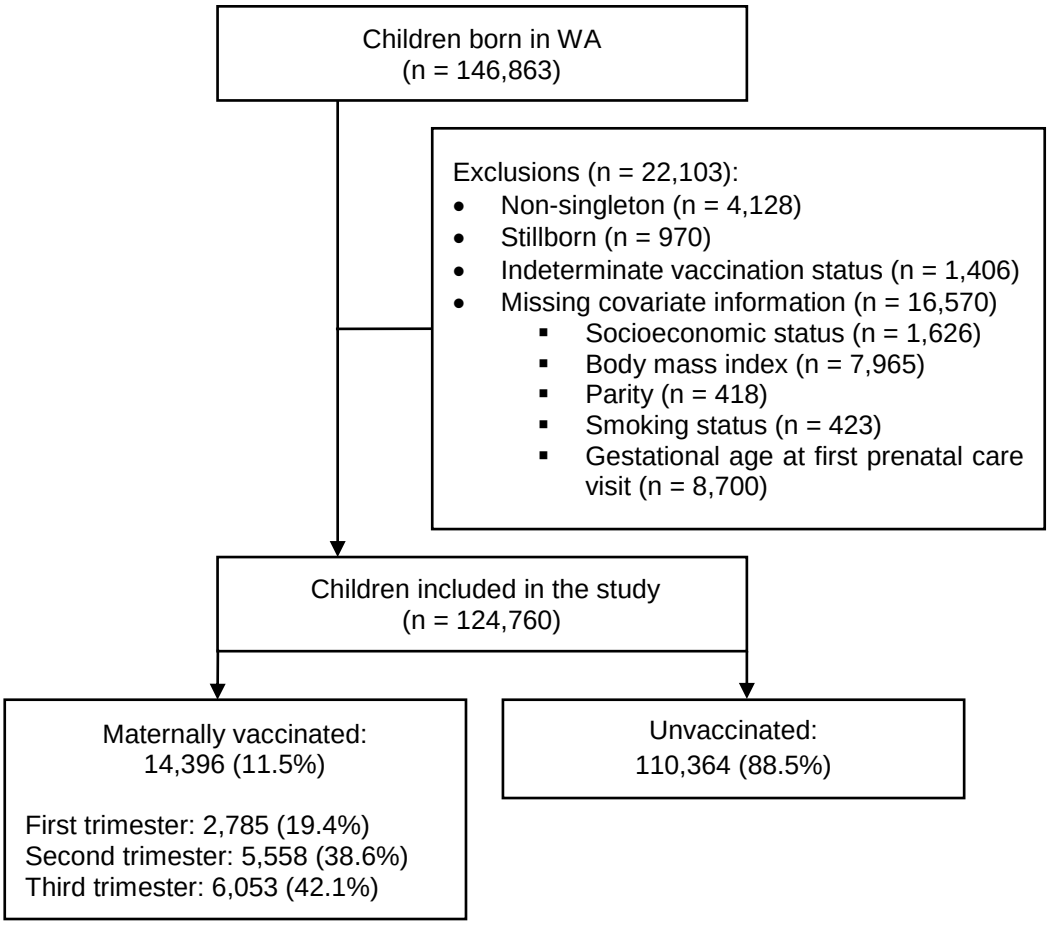

Figure 6-1. Flow diagram of study participants included in the cohort.

WANIDD is a legally mandated database of notifiable infectious diseases reported to the WA Department of Health. In Australia, LCI is a notifiable disease and WANIDD includes information on the date of specimen collection, laboratory method of confirmation, and virus type/subtype. The HMDC summarises all episodes of care provided in the state's public and private hospitals. Information details the date of admission and separation, up to 21 diagnosis codes (classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] codes).[203] Death registrations include the date and cause of all registered deaths in the state.

6.4.3 Exposure measurement

Children whose mothers had a record of receipt of prenatal seasonal IIV were considered 'maternally vaccinated'. We estimated the gestational age at vaccination as the number of completed weeks from estimated date of conception to date of vaccination. Trimesters were categorised as: first trimester (0 to ≤13 weeks gestation), second trimester (14 to ≤27 weeks gestation), and third trimester (≥28 weeks gestation). Children of mothers with no vaccination record were considered 'maternally unvaccinated'. Children whose mothers received an influenza vaccine <2 weeks prior to birth were considered to have 'indeterminate' vaccination status and were excluded from analysis.

6.4.4 Outcome measurement

We assessed three primary outcomes: 1) LCI, as reported to WANIDD, 2) influenza-associated hospitalisations, and 3) ARI-associated hospitalisations. We defined influenza-associated hospitalisations and ARI-associated hospitalisations as a hospital admission with a diagnosis code for influenza or an ARI, respectively (**Supplementary Table E-1**). Follow-up data were available up to July 2017. To assess for possible bias in the study results, we included two negative control conditions: 1) all-cause injuries, and 2) skin and soft tissue infections (hereafter referred to as skin infections), using hospital diagnosis codes (**Supplementary Table E-1**). This bias assessment was conducted to evaluate non-causal associations between prenatal exposure to seasonal IIV and the outcomes.[234]

6.4.5 Covariate measurement

Maternal covariates included age at the time of her child's birth (≤19, 20–24, 25–29, 30–34 and ≥35 years), Aboriginal status (Aboriginal, non-Aboriginal), socioeconomic status (quintiles between 1 (most disadvantaged) and 5 (least disadvantaged)), body mass index (BMI), parity (primiparous, one prior birth, ≥2 prior births), pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking during pregnancy, and gestational age at the first prenatal care visit. Child covariates included Aboriginal status, and season and year of birth. Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) Index of Relative Socioeconomic

Advantage and Disadvantage, an area-based measure of relative access to resources for households within the same census collection district.[235] Preterm birth was categorised as: moderate to late preterm (32 to <37 weeks gestation), very preterm (28 to <32 weeks gestation), and extremely preterm (<28 weeks gestation) birth. Small-for-gestational age birth was defined as birthweight <10th percentile according to Australian national birthweight percentiles by sex and gestational age.[236] All covariates were selected *a priori* because they are known indicators of maternal influenza vaccination.[16, 19, 68, 104, 237, 238]

6.4.6 Statistical analyses

Descriptive statistics were calculated to compare demographic and health characteristics between vaccinated and unvaccinated mothers and their children. The odds of vaccination were estimated using univariate logistic regression models. To control for baseline probability of vaccination, we estimated inverse-probability of treatment weights using predicted probabilities derived from a multivariate logistic regression model including all maternal covariates. Standardised mean differences were calculated to assess the balance of maternal covariates between children of vaccinated and unvaccinated mothers. Weighted Cox proportional hazard regression models were then used to estimate the aHRs of study outcomes, comparing children of vaccinated and unvaccinated mothers. Adjusted models additionally controlled for the child's Aboriginal status.

Time-at-risk commenced from birth and ended at the earliest of: a) the date the child reached five years of age, b) the last date of available data, c) the date the child died, or d) the date of event (**Figure 6-2**). Children were able to contribute more than one event of interest. Unique episodes of care were considered those with ≥2 weeks between the date of separation and subsequent admission. A random effect term was incorporated in the model to account for multiple observations within individuals (i.e. more than one event per child). Sub-group analyses compared the risk of study outcomes by trimester of vaccination and specific age groups (<6 months, 6 months to <2 years, 2 to <5 years, 6 months to <5 years).

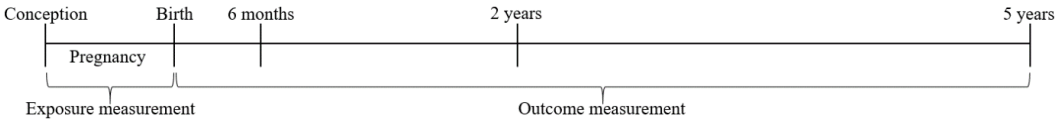

Figure 6-2. Timing of exposure measurement and outcome measurement. Exposure: maternal influenza vaccination; outcome: laboratory-confirmed influenza, influenza-associated hospitalisation, acute respiratory infection-associated hospitalisation, all-cause injury-associated hospitalisation, or skin infection-associated hospitalisation**.**

To assess the potential impact of right truncation and exposure to differential exposure to influenza seasons, we performed a sensitivity analysis restricting to children born between 1 April 2012 and 30 September 2012 which coincides with the first seasonal influenza vaccine availability during the cohort period, fixes the child's age at each influenza season and allows for up to five years of follow-up. Additional sensitivity analyses included similar analyses with LCI restricted to children aged 6 to <12 months and 1 to <2 years as the time period where infant immunisation would be least common.[207] All analyses were performed in STATA version 15.1 (StataCorp LLC, College Station, Texas, U.S.). Description of the detectable difference of risk of outcome measures between children of vaccinated and unvaccinated mothers can be found in **Supplementary Table E-2**.

6.5 Results

A total of 146,864 births were identified in WA during the study period. Of these, 22,103 (15.0%) records were excluded because the child was a non-singleton (n = 4,128), stillborn (n = 970), had missing covariate information (n = 16,570), or indeterminate vaccination status (n = 1,406). The final cohort included 124,760 singleton, live-born children from 106,206 mothers (**Figure 6-1**). Maternal characteristics were balanced between children of vaccinated and unvaccinated mothers (**Table 6-1**; **Supplementary Figure E-1**).

Table 6-1. Odds of vaccination by maternal and child characteristics of children born in Western Australia between 1 April 2012 and 1 July 2016 included in the study cohort.

Characteristic	Children of unvaccinated mothers (N = 110,364) n (%)	Children of vaccinated mothers (N = 14,396) n (%)	Unadjusted OR (95% CI)
Maternal characteristics			
Age (years):			
≤19	3,369 (3.1)	449 (3.1)	**1.13 (1.01-1.26)**
20-24	14,828 (13.4)	1,747 (12.1)	Ref
25-29	31,459 (28.5)	3,978 (27.6)	**1.07 (1.01-1.14)**
30-34	37,706 (34.2)	5,151 (35.8)	**1.16 (1.09-1.23)**
≥35	23,002 (20.8)	3,071 (21.3)	**1.13 (1.06-1.21)**
Aboriginal status:			
Aboriginal	5,296 (4.8)	717 (5.0)	1.04 (0.96-1.13)
Non-Aboriginal	105,068 (95.2)	13,679 (95.0)	Ref
Socioeconomic status:[b]			
Quintile 1 (most disadvantaged)	21,181 (19.2)	2,618 (18.2)	**0.93 (0.88-0.98)**
Quintile 2	22,674 (20.5)	3,019 (21.0)	1.00 (0.94-1.05)
Quintile 3	23,256 (21.1)	2,972 (20.6)	0.96 (0.91-1.01)
Quintile 4	22,217 (20.1)	2,979 (20.7)	1.00 (0.95-1.06)
Quintile 5 (least disadvantaged)	21,036 (19.1)	2,808 (19.5)	Ref
Body mass index:			
<18.5 (underweight)	3,532 (3.2)	450 (3.1)	0.97 (0.87-1.07)
18.5 to <25 (normal)	54,032 (49.0)	7,114 (49.4)	Ref
25 to <30 (overweight)	30,720 (27.8)	3,875 (26.9)	0.96 (0.92-1.00)
≥30 (obese)	22,080 (20.0)	2,957 (20.5)	1.02 (0.97-1.06)
Parity:			
Primiparous	47,824 (43.3)	6,764 (47.0)	Ref
1 prior birth	38,216 (34.6)	4,958 (34.4)	**0.92 (0.88-0.95)**
≥2 prior births	24,324 (22.0)	2,674 (18.6)	**0.78 (0.74-0.81)**
Pre-existing medical conditions:			
Asthma	11,523 (10.4)	1,596 (11.1)	**1.07 (1.01-1.13)**
Essential hypertension	1,417 (1.3)	261 (1.8)	**1.42 (1.24-1.62)**
Pre-existing diabetes mellitus	916 (0.8)	191 (1.3)	**1.61 (1.37-1.88)**
Pregnancy complications:			
Gestational diabetes	11,310 (10.3)	1,688 (11.7)	**1.16 (1.10-1.23)**
Gestational hypertension	5,112 (4.6)	777 (5.4)	**1.17 (1.09-1.27)**
Pre-eclampsia	3,597 (3.3)	543 (3.8)	**1.16 (1.06-1.28)**
Smoked during pregnancy	10,540 (9.6)	1,269 (8.8)	**0.92 (0.86-0.97)**
Trimester of first prenatal care visit:			
First trimester	72,857 (66.0)	*	Ref
Second trimester	32,380 (29.3)	*	**0.82 (0.79-0.85)**
Third trimester	5,053 (4.6)	*	**0.54 (0.49-0.60)**
No prenatal care	74 (0.1)	<5	0.38 (0.14-1.05)
Year of birth:			
2012	19,930 (18.1)	1,304 (9.1)	Ref
2013	25,894 (23.5)	2,909 (20.2)	**1.72 (1.60-1.84)**
2014	26,345 (23.9)	3,205 (22.3)	**1.86 (1.74-1.99)**
2015	24,726 (22.4)	5,148 (35.8)	**3.18 (2.99-3.39)**
2016	13,469 (12.2)	1,830 (12.7)	**2.08 (1.93-2.24)**
Season of birth:			
Summer (Dec-Feb)	27,325 (24.8)	2,186 (15.2)	Ref
Autumn (Mar-May)	31,716 (28.7)	2,291 (15.9)	**0.90 (0.85-0.96)**
Winter (Jun-Aug)	26,062 (23.6)	5,413 (37.6)	**2.60 (2.46-2.74)**
Spring (Sep-Nov)	25,261 (22.9)	4,506 (31.3)	**2.23 (2.11-2.35)**
Child characteristics			
Sex:[c]			
Male	56,822 (51.5)	7,347 (51.0)	Ref
Female	53,539 (48.5)	7,049 (49.0)	1.02 (0.98-1.05)
Aboriginal status:			
Aboriginal	5,779 (5.2)	787 (5.5)	1.05 (0.97-1.13)
Non-Aboriginal	104,585 (94.8)	13,609 (94.5)	Ref

Birth outcomes:			
Preterm birth	7,390 (6.7)	887 (6.2)	**0.91 (0.85-0.98)**
Moderate-to-late preterm	6,587 (6.0)	819 (5.7)	0.95 (0.88-1.02)
Very preterm	520 (0.5)	52 (0.4)	0.76 (0.57-1.01)
Extremely preterm	283 (0.3)	16 (0.1)	**0.43 (0.26-0.71)**
Small-for-gestational age[b]	9,005 (8.2)	1,191 (8.3)	1.02 (0.95-1.08)

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics [239].
* In accordance with privacy and confidentiality guidelines by the DLB, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.
[b] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age, 1998-2007 [236].
[c] The sex of <5 maternally unvaccinated children was unknown.

6.5.1 Maternal influenza vaccination

Of the 124,760 children, 14,396 (11.5%) children of mothers were vaccinated during pregnancy; 2,785 (19.4%) exposed during the first trimester, 5,558 (38.6%) during the second trimester, and 6,053 (42.1%) during the third trimester. The majority of mothers received influenza vaccine between March and July (n = 12,537; 87.1%). Vaccination was more common among primiparous women, women with pre-existing medical conditions and pregnancy complications, and non-smokers (**Table 6-1**). Women of the lowest socioeconomic status (OR: 0.93; 95% CI: 0.88-0.98) and mothers of preterm infants had lower odds of vaccination compared to term infants (OR: 0.91; 95% CI: 0.85-0.98), and women who birthed during winter had the highest odds of being vaccinated as compared to summer (OR: 2.60; 95% CI: 2.46-2.74).

6.5.2 Laboratory-confirmed influenza

There were 862 cases of LCI among 852 children aged <5 years; 670 (77.7%) cases were influenza A virus (sub-type A/H1N1: 252 (29.2%); sub-type A/H3N2: 267 (31.0%); A/unsubtyped: 151 (17.5%)) and 192 (22.3%) were influenza B virus. One hundred and sixteen cases (13.5%) occurred in the first six months of life, 431 (50.0%) between 6 months and 2 years, and 315 (36.5%) between 2 and 5 years (**Figure 6-3**). Two hundred and forty-three cases (28.2%) occurred among children born in 2012, 264 (30.6%) in 2013, 203 (23.5%) in 2014, 114 (13.2%) in 2015, and 38 (4.4%) in 2016.

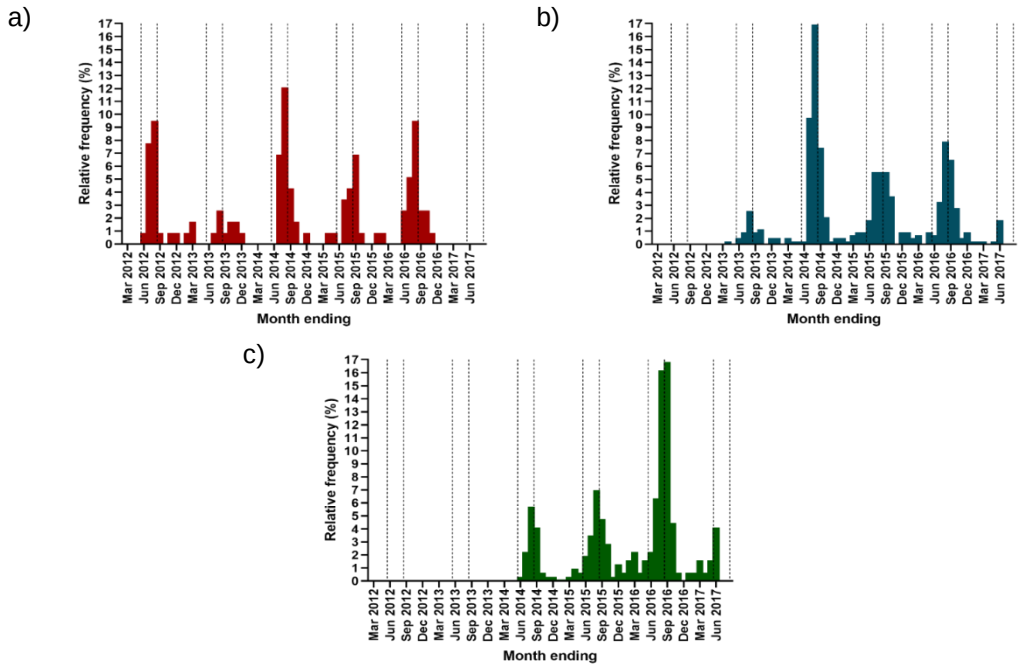

Figure 6-3. Monthly rate of laboratory-confirmed influenza notifications, by age sub-group and month/year: a) children aged 0 to <6 months, b) children aged 6 months to <2 years, or c) children aged 2 to <5 years—Western Australia, 1 April 2012-1 July 2017.
Note: dashed lines indicate influenza seasons (Jun-Aug).

We observed no difference in the risk of LCI between children of vaccinated and unvaccinated mothers from birth to 5 years of age (aHR: 1.10; 95% CI: 0.88-1.38) (**Table 6-2**). Among infants aged <6 months, we observed a lower risk of LCI associated with maternal influenza vaccination (aHR: 0.32; 95% CI: 0.12-0.84) (**Table 6-2**). There were insufficient numbers to generate estimates by trimester of vaccination.

Table 6-2. Risk of laboratory-confirmed influenza infection associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged <5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	759 (0.7)	93 (0.6)	28 (1.0)	34 (0.6)	31 (0.5)
Cases, n (%)	768 (0.7)	94 (0.7)	29 (1.0)	34 (0.6)	31 (0.5)
Unweighted HR (95% CI)	1 [Reference]	1.08 (0.87-1.35)	**1.71 (1.17-2.51)**	0.96 (0.68-1.35)	0.91 (0.63-1.30)
Weighted aHR (95% CI)[a]	1 [Reference]	1.10 (0.88-1.39)	**1.80 (1.21-2.68)**	0.97 (0.67-1.39)	0.91 (0.62-1.33)
Children aged <6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	111 (0.1)	5 (0)	<5	<5	<5
Cases, n (%)	111 (0.1)	5 (0)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	**0.35 (0.14-0.85)**	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	**0.32 (0.12-0.84)**	-	-	-
Children aged 6 months to <2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	368 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Cases, n (%)	370 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.31 (1.00-1.72)	**2.13 (1.34-3.37)**	1.23 (0.81-1.88)	1.00 (0.63-1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	1.33 (1.00-1.76)	**2.28 (1.41-3.69)**	1.20 (0.78-1.86)	1.00 (0.61-1.64)
Children aged 2 to <5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	284 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Cases, n (%)	287 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.09 (0.74-1.60)	1.54 (0.76-3.11)	0.97 (0.53-1.78)	0.98 (0.51-1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.14 (0.76-1.71)	1.52 (0.72-3.17)	1.05 (0.55-1.99)	1.04 (0.52-2.07)
Children aged 6 months to <5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	648 (0.6)	88 (0.6)	26 (0.9)	34 (0.6)	28 (0.5)
Cases, n (%)	657 (0.6)	89 (0.6)	27 (1.0)	34 (0.6)	28 (0.5)

Unweighted HR (95% CI)	1 [Reference]	1.23 (0.98-1.54)	**1.91 (1.29-2.84)**	1.13 (0.80-1.60)	1.00 (0.68-1.46)
Weighted aHR (95% CI)[a]	1 [Reference]	1.24 (0.98-1.57)	**1.96 (1.29-2.97)**	1.13 (0.79-1.63)	1.01 (0.68-1.51)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

Laboratory-confirmed influenza cases obtained from notification records reported to WANIDD.

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

Among children aged 6 months to <2 years, there was no difference in the risk of LCI between children of vaccinated and unvaccinated mothers (aHR: 1.33; 95% CI: 1.00-1.76). However, an increased risk was observed among children of mothers vaccinated during the first trimester (aHR: 2.28: 95% CI: 1.41-3.69). No associations were observed following maternal vaccination in later trimesters (**Table 6-2**). Sensitivity analyses restricting to children aged 6 to <12 months (aHR: 2.70; 95% CI: 1.40-5.98) and 1 to <2 years (aHR: 2.00; 95% CI: 1.05-3.80) similarly identified a higher risk of LCI following maternal vaccination during the first trimester (**Supplementary Table E-3**). Among children aged 2 to <5 years, no association was observed with maternal influenza vaccination (aHR: 1.14; 95% CI: 0.76-1.71) (**Table 6-2**).

6.5.3 Influenza-associated hospitalisation

A total of 360 influenza-associated hospitalisations were identified in 352 children aged < 5 years, of which 243 (67.5%) were associated with a LCI notification record. Similar to LCI, we observed no association between influenza-associated hospitalisation and maternal influenza vaccination among children from birth to age 5 years (aHR: 0.91; 95% CI: 0.62-1.33) (**Table 6-3**).I Infants aged < 6 months of vaccinated mothers had a lower risk of influenza-associated hospitalisation compared to infants of unvaccinated mothers (aHR: 0.38; 95% CI: 0.16-0.91) (**Table 6-3**). Among children aged 6 months to < 2 years and 2 to < 5 years, there was no difference in the risk of influenza-associated hospitalisation between children of vaccinated and unvaccinated mothers (aHR: 1.09; 95% CI: 0.67-1.78 and aHR: 1.40; 95% CI: 0.65-3.01, respectively) (**Table 6-3**).

Table 6-3. Risk of influenza hospitalisation associated with prenatal exposure to seasonal inactivated influenza vaccination among children <5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged <5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	318 (0.3)	34 (0.2)	7 (0.3)	12 (0.2)	15 (0.2)
Cases, n (%)	325 (0.3)	35 (0.2)	7 (0.3)	13 (0.2)	15 (0.2)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.63-1.28)	0.92 (0.43-1.95)	0.83 (0.46-1.50)	0.95 (0.56-1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.62-1.33)	1.29 (0.58-2.85)	0.80 (0.43-1.48)	0.85 (0.49-1.47)
Children aged <6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	106 (0.1)	6 (0)	<5	<5	5 (0.1)
Cases, n (%)	108 (0.1)	6 (0)	<5	<5	5 (0.1)
Unweighted HR (95% CI)	1 [Reference]	**0.43 (0.19-0.97)**	-	-	0.84 (0.34-2.07)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.38 (0.16-0.91)**	-	-	0.68 (0.26-1.73)
Children aged 6 months to <2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	145 (0.1)	20 (0.1)	<5	10 (0.2)	8 (0.1)
Cases, n (%)	146 (0.1)	21 (0.1)	<5	11 (0.2)	8 (0.1)
Unweighted HR (95% CI)	1 [Reference]	1.13 (0.70-1.82)	-	1.49 (0.77-2.89)	1.05 (0.52-2.15)
Weighted aHR (95% CI)[a]	1 [Reference]	1.09 (0.67-1.78)	-	1.36 (0.70-2.65)	0.96 (0.47-1.99)
Children aged 2 to <5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	69 (0.1)	8 (0.1)	<5	<5	<5
Cases, n (%)	71 (0.1)	8 (0.1)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	1.23 (0.59-2.56)	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.40 (0.65-3.01)	-	-	-
Children aged 6 months to <5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	212 (0.2)	28 (0.2)	6 (0.2)	12 (0.2)	10 (0.2)
Cases, n (%)	217 (0.2)	29 (0.2)	6 (0.2)	13 (0.2)	10 (0.2)

Unweighted HR (95% CI)	1 [Reference]	1.16 (0.78-1.73)	1.23 (0.54-2.78)	1.26 (0.69-2.30)	1.01 (0.54-1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.18 (0.77-1.80)	1.67 (0.69-4.01)	1.20 (0.64-2.23)	0.94 (0.48-1.83)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

Influenza-associated hospitalisation obtained from ICD-10-AM codes: J09-J11, found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table E-1**).

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

6.5.4 Acute respiratory infection-associated hospitalisation

A total of 18,643 ARI-associated hospitalisations were identified in 13,638 children <5 years of age, 5,394 in children aged <6 months, 9,776 in children aged 6 months to <2 years, and 3,495 in children aged 2 to <5 years. The distribution of ARIs is presented in **Supplementary Table E-1**. There was no association between ARI-associated hospitalisation and maternal influenza vaccination among children from birth to 5 years of age (aHR: 0.94; 95% CI: 0.88-1.01) (**Table 6-4**).I Infants aged <6 months of vaccinated mothers had a lower risk of an ARI-associated hospitalisation compared to infants of unvaccinated children (aHR: 0.85; 95% CI: 0.77-0.94); maternal vaccination during the first and second trimester were associated with a lower risk of ARI-associated hospitalisation (aHR: 0.67; 95% CI: 0.50-0.88 and aHR: 0.79; 95% CI: 0.67-0.93, respectively). This was not observed for maternal vaccination during the third trimester (aHR: 1.00; 95% CI: 0.87-1.14). We observed no associations between maternal influenza vaccination and ARI-associated hospitalisations in other age groups (**Table 6-4**).

6.5.5 Bias assessment

There were 4,162 hospitalisations for all-cause injuries in 3,975 children and 1,687 hospitalisations for skin infections in 1,559 children aged <5 years. We observed no difference in the risk of all-cause injury-hospitalisation or skin infection-associated hospitalisation between children of vaccinated and maternally unvaccinated mothers from birth to 5 years of age by trimester of vaccination or age sub-group (**Supplementary Table E-4**; **Supplementary Table E-5**).

6.5.6 Sensitivity analysis

Of the 13,834 children born between 1 April 2012 and 30 September 2012, 789 (5.7%) children of mothers were vaccinated during pregnancy; 5 (0.6%) exposed during the first trimester, 315 (39.9%) during the second trimester, and 469 (59.4%) during the third trimester. We observed no difference in the risk of LCI or hospitalisation for influenza, acute respiratory infections, all-cause injuries and skin infections between children aged <5 years and 6 months to <5 years of vaccinated and unvaccinated mothers (**Supplementary Table E-6**).

Table 6-4. Risk of acute respiratory infection hospitalisation associated with prenatal exposure to seasonal inactivated influenza vaccination among children <5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First (N = 2,785)	Second (N = 5,558)	Third (N = 6,053)
All children aged <5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	12,193 (11.0)	1,445 (10.0)	255 (9.2)	579 (10.4)	611 (10.1)
Cases, n (%)	16,706 (15.1)	1,937 (13.5)	356 (12.8)	785 (14.1)	796 (13.2)
Unweighted HR (95% CI)	1 [Reference]	0.96 (0.90-1.02)	0.90 (0.78-1.04)	0.96 (0.87-1.06)	0.97 (0.89-1.07)
Weighted aHR (95% CI)[a]	1 [Reference]	0.94 (0.88-1.01)	0.88 (0.75-1.02)	0.97 (0.87-1.07)	0.95 (0.86-1.05)
Children aged <6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	4,434 (4.0)	506 (3.5)	70 (2.5)	180 (3.2)	256 (4.2)
Cases, n (%)	4,838 (4.4)	556 (3.9)	83 (3.0)	193 (3.5)	280 (4.6)
Unweighted HR (95% CI)	1 [Reference]	**0.88 (0.80-0.97)**	**0.68 (0.53-0.88)**	**0.79 (0.68-0.92)**	1.05 (0.93-1.20)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.85 (0.77-0.94)**	**0.67 (0.50-0.88)**	**0.79 (0.67-0.93)**	1.00 (0.87-1.14)
Children aged 6 months to <2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	6,775 (6.2)	842 (5.9)	170 (6.1)	351 (6.3)	321 (5.3)
Cases, n (%)	8,702 (7.9)	1,074 (7.5)	218 (7.8)	446 (8.0)	410 (6.8)
Unweighted HR (95% CI)	1 [Reference]	0.97 (0.89-1.05)	1.02 (0.86-1.21)	1.00 (0.89-1.13)	0.91 (0.80-1.03)
Weighted aHR (95% CI)[a]	1 [Reference]	0.97 (0.90-1.06)	0.99 (0.83-1.18)	1.03 (0.91-1.16)	0.91 (0.80-1.04)
Children aged 2 to <5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	2,570 (3.0)	252 (2.8)	46 (2.5)	116 (3.3)	90 (2.6)
Cases, n (%)	3,186 (3.7)	309 (3.5)	56 (3.0)	147 (4.1)	106 (3.0)
Unweighted HR (95% CI)	1 [Reference]	1.06 (0.92-1.22)	0.93 (0.68-1.29)	1.13 (0.92-1.39)	1.03 (0.83-1.29)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.87-1.17)	0.90 (0.65-1.24)	1.06 (0.85-1.32)	1.01 (0.80-1.27)
Children aged 6 months to <5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	8,678 (7.9)	1,028 (7.2)	199 (7.2)	437 (7.9)	392 (6.5)

Cases, n (%)	11,883 (10.8)	1,383 (9.6)	274 (9.9)	593 (10.7)	516 (8.5)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.92-1.07)	1.00 (0.85-1.18)	1.03 (0.92-1.16)	0.93 (0.83-1.05)
Weighted aHR (95% CI)[a]	1 [Reference]	0.98 (0.91-1.06)	0.97 (0.82-1.14)	1.04 (0.92-1.16)	0.93 (0.83-1.05)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

Acute respiratory infection-associated hospitalisation obtained from ICD-10-AM codes: B34, J05, J06, J09-J11, J12-J18, J20, J21, J22, found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table E-1**).

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

6.6 Discussion

In this large, population-based cohort study of 124,760 children, we observed a lower risk of LCI, ARI-associated hospitalisation, and influenza-associated hospitalisation following seasonal IIV during pregnancy among infants aged <6 months. No consistent differences in risks for children aged >6 months were observed by maternal vaccination status. These findings suggest maternal vaccination is effective in preventing influenza in young infants, and does not impact the susceptibility to respiratory infections through early childhood.

We did observe a two-fold increase in the risk of LCI associated with maternal influenza vaccination when administered during the first trimester of pregnancy. The first six months of life is an important window for priming the immune system, and the influence of maternal immunisation beyond passive immunity is not well understood.[131] The presence of maternal antibodies from other maternal vaccines has been shown to inhibit the development of children's primary antibody response,[133] including blunted response to pertussis, *Haemophilus influenzae type B* and pneumococcal vaccines.[240] It is not currently known whether this is also the case with seasonal influenza vaccines. It is possible that although infants of vaccinated mothers are protected by maternal antibodies early in life, once these antibodies wane around 2–3 months after birth, this may leave a temporary window of susceptibility.[131] This may explain the temporary increased risk of LCI infection among children aged 6 months to <2 years whose mothers were vaccinated in first trimester. A Danish cohort of children whose mothers received pandemic influenza vaccine during the first trimester of pregnancy observed down-regulation of key immune mediators in airway mucosal cells, suggesting a compromised local immune defence.[176] This effect was enhanced the earlier in the pregnancy the mothers received vaccination. While this downregulation was observed in neonates and the study was not powered to examine the immune response later in infancy, it may be hypothesised that the boosted adaptive immune response in vaccinated mothers was responsible for down-regulation of the fetal immune system in this study. Whether this down-regulation is temporary, has lasting effects, or is also the case with seasonal vaccines is unknown and requires further examination.

Despite this, there are other explanations for these results, and this finding requires further evaluation. First, sensitivity analyses restricting the influence of truncation and exposure to different influenza seasons did not suggest an increased risk of LCI for children 6 months to <5 years of age. However, our cohort was too small to perform analyses specific to first trimester exposure. Second, we were unable to measure receipt of influenza vaccines during childhood in this cohort and it is possible that vaccination rates in children of vaccinated mothers varied to rates in children of unvaccinated mothers;[227] however, sensitivity analyses restricted to the time period when childhood influenza vaccination is unlikely showed similar results, suggesting this was not a strong factor in our results. Another possibility is that residual confounding influenced our results. Although we did not identify associations in our negative control analysis, and we attempted to restrict the influence of health-seeking behaviour using inverse-probability treatment weighting, we cannot entirely exclude the possible influence of confounding in our results.

The main strengths of our study include the availability of a large, population-based birth cohort and the use of record linkage to incorporate detailed information on birth, perinatal, and health care information. With the exception of antenatal vaccination registers, these registers are nationally mandated and provide data to the Australian Institute of Health and Welfare, and the quality is considered to be high.[241] Record linkage has been well established in WA since 1995.[187] The MNS is also estimated to capture 99% of all births in WA.[198] Furthermore, through the use of WANIDD data, we were able to assess laboratory-confirmed outcomes with high specificity,[242] rather than influenza identified through diagnostic codes alone which have been shown to under-report the incidence of influenza admissions.[243]

The study had some limitations: firstly, the inability to measure childhood influenza vaccination, which is a potential confounder and effect modifier. Despite this, childhood influenza vaccine coverage was low (<10%) during our study period,[207] indicating this was unlikely to have significantly influenced our results. It is possible that childhood vaccination is associated with maternal vaccination, and if this is the case, our analyses accounting for confounding maternal factors may have by proxy adjusted for some influence of childhood vaccination as a confounder. Secondly, maternal vaccination status was captured by medical

reports from immunisation providers. Although the immunisations identified by this system are likely to reflect accurate medical information, it is possible that immunisation capture was incomplete.[200] Thirdly, the use of LCI as an endpoint is a strength of our study, however, there may be some outcome misclassification, in cases where a child was not tested for influenza. For this reason, we included additional endpoints considering diagnostic coding. Finally, despite the large cohort size in our study, some outcomes were suppressed when stratifying by trimester of vaccination due to <5 cases, and post-hoc power analysis suggests some associations may not have been detected.

6.7 Conclusion

Few studies have evaluated the impacts of seasonal IIV during pregnancy on acute respiratory infectious outcomes beyond infancy and into early childhood. As maternal vaccination programs continue to expand globally, it will become increasingly important to understand the comprehensive impact of prenatal exposure to vaccines on child health, particularly the immune signature of the child.[244] Overall, our findings suggest maternal influenza vaccination prevented influenza in young infants aged <6 months and was not associated with long-term differences in the risk of acute respiratory infections among children aged <5 years. However, there was a suggested increase in the risk of LCI among children aged 6 months to <2 years following maternal influenza vaccination during the first trimester. This observed association could be due to residual confounding, differential exposure to influenza seasons, and/or the absence of vaccination information beyond six months of age implying that these results should be interpreted cautiously. Regardless, we believe our results support current vaccine policies and practices prioritizing influenza immunisation during pregnancy to protect young infants from influenza infection, and suggests the need for additional studies to further evaluate longer-term health outcomes.

Chapter Seven: Allergic/atopic and autoimmune diseases

7.1 Preamble

This chapter is based on a revised paper currently under re-review at *PLoS Medicine*. The chapter which follows is a verbatim copy of the content from the submitted manuscript, except for minor modifications for readability. Supplementary material for this manuscript is available in **Appendix F**.

7.2 Abstract

Background. Few studies have evaluated the effect of maternal influenza vaccination on the development of allergic and autoimmune diseases in children beyond six months of age. We aimed to investigate the association between *in utero* exposure to seasonal inactivated influenza vaccine (IIV) and subsequent diagnosis of allergic and autoimmune diseases.

Methods and Findings. This longitudinal, population-based linked cohort study included 124,760 singleton, liveborn children from 106,206 mothers in Western Australia born between April 2012 and July 2016, with up to 5 years of follow-up from birth. In our study cohort, 64,169 (51.4%) were male, 6,566 (5.3%) were Aboriginal and/or Torres Strait Islander children, and the mean age at the end of follow-up was 3.0 (standard deviation, 1.3) years. The exposure was receipt of seasonal IIV during pregnancy. The outcomes were diagnosis of an allergic or autoimmune disease, including asthma and anaphylaxis, identified from hospital and/or emergency department records. Inverse-probability of treatment weights accounted for baseline probability of vaccination by maternal age, Aboriginal and/or Torres Strait Islander status, socioeconomic status, body mass index, parity, medical conditions, pregnancy complications, prenatal smoking and prenatal care. The model additionally adjusted for the Aboriginal and/or Torres Strait Islander status of the child.

There were 14,396 (11.5%) children of vaccinated mothers; 913 (6.3%) and 7,655 (6.9%) children of vaccinated and unvaccinated mothers had a diagnosis of allergic or autoimmune disease, respectively. Overall, maternal influenza vaccination was not associated with diagnosis of an allergic or autoimmune disease (aHR: 1.02; 95% CI: 0.95-1.09). In trimester-specific analyses, we identified a negative association between third trimester influenza vaccination and the diagnosis of asthma (n = 40; aHR: 0.70; 95% CI: 0.50-0.97) and anaphylaxis (n = 36; aHR: 0.67; 95% CI: 0.47-0.95).We did not capture outcomes diagnosed in a primary care setting, therefore our findings are only generalizable to more severe events requiring hospitalisation or presentation to emergency department. Due to low small cell sizes (i.e., <5), estimates could not be determined for all outcomes after stratification.

Conclusion. In this study, we observed no association between *in utero* exposure to influenza vaccine and diagnosis of allergic or autoimmune diseases. Although we identified a negative association of asthma and anaphylaxis diagnosis when seasonal IIV was administered later in pregnancy, additional studies are needed to confirm this.

7.3 Introduction

Influenza is a major respiratory infection that is linked with serious morbidity and mortality through seasonal epidemics each year, particularly among children aged <5 years,[11, 24] and while seasonal IIV is the most effective preventative tool to protect against influenza infection,[228] there are no current vaccines licensed for use for infants aged less than six months.[11] Previous studies have shown that vaccine-derived antibodies cross the placenta during pregnancy and offer passive immunity to infants during their first six months of life.[11, 58] Prenatal administration of seasonal IIV is therefore recommended for pregnant women in many countries, including Australia, at any stage of pregnancy.[11, 58]

Substantial evidence supports the safety of maternal influenza vaccination with respect to health outcomes at birth, with no harmful association with preterm birth, small-for-gestational age, spontaneous abortion, stillbirth, low birthweight, congenital malformations, and fetal death.[124, 125, 127] However, according to a recent systematic review, few studies have assessed paediatric health outcomes beyond the first six months of life.[231] Previous clinical evidence has suggested that exposure to maternal vaccination *in utero* may 'prime' the innate fetal immune system, resulting in a more activated and mature immunophenotype.[133, 245] However, studies evaluating the impact of *in utero* exposure to seasonal influenza vaccines on the development of paediatric immune disorders are needed.

To our knowledge, only three studies have examined allergic or autoimmune outcomes among children >6 months of age which highlights the novelty and the need for this study. The aim of this study was to assess the risk of allergic and autoimmune diseases among children of vaccinated and unvaccinated mothers with seasonal influenza vaccines.

7.4 Methods

7.4.1 Study cohort and design

This retrospective, population-based cohort study included all singleton, live-born children born in WA between April 1, 2012, and July 1, 2016 and their mothers, as identified from birth registrations (**Figure 7-1**). Mother-child pairs were probabilistically linked with other population-based administrative health datasets

by the WA Data Linkage Branch,[188] including the Midwives Notification System (MNS),[198] the WA Antenatal Vaccination Database (WAAVD),[200] Hospital Morbidity Data Collection (HMDC),[203] Emergency Department Data Collection (EDDC),[204] and death registrations. The probabilistic linkage matches records from different sources using complex non-unique identifiers or field matching algorithms.[192] These algorithms compare common fields, such as given name, surname, date of birth and other relevant fields (dependent on the contents and context of the dataset),[193] and provides a similarity weighting which is positively associated with the likelihood that two or more records belong to the same individual.[192] Clerical review is required to assess potential non-matched records; this process has been shown to reduce the error rate of matching to less than 0.1%.[189]

The MNS is a legally mandated perinatal data collection of all children born at least 20 weeks' gestation or birthweight of ≥400g (where gestational age is unknown). This data collection includes maternal demographics and health information, obstetric history, date of delivery, gestational age, and birthweight. Death registrations includes the date and cause of all registered deaths in the state. This study received approval and a waiver or consent from the Department of Health WA Human Research Ethics Committee (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217-0808). This study is part of a larger linked cohort study and was guided by the study protocol described elsewhere.[246] This study is reported according to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.[247]

7.4.2 Maternal influenza vaccination

Data on influenza vaccination during pregnancy were obtained from the WAAVD, a state-wide database, managed by the WA Department of Health, that includes information on the date of vaccination, vaccine brand and batch number, and the estimated gestation at which vaccinations were administered as reported by their healthcare provider. In Australia, seasonal IIV during pregnancy has been recommended by the Australian Government since March 2000 and funded under the NIP since January 2010.[58, 186]

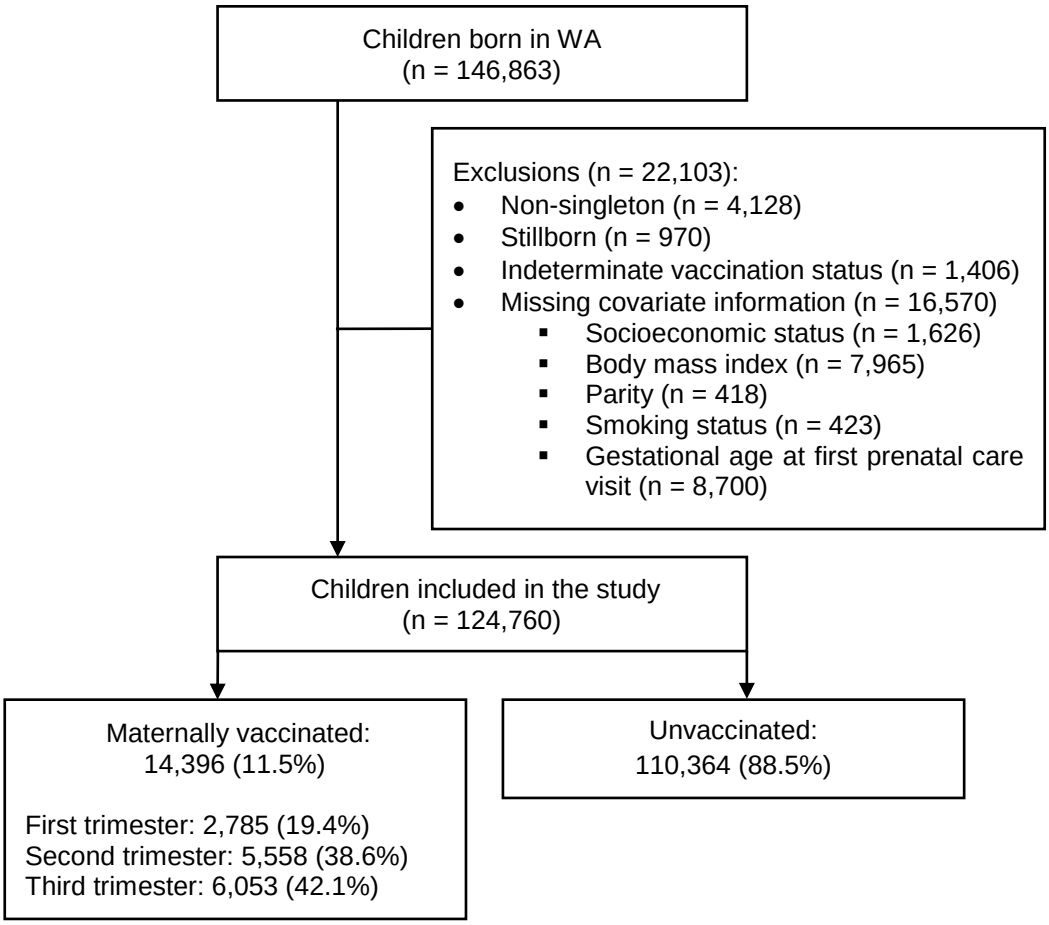

Figure 7-1. Flow diagram of study participants included in the cohort.

Children of mothers who had a record of receipt of seasonal IIV during pregnancy were considered 'maternally vaccinated'. We estimated the gestational age at vaccination from the difference of completed weeks of gestation between the estimated date of conception and date of vaccination. Trimester at vaccination was categorised as: first trimester (0 to ≤13 weeks gestation), second trimester (14 to ≤27 weeks gestation) and third trimester (≥28 weeks gestation). As antibody transfer may have been sub-optimal when administered <2 weeks prior to birth,[248] we excluded children of mothers that received an influenza vaccine <2 weeks prior to birth (i.e., 'indeterminate' vaccination status).

7.4.3 Outcomes

Outcomes were identified from hospital and emergency department records.[203, 204] The HMDC records all hospital inpatient admissions in the state's public and private hospitals, including the date of admission and separation, up to 21 diagnosis codes (classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] codes).[203] The EDDC includes all emergency department (ED) presentations in the state's metropolitan public and private hospitals, including the date of presentation, one ICD diagnosis code, and one symptom code. Outcomes evaluated in this study included: a) allergic or autoimmune diseases, b) allergic diseases, and c) autoimmune diseases, as identified by ICD-10-AM diagnostic codes in primary or additional diagnosis fields (**Supplementary Table F-1**). Within allergic diseases, we separately evaluated asthma or anaphylaxis as health outcomes. To evaluate the possible influence of bias in the study results, we included presentations for all-cause injuries as a negative control outcome, since negative controls can be used to identify non-causal associations between prenatal exposure to seasonal IIV and the outcomes (**Supplementary Table F-1**).[249]

7.4.4 Covariates

Maternal characteristics included age at the time of her child's birth (≤19, 20-24, 25-29, 30-34 and ≥35 years), Aboriginal and/or Torres Strait Islander status (hereafter respectfully referred to as Aboriginal), socioeconomic status (quintiles between 1 (most disadvantaged) and 5 (least disadvantaged)),[250] body mass index, parity (primiparous, one prior birth, ≥2 prior births), pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking during pregnancy, and gestational age at the first prenatal care visit. Socioeconomic status was based on the Socioeconomic Index for Areas Index of Relative Socioeconomic Advantage and Disadvantage, an area-based index of relative access to resources for households within the same census collection district.[239] The referent group for socioeconomic status was the least disadvantaged quintile (i.e., quintile 5).

Child characteristics considered as covariates included the child's Aboriginal status, year and season of birth, preterm birth and small-for-gestational age birth status. All covariates were selected *a priori* for their association with maternal influenza vaccination.[16, 19, 68, 104, 237, 238] Preterm birth was categorised as: moderate to late preterm (32 to <37 weeks gestation), very preterm (28 to <32 weeks gestation), and extremely preterm (<28 weeks gestation) birth. Small-for-gestational age birth was defined as birthweight <10th percentile according to Australian national birthweight percentiles by sex and gestational age.[236]

7.4.5 Participant involvement

No participants were involved in setting the research question or the exposure or outcome measures nor were they involved in the design and implementation of the study. There are no plans to directly involve study participants in the dissemination of the research findings.

7.4.6 Statistical analyses

We compared the demographic and health characteristics between vaccinated and unvaccinated mothers and their children using univariate logistic regression models. Based on the predicted probability of vaccination from multivariate logistic regression, we estimated the inverse-probability of treatment (vaccination) weights (IPTW) to control for baseline probability of vaccination in further analyses. The multivariate model included the maternal covariates: age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions, pregnancy complications, smoking during pregnancy, and gestational age at the time of first prenatal care visit. To assess the balance of maternal covariates between children of vaccinated and unvaccinated mothers, we calculated the standardised mean differences of each covariate. Inverse probability of treatment weights were applied to Cox proportional hazards regression models to estimate unadjusted and adjusted hazard ratios with 95% CIs for each of the study outcomes. Adjusted models additionally controlled for the child's Aboriginal status and year and season of birth.

Children were followed up from the date of birth and were censored at the earliest of: a) the date the child reached five years of age, b) last date of available data provided by the WA Data Linkage Branch (i.e., 1 July 2017), c) the date the child died, or d) the date of the event. Sub-group analyses compared the risk of study

outcomes by trimester of maternal vaccination. To assess the sensitivity of our definition of childhood asthma, we restricted the definition of asthma to the presence of a diagnosis code for asthma alone (i.e., J45-J46) and did not include early symptoms of asthma (i.e., wheezing). To evaluate associations with more severe clinical outcomes, additional analyses defined outcomes based on hospital inpatient admission data only. To evaluate the importance of timing of maternal vaccination and duration of exposure to maternal antibodies, stratified analyses were planned *a priori* and performed 1) by trimester of vaccination, and additional sensitivity analysis stratifying 2) by preterm birth status, to see if results differed by length of gestation. All analyses were performed in Stata version 15.1 (StataCorp LLC, College Station, Texas, USA).

As per recommendations during the peer review process, additional analyses were conducted. To evaluate the potential competing risk of all-cause mortality, the mortality rate of children of vaccinated and unvaccinated mothers was calculated. As the majority of studies in maternal influenza vaccination and early childhood health outcomes have focused on the first six months of life, we performed a sensitivity analysis restricting to children aged between 6 months and 5 years. As the study cohort includes siblings, this may imply statistical dependence of observations due to genetic factors and/or shared environment, therefore we performed an additional sensitivity analysis restricting to one randomly selected child per mother. To further evaluate the potential influence of seasonality on our findings, we performed an additional sensitivity analysis which matched children by calendar year and month of birth, allowing the assessment of outcomes comparing children born during similar time periods. These models incorporated year and month of birth as stratum and removed year and season of birth from propensity score estimates.

7.5 Results

We identified a total of 146,864 children born in WA during the study period; 22,114 (15.1%) children were excluded because the child was a non-singleton (n = 4,128), stillborn (n = 970), had indeterminate maternal vaccination status (n = 1,406), or missing covariate information (n = 16,570). The final cohort included 124,760 singleton, liveborn children from 106,206 mothers (**Figure 7-1**). Children were followed until a mean age of 3.0 (standard deviation: 1.3) years. The mortality rate was 2.4 deaths per 1,000 children of vaccinated mothers and 2.4 deaths per 1,000 children of unvaccinated mothers.

7.5.1 Maternal influenza vaccination

Among the 124,760 children, 14,396 (11.5%) children of mothers were vaccinated during pregnancy; 2,785 (19.4%) exposed during the first trimester, 5,558 (38.6%) during the second trimester, and 6,053 (42.1%) during the third trimester. Vaccine exposure varied from 6.1% for births in 2012 to 12.0% in 2015. Most mothers received their influenza vaccine between March and July (n = 12,537; 87.1%) of any given year. Primiparous women, women with pre-existing medical conditions and pregnancy complications, and women who were non-smokers during pregnancy were more likely to have been vaccinated (**Table 7-1**). Vaccination was less common among women of the lowest socioeconomic status (OR, 0.93; 95% CI: 0.88-0.98) compared to women of the highest socioeconomic status, and mothers of preterm infants compared to term infants (OR, 0.91; 95% CI: 0.85-0.98), and vaccination was more common among women who birthed during winter compared to summer (OR, 2.60; 95% CI: 2.46-2.74). After applying IPTW, standardised differences of maternal characteristics were balanced between children of vaccinated and unvaccinated mothers (**Supplementary Figure F-1**).

Table 7-1. Odds of seasonal influenza vaccination by maternal and child characteristics for children born in Western Australia between 1 April 2012 and 1 July 2016.

Characteristic	Children of unvaccinated mothers (N = 110,364) n (%)	Children of vaccinated mothers (N = 14,396) n (%)	Unadjusted OR (95% CI)
Maternal characteristics			
Age (years):			
≤19	3,369 (3.1)	449 (3.1)	**1.13 (1.01-1.26)**
20-24	14,828 (13.4)	1,747 (12.1)	Ref
25-29	31,459 (28.5)	3,978 (27.6)	**1.07 (1.01-1.14)**
30-34	37,706 (34.2)	5,151 (35.8)	**1.16 (1.09-1.23)**
≥35	23,002 (20.8)	3,071 (21.3)	**1.13 (1.06-1.21)**
Aboriginal status:			
Aboriginal	5,296 (4.8)	717 (5.0)	1.04 (0.96-1.13)
Non-Aboriginal	105,068 (95.2)	13,679 (95.0)	Ref
Socioeconomic status:[b]			
Quintile 1 (most disadvantaged)	21,181 (19.2)	2,618 (18.2)	**0.93 (0.88-0.98)**
Quintile 2	22,674 (20.5)	3,019 (21.0)	1.00 (0.94-1.05)
Quintile 3	23,256 (21.1)	2,972 (20.6)	0.96 (0.91-1.01)
Quintile 4	22,217 (20.1)	2,979 (20.7)	1.00 (0.95-1.06)
Quintile 5 (least disadvantaged)	21,036 (19.1)	2,808 (19.5)	Ref
Body mass index:			
<18.5 (underweight)	3,532 (3.2)	450 (3.1)	0.97 (0.87-1.07)
18.5 to <25 (normal)	54,032 (49.0)	7,114 (49.4)	Ref
25 to <30 (overweight)	30,720 (27.8)	3,875 (26.9)	0.96 (0.92-1.00)
≥30 (obese)	22,080 (20.0)	2,957 (20.5)	1.02 (0.97-1.06)
Parity:			
Primiparous	47,824 (43.3)	6,764 (47.0)	Ref
1 prior birth	38,216 (34.6)	4,958 (34.4)	**0.92 (0.88-0.95)**
≥2 prior births	24,324 (22.0)	2,674 (18.6)	**0.78 (0.74-0.81)**
Pre-existing medical conditions:			
Asthma	11,523 (10.4)	1,596 (11.1)	**1.07 (1.01-1.13)**
Essential hypertension	1,417 (1.3)	261 (1.8)	**1.42 (1.24-1.62)**
Pre-existing diabetes mellitus	916 (0.8)	191 (1.3)	**1.61 (1.37-1.88)**
Pregnancy complications:			
Gestational diabetes	11,310 (10.3)	1,688 (11.7)	**1.16 (1.10-1.23)**
Gestational hypertension	5,112 (4.6)	777 (5.4)	**1.17 (1.09-1.27)**
Pre-eclampsia	3,597 (3.3)	543 (3.8)	**1.16 (1.06-1.28)**
Smoked during pregnancy	10,540 (9.6)	1,269 (8.8)	**0.92 (0.86-0.97)**
Trimester of first prenatal care visit:			
First trimester	72,857 (66.0)	*	Ref
Second trimester	32,380 (29.3)	*	**0.82 (0.79-0.85)**
Third trimester	5,053 (4.6)	*	**0.54 (0.49-0.60)**
No prenatal care	74 (0.1)	<5	0.38 (0.14-1.05)
Year of birth:			
2012	19,930 (18.1)	1,304 (9.1)	Ref
2013	25,894 (23.5)	2,909 (20.2)	**1.72 (1.60-1.84)**
2014	26,345 (23.9)	3,205 (22.3)	**1.86 (1.74-1.99)**
2015	24,726 (22.4)	5,148 (35.8)	**3.18 (2.99-3.39)**
2016	13,469 (12.2)	1,830 (12.7)	**2.08 (1.93-2.24)**
Season of birth:			
Summer (Dec-Feb)	27,325 (24.8)	2,186 (15.2)	Ref
Autumn (Mar-May)	31,716 (28.7)	2,291 (15.9)	**0.90 (0.85-0.96)**
Winter (Jun-Aug)	26,062 (23.6)	5,413 (37.6)	**2.60 (2.46-2.74)**
Spring (Sep-Nov)	25,261 (22.9)	4,506 (31.3)	**2.23 (2.11-2.35)**
Child characteristics			
Sex:[c]			
Male	56,822 (51.5)	7,347 (51.0)	Ref
Female	53,539 (48.5)	7,049 (49.0)	1.02 (0.98-1.05)
Aboriginal status:			
Aboriginal	5,779 (5.2)	787 (5.5)	1.05 (0.97-1.13)
Non-Aboriginal	104,585 (94.8)	13,609 (94.5)	Ref

Birth outcomes:			
Preterm birth	7,390 (6.7)	887 (6.2)	**0.91 (0.85-0.98)**
Moderate-to-late preterm	6,587 (6.0)	819 (5.7)	0.95 (0.88-1.02)
Very preterm	520 (0.5)	52 (0.4)	0.76 (0.57-1.01)
Extremely preterm	283 (0.3)	16 (0.1)	**0.43 (0.26-0.71)**
Small-for-gestational age[b]	9,005 (8.2)	1,191 (8.3)	1.02 (0.95-1.08)

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics [239].
* In accordance with privacy and confidentiality guidelines by the DLB, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.
[b] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age, 1998-2007 [236].
[c] The sex of <5 maternally unvaccinated children was unknown.

7.5.2 Allergic diseases

There were 8,417 children with a diagnosis of an allergic disease. The most common outcomes included asthma (n = 3,538; 42.0%), urticaria (n = 2,805; 33.3%), and anaphylaxis (n = 987; 11.7%). Maternal influenza vaccination was not associated with presentation to ED or hospitalisation for an allergic disease among children aged <5 years (aHR: 1.02; 95% CI: 0.95-1.10) (**Table 7-2**). We observe similar results when stratifying by preterm birth status (**Supplementary Tables F-2 and F-3**) and when restricting to hospital admissions only (**Supplementary Table F-4**), children aged between 6 months and 5 years (**Supplementary Table F-5**) or one random child per mother (**Supplementary Table F-6**).

7.5.3 Asthma

A total of 3,757 children had an episode of care for asthma; 1,020 (27.1%) diagnoses of asthma and 2,752 (73.3%) diagnoses of wheezing were identified. We observed no difference in the risk of asthma among children of vaccinated mothers compared to children of unvaccinated mothers (aHR: 1.00; 95% CI: 0.89-1.12) (**Table 7-2**).

In the sensitivity analysis restricting the definition of asthma to the presence of an asthma diagnosis code alone, we observed a negative association of asthma following vaccination during the third trimester (aHR: 0.70; 95% CI: 0.50-0.97) (**Table 7-2**). This was mostly attributed to a negative association observed among term children following vaccination during the third trimester (aHR: 0.68; 95% CI: 0.48-0.96) (**Supplementary Table F-2**). When considering year and month of birth as a stratum, this negative association between asthma and vaccination during the third trimester was no longer significant (**Supplementary Table F-7**). No other associations were observed following vaccination during earlier trimesters (**Table 7-2**) or after stratifying by preterm birth status (**Supplementary Tables F-2 and F-3**) or

when restricting to hospital admissions only (**Supplementary Table F-4**), children aged between 6 months and 5 years (**Supplementary Table F-5**) or one random child per mother (**Supplementary Table F-6**).

7.5.4 Anaphylaxis

In total, there were 1,157 children diagnosed with an episode of anaphylaxis. We observed a negative association of anaphylaxis associated with exposure to seasonal IIV administered during the third trimester (aHR: 0.67; 95% CI: 0.47-0.95). This was attributed to a negative association observed among term children following vaccination during the third trimester (aHR: 0.62; 95% CI: 0.43-0.91) (**Supplementary Table F-2**). The negative association between anaphylaxis and vaccination during the third trimester remained even after treating year and month of birth as a stratum (aHR: 0.69; 95% CI: 0.49-0.97) (**Supplementary Table F-7**). No other associations were observed following vaccination during earlier trimesters (**Table 7-2**) or after stratifying by preterm birth status (**Supplementary Tables F-2 and F-3**) or when restricting to hospital admissions only (**Supplementary Table F-4**), children aged between 6 months and 5 years (**Supplementary Table F-5**) or one random child per mother (**Supplementary Table F-6**).

7.5.5 Autoimmune diseases

There were 174 children with a diagnosis of an autoimmune disease, including 16 (9.2%) of mothers who were vaccinated during pregnancy. The most common outcomes included diabetes mellitus (n = 54; 31.0%), coeliac disease (n = 40; 23.0%), idiopathic thrombocytopenic purpura (n = 33; 19.0%) and juvenile arthritis (n = 21; 12.1%). There was no significant difference in the risk of autoimmune diseases between children of vaccinated and unvaccinated mothers (aHR: 0.93; 95% CI: 0.55-1.59) (**Table 7-2**) nor any differences detected by trimester of vaccination (**Table 7-2**), after stratifying by preterm birth status (**Supplementary Tables F-2 and F-3**), or when restricting to hospital admissions only (**Supplementary Table F-4**), children aged between 6 months and 5 years (**Supplementary Table F-5**) or one random child per mother (**Supplementary Table F-6**).

Table 7-2. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Allergic or autoimmune disease					
Cases, n (%)	7,655 (6.9)	913 (6.3)	171 (6.1)	395 (7.1)	347 (5.7)
Unweighted HR (95% CI)	1 [Reference]	1.03 (0.96-1.11)	0.99 (0.85-1.15)	1.09 (0.99-1.21)	0.99 (0.89-1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.95-1.09)	0.97 (0.82-1.14)	1.07 (0.96-1.19)	0.98 (0.88-1.10)
Allergic disease					
Cases, n (%)	7,518 (6.8)	899 (6.2)	168 (6.0)	391 (7.0)	340 (5.6)
Unweighted HR (95% CI)	1 [Reference]	1.03 (0.96-1.11)	0.99 (0.85-1.15)	1.10 (0.99-1.22)	0.99 (0.89-1.10)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.95-1.10)	0.97 (0.82-1.14)	1.08 (0.97-1.20)	0.98 (0.87-1.10)
Asthma diagnosis or wheezing					
Cases, n (%)	3,375 (3.1)	382 (2.7)	68 (2.4)	169 (3.0)	145 (2.4)
Unweighted HR (95% CI)	1 [Reference]	1.01 (0.91-1.12)	0.92 (0.72-1.17)	1.07 (0.91-1.25)	1.00 (0.84-1.18)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.89-1.12)	0.92 (0.71-1.19)	1.07 (0.91-1.26)	0.97 (0.81-1.15)
Asthma diagnosis only[b]					
Cases, n (%)	1,425 (1.3)	131 (0.9)	30 (1.1)	61 (1.1)	40 (0.7)
Unweighted HR (95% CI)	1 [Reference]	0.89 (0.74-1.06)	1.03 (0.72-1.49)	0.97 (0.75-1.25)	**0.72 (0.52-0.98)**
Weighted aHR (95% CI)[a]	1 [Reference]	0.87 (0.73-1.05)	0.99 (0.68-1.45)	0.98 (0.75-1.28)	**0.70 (0.50-0.97)**
Anaphylaxis					
Cases, n (%)	1,043 (0.9)	114 (0.8)	30 (1.1)	48 (0.9)	36 (0.6)
Unweighted HR (95% CI)	1 [Reference]	0.95 (0.78-1.15)	1.29 (0.90-1.85)	0.98 (0.74-1.31)	0.75 (0.54-1.05)
Weighted aHR (95% CI)[a]	1 [Reference]	0.85 (0.70-1.05)	1.15 (0.78-1.68)	0.90 (0.67-1.22)	**0.67 (0.47-0.95)**
Autoimmune disease					
Cases, n (%)	158 (0.1)	16 (0.1)	<5	6 (0.1)	7 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.95 (0.57-1.59)	-	0.85 (0.37-1.92)	1.08 (0.50-2.30)
Weighted aHR (95% CI)[a]	1 [Reference]	0.93 (0.55-1.59)	-	0.89 (0.37-2.12)	1.06 (0.49-2.31)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

7.5.6 Negative control

A total of 21,730 children aged <5 years presented to ED or were hospitalised with an injury. We observed no difference in the risk of all-cause injuries between children of vaccinated and unvaccinated mothers (aHR: 1.04; 95% CI: 0.99-1.11) (**Supplementary Table F-8**).

7.6 Discussion

In this large, population-based cohort study of 124,760 children, we found no evidence of an increased risk of allergic or autoimmune disease in children following prenatal exposure to seasonal IIV. We observed a negative association of anaphylaxis and some indications of lower risk of asthma following seasonal IIV given during the third trimester. We observed no other associations between prenatal exposure to seasonal IIV and allergic or autoimmune diseases in children up to 5 years of age. These results contribute to the gap in knowledge of the potential child health impacts of maternal influenza vaccination on the development of allergic or autoimmune diseases in childhood and support the safety and continuation of existing maternal vaccination programs and policies.

To date, most studies evaluating maternal influenza vaccination have focused on outcomes in the first six months of life. To our knowledge, only three studies have assessed allergic and/or autoimmune outcomes in children beyond 6 months of age.[178, 179] Firstly, a recent Canadian study by Mehrabadi et al.[251] examined asthma in children aged <6 years, born between October 2010 and March 2014, following prenatal exposure to unadjuvanted trivalent (i.e., 2 type A strains and 1 type B strain) seasonal influenza vaccine. Another Canadian study by Walsh et al.[179] examined asthma in children aged <5 years, born between November 2009 and October 2010, following prenatal exposure to non-adjuvanted or AS03-adjuvanted pandemic A/H1N1 influenza vaccine. A Danish study by Hviid et al.[178] also examined asthma as well as other autoimmune diseases in children aged <5 years, born between November 2009 and March 2010, following prenatal exposure to AS03-adjuvanted pandemic A/H1N1 influenza vaccine. In this study, stratified analyses of outcomes were restricted to a) first trimester exposure, and b) second- or third-trimester exposure to vaccine. In Denmark, only pregnant women with chronic diseases were recommended to get vaccinated during this period, resulting in a low number of children vaccinated during the first trimester

(n = 349; 5.5%) and therefore likely lacked statistical power to detect associations. These studies identified no association between maternal influenza vaccination and the subsequent development of allergic or autoimmune diseases in offspring.

While our results evaluating seasonal influenza vaccine mostly align with those from prior pandemic vaccine studies, when stratifying by trimester of vaccination, we observed a negative association of asthma and anaphylaxis following third trimester influenza vaccination. This association persisted in a sensitivity analysis restricting to term children but not in preterm children.

While we cannot entirely rule out the possible influences of bias in the results from this observational study, several aspects of our study suggest a plausible protective relationship between maternal immunisation and the development of allergic conditions in childhood. First, early exposure to respiratory infections, in particular viral infections, are strongly linked to the development of childhood wheezing disorders and subsequent asthma in susceptible children,[252, 253] and a history of asthma is a known risk factor of anaphylaxis and severe anaphylactic episodes, not surprisingly, as there is interaction between atopic asthma and other allergic states.[254] Maternal influenza immunisation reduces the risk of all-cause respiratory infection in infants <6 months by 25%.[255, 256] Protection from respiratory infection through maternal immunisation could help to avoid exacerbation of wheezing episodes through recurrent infections and subsequent development of asthma. Given maternal antibody transfer peaks during the third trimester of pregnancy,[85] children born at term are likely to receive more maternal antibodies, and thus a higher level of protection, than children born preterm. This is consistent with our observation that a negative association of asthma was only observed among term-born children of vaccinated mothers. Second, priming of the infant's developing immune system may occur in response to exposure to environmental allergens, maternal vaccination, or infection.[245] Studies have shown an adaptive antigen-specific cellular immune response independent of antibody-mediated passive immunity associated with maternal vaccination, which suggests potential non-specific effects of maternal influenza vaccination.[245]

Our study had several strengths and limitations. The main strengths of our study include the use of a large, population-based mother-infant cohort with detailed

information on maternal sociodemographic and health characteristics, receipt of prenatal vaccine, and record linkage to several administrative health datasets permitting follow-up of outcomes up to 5 years of age. The record linkage system in WA is long-standing, with expertise in linking large administrative health data since 1995.[187] With the exception of the antenatal vaccination register, these datasets are legally mandated, feed into national data collections and the quality of data is considered to be high.[241] The MNS is also estimated to capture 99% of all births in WA.[198]

Despite these strengths, our study has several limitations. First, maternal vaccination data linked from the WAAVD relied on immunisation reports from medical providers and although these records have high specificity, they are likely to be incomplete.[200] Second, outcomes were limited by diagnoses recorded in hospital inpatient and ED presentation records, which do not capture outcomes diagnosed and treated in a primary care setting. However, because severe medical events, such as anaphylaxis, are more likely to present for secondary or tertiary care, the more severe outcomes we assessed in this study were likely to be well measured. For this reason, we considered different definitions of study outcomes to evaluate the sensitivity of diagnostic codes. Third, we cannot entirely rule out residual confounding, although we attempted to restrict the influence of health-seeking behaviour using inverse-probability treatment weighting. Finally, despite the large size of our cohort, small cell sizes (i.e., <5) made it impractical to estimate effects for first trimester or by preterm birth status for all outcomes. To our knowledge, only one other study has evaluated the impact of seasonal IIV during pregnancy on allergic or autoimmune disease development in early childhood. Overall, our findings suggest seasonal IIV during pregnancy is not associated with adverse allergic or autoimmune outcomes in children aged up to 5 years and support current global vaccine policies prioritising influenza immunisation for pregnant women. Our study observed a negative association of anaphylaxis and asthma following seasonal IIV given during the third trimester, and these results warrant further investigation. This information is useful to pregnant women and their healthcare providers when making vaccine decisions and providing vaccine counselling.

Chapter Eight: Neurodevelopmental disorders

8.1 Preamble

This chapter is a manuscript in preparation for submission to *Archives of Diseases in Childhood*, except for minor modifications for readability. Supplementary material for this manuscript is available in **Appendix G**.

8.2 Abstract

Background and Objectives. Few studies have evaluated the association between maternal influenza vaccination and the risk of a diagnosis of a neurodevelopmental disorder among children. We aimed to assess the association between *in utero* exposure to seasonal inactivated influenza vaccine (IIV) and risk of diagnosis of a neurodevelopmental disorder among young children.

Methods. This longitudinal, population-based cohort study included 124,760 singleton, liveborn children in Western Australia from April 2012 to July 2016. Exposure data on maternal influenza vaccination from conception to birth was obtained from a state-wide antenatal vaccination database. Clinical diagnosis of a neurodevelopmental disorder was recorded from hospital inpatient and emergency department records. Cox proportional hazard models, weighted by the inverse-probability of treatment (vaccination), were used to estimate the hazard ratio of neurodevelopmental disorders associated with *in utero* exposure to seasonal IIV.

Results. Overall, maternal influenza vaccination was not associated with increased risk of neurodevelopmental disorders (aHR: 1.00; 95% CI; 0.90-1.10). Children exposed in the first trimester had a lower risk of seizure disorders (aHR: 0.73; 95% CI: 0.54-0.99). However, taking multiple comparisons into account, this association was no longer significant (aHR: 0.73; 98% CI: 0.51-1.05).

Conclusion. We did not observe an increased risk of neurodevelopmental disorders following *in utero* exposure to influenza vaccine. Although we detected a lower risk of seizure disorders when seasonal IIV was administered earlier in pregnancy, additional studies are required to confirm this. These results support the safety of seasonal IIV administration during pregnancy.

8.3 Introduction

Influenza causes serious morbidity and mortality through seasonal epidemics each year. High-risk populations, particularly pregnant women and young children under the age of 5 years,[1] have a greater risk of severe influenza illness. While seasonal IIV is the most effective preventative tool to protect against influenza infection,[2] there are no current vaccines licensed for use for infants aged less than six months.[1]

To protect mothers and their infants from infection, prenatal administration of seasonal IIV is recommended for pregnant women in many countries, including Australia, at any stage of pregnancy.[1] Previous studies have reported the effectiveness of influenza vaccination during pregnancy in protecting both the mother[4, 5] and the infant[6] during their first six months of life via transplacental vaccine-derived antibodies which offer passive immunity.[1]

There is considerable evidence that supports the safety of maternal influenza vaccination in regard to adverse health outcomes at birth, including preterm birth, small-for-gestational age, spontaneous abortion, stillbirth, low birthweight, congenital malformations, and fetal death.[7] However, studies evaluating health outcomes following *in utero* exposure to seasonal influenza vaccines beyond early infancy are relatively scarce.[8]

The aim of this study was to evaluate the association between seasonal influenza vaccination during pregnancy and paediatric neurodevelopmental health outcomes.

8.4 Methods

8.4.1 Study cohort and design

This retrospective, population-based cohort study included all singleton, live-born children born in WA between April 1, 2012, and July 1, 2016 and their mothers (**Figure 8-1**). We identified the study cohort using birth registrations. Mother-child pairs were probabilistically linked with other population-based administrative health datasets by the WA Data Linkage Branch, including the Midwives Notification System (MNS), WA Antenatal Vaccination Database (WAAVD), Hospital Morbidity Data Collection (HMDC), Emergency Department Data Collection (EDDC), and death registrations.[9]

The MNS is a legally mandated perinatal data collection of all children born at least 20 weeks' gestation or birthweight of ≥400g (where gestational age is unknown). This data collection includes maternal demographics and health information, obstetric history, date of delivery, gestational age, and birthweight. Death registrations included the date and cause of all registered deaths in the state. This study received approval and a waiver of consent from the Department of Health WA Human Research Ethics Committee (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217-0808). This study is reported according to the strengthening the reporting of observational studies in epidemiology guidelines.[247]

8.4.2 Maternal influenza vaccination

Information on influenza vaccination status during pregnancy, date of vaccination and estimated gestation at which vaccinations were administered during pregnancy as reported by their healthcare provider were obtained from the WAAVD, a state-wide database managed by the WA Department of Health. In Australia, seasonal IIV during pregnancy has been recommended by the Australian Government since March 2000 and funded under the NIP since January 2010.[11]

Children of mothers who had a receipt of seasonal IIV during pregnancy were considered 'maternally vaccinated'. We calculated the gestational age at vaccination from the estimated date of conception to date of vaccination. Trimester at vaccination was categorised as: first trimester (0 to ≤13 weeks gestation), second trimester (14 to ≤27 weeks gestation), and third trimester (≥28 weeks gestation). As antibody transfer is likely to be sub-optimal when administered <2 weeks prior to birth,[12] we excluded children of mothers who received seasonal IIV <2 weeks prior to birth (i.e., 'indeterminate' vaccination status).

8.4.3 Outcomes

Outcomes were identified from hospital and emergency department records.[13, 14] The HMDC records all hospital inpatient admissions in the state's public and private hospitals, including the date of admission and separation, up to 21 diagnosis codes (classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification

[ICD-10-AM] codes).[13] The EDDC includes all emergency department (ED) presentations in the state's metropolitan public and private hospitals, including the date of presentation, one ICD-10-AM diagnosis code, and one symptom code.

Outcomes evaluated in this study included: a) neurodevelopmental disorders, b) mental or behavioural disorders, and c) neurologic disorders, as identified by ICD-10-AM diagnostic codes in primary or additional diagnosis fields (**Supplementary Table G-1**). Within neurologic disorders, we separately evaluated seizure disorders, including epilepsy, as health outcomes. To evaluate the possible influence of bias in the study results, we included presentations for all-cause injuries as a negative control outcome, since negative controls can be used to identify non-causal associations between prenatal exposure to seasonal IIV and the outcomes (**Supplementary Table G-1**).[15]

8.4.4 Covariates

Maternal characteristics included age at the time of her child's birth (≤19, 20-24, 25-29, 30-34 and ≥35 years), Aboriginal and/or Torres Strait Islander status (hereafter respectfully referred to as Aboriginal), socioeconomic status (quintiles between 1 (most disadvantaged) and 5 (least disadvantaged)),[16] body mass index, parity (primiparous, one prior birth, ≥2 prior births), pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking during pregnancy, and trimester at the first prenatal care visit. Socioeconomic status was based on the Socioeconomic Index for Areas Index of Relative Socioeconomic Advantage and Disadvantage, an area-based index of relative access to resources for households within the same census collection district.[16]

Child characteristics included Aboriginal status, year and season of birth, preterm birth, and small-for-gestational age birth status. All covariates were selected *a priori* for their association with maternal influenza vaccination.[17-21] Preterm birth was categorised as: moderate to late preterm (32 to <37 weeks gestation), very preterm (28 to <32 weeks gestation), and extremely preterm (<28 weeks gestation) birth. Small-for-gestational age birth was defined as birthweight <10th percentile according to Australian national birthweight percentiles by sex and gestational age.[22]

8.4.5 Statistical analyses

We compared the demographic and health characteristics between vaccinated and unvaccinated mothers and their children using univariate logistic regression models. Based on the predicted probability of vaccination from multivariate logistic regression, we estimated the inverse-probability of treatment (vaccination) weights (IPTW) to control for baseline probability of vaccination in further analyses. To assess the balance of maternal covariates included in the multivariate model, we calculated the standardised mean differences of each covariate between children of vaccinated and unvaccinated mothers. IPTWs were applied to weighted Cox proportional hazards regression models to estimate unadjusted and adjusted hazard ratios with 95% CIs for each of the study outcomes. Adjusted models additionally controlled for the child's Aboriginal status and year and season of birth.

Children were followed up from the date of birth and were censored at the earliest of: a) the date the child reached five years of age, b) the last date of available data, c) the date the child died, or d) the date of the event. To evaluate associations with more severe clinical outcomes, additional analyses defined outcomes based on hospital admission data only. To evaluate the importance of timing of maternal vaccination and duration of exposure to maternal antibodies, stratified analyses were planned *a priori* and performed by 1) trimester of vaccination, and additional sensitivity analysis stratifying by 2) preterm birth status, to see if results differed by length of gestation. To account for multiple comparisons (n = 5 pre-specified outcomes), we recalculated the CIs after applying a Bonferroni correction. All analyses were performed in Stata version 15.1 (StataCorp LLC, College Station, Texas, USA). A post-hoc power analysis was computed to determine the detectable difference in the risk of the outcome measures, with 90% and 80% power and an alpha of 5%, between children of vaccinated and unvaccinated mothers (**Supplementary Table G-2**).

8.5 Results

A total of 146,863 children born in WA during the study period were identified; 22,103 (15.1%) children were excluded because the child was a non-singleton (n = 4,128), stillborn (n = 970), had indeterminate vaccination status (n = 1,406), or were missing covariate information (n = 16,562); 124,760 singleton, liveborn children from 106,206 mothers were included in the study (**Figure 8-1**).

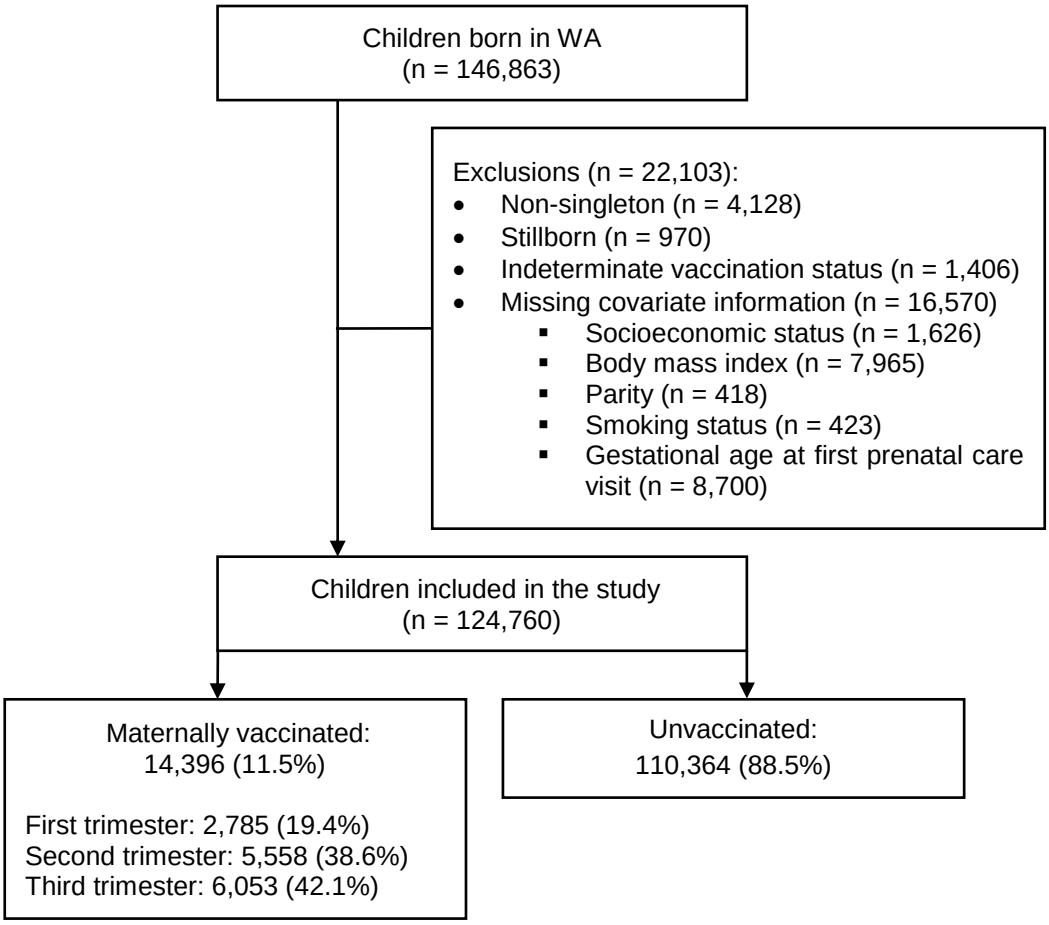

Figure 8-1. Flow diagram of study participants included in the cohort.

8.5.1 Maternal influenza vaccination

Among the 124,760 children, 14,396 (11.5%) children were vaccinated during pregnancy: 2,785 (19.4%) during the first trimester, 5,558 (38.6%) during the second trimester, and 6,053 (42.1%) during the third trimester. Vaccination during pregnancy varied from 10.1% for births in 2013 to 17.2% in 2015. The majority of mothers received their influenza vaccine between March and July (n = 12,537; 87.1%) for any given year. Vaccination was more common among primiparous women, women with pre-existing medical conditions and pregnancy complications,

and women who were non-smokers during pregnancy (**Table 8-1**). Women of the lowest socioeconomic status (OR, 0.93; 95% CI: 0.88-0.98) and mothers of preterm infants (OR, 0.91; 95% CI: 0.85-0.98) were less likely to be vaccinated, and women who gave birth during winter compared to summer were more likely to be vaccinated (OR, 2.60; 95% CI: 2.46-2.74). After weighting, maternal characteristics were balanced between children of vaccinated and unvaccinated mothers (**Supplementary Figure G-1**).

8.5.2 Neurodevelopmental disorders

During the study period, we identified 6,642 (5.3%) children with a diagnosis of a neurodevelopmental disorder. We observed no association between the risk of neurodevelopmental disorders and maternal influenza vaccination (aHR: 1.00; 95% CI: 0.90-1.10) (**Table 8-2**) nor after stratifying by trimester of vaccination (**Table 8-2**), preterm birth status (**Supplementary Tables G-3 and G-4**) or when restricting to hospital admissions only (**Supplementary Table G-5**).

8.5.3 Mental or behavioural disorders

There were 454 (0.4%) children with a diagnosis of a mental or behavioural disorder. The most common outcomes included disorders of psychological development (n = 187; 41.2%) and behavioural and emotional disorders (n = 113; 24.9%). There was no association between the risk of mental or behavioural disorders and maternal influenza vaccination (aHR: 1.00; 95% CI: 0.72-1.40) (**Table 8-2**) nor after stratifying by trimester of vaccination (**Table 8-2**), preterm birth status (**Supplementary Tables G-3 and G-4**) or when restricting to hospital admissions only (**Supplementary Table G-5**).

8.5.4 Neurologic disorders

In total, there were 6,335 (5.1%) children diagnosed with a neurologic disorder. The most common outcome included episodic and paroxysmal disorders (n = 3,929; 62.0%); 2,730 (69.5%) were episodes of a seizure disorder. No associations were observed between the risk of neurologic disorders and maternal influenza vaccination (aHR: 1.00; 95% CI: 0.91-1.09) (**Table 8-2**). Similarly, we observed no associations when stratifying by trimester of vaccination (**Table 8-2**), preterm birth status (**Supplementary Tables G-3 and G-4**) or when restricting to hospital admissions only (**Supplementary Table G-5**).

Table 8-1. Odds of seasonal influenza vaccination by maternal and child characteristics for children born in Western Australia between 1 April 2012 and 1 July 2016.

Characteristic	Children of unvaccinated mothers (N = 110,364) n (%)	Children of vaccinated mothers (N = 14,396) n (%)	Unadjusted OR (95% CI)
Maternal characteristics			
Age (years):			
≤19	3,369 (3.1)	449 (3.1)	**1.13 (1.01-1.26)**
20-24	14,828 (13.4)	1,747 (12.1)	Ref
25-29	31,459 (28.5)	3,978 (27.6)	**1.07 (1.01-1.14)**
30-34	37,706 (34.2)	5,151 (35.8)	**1.16 (1.09-1.23)**
≥35	23,002 (20.8)	3,071 (21.3)	**1.13 (1.06-1.21)**
Aboriginal status:			
Aboriginal	5,296 (4.8)	717 (5.0)	1.04 (0.96-1.13)
Non-Aboriginal	105,068 (95.2)	13,679 (95.0)	Ref
Socioeconomic status:[b]			
Quintile 1 (most disadvantaged)	21,181 (19.2)	2,618 (18.2)	**0.93 (0.88-0.98)**
Quintile 2	22,674 (20.5)	3,019 (21.0)	1.00 (0.94-1.05)
Quintile 3	23,256 (21.1)	2,972 (20.6)	0.96 (0.91-1.01)
Quintile 4	22,217 (20.1)	2,979 (20.7)	1.00 (0.95-1.06)
Quintile 5 (least disadvantaged)	21,036 (19.1)	2,808 (19.5)	Ref
Body mass index:			
<18.5 (underweight)	3,532 (3.2)	450 (3.1)	0.97 (0.87-1.07)
18.5 to <25 (normal)	54,032 (49.0)	7,114 (49.4)	Ref
25 to <30 (overweight)	30,720 (27.8)	3,875 (26.9)	0.96 (0.92-1.00)
≥30 (obese)	22,080 (20.0)	2,957 (20.5)	1.02 (0.97-1.06)
Parity:			
Primiparous	47,824 (43.3)	6,764 (47.0)	Ref
1 prior birth	38,216 (34.6)	4,958 (34.4)	**0.92 (0.88-0.95)**
≥2 prior births	24,324 (22.0)	2,674 (18.6)	**0.78 (0.74-0.81)**
Pre-existing medical conditions:			
Asthma	11,523 (10.4)	1,596 (11.1)	**1.07 (1.01-1.13)**
Essential hypertension	1,417 (1.3)	261 (1.8)	**1.42 (1.24-1.62)**
Pre-existing diabetes mellitus	916 (0.8)	191 (1.3)	**1.61 (1.37-1.88)**
Pregnancy complications:			
Gestational diabetes	11,310 (10.3)	1,688 (11.7)	**1.16 (1.10-1.23)**
Gestational hypertension	5,112 (4.6)	777 (5.4)	**1.17 (1.09-1.27)**
Pre-eclampsia	3,597 (3.3)	543 (3.8)	**1.16 (1.06-1.28)**
Smoked during pregnancy	10,540 (9.6)	1,269 (8.8)	**0.92 (0.86-0.97)**
Trimester of first prenatal care visit:			
First trimester	72,857 (66.0)	*	Ref
Second trimester	32,380 (29.3)	*	**0.82 (0.79-0.85)**
Third trimester	5,053 (4.6)	*	**0.54 (0.49-0.60)**
No prenatal care	74 (0.1)	<5	0.38 (0.14-1.05)
Year of birth:			
2012	19,930 (18.1)	1,304 (9.1)	Ref
2013	25,894 (23.5)	2,909 (20.2)	**1.72 (1.60-1.84)**
2014	26,345 (23.9)	3,205 (22.3)	**1.86 (1.74-1.99)**
2015	24,726 (22.4)	5,148 (35.8)	**3.18 (2.99-3.39)**
2016	13,469 (12.2)	1,830 (12.7)	**2.08 (1.93-2.24)**
Season of birth:			
Summer (Dec-Feb)	27,325 (24.8)	2,186 (15.2)	Ref
Autumn (Mar-May)	31,716 (28.7)	2,291 (15.9)	**0.90 (0.85-0.96)**
Winter (Jun-Aug)	26,062 (23.6)	5,413 (37.6)	**2.60 (2.46-2.74)**
Spring (Sep-Nov)	25,261 (22.9)	4,506 (31.3)	**2.23 (2.11-2.35)**
Child characteristics			
Sex:[c]			
Male	56,822 (51.5)	7,347 (51.0)	Ref
Female	53,539 (48.5)	7,049 (49.0)	1.02 (0.98-1.05)
Aboriginal status:			
Aboriginal	5,779 (5.2)	787 (5.5)	1.05 (0.97-1.13)
Non-Aboriginal	104,585 (94.8)	13,609 (94.5)	Ref

Birth outcomes:			
Preterm birth	7,390 (6.7)	887 (6.2)	**0.91 (0.85-0.98)**
Moderate-to-late preterm	6,587 (6.0)	819 (5.7)	0.95 (0.88-1.02)
Very preterm	520 (0.5)	52 (0.4)	0.76 (0.57-1.01)
Extremely preterm	283 (0.3)	16 (0.1)	**0.43 (0.26-0.71)**
Small-for-gestational age[b]	9,005 (8.2)	1,191 (8.3)	1.02 (0.95-1.08)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics [239].

* In accordance with privacy and confidentiality guidelines by the DLB, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.

[b] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age, 1998-2007 [236].

[c] The sex of <5 maternally unvaccinated children was unknown.

Table 8-2. Risk of neurodevelopmental disorders associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Neurodevelopmental disorder					
Cases, n (%)	5,964 (5.4)	677 (4.7)	132 (4.7)	288 (5.2)	257 (4.2)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.94-1.10)	1.02 (0.86-1.21)	1.05 (0.93-1.18)	0.99 (0.87-1.12)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.91-1.08)	0.98 (0.82-1.18)	1.03 (0.91-1.16)	0.96 (0.84-1.10)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.00 (0.90-1.10)	0.98 (0.79-1.22)	1.03 (0.89-1.19)	0.96 (0.82-1.12)
Mental or behavioural disorder					
Cases, n (%)	407 (0.4)	47 (0.3)	6 (0.2)	23 (0.4)	18 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.78-1.43)	0.70 (0.31-1.56)	1.25 (0.82-1.90)	1.02 (0.64-1.64)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.72-1.40)	0.67 (0.28-1.61)	1.20 (0.76-1.89)	0.97 (0.57-1.66)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.00 (0.68-1.49)	0.67 (0.24-1.89)	1.20 (0.69-2.06)	0.97 (0.51-1.83)
Neurologic disorder					
Cases, n (%)	5,689 (5.2)	646 (4.5)	128 (4.6)	275 (4.9)	243 (4.0)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.94-1.11)	1.04 (0.87-1.24)	1.05 (0.93-1.18)	0.98 (0.86-1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.91-1.09)	1.00 (0.83-1.20)	1.03 (0.91-1.17)	0.95 (0.83-1.09)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.00 (0.90-1.10)	1.00 (0.80-1.24)	1.03 (0.89-1.20)	0.95 (0.81-1.12)
Seizure disorder					
Cases, n (%)	2,441 (2.2)	289 (2.0)	45 (1.6)	126 (2.3)	118 (1.9)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.88-1.12)	0.79 (0.59-1.06)	1.06 (0.88-1.26)	1.02 (0.85-1.23)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.87-1.13)	**0.73 (0.54-0.99)**	1.11 (0.91-1.34)	0.99 (0.81-1.20)
Weighted aHR (98% CI)[ab]	1 [Reference]	0.99 (0.85-1.15)	0.73 (0.51-1.05)	1.11 (0.88-1.39)	0.99 (0.78-1.24)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table G-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.
[b] Adjusted models accounted for multiple comparisons using Bonferroni-corrected confidence intervals.

8.5.5 Seizure disorder

A total of 2,730 (2.2%) children were diagnosed with a seizure disorder; 642 (23.5%) diagnoses were 'epilepsy' or 'status epileptus' and 2,507 (91.8%) were convulsions. We observed no association between the risk of seizure disorders and maternal influenza vaccination (aHR: 1.00; 95% CI: 0.90-1.10). When stratifying by trimester, we observed a lower risk of seizure disorders following vaccination during the first trimester (aHR: 0.73; 95% CI: 0.54-0.99) (**Table 8-2**). This association was only observed among term children vaccinated during the first trimester (aHR: 0.72; 95% CI: 0.51-1.00) (**Supplementary Table G-3**). However, these associations were attenuated when taking multiple comparisons into account using Bonferroni-corrected CIs (**Table 8-2** and **Supplementary Table G-3**). No other associations were observed following vaccination during later trimesters (**Table 8-2**), when stratifying by preterm birth status (**Supplementary Tables G-3 and G-4**) or when restricting to hospital admissions only (**Supplementary Table G-5**).

8.5.6 Negative control

There were 21,730 (17.4%) children aged <5 years that presented to ED or were hospitalised with an injury. There was no association between the risk of all-cause injuries and maternal influenza vaccination (aHR: 1.04; 95% CI: 0.99-1.09) (**Supplementary Table G-6**), nor when stratifying by trimester of vaccination (**Supplementary Table G-6**).

8.6 Discussion

In this large, population-based cohort study of 124,760 children, we found no evidence of an increased risk of neurodevelopmental disorders among children aged <5 years following prenatal exposure to seasonal IIV. However, we did observe an indication of a lower risk of seizure disorders following seasonal IIV administered during the first trimester. There were no other associations between prenatal exposure to seasonal IIV and neurodevelopmental disorders. These results support the safety of maternal influenza vaccination and support continuance of existing maternal vaccination programs and policies.

To date, most studies evaluating maternal influenza vaccination have focused on outcomes in the first six months of life.[7] To our knowledge, only three studies

have assessed neurodevelopmental outcomes among children more than 6 months of age, two examining pandemic vaccines and one examining seasonal IIV exposure.[23-25] A recent Swedish study by Ludvigsson et al[23] examined autism spectrum disorder (ASD) among children aged <7 years from 2009 to 2016, following pandemic A/H1N1 influenza vaccination. Another study by Zerbo et al,[25] conducted in the United States, also examined ASD among children aged <15 years from 2000 to 2010, following prenatal exposure to seasonal IIV. A Danish study by Hviid et al[24] also examined ASD and autistic disorder as well as other behavioural (i.e., intellectual disability) and neurologic (i.e., bell palsy, epilepsy, Guillain-Barré syndrome) disorders among children aged <5 years from 2009 to 2010, following pandemic A/H1N1 influenza vaccination.

Overall, these studies identified no association between maternal influenza vaccination and neurodevelopmental disorder development in childhood. When stratifying by trimester, Zerbo et al[25] observed a suggestion of increased risk of ASD following prenatal exposure to seasonal IIV in the first trimester (aHR: 1.20; 95% CI: 1.04-1.39). However, accounting for multiple comparisons using Bonferroni-corrected CIs, this association was no longer significant (P = 0.1). In our study cohort, we identified 22 children with a diagnosis for ASD. However, due to an insufficient number of cases among the vaccinated cohort (n <5), analysis of ASD as an outcome was not possible. Hviid et al[24] reported no association between epilepsy among children exposed to pandemic influenza vaccine in the first trimester (aRR: 1.01; 95% CI: 0.21-4.74) nor in the second or third trimester (aRR: 1.22; 95% CI: 0.79-1.86).

While our results examining composite outcomes and seizure disorders mostly align with previous studies examining individual outcomes, when stratifying by trimester of vaccination, we observed a decreased risk of seizure disorders following first trimester influenza vaccination. Similarly, a post-hoc analysis that additionally adjusted for preterm birth categories and fetal growth restriction also showed a decreased association (aHR: 0.73; 95% CI: 0.53-0.99). This association was not significant when taking multiple comparisons into account using Bonferroni-corrected CIs. While we cannot entirely rule out the possible influences of bias and Type I error in the results from this observational study, several aspects of our study suggest a plausible protective relationship between

maternal immunisation and the subsequent development of neurodevelopmental conditions in offspring.

Previous studies have observed adverse neurodevelopmental outcomes, including ASD, schizophrenia, microcephaly and psychotic disorders, following prenatal exposure to viral or bacterial infections in offspring, including influenza infection.[3] Influenza virus infection and subsequent maternal immune activation during pregnancy has been implicated in the development of seizure disorders in offspring.[26, 27] A recent retrospective cohort study using data from Norway, Canada and Australia identified a higher risk of seizure disorders (aHR: 1.17; 95% CI: 1.07-1.28) and febrile seizures (aHR: 1.20; 95% CI: 1.07-1.34) following maternal influenza infection.[28]

Vaccination during pregnancy is effective in preventing maternal influenza infection. A meta-analysis of 19 studies from 11 countries identified a lower incidence of laboratory-confirmed influenza among pregnant women following exposure to seasonal IIV during pregnancy (unadjusted vaccine effectiveness [VE], 63%; 95% CI: 29-69%).[4] Another, retrospective study from 4 countries, utilizing a test-negative design and data over 25 influenza seasons, also identified a lower incidence of laboratory-confirmed influenza-associated hospitalisations following maternal influenza vaccination (VE, 40%; 95% CI: 12-59%).[5]

Given maternal antibody transfer peaks during the third trimester of pregnancy,[29] children born at term are likely to receive a higher titer of maternal antibodies, thereby offering a higher level of protection compared to children born preterm. Protection against influenza virus infection through maternal immunisation could result in the reduced risk of influenza infection during pregnancy, and as a result prevent neurological harm to the fetal brain.

The main strengths of our study include the use of a large, population-based mother-infant cohort with detailed information on maternal sociodemographic and health characteristics, receipt of prenatal vaccine, and record linkage to several administrative health datasets permitting follow-up of outcomes up to 5 years of age. The record linkage system in WA is long-standing, with expertise in linking large administrative health data since 1995.[30] With the exception of the antenatal vaccination database, these datasets are legally mandated, and have high data quality.[31] The MNS is also estimated to capture 99% of all births in WA.[32]

Despite these strengths, our study has several limitations. First, maternal vaccination data linked from the WAAVD relied on immunisation reports from medical providers and although these records have high specificity, they are likely to be incomplete.[33] Second, outcomes were limited by diagnoses recorded in hospital inpatient and ED presentation records, which do not capture outcomes diagnosed and treated in a primary care setting. However, as severe medical events are unlikely to be managed entirely through primary care, especially in young children, we believe the majority of severe events are captured in our dataset. For this reason, our results may be more reflective of severe neurodevelopmental conditions in childhood. Third, we cannot entirely rule out residual confounding from differential health-seeking behaviour, although we attempted to restrict the influence of health-seeking behaviour using inverse-probability treatment weighting. Finally, despite the large size of our cohort, small cell sizes (i.e., <5) made it impractical to estimate effects by preterm birth status or when restricting to hospital admissions for all outcomes.

8.7 Conclusions

Our findings affirm seasonal IIV during pregnancy is not associated with adverse neurodevelopmental outcomes among children aged up to 5 years and support current global vaccine policies prioritizing influenza immunisation for pregnant women. Our study detected a potential lower risk of seizure disorders following seasonal IIV administered in the first trimester, and this finding warrants further investigation. This information may be useful to reassure pregnant women and inform their healthcare providers when making vaccine decisions and providing vaccine counselling.

Chapter Nine: Child mortality

9.1 Preamble

This chapter is a manuscript in preparation for submission to *Vaccine* as a short communication article, except for minor modifications for readability. Supplementary material for this manuscript is available in **Appendix H**.

9.2 Abstract

Influenza vaccination is recommended to protect mothers and their infants from influenza. However, few studies have evaluated the association between maternal influenza vaccination and child mortality. We aimed to evaluate the association between *in utero* exposure to seasonal inactivated influenza vaccine (IIV) and child mortality among young children. This longitudinal, population-based cohort linked study of 191,247 singleton, liveborn children born between April 2012 and December 2017 in Western Australia. We found no association between *in utero* exposure to seasonal IIV and child mortality through age five years. In this population-based study, we found no evidence of harm following seasonal influenza vaccination during pregnancy in regard to child mortality and our findings support the continued implementation of existing vaccine programs and policies promoting the provision of seasonal influenza vaccines to pregnant women

Keywords. maternal vaccination, child health, seasonal influenza vaccine, vaccine safety, mortality

9.3 Introduction

Influenza is associated with severe morbidity and mortality through annual seasonal epidemics, particularly among children <5 years of age.[11, 24] In the absence of a currently licensed influenza vaccine for infants aged <6 months, transplacental vaccine-derived antibodies transferred following prenatal administration of seasonal IIV can offer protection during the early months of life.[11]

While maternal influenza vaccination has not been previously associated with an increased risk of adverse outcomes during pregnancy or at birth,[122] few studies have assessed child health outcomes beyond the first six months of life.[231] Limited research has assessed the risk of child mortality associated with *in utero* exposure to influenza vaccines, and to our knowledge, no studies have evaluated the impact of seasonal influenza vaccines.[231] The objective of this study was to evaluate whether seasonal influenza vaccination during pregnancy increases the risk of all-cause child mortality.

9.4 Methods

9.4.1 Study design, cohort, and data sources

We conducted a retrospective, population-based cohort study of singleton, liveborn children born in WA between April 2012 and December 2017.[246] Mother-child pairs were identified from birth registrations[195] and were probabilistically linked with other population-based administrative health datasets by the WA Data Linkage Branch,[187] including the Midwives Notification System (MNS),[197] the WA Antenatal Vaccination Database (WAAVD),[200] and death registrations.[205]

The MNS is a legally mandated perinatal data collection of all children born ≥20 weeks of gestation or birthweight of ≥400g (where gestational age is unknown). The MNS includes maternal sociodemographic and health information, obstetric history, date of delivery, gestational age, birthweight, and in July 2016, it introduced data collection on maternal vaccination status.[197] The WAAVD is a state-wide database including information on the date of vaccination, vaccine brand and batch number, and the estimated gestation at which vaccinations were administered as reported by their healthcare provider.[200] Death registrations included the date and cause of all registered deaths in the state.[205] This study

received approval from the Department of Health WA (RA#2016.56) and the Curtin University Human Research Ethics Committees (RA#20217-0808) and is reported according to the 'Strengthening of Observational Studies in Epidemiology' guidelines.[247]

9.4.2 Variable definition

Maternal vaccination status (exposure of interest) was derived from WAAVD for children born between 1 April 2012 and 1 July 2016 and from MNS for children born between 2 July 2016 and 31 December 2017. We estimated the gestational age at vaccination as the number of completed weeks of gestation between the estimated date of conception and date of vaccination. Trimesters were categorised as: first trimester (0 to ≤$13^{6/7}$ weeks gestation), second trimester (14 to ≤$27^{6/7}$ weeks gestation) and third trimester (≥$28^{6/7}$ weeks gestation). Child mortality (outcome of interest) was defined as a record of a death registration from birth to the end of the study period (i.e., 31 March 2018). Covariates included socioeconomic status, pre-existing asthma, hypertension and diabetes mellitus, and trimester at the first prenatal care visit as derived from perinatal data collections and hospital admission records (i.e., Hospital Morbidity Data Collection). Maternal Aboriginal and/or Torres Strait Islander status was derived from a combination of routine data sources using a pre-validated algorithm.[187]

9.4.3 Statistical analyses

Children were followed from birth and were censored at the earliest of the: a) death, b) age five years; or c) last date of available data. The risk of mortality was estimated using stratified Cox proportional hazards regression. Adjustment variables were selected based on the minimum adjustment set identified with a directed acyclic graph (**Supplementary Figure H-1**) and included all maternal covariates. For children with missing necessary covariate information (n = 13,662; 7.1%), we used multiple imputation by chained equations with 20 generated datasets. Stratified models were used to estimate the risk of child mortality by trimester of vaccination. As antibody transfer is likely to be sub-optimal when administered <2 weeks prior to birth,[248] we conducted a sensitivity analysis which excluded children of mothers that received an influenza vaccine within 2 weeks prior to birth (i.e., 'indeterminate' vaccination status). Since maternal vaccination has been well evaluated in relation to perinatal mortality,

and deaths occurring in the first 28 days of life are strongly linked with perinatal conditions,[257] we performed an additional sensitivity analysis excluding neonatal deaths. Finally, since the dataset commenced in April 2012, to allow all children to have the opportunity to be maternally vaccinated during any trimester throughout the study, additional sensitivity analyses restricting to children born between 1 December 2012 and 31 December 2017 were performed. All analyses were performed in Stata version 15.1 (StataCorp LLC, College Station, Texas, USA). A post-hoc power analysis was used to determine the detectable difference in the risk of the outcome measures, with 90% and 80% power and an alpha of 5%, between children of vaccinated and unvaccinated mothers (**Supplementary Table H-1**).

9.5 Results

Of the 198,037 children born from 149,163 mothers, 6,790 (3.4%) children were excluded because the child was a non-singleton (n = 5,585), was stillborn (n = 1,322), or was born before 22 or after 44 completed weeks of gestation (n = 425) (**Supplementary Figure H-2**). A total of 191,247 singleton, liveborn children born from 146,883 mothers were eligible for inclusion in the study cohort; 35,665 (18.7%) children were exposed to seasonal IIV *in utero*: 5,989 (16.8%) children during the first trimester, 12,140 (34.0%) during the second trimester, 15,353 (43.1%) during the third trimester, and 2,183 (6.1%) were exposed to vaccine during pregnancy but the trimester was not recorded. Demographic characteristics of the study cohort are presented in **Supplementary Table H-2**.

Children were followed until a median age of 37.2 months (interquartile range [IQR], 20.2-54.4). During the study period, we observed 486 all-cause deaths prior to age five years; 251 children (51.6%) died in the first 28 days, 173 (35.6%) children were aged between 1 month to <1 year, 35 (7.2%) children were aged between 1 to <2 years, 16 (3.3%) children were aged between 2 to <3 years, and 11 (2.3%) children were aged between 3 to <5 years. The median age at death was 1.0 month (IQR, 0.1-6.4) in the vaccinated cohort and 0.7 months (IQR, 0.0-4.1) in the unvaccinated cohort. The cumulative incidence of child mortality was 9 cases per 10,000 child-years for children of vaccinated mothers and 8 cases per 10,000 child-years for children of unvaccinated mothers. We observed no association between maternal influenza vaccination and the risk of child mortality

(aHR: 0.89; 95% CI: 0.68-1.17) (**Figure 9-1; Supplementary Table H-3**). We observed similar results when stratifying by trimester of vaccination (**Supplementary Table H-3**), when excluding children of mothers with indeterminate vaccination status and/or death in the first 28 days, and when restricting the cohort to children born between 1 December 2012 and 31 December 2017 (**Supplementary Tables H-4 to H-6**).

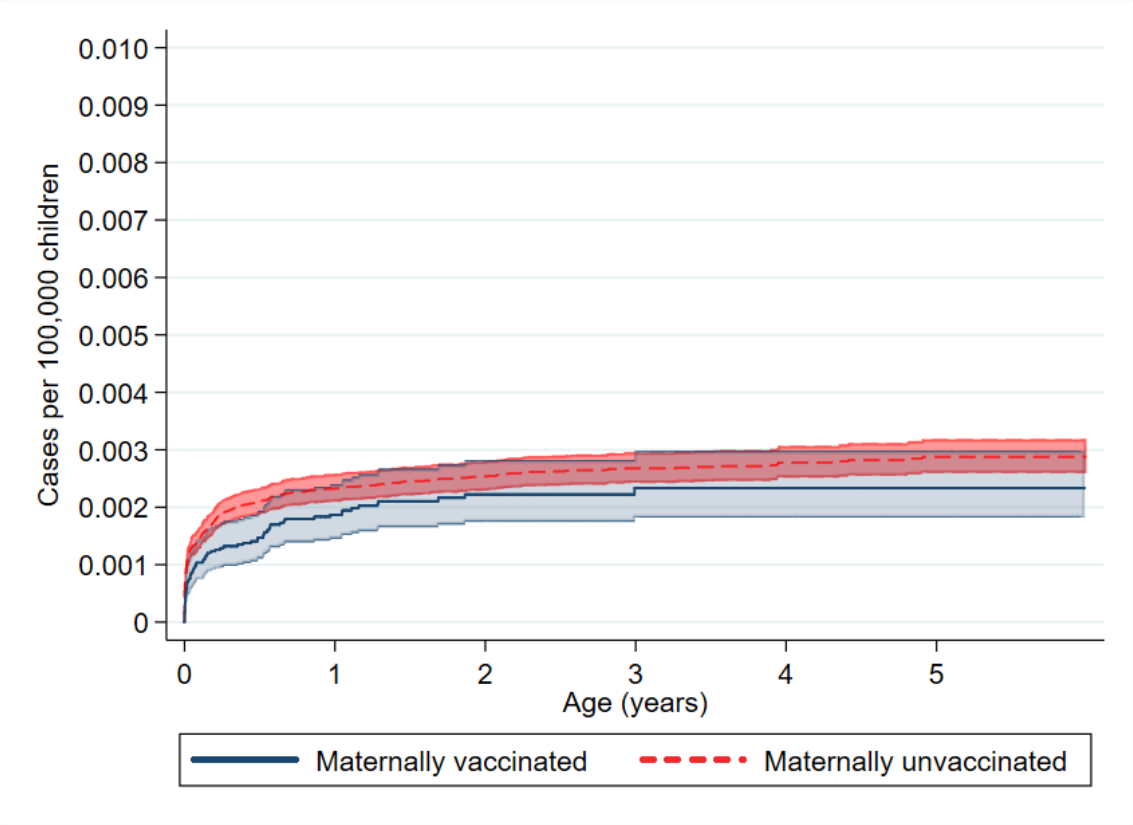

Figure 9-1. Cumulative incidence of child mortality with 95% CIs, by maternal vaccination status, WA, 1 April 2012-31 December 2017.

9.6 Discussion

In this large, population-based cohort study of 191,247 maternal-infant pairs, we found no evidence of an increased risk of all-cause child mortality following maternal seasonal influenza vaccination. Two other previous studies have reported similar results in relation to pandemic influenza vaccination. A recent Canadian study showed no risk of death among children aged 1 day to <5 years following prenatal exposure to non-adjuvanted or AS03-adjuvanted pandemic

A/H1N1 influenza vaccine (aHR: 0.83; 95% CI: 0.64-1.08);[179] similarly, a Swedish study showed no risk of death among children aged 7 days to <4.6 years following prenatal exposure to AS03-adjuvanted pandemic A/H1N1 influenza vaccine (aHR: 0.97; 95% CI: 0.69-1.36).[180] To our knowledge, this is the first population-based study to examine child mortality associated with seasonal influenza vaccines and we report a similar effect estimate among children 1 day to <5 years. These results confirm the safety of seasonal influenza vaccination during pregnancy, supporting current recommendations and immunisation policies.

The strengths of this study include the use of a high-quality large, population-based birth cohort and the use of record linkage to incorporate detailed information on maternal sociodemographic and health characteristics, and receipt of prenatal vaccine.[241] Despite these strengths, our study had some limitations. First, maternal vaccination data prior to 2016 relied on immunisation reports from medical providers and while considered to be highly specific, it may be incomplete.[200] Second, we did not have information on childhood vaccination status. However, given vaccine-preventable disease is an uncommon cause of child death in Australia and childhood immunisation rates in WA are high for vaccines listed on the NIP,[258] we do not believe incorporating information on childhood immunisation would have strongly influenced our findings.

Despite these limitations, we believe this study can be used to support public and provider confidence in maternal influenza vaccination programs. Concerns about the safety of exposure to vaccines *in utero* is a commonly cited deterrent to accepting maternal vaccines.[103] This is particularly important, considering the low uptake of effective vaccines among pregnant individuals globally.[103] Our findings support the long-term safety of maternal influenza vaccination and support current immunisation programs and policies.

Chapter Ten: Summary of Findings

10.1 Preamble

This final chapter synthesises the findings presented in Chapters Five through Nine (Sections 10.2-10.3) and incorporates these findings into the current context of maternal influenza vaccination. Sections 10.4-10.5 address the strengths and limitations of the studies presented, and Sections 10.6-10.7 highlight the potential implications for public health practice and future directions in research. The overall goal of this research was to evaluate the association between seasonal influenza vaccination during pregnancy and early childhood health outcomes using a large population-based cohort and longitudinal linked data in WA.

10.2 Major findings

A summary of the key findings related to the safety of seasonal influenza vaccination during pregnancy among children in WA has been provided in **Tables 10-1** and **10-2**.

Table 10-1. Summary of the Key Findings

Objective 1.1: To systematically search, compile, synthesise and critically review the current evidence on the association between maternal influenza vaccination and early childhood health outcomes (Chapter Five).
Maternal influenza vaccination and early childhood health outcomes: As of 24 July 2019, only 9 studies evaluating the association between maternal influenza vaccination and early childhood health outcomes were identified. The studies included in the review were highly diverse in regards to study quality, vaccine type and method of exposure ascertainment, and study outcomes and method of outcome ascertainment. Key findings: Of the included studies, no significant difference in the risk of early childhood health outcomes was observed between children of vaccinated and unvaccinated mothers. Interpretation: This review found insufficient evidence of any associations between maternal influenza vaccination and early childhood health outcomes.
Objective 2.1: Estimate the association between prenatal exposure to seasonal influenza vaccine and laboratory-confirmed influenza and hospitalisation for influenza and other acute respiratory infections in childhood (Chapter Six).

Key findings:

Seasonal influenza vaccination had a protective association with laboratory-confirmed influenza and hospitalisation for influenza and acute respiratory infections among infants aged <6 months, followed by a slight adverse association with laboratory-confirmed influenza among children aged 6 months to <2 years of mothers who were vaccinated during the first trimester.

Interpretation:

This study provides confirmatory evidence that maternal immunisation can protect infants from influenza during the first six months of life and identified a potential transient risk of laboratory-confirmed influenza among children aged 6 months to <2 years. Study findings are consistent with previous research in regard to the effectiveness of seasonal influenza vaccination during pregnancy in preventing laboratory-confirmed influenza and hospitalisation for influenza and acute respiratory infections among infants.

Objective 2.2: Estimate the association between prenatal exposure to seasonal influenza vaccine and allergic/atopic and autoimmune diseases in childhood (Chapter Seven).

Key findings:

There was a modest reduction in the risk of diagnosis for asthma and anaphylaxis among children aged <5 years of mothers that were vaccinated during the third trimester.

Interpretation:

This study suggests a potential protective effect of seasonal influenza vaccination during pregnancy, particularly during the third trimester, against the development of asthma and anaphylaxis.

Objective 2.3: Estimate the association between prenatal exposure to seasonal influenza vaccine and neurodevelopmental disorders in childhood (Chapter Eight).

Key findings:

There was a modest reduction in the risk of diagnosis for a seizure disorder among children aged <5 years of mothers that were vaccinated during the first trimester.

Interpretation:

This study suggests a potential protective effect of seasonal influenza vaccination during pregnancy, particularly during the first trimester, against the development of seizure disorders.

Objective 2.4: Estimate the association between prenatal exposure to seasonal influenza vaccine and all-cause child mortality (Chapter Nine).

Key findings:

There was no association between seasonal influenza vaccination and child mortality among children aged <6 years and children aged 1 month to <6 years.

Interpretation:

This study identified no association between seasonal influenza vaccination and all-cause child mortality.

Table 10-2. The Associations between Maternal Influenza Vaccination and Early Childhood Health Outcomes, by trimester of prenatal vaccination.

Outcomes	Any trimester	First trimester	Second trimester	Third trimester
Study Two (Chapter Six)				
Laboratory-confirmed influenza				
6 month infection[a]	0.32 (0.12-0.84)	-	-	-
6 month to <2 year infection[a]	1.33 (1.00-1.76)	2.28 (1.41-3.69)	1.20 (0.78-1.86)	1.00 (0.61-1.64)
2 to <5 year infection[a]	1.14 (0.76-1.71)	1.52 (0.72-3.17)	1.05 (0.55-1.99)	1.04 (0.52-2.07)
ICD-coded influenza				
6 month infection[b]	0.38 (0.16-0.91)	-	-	0.68 (0.26-1.73)
6 month to <2 year infection[b]	1.09 (0.67-1.78)	-	1.36 (0.70-2.65)	0.96 (0.47-1.99)
2 to <5 year infection[b]	1.40 (0.65-3.01)	-	-	-
ICD-coded acute respiratory infection				
6 month infection[b]	0.85 (0.77-0.94)	0.67 (0.50-0.88)	0.79 (0.67-0.93)	1.00 (0.87-1.14)
6 month to <2 year infection[b]	0.97 (0.90-1.06)	0.99 (0.83-1.18)	1.03 (0.91-1.16)	0.91 (0.80-1.04)
2 to <5 year infection[b]	1.01 (0.87-1.17)	0.90 (0.65-1.24)	1.06 (0.85-1.32)	1.01 (0.80-1.27)
Study Three (Chapter Seven)				
Allergic or autoimmune disease[c]	1.02 (0.95-1.09)	0.97 (0.82-1.14)	1.07 (0.96-1.19)	0.98 (0.88-1.10)
Allergic disease[c]	1.02 (0.95-1.10)	0.97 (0.82-1.14)	1.08 (0.97-1.20)	0.98 (0.87-1.10)

Asthma and wheezing[c]	1.00 (0.89-1.12)	0.92 (0.71-1.19)	1.07 (0.91-1.26)	0.97 (0.81-1.15)
Asthma[c]	0.87 0.73-1.05)	0.99 (0.68-1.45)	0.98 (0.75-1.28)	0.70 0.50-0.97)
Anaphylaxis[c]	0.85 (0.70-1.05)	1.15 (0.78-1.68)	0.90 (0.67-1.22)	0.67 0.47-0.95)
Autoimmune disease[c]	0.93 (0.55-1.59)	-	0.89 (0.37-2.12)	1.06 (0.49-2.31)
Study Four (Chapter Eight)				
Neurodevelopmental disorder[d]	1.00 (0.91-1.08)	0.98 (0.82-1.18)	1.03 (0.91-1.16)	0.96 (0.84-1.10)
Mental or behavioural disorder[d]	1.00 (0.72-1.40)	0.67 (0.24-1.89)	1.20 (0.76-1.89)	0.97 (0.57-1.66)
Neurologic disorder[d]	1.00 (0.91-1.09)	1.00 (0.83-1.20)	1.03 (0.91-1.17)	0.95 (0.83-1.09)
Seizure disorder[d]	0.99 (0.87-1.13)	0.73 (0.54-0.99)	1.11 (0.91-1.34)	0.99 (0.81-1.20)
Study Five (Chapter Nine)				
Child mortality				
<6 year mortality[e]	0.89 (0.68-1.17)	1.01 (0.58-1.77)	0.84 (0.54-1.31)	0.85 (0.58-1.24)
1 month to <6 year mortality[e]	1.08 (0.74-1.58)	0.87 (0.35-2.16)	0.94 (0.49-1.81)	1.30 (0.79-2.14)

Abbreviations: ICD, International Classification of Diseases.

Effect estimates are presented as adjusted hazard ratios (95% CI).

Except where indicated, effect estimates presented are among children aged <5 years.

Effect estimates are displayed as colours ranging from green (protective association) to red (adverse association).

[a] Outcome was obtained from notification records reported to WANIDD.

[b] Outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient records (**Supplementary Table E-1**).

[c] Outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and ED presentation records, and from the presenting symptom code found in the ED presentation records (**Supplementary Table F-1**).

[d] Outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and ED presentation records, and from

the presenting symptom code found in the ED presentation records (**Supplementary Table G-1**).

[e] Outcomes were identified from death records reported to Death Registrations.

Based on the systematic review carried out at the beginning of this PhD (Study One) there was limited research on the association between maternal influenza vaccination and health outcomes beyond the perinatal period, particularly in relation to the seasonal influenza vaccine and childhood health outcomes beyond one year of age. The published studies included in this review were highly diverse in regards to study quality, vaccine type and method of exposure ascertainment, study outcomes, and method of outcome ascertainment. Although limited, this review indicated no adverse effects of maternal influenza vaccination on early childhood health outcomes and highlighted the need for additional research.

Since the publication of this systematic review (Study One), two studies evaluating the association between maternal influenza vaccination and early childhood health outcomes have been published. A population-based cohort study by Ludvigsson et al,[259] assessed the association between pandemic influenza vaccination during pregnancy and ASD and autistic disorder among children aged <7 years that were born between October 2009 and November 2010. This study prospectively followed 39,726 (57.6%) children of vaccinated mothers, of which 13,845 (34.9%) were exposed during the first trimester, and 29,293 children of unvaccinated mothers. This study reported no difference in the risk of ASD and autistic disorder between children of vaccinated and unvaccinated mothers. Furthermore, no associations were observed when considering first trimester vaccination, truncating follow-up at 6 years, excluding children with incomplete vaccination status, and restricting to children of mothers born in Sweden.[259]

A more recent Canadian study by Mehrabadi et al,[251] using a retrospective cohort design, estimated the risk and incidence of multiple early childhood health outcomes among children aged <6 years of vaccinated mothers with children of unvaccinated mothers. This study reported no difference in the risk of asthma, upper respiratory tract infections, lower respiratory tract infections, gastrointestinal infections, otitis media, all-cause infections, neoplasms, sensory impairment and urgent and inpatient health services utilisation between children

of vaccinated and unvaccinated mothers. In trimester-specific analyses, there was an increased incidence of lower respiratory infections among children of mothers vaccinated during the third trimester (aIRR: 1.19; 95% CI: 1.01-1.40). There were no significant differences in the incidence of early childhood health outcomes following seasonal influenza vaccination during pregnancy.

As part of this thesis, my longitudinal cohort studies evaluated the association between seasonal influenza vaccination during pregnancy and multiple health outcomes in childhood. As summarised in **Table 10-1**, my results suggest that maternal influenza vaccination may be beneficial in reducing the development of asthma, anaphylaxis, and seizure disorders. Given the novelty of these findings that have not been reported elsewhere, the lack of studies evaluating the association between maternal influenza vaccination and early childhood health outcomes, and inconclusive results reported in other studies, further research is needed to confirm these findings.

10.3 Strengths

The body of work had numerous methodological and analytical strengths. While RCTs are typically considered the 'gold standard' for investigating causal relationships, this study design was not feasible in this population sub-group. Seasonal influenza vaccines are recommended for all pregnant women to protect both the mother and infant from influenza infection,[10, 11, 58] and withholding vaccination from a control group in a randomised controlled trial would be unethical. Observational studies are typically carried out due to feasibility, efficiency, and ethical considerations. Compared to RCTs, observational studies include a more 'real-world' study cohort with a wider band of participant characteristics in real-world conditions, and the ability to assess for a broader range of outcomes with sufficient statistical power which is particularly important in regard to rarer outcomes.

We employed multiple epidemiological approaches to investigate the link between seasonal influenza vaccination during pregnancy and multiple early childhood health outcomes, each of which have several strengths. In the absence of an RCT design, we attempted to consider causality by using causal inference techniques including IPTW (i.e., propensity scores) and negative control conditions. By accounting for measured characteristics between children of vaccinated and unvaccinated mothers, the propensity scores minimise the influence of health-seeking behaviour and aimed to estimate a robust effect estimate using IPTW.[260, 261] Negative control conditions were used to rule out possible non-causal associations between seasonal influenza vaccination and early childhood health outcomes.[262]

These studies relied on record linkage which has been well established in WA since the 1970s, has high specificity and sensitivity, uses highly robust methodology, and is considered to be highly cost-effective.[188-190] This method allowed the creation of a large, population-based mother-child cohort linked with several administrative datasets comprising midwives, vaccination, infectious disease notification, hospital admission, emergency department, and death records, for a rich dataset with a variety of data fields. The majority of these data collections are legally mandated and a minimum dataset is provided to the Australian Institute of Health and Welfare, and the quality of the metadata are

estimated to be high.[241] The health department datasets used to conduct these studies are routinely validated and are of high quality.[241]

The MNS has been reported to have a high completeness of key variables, including maternal demographic, obstetric, labour and delivery, and infant information.[263] Vaccination information from the WAAVD was used to identify maternal influenza vaccination as the exposure with high specificity (99.6%; 95% CI: 97.8-99.9%) and positive predictive value (99.3%; 95% CI: 96.2-99.9%).[200] Data from the WANIDD was used to identify LCI as an outcome, the 'gold standard' for diagnosis of influenza infection, with high specificity.[242] We supplemented our analysis with ICD-10-AM diagnosis coded outcomes (i.e., influenza, acute respiratory infections). In WA, diagnosis of influenza using the ICD-10-AM diagnosis codes has been estimated to have a high specificity (98.6%; 95% CI: 98.4-98.9%), positive predictive value (84.1%; 95% CI: 81.2-86.7%), and sensitivity (86.1%; 95% CI: 83.4-88.6%).[264]

10.4 Limitations

This research has some limitations which include the inherent difficulties with attributing causality from observational studies, and potential misclassifications of maternal influenza vaccination status, laboratory-confirmed influenza, and less severe outcomes.

While my research used causal inference techniques, including IPTW (i.e., propensity scores) and negative control conditions to attempt to consider causality in our analytical models, unlike RCTs, the analytical model is limited by its reliance of available measured confounders. There is a potential for confounding due to unmeasured confounders which limits the ability of the analytical models to estimate causal inference.[260, 261]

In April 2012, the WAAVD was established to routinely monitor antenatal vaccinations administered by the state immunisation program. Although the specificity of influenza vaccination data derived from the WAAVD is high at 99.6% (95% CI: 97.8-99.9%), the sensitivity at 45.7% (95% CI: 40.1-51.4%).[200] This under-detection of vaccination indicates the presence of exposure misclassification bias in the studies included in this thesis. This misclassification would have biased all effect estimates toward the null which indicates any

significant effects may underestimate the true effect of maternal influenza vaccination.[265]

From July 2016, the antenatal vaccination database was discontinued after the Department of Health introduced influenza vaccination status and trimester of vaccination variables on the midwives' notification form and this information is now routinely collected as part of the MNS database. Although the specificity and sensitivity of influenza vaccination data derived from the MNS has been estimated to be 53.0% (95% CI: 42.4-63.4%) and 65.7% (95% CI: 56.0-74.2%), respectively.[201] However, when restricting to records with complete vaccination information (i.e., documented as either vaccinated or not vaccinated), the specificity and sensitivity increases to 88.0% (95% CI: 76.7-95.5%) and 91.8% (95% CI: 83.0-96.9%), respectively. For the study cohort in Chapter Nine, of the 51,174 mothers of children born between 2 July 2016 and 31 December 2017, only 584 (1.1%) were excluded due to missing influenza vaccination status. Therefore, it is likely that maternal influenza vaccination status was likely to be reliable for our study cohort.[201]

In addition to exposure misclassification, we did not have information on all possible confounding variables. We did not have access to the Australian Immunisation Register and therefore information on childhood vaccinations. Studies have shown that the presence of maternal antibodies from other maternal vaccines, such as pertussis, can interfere with the child's humoral immune response to primary vaccination via immunological blunting.[133] Despite the inability to account for childhood influenza vaccination, which is a potential confounder and effect modifier, childhood influenza vaccine coverage among children aged 6 months and 5 years was low (<10%) during our study period[207] and was unlikely to influence our results. Additionally, sensitivity analysis restricting to the time period when childhood influenza vaccination is unlikely (Chapter Six), observed similar results compared to the primary analysis which suggests that childhood influenza vaccination was not a strong factor in our results.

Although the specificity of a LCI test is high which is a strength of these studies,[242] there is likely some outcome misclassification in the case where a child was not tested for influenza. As most respiratory illnesses are self-limiting, they are

treated empirically, and are under-tested unless children have significant comorbid features.[266] For this reason, I included additional endpoints for influenza and acute respiratory infections using diagnostic coding.

While this research relied on the diagnosis of multiple outcomes found in hospital admission and emergency department records which would likely capture more severe events, I did not have access to primary care data which would likely be more appropriate for the capture of less severe events of outcomes. Due to small numbers or cells sizes (i.e., <5), effect estimates for some outcomes, particularly rarer outcomes, could not be determined when stratifying by trimester of vaccination, age, or preterm birth status, or when restricting to hospital admissions only. Larger population-based datasets with sufficient follow-up time are necessary for sufficiently powered analyses evaluating the safety of maternal influenza vaccination in regard to early childhood health outcomes.

10.5 Implications for public health practice

These results outlined have several implications for public health practice (**Table 10-3**). The findings highlight the potential benefits of and support the safety of maternal influenza vaccination. However, additional research is required that accounts for the child's own influenza vaccination status after 6 months of age to confirm the potential transient risk of LCI following seasonal influenza vaccination among children aged 6 months to <2 years. Given the high disease burden of influenza and ARI among infants, the benefits of seasonal influenza vaccination during pregnancy are likely to outweigh any potential long-term risk. Therefore, these results support the continued implementation of existing vaccine programs and policies that promote the provision of seasonal influenza vaccines to pregnant women.

These findings can be used to communicate with pregnant patients around the long-term health outcomes of children exposed to seasonal influenza vaccine *in utero*. This information may be useful for women who are hesitant towards accepting vaccines during pregnancy, since safety concerns are the most frequent reason for refusing or delaying vaccination during pregnancy.[15] In WA, the WA Department of Health provides influenza immunisation education to health professionals, including general practitioners, nurses and midwives.[267] Education and support for prenatal care providers is essential to increase

recommendations of seasonal influenza vaccination to pregnant women. Intervention programs should include education of the health benefits of seasonal influenza vaccination during pregnancy, particularly the effectiveness in preventing influenza infection in pregnant women and infants in the first six months of life and the safety of influenza vaccination during pregnancy, and the importance of promoting and communicating the health benefits, effectiveness, and safety of influenza vaccination during pregnancy to prospective parents.

Table 10-3. Implications for public health.

Public health action	Conclusion/Recommendation
Determining the optimal timing for maternal influenza vaccination	Significant reductions of asthma and anaphylaxis could only be observed following maternal influenza vaccination during the third trimester and of seizure disorders could only be observed following maternal influenza vaccination during the first trimester. Although no associations were observed for second trimester vaccination specifically, my findings indicate potential on-target and off-target benefits of maternal influenza vaccination regardless of trimester of vaccination. Our findings may suggest that via the protection of maternal influenza infection, this may reduce exacerbations of asthma, anaphylaxis, and seizure disorders. Thus, public health programs and policies should promote seasonal influenza vaccination during pregnancy in any trimester.
Addressing concerns around safety of maternal immunisation as a barrier of vaccine uptake	Generally, we observed no evidence of long-term harm following maternal influenza vaccination. Our findings may be reassuring to prospective parents, particularly pregnant women. Therefore, health promotion by prenatal care providers of the safety of seasonal influenza vaccination during pregnancy may improve vaccine uptake among pregnant women.
Promoting seasonal influenza vaccines to vaccine providers and prospective parents, particularly pregnant women	Several outcomes examined in this body of research could be used by public health authorities to promote maternal vaccination in pregnant women. Protection of infants from infection is a key motivator of decision making for pregnant women. Prenatal care providers and vaccine providers should communicate the neonatal health benefits of maternal influenza vaccination and address parent's concerns around maternal vaccines.

10.6 Recommendations for future research

This thesis contributes to the gap in knowledge of the potential health impacts of maternal influenza vaccination regarding the seasonal influenza vaccine on early childhood health outcomes and identifies several areas where future research is required (**Table 10-4**).

Given that safety of maternal immunisation is a commonly cited barrier of vaccine uptake among pregnant women[15] and while our findings were mostly supportive of the safety of prenatal administration of seasonal influenza vaccine, replication of this research would be highly valuable. Although we identified a potential transient risk of laboratory-confirmed influenza among children aged 6 months to <2 years of mothers that were vaccinated during the first trimester. To confirm this finding, additional research should explore the effect of maternal antibodies in dampening or blunting the immune response to viral pathogens following childhood vaccination after six months of age and replicate our research accounting for childhood influenza vaccination status. Our body of research observed differential benefits by trimester of maternal influenza vaccination among children of mothers. However, additional research that accounts for both maternal influenza infection and maternal influenza vaccination to confirm these findings.

Given the introduction of maternal immunisation of the pertussis vaccine in 2015, the recent introduction of the COVID-19 vaccines in 2021 and future respiratory syncytial virus (RSV) vaccine, the methodology and statistical approaches I used could be applied to future epidemiological studies assessing vaccine effectiveness and safety of maternal vaccines. The standardisation of methods for the analysis of effectiveness and safety following maternal immunisation would increase the comparability between studies and would allow future meta-analyses to be performed.

While this research relied on the diagnosis of outcomes found in hospital admission and emergency department records which likely captured more severe events, future studies should consider incorporating primary care data and other non-specific outcomes (i.e., influenza-like illness, respiratory infection with fever) to also capture less severe events of outcomes). Future studies evaluating the safety of vaccination during pregnancy should incorporate a much larger

population-based sample with longer follow-up duration. Unfortunately, during the five-year study period included in this research, there were insufficient number of some outcomes among children of vaccinated mothers, particularly when stratifying by trimester of vaccination. However, it is unlikely that a single site population will have a large enough sample to evaluate trimester-specific effects or to examine rarer outcomes, such as autism spectrum disorder. Therefore future research should consider the establishment of a national or international cohort to sufficiently evaluate the safety of vaccination during pregnancy, or alternatively, the standardisation of methodology of epidemiological studies in the area of maternal influenza vaccination to allow for pooled meta-analyses.

Table 10-4. Recommendations for future research.

Research area	Additional research needed
Vaccine safety	Future research should continue to evaluate other early childhood health outcomes associated with seasonal influenza vaccination during pregnancy, including rare outcomes (e.g., autism spectrum disorder). Larger population-based datasets with sufficient follow-up time will be needed to detect the associations of childhood health outcomes, particularly rarer outcomes, with sufficient power, and would also allow appropriately powered analyses of outcomes when stratifying by trimester of vaccination or preterm birth status or when restricting to age sub-groups. Further evidence in other southern hemisphere countries and low and middle-income countries with maternal immunisation policies would also be welcome additions to the literature.
Accounting for other factors	Replication and additional studies exploring the biological mechanisms are required to confirm the potential transient risk of laboratory-confirmed influenza among children aged 6 months to <2 years of mothers that were vaccinated during the first trimester. These studies should consider vaccination status of other maternal and childhood vaccines to account for the intended and unintended effects (i.e., immunological blunting) of other vaccines.

	The inclusion of siblings in maternal vaccine safety studies may imply statistical dependence between observations due to shared environmental and/or genetic factors. Future studies should consider accounting for these shared factors to minimise the impact of statistical dependence (e.g., sensitivity analyses restricting to one random child per mother).
Other vaccines administered during pregnancy	The methodology and statistical approach used as part of this body of research could be applied to future epidemiological studies of other maternal vaccines during pregnancy, including the existing pertussis and COVID-19 vaccine, and future RSV vaccines. Standardisation of methods analysing maternal vaccine effectiveness and safety would increase comparability between studies and would allow for future meta-analyses.

10.7 Conclusion

The findings from this body of research contributes to the scientific gap in knowledge of the potential health impacts of maternal influenza vaccination, particularly seasonal influenza vaccines, on early childhood health outcomes. This thesis has confirmed the effectiveness of maternal influenza vaccination in preventing influenza in the first six months of life and makes novel contributions to the literature through evidence identifying limited effects of maternal influenza vaccination on the health of children through five years of age. Further large-scale epidemiological studies incorporating a range of geographical areas and populations should now be conducted to confirm these findings. Overall, this body of research observed no consistent evidence for long-term harm and the findings support the safety of seasonal influenza vaccination during pregnancy and the continued implementation of existing vaccine programs and policies that promote the provision of seasonal influenza vaccines to pregnant women.

Chapter Eleven: References

1. Blacker BF, Abate D, Adhikari TB, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2019; 7: 69-89. doi: 10.1016/S2213-2600(18)30496-X.
2. Meijer WJ, van Noortwijk AGA, Bruinse HW, et al. Influenza virus infection in pregnancy: a review. *Acta Obstet Gynecol Scand* 2015; 94: 797-819. doi: 10.1111/aogs.12680.
3. Rasmussen SA, Jamieson DJ and Uyeki TM. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol* 2012; 207: S3-S8. doi: 10.1016/j.ajog.2012.06.068.
4. Mertz D, Lo CK-F, Lytvyn L, et al. Pregnancy as a risk factor for severe influenza infection: an individual participant data meta-analysis. *BMC Infect Dis* 2019; 19: 683-683. doi: 10.1186/s12879-019-4318-3.
5. Munoz FM. Influenza Vaccination During Pregnancy Can Protect Women Against Hospitalization Across Continents. *Clin Infect Dis* 2019; 68: 1454-1455. 2018/10/12. doi: 10.1093/cid/ciy740.
6. Mertz D, Geraci J, Winkup J, et al. Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies. *Vaccine* 2017; 35: 521-528. 2016/12/28. doi: 10.1016/j.vaccine.2016.12.012.
7. Australian Government: Department of Health. National Immunisation Program Schedule, 2021. https://www.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule (accessed 6/12/2021).
8. Englund J, Paul Glezen W and Piedra PA. Maternal immunization against viral disease. *Vaccine* 1998; 16: 1456-1463. doi: 10.1016/S0264-410X(98)00108-X.
9. Chu H and Englund J. Maternal Immunization. *Clin Infect Dis* 2014; 59: 560. doi: 10.1093/cid/ciu327.
10. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Influenza vaccination during pregnancy (and in women planning pregnancy). 2017.
11. World Health Organization. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec* 2012; 87: 461-476.
12. Irving SA, Ball SW, Booth SM, et al. A multi-country investigation of influenza vaccine coverage in pregnant individuals, 2010-2016. *Vaccine* 2021; 39: 7598-7605. 2021/11/23. doi: 10.1016/j.vaccine.2021.11.018.
13. Schmid P, Rauber D, Betsch C, et al. Barriers of Influenza Vaccination Intention and Behavior - A Systematic Review of Influenza Vaccine Hesitancy, 2005 - 2016. *PLoS One* 2017; 12: e0170550. 2017/01/27. doi: 10.1371/journal.pone.0170550.
14. Okoli GN, Reddy VK, Al-Yousif Y, et al. Sociodemographic and health-related determinants of seasonal influenza vaccination in pregnancy: A systematic review and meta-analysis of the evidence since 2000. *Acta Obstet Gynecol Scand* 2021; 100: 997-1009. doi: 10.1111/aogs.14079.
15. Kilich E, Dada S, Francis MR, et al. Factors that influence vaccination decision-making among pregnant women: A systematic review and meta-analysis. *PLoS One* 2020; 15: e0234827. 2020/07/10. doi: 10.1371/journal.pone.0234827.
16. Yuen CYS and Tarrant M. Determinants of uptake of influenza vaccination among pregnant women – A systematic review. *Vaccine* 2014; 32: 4602-4613. doi: 10.1016/j.vaccine.2014.06.067.
17. Wilson RJ, Paterson P, Jarrett C, et al. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. *Vaccine* 2015; 33: 6420-6429. doi: 10.1016/j.vaccine.2015.08.046.
18. Myers K. Predictors of maternal vaccination in the United States: An integrative review of the literature. *Vaccine* 2016; 34: 3942-3949. doi: 10.1016/j.vaccine.2016.06.042.
19. Lutz CS, Carr W, Cohn A, et al. Understanding barriers and predictors of maternal immunization: Identifying gaps through an exploratory literature review. *Vaccine* 2018; 36: 7445-7455. doi: 10.1016/j.vaccine.2018.10.046.
20. Poliquin V, Greyson D and Castillo E. A Systematic Review of Barriers to Vaccination During Pregnancy in the Canadian Context. *J Obstet Gynaecol Can* 2019; 41: 1344-1355. 2018/10/27. doi: 10.1016/j.jogc.2018.05.042.

21. Mayor S. Acute respiratory infections are world's third leading cause of death. *BMJ* 2010; 341: c6360-c6360. doi: 10.1136/bmj.c6360.
22. Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Infectious Diseases* 2018; 18: 1191-1210. doi: 10.1016/s1473-3099(18)30310-4.
23. World Health Organization. Influenza (Seasonal), 2018. http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal) (accessed 31 December 2018).
24. Zhou F, Trieu M, Davies R, et al. Improving influenza vaccines: challenges to effective implementation. *Curr Opin Immunol* 2018; 53: 88-95. doi: 10.1016/j.coi.2018.04.010.
25. Australian Government: Department of Health. Influenza Laboratory Case Definition (LCD), 2020. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-phlncd-influenza.htm (accessed 29/11/2021).
26. Government of Western Australia: Department of Health. Statutory medical notification, https://ww2.health.wa.gov.au/Health-for/Health-professionals/Statutory-medical-notification (accessed 6/12/2021).
27. Barr IG, Deng YM, Grau ML, et al. Intense interseasonal influenza outbreaks, Australia, 2018/19. *Euro Surveill* 2019; 24 2019/08/23. doi: 10.2807/1560-7917.ES.2019.24.33.1900421.
28. NNDSS Annual Report Writing Group. Australia's notifiable disease status, 2012: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2015; 39: E46-E136.
29. NNDSS Annual Report Writing Group. Australia's notifiable disease status, 2013: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2015; 39: E387-E478.
30. NNDSS Annual Report Working Group. Australia's notifiable disease status, 2014: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2016; 40: E48-E145.
31. NNDSS Annual Report Working Group. Australia's notifiable disease status, 2015: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2019; 43. doi: 10.33321/cdi.2019.43.6.
32. NNDSS Annual Report Working Group. Australia's notifiable disease status, 2016: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2021; 45. doi: 10.33321/cdi.2021.45.28.
33. Leung VKY, Wong JY, Barnes R, et al. Excess respiratory mortality and hospitalizations associated with influenza in Australia, 2007-2015. *Int J Epidemiol* 2021 2021/08/02. doi: 10.1093/ije/dyab138.
34. Takeda S, Hisano M, Komano J, et al. Influenza vaccination during pregnancy and its usefulness to mothers and their young infants. *J Infect Chemother* 2015; 21: 238-246. 2015/02/25. doi: 10.1016/j.jiac.2015.01.015.
35. Jamieson DJ, Theiler RN and Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis* 2006; 12: 1638-1643. doi: 10.3201/eid1211.060152.
36. Abu-Raya B, Michalski C, Sadarangani M, et al. Maternal Immunological Adaptation During Normal Pregnancy. *Front Immunol* 2020; 11: 575197. 2020/11/03. doi: 10.3389/fimmu.2020.575197.
37. Raj RS, Bonney EA and Phillippe M. Influenza, immune system, and pregnancy. *Reprod Sci* 2014; 21: 1434-1451. 2014/06/06. doi: 10.1177/1933719114537720.
38. Robinson DP and Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. *Horm Behav* 2012; 62: 263-271. 2012/03/13. doi: 10.1016/j.yhbeh.2012.02.023.
39. Buchy P, Badur S, Kassianos G, et al. Vaccinating pregnant women against influenza needs to be a priority for all countries: An expert commentary. *Int J Infect Dis* 2020; 92: 1-12. doi: 10.1016/j.ijid.2019.12.019.
40. Puig-Barbera J, Natividad-Sancho A, Launay O, et al. 2012-2013 Seasonal influenza vaccine effectiveness against influenza hospitalizations: results from the global

influenza hospital surveillance network. *PLoS One* 2014; 9: e100497. 2014/06/20. doi: 10.1371/journal.pone.0100497.
41. Puig-Barbera J, Natividad-Sancho A, Trushakova S, et al. Epidemiology of Hospital Admissions with Influenza during the 2013/2014 Northern Hemisphere Influenza Season: Results from the Global Influenza Hospital Surveillance Network. *PLoS One* 2016; 11: e0154970. 2016/05/20. doi: 10.1371/journal.pone.0154970.
42. Puig-Barbera J, Burtseva E, Yu H, et al. Influenza epidemiology and influenza vaccine effectiveness during the 2014-2015 season: annual report from the Global Influenza Hospital Surveillance Network. *BMC Public Health* 2016; 16 Suppl 1: 757. 2016/08/25. doi: 10.1186/s12889-016-3378-1.
43. Puig-Barbera J, Mira-Iglesias A, Burtseva E, et al. Influenza epidemiology and influenza vaccine effectiveness during the 2015-2016 season: results from the Global Influenza Hospital Surveillance Network. *BMC Infect Dis* 2019; 19: 415. 2019/05/16. doi: 10.1186/s12879-019-4017-0.
44. Baselga-Moreno V, Trushakova S, McNeil S, et al. Influenza epidemiology and influenza vaccine effectiveness during the 2016-2017 season in the Global Influenza Hospital Surveillance Network (GIHSN). *BMC Public Health* 2019; 19: 487. 2019/05/03. doi: 10.1186/s12889-019-6713-5.
45. Lina B, Georges A, Burtseva E, et al. Complicated hospitalization due to influenza: results from the Global Hospital Influenza Network for the 2017-2018 season. *BMC Infect Dis* 2020; 20: 465. 2020/07/04. doi: 10.1186/s12879-020-05167-4.
46. Katz MA, Gessner BD, Johnson J, et al. Incidence of influenza virus infection among pregnant women: a systematic review. *BMC Pregnancy Childbirth* 2017; 17. doi: 10.1186/s12884-017-1333-5.
47. Fell D, Savitz D, Kramer M, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. *BJOG* 2017; 124: 48-59. doi: 10.1111/1471-0528.14143.
48. He J, Liu ZW, Lu YP, et al. A Systematic Review and Meta-Analysis of Influenza A Virus Infection During Pregnancy Associated with an Increased Risk for Stillbirth and Low Birth Weight. *Kidney Blood Press Res* 2017; 42: 232-243. 2017/05/18. doi: 10.1159/000477221.
49. Luteijn JM, Brown MJ and Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. *Hum Reprod* 2014; 29: 809-823. doi: 10.1093/humrep/det455.
50. Wang R, Yan W, Du M, et al. The effect of influenza virus infection on pregnancy outcomes: A systematic review and meta-analysis of cohort studies. *Int J Infect Dis* 2021; 105: 567-578. 2021/03/02. doi: 10.1016/j.ijid.2021.02.095.
51. Poehling KA, Edwards KM, Weinberg GA, et al. The Underrecognized Burden of Influenza in Young Children. *N Engl J Med* 2006; 355: 31-40. doi: 10.1056/NEJMoa054869.
52. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; 378: 1917-1930. doi: 10.1016/S0140-6736(11)61051-9.
53. Li Y, Widdowson M-A, Omer SB, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Health* 2020; 8: e497-e510. doi: 10.1016/S2214-109X(19)30545-5.
54. Lafond KE, Nair H, Rasooly MH, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982–2012: A Systematic Analysis. *PLoS Med* 2016; 13. doi: 10.1371/journal.pmed.1001977.
55. Albrecht M and Arck PC. Vertically Transferred Immunity in Neonates: Mothers, Mechanisms and Mediators. *Front Immunol* 2020; 11: 555. 2020/04/17. doi: 10.3389/fimmu.2020.00555.
56. Zinkernagel RM. Maternal Antibodies, Childhood Infections, and Autoimmune Diseases. *N Engl J Med* 2001; 345: 1331-1335. doi: 10.1056/NEJMra012493.
57. World Health Organization. Immunization, 2019. https://www.who.int/news-room/facts-in-pictures/detail/immunization (accessed 6/12/2021).

58. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook: 10th Edition*. Canberra, Australia: Australian Government: Department of Health, 2013.
59. Australian Government: Department of Health: Therapeutic Goods Administration. AIVC recommendations for the composition of influenza vaccine for Australia in 2014, 2013. https://www.tga.gov.au/aivc-recommendations-composition-influenza-vaccine-australia-2014 (accessed 6/12/2021).
60. Australian Government: Department of Health: Therapeutic Goods Administration. AIVC recommendations for the composition of influenza vaccine for Australia in 2015, 2014. https://www.tga.gov.au/aivc-recommendations-composition-influenza-vaccine-australia-2015 (accessed 6/12/2021).
61. Australian Government: Department of Health: Therapeutic Goods Administration. AIVC recommendations for the composition of influenza vaccine for Australia in 2016, 2016. https://www.tga.gov.au/aivc-recommendations-composition-influenza-vaccine-australia-2016 (accessed 6/12/2021).
62. Australian Government: Department of Health. Composition of Australian Influenza Vaccine for the 2013 season, 2012. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-fluvacc.htm (accessed 6/12/2021).
63. World Health Organization. The Global Action Plan for Influenza Vaccines. Geneva: World Health Organization, 2016.
64. Lafond KE, Tam JS, Bresee JS, et al. International meeting on influenza vaccine effectiveness, 3–4 December 2012, Geneva, Switzerland. *Vaccine* 2014; 32: 6591-6595. doi: 10.1016/j.vaccine.2014.09.069.
65. Sambala EZ, Ngcobo N, Machingaidze S, et al. A global review of seasonal influenza vaccine introduction: analysis of the WHO/UNICEF Joint Reporting Form. *Expert Rev Vaccines* 2019; 18: 859-865. 2019/07/19. doi: 10.1080/14760584.2019.1640119.
66. Ortiz JR, Perut M, Dumolard L, et al. A global review of national influenza immunization policies: Analysis of the 2014 WHO/UNICEF Joint Reporting Form on immunization. *Vaccine* 2016; 34: 5400-5405. doi: 10.1016/j.vaccine.2016.07.045.
67. Australian Government: Department of Health. Flu vaccination in 2021, 2021. https://www.health.gov.au/news/flu-vaccination-in-2021 (accessed 6/12/2021).
68. Mak DB, Regan AK, Vo DT, et al. Antenatal influenza and pertussis vaccination in Western Australia: a cross-sectional survey of vaccine uptake and influencing factors. *BMC Pregnancy Childbirth* 2018; 18: 416. Article. doi: 10.1186/s12884-018-2051-3.
69. Department of Health WA. OD 0363/12 Influenza vaccination for pregnant women. Perth: Department of Health, Western Australia, 2012.
70. Belshe RB, Newman FK, Wilkins K, et al. Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. *Vaccine* 2007; 25: 6755-6763. 2007/08/19. doi: 10.1016/j.vaccine.2007.06.066.
71. Englund JA, Walter EB, Gbadebo A, et al. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics* 2006; 118: e579-585. 2006/09/05. doi: 10.1542/peds.2006-0201.
72. Walter EB, Neuzil KM, Zhu Y, et al. Influenza vaccine immunogenicity in 6- to 23-month-old children: are identical antigens necessary for priming? *Pediatrics* 2006; 118: e570-578. 2006/09/05. doi: 10.1542/peds.2006-0198.
73. Nakphook S, Patumanond J, Shrestha M, et al. Antibody responses induced by trivalent inactivated influenza vaccine among pregnant and non-pregnant women in Thailand: A matched cohort study. *PLoS One* 2021; 16: e0253028. 2021/06/10. doi: 10.1371/journal.pone.0253028.
74. Naleway AL, Ball S, Kwong JC, et al. Estimating Vaccine Effectiveness Against Hospitalized Influenza During Pregnancy: Multicountry Protocol for a Retrospective Cohort Study. *JMIR Res Protoc* 2019; 8: 14. Article. doi: 10.2196/11333.
75. Munoz FM, Patel SM, Jackson LA, et al. Safety and immunogenicity of three seasonal inactivated influenza vaccines among pregnant women and antibody persistence in their infants. *Vaccine* 2020; 38: 5355-5363. doi: 10.1016/j.vaccine.2020.05.059.

76. Mutsaerts E, Madhi SA, Cutland CL, et al. Influenza vaccination of pregnant women protects them over two consecutive influenza seasons in a randomized controlled trial. *Expert Rev Vaccines* 2016; 15: 1055-1062. 2016/05/24. doi: 10.1080/14760584.2016.1192473.
77. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza Vaccination of Pregnant Women and Protection of Their Infants. *N Engl J Med* 2014; 371: 918-931. doi: 10.1056/NEJMoa1401480.
78. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis* 2016; 16: 1026-1035. doi: 10.1016/S1473-3099(16)30054-8.
79. Demers-Mathieu V, Underwood MA, Beverly RL, et al. Comparison of Human Milk Immunoglobulin Survival during Gastric Digestion between Preterm and Term Infants. *Nutrients* 2018; 10 2018/05/19. doi: 10.3390/nu10050631.
80. Vazquez-Pagan A and Schultz-Cherry S. Serological Responses to Influenza Vaccination during Pregnancy. *Microorganisms* 2021; 9 2021/11/28. doi: 10.3390/microorganisms9112305.
81. Brady RC, Jackson LA, Frey SE, et al. Randomized trial comparing the safety and antibody responses to live attenuated versus inactivated influenza vaccine when administered to breastfeeding women. *Vaccine* 2018; 36: 4663-4671. 2018/07/03. doi: 10.1016/j.vaccine.2018.06.036.
82. Maertens K, De Schutter S, Braeckman T, et al. Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. *Vaccine* 2014; 32: 1786-1792. 2014/02/18. doi: 10.1016/j.vaccine.2014.01.083.
83. Demers-Mathieu V, Huston RK, Markell AM, et al. Antenatal Influenza A-Specific IgA, IgM, and IgG Antibodies in Mother's Own Breast Milk and Donor Breast Milk, and Gastric Contents and Stools from Preterm Infants. *Nutrients* 2019; 11 2019/07/25. doi: 10.3390/nu11071567.
84. Schlaudecker EP, Steinhoff MC, Omer SB, et al. IgA and neutralizing antibodies to influenza a virus in human milk: a randomized trial of antenatal influenza immunization. *PLoS One* 2013; 8: e70867. 2013/08/24. doi: 10.1371/journal.pone.0070867.
85. Cuningham W, Geard N, Fielding JE, et al. Optimal timing of influenza vaccine during pregnancy: A systematic review and meta-analysis. *Influenza Other Respir Viruses* 2019; 13: 438-452. doi: 10.1111/irv.12649.
86. Malek A, Sager R and Schneider H. Maternal-Fetal Transport of Immunoglobulin G and Its Subclasses During the Third Trimester of Human Pregnancy. *Am J Reprod Immunol* 1994; 32: 8-14. Accepted December 1, 1993. doi: 10.1111/j.1600-0897.1994.tb00873.x.
87. Maertens K, Orije MRP, Van Damme P, et al. Vaccination during pregnancy: current and possible future recommendations. *Eur J Pediatr* 2020; 179: 235-242. 2020/01/09. doi: 10.1007/s00431-019-03563-w.
88. Omer SB, Clark DR, Madhi SA, et al. Efficacy, duration of protection, birth outcomes, and infant growth associated with influenza vaccination in pregnancy: a pooled analysis of three randomised controlled trials. *The Lancet Respiratory Medicine* 2020; 8: 597-608. doi: 10.1016/s2213-2600(19)30479-5.
89. Laurie L, Lambert SB, Jones L, et al. Influenza and pertussis vaccine uptake during pregnancy among Australian women in south-east Queensland, Australia. *Aust N Z J Public Health* 2021; 45: 443-448. 2021/06/29. doi: 10.1111/1753-6405.13133.
90. Rowe SL, Perrett KP, Morey R, et al. Influenza and pertussis vaccination of women during pregnancy in Victoria, 2015-2017. *Med J Aust* 2019; 210: 454-462. 2019/04/22. doi: 10.5694/mja2.50125.
91. Regan AK, Mak DB, Hauck YL, et al. Trends in seasonal influenza vaccine uptake during pregnancy in Western Australia: Implications for midwives. *Women Birth* 2016; 29: 423-429. doi: 10.1016/j.wombi.2016.01.009.
92. McCarthy EA, Pollock WE, Tapper L, et al. Increasing uptake of influenza vaccine by pregnant women post H1N1 pandemic: a longitudinal study in Melbourne, Australia,

2010 to 2014. *BMC Pregnancy Childbirth* 2015; 15: 53-59. doi: 10.1186/s12884-015-0486-3.
93. Ding H, Kahn KE, Black CL, et al. Influenza Vaccination Coverage Among Pregnant Women in the U.S., 2012-2015. *Am J Prev Med* 2019; 56: 477-486. 2019/02/20. doi: 10.1016/j.amepre.2018.11.020.
94. Ding H, Black CL, Ball S, et al. Influenza Vaccination Coverage Among Pregnant Women — United States, 2016–17 Influenza Season. *MMWR Morbidity Mortality Weekly Report* 2017; 66: 1016-1022. doi: 10.15585/mmwr.mm6638a2.
95. Groom HC, Henninger ML, Smith N, et al. Influenza Vaccination During Pregnancy: Influenza Seasons 2002–2012, Vaccine Safety Datalink: Influenza Seasons 2002–2012, Vaccine Safety Datalink. *Am J Prev Med* 2016; 50: 480-488. doi: 10.1016/j.amepre.2015.08.017.
96. Kennedy ED, Ahluwalia IB, Ding H, et al. Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. *Am J Obstet Gynecol* 2012; 207: S9-S16. doi: 10.1016/j.ajog.2012.06.069.
97. Annunziata K, Rak A, Del Buono H, et al. Vaccination rates among the general adult population and high-risk groups in the United States. *PLoS One* 2012; 7: e50553. 2012/12/12. doi: 10.1371/journal.pone.0050553.
98. Walker D, Ball S, Black R, et al. Influenza Vaccination Coverage Among Pregnant Women— United States, 2010-11 Influenza Season. *MMWR Morbidity Mortality Weekly Report* 2011; 60: 1078-1082.
99. Liu N, Sprague AE, Yasseen AS, et al. Vaccination patterns in pregnant women during the 2009 H1N1 influenza pandemic: a population-based study in Ontario, Canada. *Can J Public Health* 2012; 103: 353-358. doi: 10.1016/j.jpeds.2013.02.049.
100. Fabry P, Gagneur A and Pasquier J-C. Determinants of A (H1N1) vaccination: cross-sectional study in a population of pregnant women in Quebec. *Vaccine* 2011; 29: 1824-1829. doi: 10.1016/j.vaccine.2010.12.109.
101. Walker JL, Rentsch CT, McDonald HI, et al. Social determinants of pertussis and influenza vaccine uptake in pregnancy: a national cohort study in England using electronic health records. *BMJ Open* 2021; 11: e046545. 2021/06/23. doi: 10.1136/bmjopen-2020-046545.
102. Dabrera G, Zhao H, Andrews N, et al. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. *Euro Surveill* 2014; 19: 20959. doi: 10.2807/1560-7917.ES2014.19.45.20959.
103. Lane S, Macdonald NE, Marti M, et al. Vaccine hesitancy around the globe: Analysis of three years of WHO/UNICEF Joint Reporting Form data-2015–2017. *Vaccine* 2018; 36: 3861-3867. doi: 10.1016/j.vaccine.2018.03.063.
104. Kahn KE, Black CL, Ding H, et al. Influenza and Tdap Vaccination Coverage Among Pregnant Women — United States, April 2018. *MMWR Morbidity Mortality Weekly Report* 2018; 67: 1055-1059. doi: 10.15585/mmwr.mm6738a3.
105. Regan AK, Hauck Y, Nicolaou L, et al. Midwives' knowledge, attitudes and learning needs regarding antenatal vaccination. *Midwifery* 2018; 62: 199-204. doi: 10.1016/j.midw.2018.04.004.
106. Morales KF, Menning L and Lambach P. The faces of influenza vaccine recommendation: A Literature review of the determinants and barriers to health providers' recommendation of influenza vaccine in pregnancy. *Vaccine* 2020; 38: 4805-4815. 2020/06/06. doi: 10.1016/j.vaccine.2020.04.033.
107. Quach THT, Mallis NA and Cordero JF. Influenza Vaccine Efficacy and Effectiveness in Pregnant Women: Systematic Review and Meta-analysis. *Matern Child Health J* 2020; 24: 229-240. doi: 10.1007/s10995-019-02844-y.
108. Nunes MC and Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: A systematic review and meta-analysis. *Hum Vaccin Immunother* 2018; 14: 758-766. doi: 10.1080/21645515.2017.1345385.
109. Omer SB, Clark DR, Aqil AR, et al. Maternal Influenza Immunization and Prevention of Severe Clinical Pneumonia in Young Infants Analysis of Randomized

Controlled Trials Conducted in Nepal, Mali and South Africa. *Pediatr Infect Dis J* 2018; 37: 436-440. Article. doi: 10.1097/inf.0000000000001914.
110. Mazagatos C, Godoy P, Munoz Almagro C, et al. Effectiveness of influenza vaccination during pregnancy to prevent severe infection in children under 6 months of age, Spain, 2017-2019. *Vaccine* 2020; 38: 8405-8410. 2020/08/04. doi: 10.1016/j.vaccine.2020.07.014.
111. Regan AK and Munoz FM. Efficacy and safety of influenza vaccination during pregnancy: realizing the potential of maternal influenza immunization. *Expert Rev Vaccines* 2021 2021/04/10. doi: 10.1080/14760584.2021.1915138.
112. Nunes MC, Cutland CL, Moultrie A, et al. Immunogenicity and safety of different dosing schedules of trivalent inactivated influenza vaccine in pregnant women with HIV: a randomised controlled trial. *The Lancet HIV* 2020; 7: e91-e103. doi: 10.1016/s2352-3018(19)30322-4.
113. Munoz FM, Jackson LA, Swamy GK, et al. Safety and immunogenicity of seasonal trivalent inactivated influenza vaccines in pregnant women. *Vaccine* 2018; 36: 8054-8061. 2018/11/13. doi: 10.1016/j.vaccine.2018.10.088.
114. Glover C, Crawford N, Leeb A, et al. Active SMS-based surveillance of adverse events following immunisation with influenza and pertussis-containing vaccines in Australian pregnant women using AusVaxSafety. *Vaccine* 2020; 38: 4892-4900. 2020/06/06. doi: 10.1016/j.vaccine.2020.04.056.
115. Regan AK, Tracey L, Blyth CC, et al. A prospective cohort study comparing the reactogenicity of trivalent influenza vaccine in pregnant and non-pregnant women. *BMC Pregnancy Childbirth* 2015; 15: 61. 2015/04/17. doi: 10.1186/s12884-015-0495-2.
116. Naleway AL, Irving SA, Henninger M, et al. Safety of influenza vaccination during pregnancy: A review of subsequent maternal obstetric events and findings from two recent cohort studies. *Vaccine* 2014; 32: 3122-3127. doi: 10.1016/j.vaccine.2014.04.021.
117. Henninger M, Naleway A, Crane B, et al. Predictors of seasonal influenza vaccination during pregnancy. *Obstet Gynecol* 2013; 121: 741-749. 2013/05/03. doi: 10.1097/AOG.0b013e3182878a5a.
118. Thompson M, Williams J, Naleway A, et al. The Pregnancy and Influenza Project: design of an observational case-cohort study to evaluate influenza burden and vaccine effectiveness among pregnant women and their infants. *Am J Obstet Gynecol* 2011; 204: S69-76. 2011/03/18. doi: 10.1016/j.ajog.2011.01.006.
119. Kharbanda EO, Vazquez-Benitez G, Lipkind H, et al. Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events. *Obstet Gynecol* 2013; 122: 659-667. 2013/08/08. doi: 10.1097/AOG.0b013e3182a1118a.
120. Clark DR, Omer SB, Tapia MD, et al. Influenza or Meningococcal Immunization During Pregnancy and Mortality in Women and Infants: A Pooled Analysis of Randomized Controlled Trials. *Pediatr Infect Dis J* 2020; 39: 641-644. 2020/05/08. doi: 10.1097/INF.0000000000002629.
121. Lu QC, Zhang TY, Bundhun PK, et al. One "misunderstood" health issue: demonstrating and communicating the safety of influenza a vaccination in pregnancy: a systematic review and meta-analysis. *BMC Public Health* 2021; 21: 703-703. doi: 10.1186/s12889-021-10740-w.
122. Giles ML, Krishnaswamy S, Macartney K, et al. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. *Hum Vaccin Immunother* 2019; 15: 687-699. 2018/11/02. doi: 10.1080/21645515.2018.1540807.
123. Jeong S, Jang EJ, Jo J, et al. Effects of maternal influenza vaccination on adverse birth outcomes: A systematic review and Bayesian meta-analysis. *PLoS One* 2019; 14: e0220910. 2019/08/15. doi: 10.1371/journal.pone.0220910.
124. Zhang C, Wang X, Liu D, et al. A systematic review and meta-analysis of fetal outcomes following the administration of influenza A/H1N1 vaccination during pregnancy. *International Journal of Gynaecology and Obstetrics* 2018; 141: 141-150. doi: 10.1002/ijgo.12394.

125. Nunes MC, Aqil AR, Omer SB, et al. The Effects of Influenza Vaccination during Pregnancy on Birth Outcomes: A Systematic Review and Meta-Analysis. *Am J Perinatol* 2016; 33: 1104-1114. doi: 10.1055/s-0036-1586101.
126. Fell D, Platt R, Lanes A, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. *BJOG* 2015; 122: 17-26. doi: 10.1111/1471-0528.12977.
127. Bratton KN, Wardle MT, Orenstein WA, et al. Maternal Influenza Immunization and Birth Outcomes of Stillbirth and Spontaneous Abortion: A Systematic Review and Meta-analysis. *Clin Infect Dis* 2015; 60: E11-E19.
128. McMillan M, Porritt K, Kralik D, et al. Influenza vaccination during pregnancy: A systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. *Vaccine* 2015; 33: 2108-2117. doi: 10.1016/j.vaccine.2015.02.068.
129. Macias Saint-Gerons D, Sola Arnau I, De Mucio B, et al. Adverse events associated with the use of recommended vaccines during pregnancy: An overview of systematic reviews. *Vaccine* 2021; 39 Suppl 2: B12-B26. 2020/09/26. doi: 10.1016/j.vaccine.2020.07.048.
130. Arora M and Lakshmi R. Vaccines - safety in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2021; 76: 23-40. 2021/03/29. doi: 10.1016/j.bpobgyn.2021.02.002.
131. Marchant A, Sadarangani M, Garand M, et al. Maternal immunisation: collaborating with mother nature. *Lancet Infect Dis* 2017; 17: e197-e208. Article. doi: 10.1016/s1473-3099(17)30229-3.
132. Vojtek I, Dieussaert I, Doherty TM, et al. Maternal immunization: where are we now and how to move forward? *Ann Med* 2018; 50: 193-208. 2018/01/09. doi: 10.1080/07853890.2017.1421320.
133. Orije MRP, Maertens K, Corbière V, et al. The effect of maternal antibodies on the cellular immune response after infant vaccination: A review. *Vaccine* 2020; 38: 20-28. doi: 10.1016/j.vaccine.2019.10.025.
134. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Front Immunol* 2014; 5. doi: 10.3389/fimmu.2014.00446.
135. Zimmermann P, Perrett KP, Messina NL, et al. The Effect of Maternal Immunisation During Pregnancy on Infant Vaccine Responses. *EClinicalMedicine* 2019; 13: 21-30. 2019/09/14. doi: 10.1016/j.eclinm.2019.06.010.
136. Fitzgerald E, Hor K and Drake AJ. Maternal influences on fetal brain development: The role of nutrition, infection and stress, and the potential for intergenerational consequences. *Early Hum Dev* 2020; 150: 105190-105190. doi: 10.1016/j.earlhumdev.2020.105190.
137. Racicot K and Mor G. Risks associated with viral infections during pregnancy. *J Clin Invest* 2017; 127: 1591-1599. 2017/05/02. doi: 10.1172/JCI87490.
138. Al-Haddad BJS, Oler E, Armistead B, et al. The fetal origins of mental illness. *Am J Obstet Gynecol* 2019; 221: 549-562. 2019/06/18. doi: 10.1016/j.ajog.2019.06.013.
139. Meyer U. Neurodevelopmental Resilience and Susceptibility to Maternal Immune Activation. *Trends Neurosci* 2019; 42: 793-806. doi: 10.1016/j.tins.2019.08.001.
140. Goeden N, Velasquez J, Arnold KA, et al. Maternal Inflammation Disrupts Fetal Neurodevelopment via Increased Placental Output of Serotonin to the Fetal Brain. *J Neurosci* 2016; 36: 6041-6049. 2016/06/03. doi: 10.1523/JNEUROSCI.2534-15.2016.
141. Al-Haddad BJS, Jacobsson B, Chabra S, et al. Long-term Risk of Neuropsychiatric Disease After Exposure to Infection In Utero. *JAMA Psychiatry* 2019; 76: 594-602. 2019/03/07. doi: 10.1001/jamapsychiatry.2019.0029.
142. Bergdolt L and Dunaevsky A. Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. *Prog Neurobiol* 2019; 175: 1-19. doi: 10.1016/j.pneurobio.2018.12.002.
143. Ellman LM, Yolken RH, Buka SL, et al. Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. *Biological Psychiatry* 2009; 65: 1040-1047. 2009/02/07. doi: 10.1016/j.biopsych.2008.12.015.

144. Byrne M, Agerbo E, Bennedsen B, et al. Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. *Schizophr Res* 2007; 97: 51-59. 2007/09/04. doi: 10.1016/j.schres.2007.07.018.
145. Brown AS, Begg MD, Gravenstein S, et al. Serologic Evidence of Prenatal Influenza in the Etiology of Schizophrenia. *Arch Gen Psychiatry* 2004; 61: 774-780. doi: 10.1001/archpsyc.61.8.774.
146. Limosin F, Rouillon F, Payan C, et al. Prenatal exposure to influenza as a risk factor for adult schizophrenia. *Acta Psychiatr Scand* 2003; 107: 331-335. Accepted for publication October 23, 2002. doi: 10.1034/j.1600-0447.2003.00052.x.
147. Brown AS, Schaefer CA, Wyatt RJ, et al. Maternal Exposure to Respiratory Infections and Adult Schizophrenia Spectrum Disorders: A Prospective Birth Cohort Study. *Schizophr Bull* 2000; 26: 287-295. doi: 10.1093/oxfordjournals.schbul.a033453.
148. Selten J-P, Brown AS, Moons KGM, et al. Prenatal exposure to the 1957 influenza pandemic and non-affective psychosis in The Netherlands. *Schizophr Res* 1999; 38: 85-91. doi: 10.1016/S0920-9964(99)00005-5.
149. Selten J-P, Slaets J and Kahn R. Prenatal exposure to influenza and schizophrenia in Surinamese and Dutch Antillean immigrants to The Netherlands. *Schizophr Res* 1998; 30: 101-103. doi: 10.1016/S0920-9964(97)00105-9.
150. Morgan V, Castle D, Page A, et al. Influenza epidemics and the incidence of schizophrenia, affective disorders and mental retardation: Further data from Western Australia. *Schizophrenia Res* 1998; 29: 18-18. doi: 10.1016/S0920-9964(97)88333-8.
151. Morgan V, Castle D, Page A, et al. Influenza epidemics and incidence of schizophrenia, affective disorders and mental retardation in Western Australia: no evidence of a major effect. *Schizophr Res* 1997; 26: 25-39. doi: 10.1016/S0920-9964(97)00033-9.
152. Cannon M, Cotter D, Coffey VP, et al. Prenatal Exposure to the 1957 Influenza Epidemic and Adult Schizophrenia: A Follow-Up Study. *Br J Psychiatry* 1996; 168: 368-371. doi: 10.1192/bjp.168.3.368.
153. Susser E, Lin SP, Brown AS, et al. No relation between risk of schizophrenia and prenatal exposure to influenza in Holland. *Am J Psychiatry* 1994; 151: 922-924. doi: 10.1176/ajp.151.6.922.
154. Takei N, O'Callaghan E, Sham PC, et al. Does prenatal influenza divert susceptible females from later affective psychosis to schizophrenia? *Acta Psychiatr Scand* 1993; 88: 328-336. Accepted for publication June 28, 1993. doi: 10.1111/j.1600-0447.1993.tb03468.x.
155. Takei N, Sham P, O'Callaghan E, et al. Prenatal influenza and schizophrenia: Is the effect confined to females? *Schizophrenia research* 1993; 9: 141-141. doi: 10.1016/0920-9964(93)90243-C.
156. O'Callaghan E, Sham P, Takei N, et al. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet* 1991; 337: 1248-1250. doi: 10.1016/0140-6736(91)92919-S.
157. Mednick SA, Machon RA, Huttunen MO, et al. Adult Schizophrenia Following Prenatal Exposure to an Influenza Epidemic. *Arch Gen Psychiatry* 1988; 45: 189-192. doi: 10.1001/archpsyc.1988.01800260109013.
158. Guisso DR, Saadeh FS, Saab D, et al. Association of Autism with Maternal Infections, Perinatal and Other Risk Factors: A Case-Control Study. *J Autism Dev Disord* 2018; 48: 2010-2021. 2018/01/15. doi: 10.1007/s10803-017-3449-x.
159. Brucato M, Ladd-Acosta C, Li M, et al. Prenatal exposure to fever is associated with autism spectrum disorder in the boston birth cohort. *Autism Res* 2017; 10: 1878-1890. 2017/08/12. doi: 10.1002/aur.1841.
160. Zerbo O, Qian Y, Yoshida C, et al. Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder. *JAMA Pediatr* 2017; 171: e163609. doi: 10.1001/jamapediatrics.2016.3609.
161. Mahic M, Che X, Susser E, et al. Epidemiological and Serological Investigation into the Role of Gestational Maternal Influenza Virus Infection and Autism Spectrum Disorders. *mSphere* 2017; 2 2017/06/29. doi: 10.1128/mSphere.00159-17.

162. Jiang H-Y, Xu L-L, Shao L, et al. Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. *Brain Behav Immun* 2016; 58: 165-172. doi: 10.1016/j.bbi.2016.06.005.
163. Atladóttir HÓ, Henriksen TB, Schendel DE, et al. Autism after infection, febrile episodes, and antibiotic use during pregnancy: An exploratory study. *Pediatrics* 2012; 130: e1447-e1454. doi: 10.1542/peds.2012-1107.
164. Fang SY, Wang S, Huang N, et al. Prenatal Infection and Autism Spectrum Disorders in Childhood: A Population-Based Case–Control Study in Taiwan. *Paediatric and Perinatal Epidemiology* 2015; 29: 307-316. doi: 10.1111/ppe.12194.
165. Zerbo O, Iosif A-M, Walker C, et al. Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Developmental Delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) Study. *J Autism Dev Disord* 2013; 43: 25-33. doi: 10.1007/s10803-012-1540-x.
166. Anderson JJ, Hoath S, Zammit S, et al. Gestational influenza and risk of hypomania in young adulthood: prospective birth cohort study. *J Affect Disord* 2016; 200: 182-188. 2016/05/03. doi: 10.1016/j.jad.2016.04.048.
167. Mortensen PB, Pedersen CB, Melbye M, et al. Individual and Familial Risk Factors for Bipolar Affective Disorders in Denmark. *Arch Gen Psychiatry* 2003; 60: 1209-1215. doi: 10.1001/archpsyc.60.12.1209.
168. Mino Y, Oshima I and Okagami K. Mood disorders and influenza epidemics in Japan. *Psychiatry Clin Neurosci* 2000; 54: 59-65. doi: 10.1046/j.1440-1819.2000.00638.x.
169. Dreier JW, Berg-Beckhoff G, Andersen AMN, et al. Fever and infections during pregnancy and psychosis-like experiences in the offspring at age 11. A prospective study within the Danish National Birth Cohort. *Psychol Med* 2018; 48: 426-436. 2017/07/25. doi: 10.1017/S0033291717001805.
170. Zammit S, Odd D, Horwood J, et al. Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. *Psychol Med* 2009; 39: 1457-1467. 2009/02/14. doi: 10.1017/S0033291708005126.
171. Pineda DA, Palacio LG, Puerta IC, et al. Environmental influences that affect attention deficit/hyperactivity disorder: Study of a genetic isolate. *Eur Child Adolesc Psychiatry* 2007; 16: 337-346. doi: 10.1007/s00787-007-0605-4.
172. Takei N, Murray G, O'Callaghan E, et al. Prenatal exposure to influenza epidemics and risk of mental retardation. *Eur Arch Psychiatry Clin Neurosci* 1995; 245: 255-259. doi: 10.1007/BF02191805.
173. Pang D, Syed S, Fine P, et al. No Association between Prenatal Viral Infection and Depression in Later Life—A Long-Term Cohort Study of 6152 Subjects. *Can J Psychiatry* 2009; 54: 565-570. doi: 10.1177/070674370905400809.
174. Favaro A, Tenconi E, Ceschin L, et al. In utero exposure to virus infections and the risk of developing anorexia nervosa. *Psychol Med* 2011; 41: 2193-2199. doi: 10.1017/S0033291710002655.
175. Cocoros NM, Ording AG, Horváth-Puhó E, et al. In utero exposure to the 1918 pandemic influenza in Denmark and risk of dementia. *Influenza Other Respir Viruses* 2018; 12: 314-318. doi: 10.1111/irv.12542.
176. Bischoff AL, Følsgaard NV, Vissing NH, et al. Airway Mucosal Immune-suppression in Neonates of Mothers Receiving A(H1N1)pnd09 Vaccination During Pregnancy. *Pediatr Infect Dis J* 2015; 34: 84-90. doi: 10.1097/INF.0000000000000529.
177. Fell D, Wilson K, Ducharme R, et al. Infant Respiratory Outcomes Associated with Prenatal Exposure to Maternal 2009 A/H1N1 Influenza Vaccination. *PLoS One* 2016; 11: e0160342. doi: 10.1371/journal.pone.0160342.
178. Hviid A, Svanström H, Mølgaard-Nielsen D, et al. Association Between Pandemic Influenza A(H1N1) Vaccination in Pregnancy and Early Childhood Morbidity in Offspring. *JAMA Pediatr* 2017; 171: 239-248. doi: 10.1001/jamapediatrics.2016.4023.
179. Walsh LK, Donelle J, Dodds L, et al. Health outcomes of young children born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: retrospective cohort study. *BMJ* 2019; 366: 1-9. doi: 10.1136/bmj.l4151.

180. Ludvigsson JF, Strom P, Lundholm C, et al. Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design. *BMJ* 2015; 351: 1-6. 2015/11/18. doi: 10.1136/bmj.h5585.
181. Benowitz I, Esposito DB, Gracey KD, et al. Influenza Vaccine Given to Pregnant Women Reduces Hospitalization Due to Influenza in Their Infants. *Clin Infect Dis* 2010; 51: 1355-1361. doi: 10.1086/657309.
182. Van Santen KL, Bednarczyk RA, Adjaye-Gbewonyo D, et al. Effectiveness of Pneumococcal Conjugate Vaccine in Infants by Maternal Influenza Vaccination Status. *Pediatr Infect Dis J* 2013; 32: 1180-1184. doi: 10.1097/INF.0b013e3182a26752.
183. Government of Western Australia: Department of Health. About Us, 2022. https://ww2.health.wa.gov.au/About-us.
184. Australian Bureau of Statistics. Births, summary, by state, 2018. http://stat.data.abs.gov.au/Index.aspx?DatasetCode=BIRTHS_SUMMARY (accessed 12/09/2021).
185. Australian Government: Department of Health. Clinical update: 2020 seasonal influenza vaccines – early advice for vaccination providers, 2020. https://www.health.gov.au/news/clinical-update-2020-seasonal-influenza-vaccines-early-advice-for-vaccination-providers (accessed 1/9/2020).
186. National Centre for Immunisation Research and Surveillance. Significant events in influenza vaccination practice in Australia. 2020.
187. Western Australian Data Linkage Branch. About Data Linkage Branch WA, https://www.datalinkage-wa.org.au/about/ (accessed 1/6/2021).
188. Holman CDJ, Bass AJ, Rosman DL, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. *Aust Health Rev* 2008; 32: 766-777. doi: 10.1071/AH080766.
189. Holman C, Bass A, Rouse I, et al. Population-based linkage of health records in Western Australia: Development of a health services research linked database. *Aust NZ J Obstet Gyn* 1999; 23: 453-459.
190. Brook EL, Rosman DL and Holman CD. Public good through data linkage: measuring research outputs from the Western Australian Data Linkage System. *Aust N Z J Public Health* 2008; 32: 19-23. 2008/02/23. doi: 10.1111/j.1753-6405.2008.00160.x.
191. Western Australian Data Linkage Branch. Linkage, https://www.datalinkage-wa.org.au/dlb-services/linkage/ (accessed 17/9/2021).
192. Eitelhuber T, Thackray J, Hodges S, et al. Fit for purpose - developing a software platform to support the modern challenges of data linkage in Western Australia. *International Journal of Population Data Science* 2018; 3: 435-435. doi: 10.23889/ijpds.v3i3.435.
193. Kelman CW, Bass AJ and Holman CDJ. Research use of linked health data - a best practice protocol. *Aust N Z J Public Health* 2002; 26: 251-255. doi: 10.1111/j.1467-842X.2002.tb00682.x.
194. National Health and Medical Research Council. Guidelines Under Section 95 of the Privacy Act 1988. 2014.
195. Western Australian Data Linkage Branch. Birth registrations: linkage quality statement. 2017.
196. Parliamentary Counsel's Office. Births, Deaths and Marriages Registration Act 1998. In: Justice GoWADo, (ed.). 2020.
197. Government of Western Australia: Department of Health. Midwives Notification System, 2018. http://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System (accessed 12/7/2018).
198. Gee V and Dawes V. Validation study of the Western Australian Midwives' Notification System 1992. Perth, WA: Western Australia Department of Health, 1994.
199. Government of Western Australia: Department of Health. Data Quality Statement: Midwives Notification System. 2021.
200. Regan AK, Mak DB, Moore HC, et al. Surveillance of antenatal influenza vaccination: validity of current systems and recommendations for improvement. *BMC Public Health* 2015; 15: 1155. doi: 10.1186/s12889-015-2234-z.

201. Regan AK, Effler PV, Thomson C, et al. Potential use of Western Australia's mandatory Midwives Notification System for routinely monitoring antenatal vaccine coverage. *Commun Dis Intell* 2019; 43 2019/06/18. doi: 10.33321/cdi.2019.43.21.
202. Communicable Disease Control Directorate. Guide to interpreting notifiable infections disease data for Western Australia. Western Australia Department of Health, 2021.
203. Government of Western Australia: Department of Health. Hospital Morbidity Data System. Reference Manual Part A: Contacts, Hospital Responsibilities, Data Element Definitions. 2017.
204. Government of Western Australia: Department of Health. Process For Emergency Department Patient Statistics – Emergency Department Data Collections. Data Collections Directorate, 2018.
205. Western Australian Data Linkage Branch. Death registrations: linkage quality statement. 2017.
206. Australian Bureau of Statistics. 3303.0 - Causes of Death, Australia, 2017: Explanatory notes, 2018. https://www.abs.gov.au/ausstats/abs@.nsf/Previousproducts/3303.0Explanatory%20Notes12017?opendocument&tabname=Notes&prodno=3303.0&issue=2017&num=&view= (accessed 25/01/2022).
207. Blyth CC, Macartney KK, Hewagama S, et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). *Euro Surveill* 2016; 21: 30301. doi: 10.2807/1560-7917.ES.2016.21.30.30301.
208. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of Maternal Influenza Immunization in Mothers and Infants. *N Engl J Med* 2008; 359: 1555-1564. doi: 10.1056/NEJMoa0708630.
209. Macdonald N and Bortolussi R. Protecting young babies from influenza. *Paediatr Child Health* 2009; 14: 612-614.
210. Halasa N, Gerber MA, Chen Q, et al. Safety and Immunogenicity of Trivalent Inactivated Influenza Vaccine in Infants. *J Infect Dis* 2008; 197: 1448-1454. doi: 10.1086/587643.
211. Steinhoff MC, Omer SB, Roy E, et al. Influenza Immunization in Pregnancy — Antibody Responses in Mothers and Infants. *N Engl J Med* 2010; 362: 1644-1646. doi: 10.1056/NEJMc0912599.
212. Sperling SR, Engel MS, Wallenstein AS, et al. Immunogenicity of Trivalent Inactivated Influenza Vaccination Received During Pregnancy or Postpartum. *Obstet Gynecol* 2012; 119: 631-639. doi: 10.1097/AOG.0b013e318244ed20.
213. Jackson LA, Patel SM, Swamy GK, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. *J Infect Dis* 2011; 204: 854-863. doi: 10.1093/infdis/jir440.
214. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. *MMWR Morbidity Mortality Weekly Report* 2018; 67: 1-20. doi: 10.15585/mmwr.rr6703a1.
215. Silverman N and Beigi R. ACOG Committee Opinion No. 732: Influenza Vaccination During Pregnancy. *Obstet Gynecol* 2018; 131: e109-e114. doi: 10.1097/AOG.0000000000002588.
216. Macias AE, Precioso AR and Falsey AR. The Global Influenza Initiative recommendations for the vaccination of pregnant women against seasonal influenza. *Influenza Other Respir Viruses* 2015; 9: 31-37. doi: 10.1111/irv.12320.
217. Polyzos AK, Konstantelias AA, Pitsa EC, et al. Maternal Influenza Vaccination and Risk for Congenital Malformations: A Systematic Review and Meta-analysis. *Obstet Gynecol* 2015; 126: 1075-1084. doi: 10.1097/AOG.0000000000001068.
218. Jarvis JR, Dorey RB, Warricker FDM, et al. The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: Systematic review and meta-analysis. *Vaccine* 2020; 38: 1601-1613. doi: 10.1016/j.vaccine.2019.12.056.

219. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015; 4: 1. journal article 2015/01/03. doi: 10.1186/2046-4053-4-1.
220. Desmeules R, Campbell S and Dorgan M. Acknowledging Librarians' Contributions to Systematic Review Searching. *Journal of the Canadian Health Libraries Association / Journal de l'Association des bibliothèques de la santé du Canada* 2016; 37. doi: 10.5596/c16-014.
221. Higgins JPT and Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 [updated June 2017]. The Cochrane Collaboration, 2011.
222. Wells G, Shea B and O'Connell J. *The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses*. 2014.
223. Wells GA, Shea BOD, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 14 May 2019).
224. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev* 2016; 10 (Suppl 1). doi: 10.1002/14651858.CD201601.
225. van der Maas N, Dijs-Elsinga J, Kemmeren J, et al. Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross-sectional linkage study. *BJOG* 2016; 123: 709. doi: 10.1111/1471-0528.13329.
226. Hviid A. Vaccine Safety in Pregnancy: Going Beyond the Perinatal Period. *Ann Intern Med* 2020; 173: 658-659. doi: 10.7326/M20-5489.
227. Danchin MH, Costa-Pinto J, Attwell K, et al. Vaccine decision-making begins in pregnancy: Correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. *Vaccine* 2018; 36: 6473-6479. doi: 10.1016/j.vaccine.2017.08.003.
228. Kachikis A, Eckert LO and Englund J. Who's the Target: Mother or Baby? *Viral Immunol* 2018; 31: 184-194. doi: 10.1089/vim.2017.0135.
229. Kay AW and Blish CA. Immunogenicity and Clinical Efficacy of Influenza Vaccination In Pregnancy. *Front Immunol* 2015; 6: 289. doi: 10.3389/fimmu.2015.00289.
230. Regan AK, de Klerk N, Moore HC, et al. Effectiveness of seasonal trivalent influenza vaccination against hospital-attended acute respiratory infections in pregnant women: A retrospective cohort study. *Vaccine* 2016; 34: 3649-3656. doi: 10.1016/j.vaccine.2016.05.032.
231. Foo DYP, Sarna M, Pereira G, et al. Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review. *Pediatrics* 2020; 146: e20200375. doi: 10.1542/peds.2020-0375.
232. Glezen WP. Effect of maternal antibodies on the infant immune response. *Vaccine* 2003; 21: 3389-3392. doi: 10.1016/S0264-410X(03)00339-6.
233. Australian Bureau of Statistics. 3301.0 - Births, Australia, 2016, 2017. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3301.02016?OpenDocument (accessed 1 September 2020).
234. Lipsitch M, Tchetgen ET and Cohen T. Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. *Epidemiology* 2010; 21: 383-388. doi: 10.1097/EDE.0b013e3181d61eeb.
235. Pink B. Socio-Economic Indexes for Areas. Canberra: Australia Bureau of Statistics, 2011.
236. Dobbins TA, Sullivan EA, Roberts CL, et al. Australian national birthweight percentiles by sex and gestational age, 1998–2007. *Med J Aust* 2012; 197: 291-294. doi: 10.5694/mja11.11331.
237. Lindley MC, Kahn KE, Bardenheier BH, et al. Vital Signs: Burden and Prevention of Influenza and Pertussis Among Pregnant Women and Infants - United States. *MMWR Morbidity Mortality Weekly Report* 2019; 68: 885-892. doi: 10.15585/mmwr.mm6840e1.

238. Barber A, Muscoplat MH and Fedorowicz A. Coverage with Tetanus, Diphtheria, and Acellular Pertussis Vaccine and Influenza Vaccine Among Pregnant Women — Minnesota, March 2013–December 2014. *MMWR Morbidity Mortality Weekly Report* 2017; 66: 56-59. doi: 10.15585/mmwr.mm6602a4.
239. Australian Bureau of Statistics. 2033.0.55.001 - Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2016, 2018. https://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001 (accessed 1 September 2020).
240. Maertens K, Burbidge P, Van Damme P, et al. Pneumococcal Immune Response in Infants Whose Mothers Received Tetanus, Diphtheria and Acellular Pertussis Vaccination During Pregnancy. *Pediatr Infect Dis J* 2017; 36: 1186-1192. doi: 10.1097/INF.0000000000001601.
241. Australian Government: Australian Institute of Health and Welfare. Metadata standards, 2019. https://www.aihw.gov.au/about-our-data/metadata-standards (accessed 1/6/2021).
242. Lim FJ, Blyth CC, Levy A, et al. Using record linkage to validate notification and laboratory data for a more accurate assessment of notifiable infectious diseases. *BMC Med Inform Decis Mak* 2017; 17: 86. doi: 10.1186/s12911-017-0484-7.
243. Communicable Disease Control Directorate. Surveillance Case Definitions for Notifiable Infectious Diseases and Related Conditions in Western Australia. 2021.
244. Munoz FM and Long SS. The Safety of Maternal Influenza Vaccination and Infant Health Outcomes. *Pediatrics* 2020; 146: e2020006916. doi: 10.1542/peds.2020-006916.
245. Wilcox CR and Jones CE. Beyond Passive Immunity: Is There Priming of the Fetal Immune System Following Vaccination in Pregnancy and What Are the Potential Clinical Implications? *Front Immunol* 2018; 9: 1548. 2018/08/01. doi: 10.3389/fimmu.2018.01548.
246. Sarna M, Andrews R, Moore H, et al. 'Links2HealthierBubs' cohort study: protocol for a record linkage study on the safety, uptake and effectiveness of influenza and pertussis vaccines among pregnant Australian women. *BMJ Open* 2019; 9: 030277. doi: 10.1136/bmjopen-2019-030277.
247. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453-1457. doi: 10.1016/S0140-6736(07)61602-X.
248. Blanchard-Rohner G, Meier S, Bel M, et al. Influenza vaccination given at least 2 weeks before delivery to pregnant women facilitates transmission of seroprotective influenza-specific antibodies to the newborn. *Pediatr Infect Dis J* 2013; 32: 1374-1380. doi: 10.1097/01.inf.0000437066.40840.c4.
249. Lipsitch M, Jha A and Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. *Int J Epidemiol* 2016; 45: 2060-2074. 2016/07/28. doi: 10.1093/ije/dyw124.
250. Australian Bureau of Statistics. 2071.0 - Census of Population and Housing: Reflecting Australia - Stories from the Census, 2016, 2018. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2071.0~2016~Main%20Features~Socio-Economic%20Advantage%20and%20Disadvantage~123 (accessed 1/6/2021).
251. Mehrabadi A, Dodds L, MacDonald NE, et al. Association of Maternal Influenza Vaccination During Pregnancy With Early Childhood Health Outcomes. *JAMA* 2021; 325: 2285-2293. doi: 10.1001/jama.2021.6778.
252. Bonner K, Scotney E and Saglani S. Factors and mechanisms contributing to the development of preschool wheezing disorders. *Expert Rev Respir Med* 2021: 1-16. doi: 10.1080/17476348.2021.1913057.
253. Wu P, Dupont WD, Griffin MR, et al. Evidence of a Causal Role of Winter Virus Infection during Infancy in Early Childhood Asthma. *Am J Respir Crit Care Med* 2008; 178: 1123-1129. doi: 10.1164/rccm.200804-579OC.

254. Tanno LK, Demoly P and Marseglia GL. Anaphylaxis in children. *Pediatr Allergy Immunol* 2020; 31: 8-10. doi: 10.1111/pai.13336.
255. Regan AK, de Klerk N, Moore H, et al. Effect of Maternal Influenza Vaccination on Hospitalization for Respiratory Infections in Newborns: A Retrospective Cohort Study. *Pediatr Infect Dis J* 2016; 35: 1097-1103. doi: 10.1097/INF.0000000000001258.
256. Nunes MC, Cutland CL, Jones S, et al. Efficacy of Maternal Influenza Vaccination Against All-Cause Lower Respiratory Tract Infection Hospitalizations in Young Infants: Results From a Randomized Controlled Trial. *Clin Infect Dis* 2017; 65: 1066-1071. Article. doi: 10.1093/cid/cix497.
257. Sankar MJ, Natarajan CK, Das RR, et al. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. *J Perinatol* 2016; 36 Suppl 1: S1-S11. doi: 10.1038/jp.2016.27.
258. Australian Institute of Health and Welfare. Immunisation rates for children in 2016–17. Canberra: Australian Institute of Health and Welfare, 2018.
259. Ludvigsson JF, Winell H, Sandin S, et al. Maternal Influenza A(H1N1) Immunization During Pregnancy and Risk for Autism Spectrum Disorder in Offspring: A Cohort Study. *Ann Intern Med* 2020; 173: 597-604. doi: 10.7326/M20-0167.
260. Lash TL. *Applying Quantitative Bias Analysis to Epidemiologic Data / by Timothy L. Lash, Matthew P. Fox, Aliza K. Fink*. New York, NY: New York, NY : Springer New York, 2009.
261. VanderWeele TJ and Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017; 167: 268-274. 2017/07/12. doi: 10.7326/M16-2607.
262. Richmond RC, Al-Amin A, Smith GD, et al. Approaches for drawing causal inferences from epidemiological birth cohorts: a review. *Early Hum Dev* 2014; 90: 769-780. 2014/09/28. doi: 10.1016/j.earlhumdev.2014.08.023.
263. Downey F. Validation Study of the Western Australian Midwives Notification System: 2005 Birth Data. Perth, WA: Western Australia Department of Health, 2007.
264. Moore HC, Lehmann D, de Klerk N, et al. How Accurate Are International Classification of Diseases-10 Diagnosis Codes in Detecting Influenza and Pertussis Hospitalizations in Children? *J Pediatric Infect Dis Soc* 2014; 3: 255-260. doi: 10.1093/jpids/pit036.
265. Whitcomb BW and Naimi AI. Things Don't Always Go as Expected: The Example of Nondifferential Misclassification of Exposure—Bias and Error. *Am J Epidemiol* 2020; 189: 365-368. doi: 10.1093/aje/kwaa020.
266. Lim FJ, Blyth CC, Fathima P, et al. Record linkage study of the pathogen-specific burden of respiratory viruses in children. *Influenza Other Respir Viruses* 2017; 11: 502-510. doi: 10.1111/irv.12508.
267. Government of Western Australia: Department of Health. Immunisation education, 2021. https://ww2.health.wa.gov.au/Articles/F_I/Immunisation-education (accessed 18/10/2021).

Appendices

Appendix A. Acknowledgement of co-authored publications

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To whom it may concern,

We the undersigned are writing this letter to stipulate the role of Damien Foo in the preparation and submission of the following manuscript:

- **Foo, D. Y. P.**, Sarna, M. Pereira, G., Moore, H. C., Fell, D. B., & Regan, A. K. (2020). Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review. *Pediatrics, 146*(2), e20200375. doi:10.1542/peds.2020-0375

Task	Role of Co-author
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- **Foo, D. Y. P.**, Sarna, M. Pereira, G., Moore, H. C., & Regan, A. K. (2022). Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood. *Vaccine, 40*, 656-665. doi: 10.1016/j.vaccine.2021.11.084

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Appendix B. Study One (Chapter Five)

Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review

Damien Y.P. Foo, BSc (Hons),[a,b] Mohinder Sarna, PhD,[a,b] Gavin Pereira, PhD,[a,c,d] Hannah C. Moore, PhD,[b] Deshayne B. Fell, PhD,[e,f] Annette K. Regan, PhD[a,b,g]

abstract

CONTEXT: Vaccination during pregnancy is an effective strategy for preventing infant disease; however, little is known about early childhood health after maternal vaccination.

OBJECTIVES: To systematically review the literature on early childhood health associated with exposure to influenza vaccines in utero.

DATA SOURCES: We searched CINAHL Plus, Embase, Medline, Scopus, and Web of Science for relevant articles published from inception to July 24, 2019.

STUDY SELECTION: We included studies published in English reporting original data with measurement of in utero exposure to influenza vaccines and health outcomes among children <5 years of age.

DATA EXTRACTION: Two authors independently assessed eligibility and extracted data on study design, setting, population, vaccines, outcomes, and results.

RESULTS: The search yielded 3647 records, of which 9 studies met the inclusion criteria. Studies examined infectious, atopic, autoimmune, and neurodevelopmental outcomes, and all-cause morbidity and mortality. Authors of 2 studies reported an inverse association between pandemic influenza vaccination and upper respiratory tract infections, gastrointestinal infections, and all-cause hospitalizations; and authors of 2 studies reported modest increased association between several childhood disorders and pandemic or seasonal influenza vaccination, which, after adjusting for confounding and multiple comparisons, were not statistically significant.

LIMITATIONS: Given the small number of studies addressing similarly defined outcomes, meta-analyses were deemed not possible.

CONCLUSIONS: Results from the few studies in which researchers have examined outcomes in children older than 6 months of age did not identify an association between exposure to influenza vaccines in utero and adverse childhood health outcomes.

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Influenza is a major respiratory infection that can lead to severe illness and death at any age,[1] but high-risk populations such as pregnant women and infants <6 months of age have a greater risk of severe illness.[2,3] No vaccines are currently licensed for infants in this age group.[4–6] Because maternal antibodies cross the placenta during pregnancy,[7] influenza vaccines administered to pregnant women are an effective means of protecting both mothers and their infants from influenza infection.[8–10] Given these benefits, the 2012 World Health Organization position paper on influenza vaccines recommended pregnant women be considered the highest priority risk group for countries considering expansion of their seasonal influenza vaccination program.[6] Globally, >50% of countries have policies recommending influenza vaccines to pregnant women.[6,11–14]

Despite these widespread recommendations, vaccine uptake is poor in many countries,[15–22] with concerns around vaccine safety cited as the most common reason for vaccine hesitancy.[23] These concerns stand in contrast to the substantial evidence supporting the safety of administration of inactivated influenza vaccines (IIVs) during pregnancy on maternal, fetal, and early infant outcomes. The safety of influenza vaccination during pregnancy has been consistently highlighted in systematic reviews and meta-analyses.[24–26] These studies concluded that influenza vaccination during pregnancy was not associated with increased risk of congenital anomalies, stillbirth, preterm birth, fetal growth restriction, and/or low birth weight.[24–27] Although a recent review assessed influenza and other respiratory outcomes in early childhood, no study has comprehensively assessed longer-term child health outcomes in association with in utero exposure to IIV.[28]

METHODS

We conducted a systematic review of the literature related to IIV during pregnancy and childhood health outcomes, as guided by the minimum evidence-based set of items for reporting in systematic reviews outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews (CRD42014014384) before commencing the review.

Data Sources and Search Strategy

We searched CINAHL Plus, Embase, Medline, Scopus, and Web of Science databases for peer-reviewed literature from inception to July 24, 2019, using a combination of medical subject headings and keywords related to prenatal influenza vaccination and early childhood health outcomes (Supplemental Tables 6–10). Our search included experimental and observational studies, including cross-sectional, case-control, and cohort studies. As recommended,[30,31] we consulted with a medical librarian to develop our search strategy.

Study Selection

Eligible studies included those investigating any mother–child pair population, in which exposure to influenza vaccines in utero (pandemic or seasonal) was reported, an unexposed mother–child pair control group is present, and ≥1 health outcome in children aged 6 months to 5 years was investigated. We made the following exclusions: articles not published in peer-reviewed journals, articles published in languages other than English, studies not conducted in humans, reviews, editorials, commentaries, letters, case studies, and case series. First, two independent reviewers (D.Y.P.F. and M.S.) screened and reviewed the titles and abstracts of records retrieved during the search for inclusion criteria. Second, the reviewers screened and reviewed the full-text articles for eligibility in accordance with study inclusion and exclusion criteria. Studies deemed to meet the inclusion criteria by the two reviewers were included in the final review. A third reviewer (A.K.R.) resolved any conflicts between the two reviewers during each screening and review stage.

Data Extraction and Risk-of-Bias Assessment

We developed a standardized data collection form to extract information on study characteristics, including study design, geographic location, participant demographics, definition and ascertainment of exposure and outcomes (including type of influenza vaccine), effect sizes and confidence intervals (CIs), and confounding variables. Two reviewers (D.Y.P.F. and M.S.) independently extracted information from each of the included articles.

For observational studies, we used the Newcastle–Ottawa scale to assess risk of bias (Tables 1–3).[32] The Newcastle–Ottawa scale has a maximum score of 9, with a greater score indicating the lowest risk of bias. The scoring system is based on the following criteria: selection bias (maximum score: 4), comparability of study groups (maximum score: 2), and ascertainment of exposure for case-control studies or outcome for observational studies (maximum score: 3).[32] Observational studies were considered at low risk of bias if they scored ≥8 and moderate-high risk of bias if they scored <8.

For randomized controlled trials (RCTs), we used the Cochrane risk-of-bias tool to assess risk of bias.[31] The Cochrane risk-of-bias tool addressed 5 major domains: selection bias

TABLE 1 Results of Risk-of-Bias Assessment for Cohort Studies

Cohort Studies[a]	Overall Risk-of-Bias score	Risk of Bias[b]	Criteria							
			Selection				Comparability[c]	Outcome		
			Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Cases	Outcome of Interest Was Not Present at Start of Study	Comparability of the Design and Analysis for Cohorts	Assessment of Outcome	Sufficient Follow-up Duration	Adequacy of Follow-up of Cohorts
van Santen et al[33] (2013)	6 of 9	High	—	X	X	X	X	X	X	—
Ludvigsson et al[34] (2015)	8 of 9	Low	X	X	X	X	XX	X	X	—
van der Maas et al[35] (2016)	7 of 9	High	—	X	—	X	XX	X	X	X
Fell et al[36] (2016)	8 of 9	Low	X	X	X	X	XX	X	X	—
Zerbo et al[37] (2017)	7 of 9	High	—	X	X	X	XX	X	X	—
Hviid et al[38] (2017)	8 of 9	Low	X	X	X	X	XX	X	X	—
Walsh et al[39] (2019)	8 of 9	Low	X	X	X	X	XX	X	X	—

[a] Cohort studies were assessed using the Newcastle–Ottawa scale. Each X represents whether an individual criterion is satisfied. Each — represents whether an individual criterion is not satisfied.
[b] Low risk of bias: overall risk of bias score ≥8; high risk of bias: overall risk of bias score <8.
[c] All criteria receives a maximum score of 1 X except for comparability of study groups where an additional X may be allocated for the control of additional important confounders.[30]

(random sequence generation and allocation concealment), performance bias (blinding of participants and personnel and other potential threats to validity), detection bias (blinding of outcome assessment and other potential threats to validity), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting).[31] Consistent with the Cochrane risk-of-bias tool scoring, articles were classified as low risk of bias, some concerns of bias, or high risk of bias.[31] Two reviewers (D.Y.P.F. and M.S.) independently assessed the quality of case-control and cohort studies and RCTs using the Newcastle–Ottawa Scale[42] and Cochrane risk-of-bias tool,[43] respectively. Any conflicts between the two reviewers during the quality assessment process were resolved by a third reviewer (A.K.R.).

Data Synthesis and Analysis

We developed a narrative description of the characteristics and results of included studies. Where possible, results were provided by trimester of vaccination and type of vaccine. To generate pooled effect estimates for each outcome, a random effects meta-analysis was planned a priori, dependent on whether a sufficient number of studies were retrieved using commonly defined end-points ($n > 2$).

TABLE 2 Results of Risk-of-Bias Assessment for Case-Control Studies

Case-Control Studies[a]	Overall Risk-of-Bias Score	Risk of Bias[b]	Selection				Comparability[c]	Exposure		
			Representativeness of the Cases	Selection of the Controls	Adequacy of Case Definition	Definition of Controls	Comparability of the Design and Analysis for Cohorts	Ascertainment of Exposure	Comparability of Ascertainment of Exposure for Cohorts	Comparability of Nonresponse Rate for Cohorts
Benowitz et al[40] (2010)	7 of 9	High	X	—	X	X	X	X	X	X

[a] Case-control studies were assessed using the Newcastle–Ottawa scale. Each X represents whether an individual criterion is satisfied. Each — represents whether an individual criterion is not satisfied.
[b] Low risk of bias: overall risk of bias score ≥8; high risk of bias: overall risk of bias score <8.
[c] All criteria receives a maximum score of 1 X except for comparability of study groups where an additional X may be allocated for the control of additional important confounders.[30]

TABLE 3 Results of Risk-of-Bias Assessment for RCTs

RCTs[a]	Risk of Bias[b]	Selection Bias		Performance Bias	Attrition Bias	Detection Bias	Reporting Bias
		Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel and Other Potential Threats to Validity	Incomplete Outcome Data	Blinding of Outcome Assessment and Other Potential Threats to Validity	Selective Outcome Reporting
Bischoff et al[41] (2015)	High	Low	Low	Low	Low	High	High

[a] RCTs were assessed using the Cochrane risk-of-bias tool. Each risk of bias item receives a judgement on risk of bias.
[b] Risk of bias judgement given by algorithm.[51]

Role of the Funding Source

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RESULTS

Study Selection

We identified 3647 records, of which 3551 were excluded after initial title and abstract screening. We reviewed 96 full-text articles, of which 9 were deemed eligible for inclusion (Fig 1). Reasons for exclusions included no measurement of influenza vaccination during pregnancy (n = 4), no reported outcome measure of early childhood health (n = 33), not a comparative observational study or RCT (n = 44), or not published in English (n = 6).

Study Characteristics

Of the 9 included studies, methodology and study outcomes were highly diverse (Table 4). All of the studies originated from high-income countries in North America[33,36,37,39,40] (n = 5) or Europe[34,35,38,41] (n = 4), and study periods ranged between 1980 and 2012. Estimates from the same population were reported in 2 articles.[33,37] One study was an RCT,[41] 5 studies were retrospective cohort studies,[33,35,36,38,39] and 2 were prospective cohort studies[34,37]; 1 study used a case-control design.[40] Record linkage was used in most studies to measure prenatal influenza vaccination and early childhood health outcomes (n = 7). Studies ranged in sample size from 306 to 275 500 mother–infant pairs. With the exception of 1 study in which children 6 to 12 months of age were specifically examined,[40] the follow-up period of included studies began at birth and ranged from 1 to 15 years of age.

Exposure Assessment

Researchers in 6 studies investigated pandemic[34,36,38,39,41] influenza vaccines, and researchers in 3 investigated seasonal[33,37,40] influenza vaccines (Table 4). Of the 6 studies on 2009 monovalent pandemic influenza A virus subtype H1N1 (A/H1N1) vaccines, researchers of 4 studies exclusively investigated adjuvanted vaccines (MF59-adjuvant: n = 2[35,41]; AS03-adjuvant: n = 2[34,38]). Vaccination status during pregnancy was ascertained by self-report (n = 1),[35] random allocation (n = 1),[41] written or electronic health records (n = 3),[33,37,40] and registry information (n = 4).[34,36,38,39]

Outcome Assessment

Outcomes included infectious (n = 7), atopic (n = 2), autoimmune (n = 2), and neurodevelopmental (n = 3) conditions, neoplasms (n = 1), and all-cause morbidity (n = 2) and mortality (n = 2) (Table 5). Infections or infectious conditions included influenza, pneumonia, otitis media, sepsis, acute respiratory infections, gastrointestinal infections, viral infections, and all-cause infection-related primary care contact. Atopic conditions included asthma. Autoimmune conditions included celiac disease, ulcerative colitis, Crohn disease, juvenile arthritis, Sjögren syndrome, vasculitis, reactive arthropathy, idiopathic thrombocytopenic purpura, type-1 diabetes, Bell palsy, and Guillain-Barré syndrome. Neurodevelopmental conditions included epilepsy, autism spectrum disorder, intellectual disability, and sensory disorders. All-cause morbidity outcomes included 1-year all-cause hospitalization, 3-year all-cause hospitalization, 5-year all-cause hospitalization, urgent and inpatient health services used, and pediatric complex chronic conditions. International Classification of Diseases (ICD) clinical diagnosis codes were used in the majority of studies (n = 5) to identify outcomes.

Given the small number of studies in which similarly defined outcomes were addressed, meta-analyses were deemed not possible.

Confounder Assessment

Among the 9 included studies, several maternal and child characteristics were included as potential confounders (Supplemental

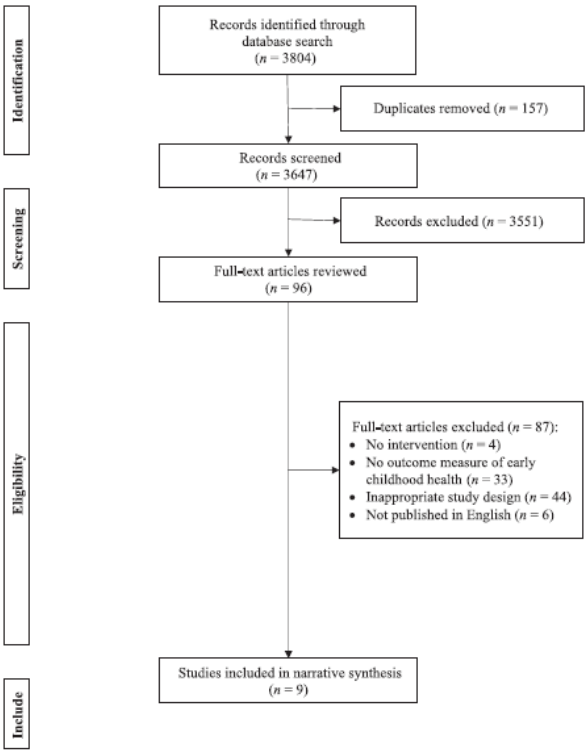

FIGURE 1
Flow diagram of study selection process for systematic review of the literature on early childhood health outcomes associated with in utero exposure to influenza vaccines.

Table 11). Maternal characteristics included maternal age (n = 6), ethnicity (n = 2), place of birth (n = 3), place of residence (n = 3), socioeconomic status and income (n = 4), education (n = 3), BMI (n = 2), parity (n = 5), medical comorbidities (n = 5), pregnancy complications (n = 3), multiple gestations and/or births (n = 3), smoking during pregnancy (n = 4), season of conception (n = 2), and gestational age (n = 2). Child characteristics mostly included sex (n = 4). Other characteristics, such as marital status, calendar year of conception, use of antenatal care, medication use, the child's ethnicity, and other birth outcomes, were less commonly controlled for as confounders (n = 1) (Supplemental Table 11). One study accounted for the potential influence of childhood influenza immunization by censoring at age at influenza vaccination.[33]

Infectious Conditions

In the 2 studies in which researchers examined influenza infection, infection status was ascertained either by a positive result by direct fluorescent antibody test (for laboratory-confirmed influenza)[40] or by using primary or secondary diagnostic codes for (1) influenza alone or (2) influenza and pneumonia.[36] Outcome measures were expressed as vaccine effectiveness (VE; calculated as [1 − odds ratio comparing the odds of infection in exposed versus unexposed] × 100%) or crude incidence rates for influenza infection among children exposed to IIV in utero versus unexposed. Benowitz et al[40] assessed laboratory-confirmed influenza and did not identify an association between IIV exposure in utero and VE in infants aged ≥6 months (unadjusted VE: −41.4%; 95% CI: −2257.4% to 91.5%) (Table 5). However, as noted by Benowitz et al,[40] because of the small sample size of infants aged ≥6 months, there was low statistical power to assess VE. In a study that followed infants ≤1 year of age, Fell et al[36] observed incidence rates of influenza that did not differ between children exposed to IIV in utero compared with unexposed children for each influenza time period examined, including the 2009 A/H1N1 pandemic season (incidence rate ratio: 0.61; 95% CI: 0.32 to 1.17) and the post-2009 A/H1N1 pandemic period (adjusted incidence rate ratio [aIRR]: 1.05; 95% CI: 0.81 to 1.37). Incidence rates for influenza and pneumonia were significantly higher among infants exposed to IIV in utero compared with unexposed infants in the post-2009 A/H1N1 pandemic period (aIRR: 1.17; 95% CI: 1.05 to 1.31). However, incidence rates for influenza and pneumonia did not differ significantly during the 2009 A/H1N1 pandemic season (aIRR: 1.04; 95% CI: 0.84 to 1.29) (Table 5).

Researchers of two studies assessed infection-related primary care contact (fever, symptoms of infection of ≥1 organ system, or prescriptions for infectious symptoms) by examining medical records given by primary care providers[35] and infections (common cold, pharyngitis, otitis,

TABLE 4 Characteristics of Studies Included in a Systematic Review of the Literature on Early Childhood Health Outcomes Associated With In Utero Exposure to Influenza Vaccines

Author(s) (y), Country	Study Design	Ascertainment of Exposure	Type of Vaccine	Study Period	Age of Follow-up	No. Participants		Trimester of Exposure, n (%)			Ascertainment of Outcome	Outcome(s)
						Exposed	Unexposed	First	Second	Third		
Pandemic influenza vaccine												
Bakken et al[41] (2013), Denmark	Matched RCT	Random allocation	MF59-adjuvanted pandemic A/H1N1 influenza vaccine	2009–2010	0–1 y	51	352	Not specified	Not specified	Not specified	Parent-reported daily diary cards reviewed by research doctor	Infections (common cold, laryngitis, otitis, pneumonia, fever, and gastrointestinal infection)
Ludvigsson et al[34] (2013), Sweden	Prospective cohort	Register	AS03-adjuvanted pandemic A/H1N1 influenza vaccine	October 2, 2009, to November 26, 2010	0–6.4 y	41 183	284 317	Not specified	Not specified	Not specified	Death register	Mortality
van der Maas et al[35] (2016), Netherlands	Retrospective cohort	Self-report	MF59-adjuvanted pandemic A/H1N1 influenza vaccine	November 2009 to December 2009	0–1 y	3357	669	—	1332 (100) across the second and third trimester		Register and medical records	Infection-related primary care contact (fever, symptoms of infection of ≥1 organ system, or prescriptions for infection treatment)
Fell et al[36] (2016), Canada	Retrospective cohort	Register	Pandemic A/H1N1 influenza vaccine[a]	November 2, 2009 to October 31, 2010	0–1 y	36 044	81 302	Not specified	Not specified	Not specified	Medical records	Influenza, combination of pneumonia and influenza
Nohr et al[38] (2017), Denmark	Retrospective cohort	Register	AS03-adjuvanted pandemic A/H1N1 influenza vaccine	November 2, 2009 to March 31, 2010	0–5 y	6511	35 048	349 (5.3)	3982 (84.3) across the second and third trimester		Register and medical records	Hospitalizations, infectious diseases, autoimmune diseases, neurologic diseases, behavioral disorders
Vellar et al[39] (2019), Canada	Retrospective cohort	Register	Pandemic A/H1N1 influenza vaccine[a]	November 2, 2009 to October 31, 2010	0–5 y	31 295	72 994	Not specified	Not specified	Not specified	Medical records	Infectious diseases, atopic diseases, neoplasms, sensory disorders, urgent and non-urgent health services use, complex chronic conditions, mortality
Seasonal influenza vaccine												
Benowitz et al[40] (2010), United States	Matched case-control	Medical records	IIV	October 1, 2000 to April 30, 2009	0–1 y	113[b]	193	—	8 (22.2)	28 (77.8)	Direct fluorescent antibody test	Laboratory-confirmed influenza
van Santen et al[33] (2013), United States	Retrospective cohort	Medical records	Trivalent IIV	June 2, 2002 to December 31, 2009	0–1 y	2416	7391	Not specified	Not specified	Not specified	Medical records	Acute otitis media, medically attended acute respiratory infections
Zerbo et al[37] (2017), United States	Prospective cohort	Medical records	IIV[c]	2000–2010	0–15 y	45 231	151 698	13 477 (29.8)	17 475 (38.6)	14 665 (32.4)	Medical records	Autism spectrum disorder

IIV, inactivated influenza vaccine; —, indicates no participants in the exposure group.
[a] Study did not distinguish between non-adjuvanted pandemic influenza vaccine (targeted at pregnant women) and AS03-adjuvanted pandemic influenza vaccine (targeted at the general population).
[b] Number of case participants (infants hospitalized for laboratory-confirmed influenza).
[c] Study included the 2009 A/H1N1 pandemic year; investigators did not distinguish between the seasonal trivalent influenza vaccine from the pandemic monovalent vaccine during this period of time.

TABLE 5 Adjusted Effect Estimates of Early Childhood Health Outcomes Associated With In Utero Exposure to Influenza Vaccine, by Pandemic and Seasonal Influenza Vaccines

Author(s) (y)	Outcome Assessed	Effect Estimate for Vaccination at Any Time During Pregnancy	Effect Estimate by Trimester		
			First Trimester	Second Trimester	Third Trimester
Pandemic influenza vaccine					
Bischoff et al[41] (2015)	All infections (common cold, pharyngitis, otitis, pneumonia, fever, gastrointestinal infection)	aIRR: 0.99 (0.84–1.18)	—	—	—
Ludvigsson et al[34] (2015)	Mortality	aHR: 0.97 (0.69–1.36) vs sibling control: aHR: 0.78 (0.52–1.19)[a]	aHR: 0.86 (0.51–1.47) versus sibling control: aHR: 0.47 (0.22–1.01)[a]	aHR: 1.10 (0.69–1.76) versus sibling control: aHR: 1.44 (0.74–2.78)[a]	aHR: 0.93 (0.54–1.60) versus sibling control: aHR: 0.65 (0.30–1.39)[a]
van der Maas et al[35] (2016)	Infection-related primary care contact	aIRR: 1.07 (0.91–1.28)	—	—	—
Fell et al[36] (2016)	Influenza, by season				
	2009 A/H1N1 pandemic season	IRR: 0.61 (0.32–1.17)	—	—	—
	Post 2009 A/H1N1 pandemic period	aIRR: 1.05 (0.81–1.37)	—	—	—
	Pre-2010–2011 period	aIRR: 1.08 (0.80–1.44)	—	—	—
	2010–2011 period	aIRR: 0.88 (0.76–1.02)	—	—	—
	Post-2010–2011 period	aIRR: 0.72 (0.50–1.04)	—	—	—
	Pre-2011–2012 period	—	—	—	—
	Influenza and pneumonia, by season				
	2009 A/H1N1 pandemic season	aIRR: 1.04 (0.84–1.29)	—	—	—
	Post 2009 A/H1N1 pandemic period	aIRR: 1.17 (1.05–1.31)	—	—	—
	Pre-2010–2011 period	aIRR: 1.07 (0.93–1.25)	—	—	—
	2010–2011 period	aIRR: 0.99 (0.92–1.07)	—	—	—
	Post-2010–2011 period	aIRR: 1.00 (0.85–1.17)	—	—	—
	Pre-2011–2012 period	aIRR: 0.81 (0.38–1.70)	—	—	—
Hviid et al[38] (2017)	1-y hospitalization		aHR: 1.10 (0.89–1.37); aRR: 1.15 (0.90–1.48)	aHR: 0.94 (0.89–0.99); aRR: 0.93 (0.87–0.99)	
	3-y hospitalization		aHR: 1.15 (0.97–1.37); aRR: 1.21 (0.98–1.50)	aHR: 0.95 (0.90–0.99); aRR: 0.96 (0.90–1.01)	
	5-y hospitalization		aHR: 1.13 (0.96–1.32); aRR: 1.17 (0.94–1.45)	aHR: 0.95 (0.91–0.99); aRR: 0.93 (0.87–0.99)	
	Upper respiratory tract infections	—	aRR: 1.08 (0.80–1.46)	aRR: 0.92 (0.85–0.99); aRR: 0.92 (0.81–1.03)[b]	
	Lower respiratory tract infections	—	aRR: 0.90 (0.63–1.28)	aRR: 0.92 (0.84–1.00)	
	Gastrointestinal infections		aRR:1.03 (0.68–1.55)	aRR: 0.84 (0.74–0.94); aRR: 0.84 (0.70–1.00)[b]	
	Meningitis	—	—	aRR: 1.17 (0.61–2.24)	
	Sepsis	—	—	aRR: 1.96 (1.26–3.05); aRR: 1.96 (0.98–3.91)[b]	
	Viral infections	—	aRR: 1.20 (0.82–1.73)	aRR: 0.91 (0.82–1.00)	
	Other infections	—	aRR: 1.71 (1.08–2.73); aRR: 1.71 (0.83–3.56)[b]	aRR: 0.92 (0.81–1.05)	
	Asthma	—	aRR: 1.50 (0.99–2.29)	aRR: 1.02 (0.89–1.16)	
	Celiac disease	—	—	aRR: 0.81 (0.31–2.12)	
	Crohn disease	—	—	aRR: 1.24 (0.31–11.90)	
	Ulcerative colitis	—	—	aRR: 2.48 (0.41–14.82)	
	Juvenile arthritis	—	—	aRR: 0.60 (0.23–1.54)	
	Sjögren syndrome		aRR: 1.15 (0.24–5.53)	aRR: 1.59 (1.04–2.44); aRR: 1.59 (0.82–3.11)[b]	
	Vasculitis	—	—	—	—
	Reactive arthropathy	—	aRR: 0.80 (0.09–6.88)	aRR: 1.40 (0.96–2.05)	
	Idiopathic thrombocytopenic purpura	—	—	aRR: 0.68 (0.15–3.05)	
	Idiopathic urticaria	—	—	aRR: 1.03 (0.38–2.78)	
	Type-1 diabetes	—	—	aRR: 0.80 (0.23–2.77)	
	Bell palsy	—	—	aRR: 1.24 (0.34–4.57)	
	Epilepsy	—	aRR: 1.01 (0.21–4.74)	aRR: 0.86 (0.58–1.27)	

TABLE 5 Continued

Author(s) (y)	Outcome Assessed	Effect Estimate for Vaccination at Any Time During Pregnancy	Effect Estimate by Trimester		
			First Trimester	Second Trimester	Third Trimester
	Guillain-Barré syndrome	—	—	—	
	Autism spectrum disorder	—	—	aRR: 1.22 (0.79–1.86)	
	Intellectual disability	—	—	aRR: 0.66 (0.28–1.56)	
Walsh et al[39] (2019)	Upper respiratory tract infections	aIRR: 1.01 (0.98–1.03)	—	—	—
	Lower respiratory tract infections	aIRR: 0.99 (0.95–1.03)	—	—	—
	Gastrointestinal infections	aIRR: 0.94 (0.91–0.98); aIRR: 0.94 (0.88–1.00)[b]	—	—	—
	Otitis media	aIRR: 1.03 (1.00–1.06)	—	—	—
	All infections	aIRR: 1.01 (0.98–1.03)	—	—	—
	Asthma	aHR: 1.05 (1.02–1.09); aHR: 1.05 (1.00–1.11)[b]	—	—	—
	Neoplasms	aHR: 1.12 (0.79–1.59)	—	—	—
	Sensory disorders	aHR: 0.94 (0.67–1.33)	—	—	—
	Urgent and inpatient health services used	aIRR: 0.99 (0.98–1.01)	—	—	—
	Pediatric complex chronic conditions	aRR: 0.98 (0.80–1.20)	—	—	—
	5-y mortality	aHR: 0.83 (0.64–1.08)	—	—	—
Seasonal influenza vaccine					
Benowitz et al[40] (2010)	Laboratory-confirmed influenza	VE: −41.4% (−2257.4% to 91.5%)	—	—	—
van Santen et al[33] (2013)	Acute otitis media	aVE: 47.9% (42.0% to 53.3%)	—	—	—
	Medically attended acute respiratory infections	aVE: 39.6% (31.6% to 46.7%)	—	—	—
Zerbo et al[37] (2017)	Autism spectrum disorder	aHR: 1.10 (1.00–1.21)	aHR: 1.20 (1.04–1.39)	aHR: 1.03 (0.90–1.19)	aHR: 1.03 (0.90–1.20)

aIRR, adjusted incidence rate ratio; aHR, adjusted hazard ratio; aRR, adjusted rate ratio; aVE, adjusted vaccine effectiveness; VE, unadjusted vaccine effectiveness; —, not applicable.
[a] Overall estimates are compared with unexposed children; an additional comparison with unexposed siblings also provided.
[b] Adjusted for multiplicity using Bonferroni correction.

pneumonia, and gastrointestinal infection) or fever by parent-reported daily diary cards reviewed by a research doctor.[41] Neither van der Maas et al[35] (aIRR: 1.07; 95% CI: 0.91 to 1.28) nor Bischoff et al[41] (aIRR: 0.99; 95% CI: 0.84 to 1.18) found a difference in incidence of infections between children of vaccinated and unvaccinated mothers in their studies (Table 5).

Studies in which upper respiratory tract infections, lower respiratory tract infections, and all-cause infections were examined found a statistically significant reduction in risk of upper respiratory tract infections (adjusted rate ratio [aRR]: 0.92; 95% CI: 0.85 to 0.99)[38] and all-cause infections (aRR: 1.71; 95% CI: 1.08 to 2.44)[38] but not lower respiratory tract infections (Table 5).[38,39] Hviid et al[38] observed an inverse association with upper respiratory tract infections and all-cause infections in children whose mothers were vaccinated with pandemic influenza vaccine in the second or third trimester and in the first trimester, respectively. However, after adjusting for multiplicity using a Bonferroni correction, these associations were no longer significant. Data from one of 2 studies[33,39] that investigated otitis media in infants ≤1 year of age reported a lower absolute adjusted VE (calculated as 1 − the ratio of the incidence of otitis media in exposed versus unexposed children) for children whose mothers received a pneumococcal conjugate vaccine while pregnant (37.6%; 95% CI: 23.1 to 49.4) than children whose mothers received a pneumococcal conjugate vaccine and trivalent IIV while pregnant (47.9%; 95% CI: 42.0 to 53.3), as compared with the children whose mothers received no vaccines during pregnancy.[33] The second

study, by Walsh et al,[39] followed offspring ≤5 years of age and found no difference in incidence rates between children exposed to IIV in utero and unexposed children (aIRR: 1.03; 95% CI: 1.00 to 1.06). Walsh et al[39] and Hviid et al[38] each observed a statistically significant reduction in the risk of gastrointestinal infections (adjusted hazard ratio [aHR]: 0.94; 95% CI: 0.91 to 0.98 and aRR: 0.84; 95% CI: 0.74 to 0.94, respectively). Hviid et al[38] observed this association in children whose mothers were vaccinated in either the second or third trimester but not in the first trimester. Second or third trimester prenatal influenza vaccination was also associated with a significant increase in risk of sepsis (aRR: 1.96; 95% CI: 1.26 to 3.05).[38] However, after taking multiple comparisons into account using Bonferroni-corrected CIs, associations for gastrointestinal infections and sepsis were not significant and could have been due to chance (Table 5).[38,39]

Atopic, Autoimmune, and Neurodevelopmental Conditions

In the 2 studies in which asthma was examined, asthma status was identified from a regional asthma database[39] or by using primary or secondary ICD diagnostic codes.[38,39] Walsh et al[39] reported a small, but significant, increase in asthma among children exposed to IIV in utero compared with unexposed children (aHR: 1.05; 95% CI: 1.02 to 1.09) (Table 5). However, results were no longer statistically significant after adjusting for multiplicity using Bonferroni correction (aHR: 1.05; 95% CI: 1.00 to 1.11).[39] Hviid et al[38] reported no significant difference in asthma for first trimester vaccination (aRR: 1.50; 95% CI: 0.99 to 2.29) or second or third trimester vaccination (aRR: 1.02; 95% CI: 0.89 to 1.16).

Estimates on rates of autism spectrum disorder were provided in 2 studies, of which 1 group evaluated pandemic influenza vaccine[39] and the other evaluated seasonal influenza vaccine.[37] For both studies, autism spectrum disorder was identified using ICD diagnostic codes. Zerbo et al[37] reported a slightly elevated risk of autism spectrum disorder after prenatal influenza vaccination in the first trimester (aHR: 1.20; 95% CI: 1.04 to 1.39) but not in the second or third trimester (Table 5). However, this association was no longer significant after adjusting for multiplicity using a Bonferroni correction ($P = .1$). Hviid et al[38] found no significant association between IIV exposure in utero and autism spectrum disorder. Additionally, Hviid et al[38] observed an increase of risk in Sjögren syndrome, only after prenatal influenza vaccination in the second or third trimester (aRR: 1.59; 95% CI: 1.04 to 2.44) but not in the first trimester. After adjusting for multiplicity using a Bonferroni correction, this association for Sjögren syndrome was no longer significant (aRR: 1.59; 95% CI: 0.82 to 3.11).

Across all studies, there were no other significant associations between prenatal influenza vaccination and celiac disease,[38] Crohn disease,[38] ulcerative colitis,[38] juvenile arthritis,[38] vasculitis,[38] reactive arthropathy,[38] idiopathic thrombocytopenic purpura,[38] idiopathic urticaria,[38] type-1 diabetes,[38] Bell palsy,[38] epilepsy,[38] Guillain-Barré syndrome,[38] intellectual disability,[38] neoplasms,[39] and sensory disorders (Table 5).[39]

All-Cause and Nonspecific Childhood Morbidity

All-cause childhood morbidity outcomes included all-cause hospitalizations and urgent care services; researchers in 1 study examined a nonspecific outcome, including a complex of pediatric chronic conditions.[39] Walsh et al[39] found no significant associations between IIV exposure in utero and urgent and inpatient health services used[39] or the nonspecific complex of chronic conditions (Table 5).[39] Hviid et al[38] observed a statistically significant reduction in the risk of 1-year all-cause hospitalization (aHR: 0.94; 95% CI: 0.89 to 0.99), 3-year all-cause hospitalization (aHR: 0.95; 95% CI: 0.90 to 0.99), and 5-year all-cause hospitalization (aHR: 0.95; 95% CI: 0.91 to 0.99) in children whose mothers were vaccinated in the second or third trimester.

Pediatric Mortality

Pediatric mortality was defined as death occurring from birth through 5 years of age[39] or from 7 days to 4.6 years of age.[34] No significant associations were identified in the 2 studies that examined mortality as an outcome. Although Walsh et al[39] reported a reduced association between pandemic influenza vaccine given during pregnancy and pediatric mortality (aHR: 0.83; 95% CI: 0.64 to 1.08), this result was not statistically significant (Table 5). Similarly, Ludvigsson et al[34] reported no significant association between pandemic influenza vaccine during pregnancy and pediatric mortality overall (aHR: 0.97; 95% CI: 0.69 to 1.36) or by trimester of vaccination (first trimester: aHR: 0.86; 95% CI: 0.51 to 1.47; second trimester: aHR: 1.10; 95% CI: 0.69 to 1.76; third trimester: aHR: 0.93; 95% CI: 0.54 to 1.60). Secondary analyses, using unvaccinated siblings as controls, also revealed no significant associations (overall: aHR: 0.78; 95% CI: 0.52 to 1.19; first trimester: aHR: 0.47; 95% CI: 0.22 to 1.01; second trimester: aHR: 1.44; 95% CI: 0.74 to 2.78; third trimester: aHR; 0.65; 95% CI: 0.30 to 1.39).[34]

Risk of Bias

For observational studies, risk of bias scores ranged from 6 to 8 on the Newcastle–Ottawa scale, of which 4 studies were deemed to be at low risk of bias,[34,36,38,39] and 4 studies were deemed to be at moderate-high risk

of bias (Tables 1–3).[33,35,37,40] Common causes of potential bias included inadequate representativeness of the exposed cohort (n = 3)[33,35,37] and inadequately described follow-up of exposed and nonexposed cohorts (n = 6). The 1 RCT included was deemed to be at high risk of bias because of the lack of blinding of outcome assessment (detection bias) and inadequate ascertainment of outcomes (reporting bias).[41]

DISCUSSION

Although there has been increasing interest in the potential impacts of IIV exposure in utero on later child health, we identified relatively few studies in which health outcomes through the age of 5 years have been evaluated. In this systematic review, we summarized results from 9 studies including information on over 750 000 children, 163 924 of whom were exposed to IIV in utero. Researchers in 2 studies suggested lower risk of upper respiratory tract infection, all-cause infections, all-cause hospitalization, and gastrointestinal infection associated with pandemic IIV exposure in utero. While the data from some studies suggested a potential increase in the risk of asthma, sepsis, and Sjögren syndrome after exposure to pandemic IIV in utero and an increased risk of autism spectrum disorder after exposure to seasonal IIV in utero, after adjusting for multiple comparisons using Bonferroni-corrected CIs, these associations were no longer statistically significant.

Narrative synthesis of these few studies indicates there is limited evidence evaluating health outcomes through the age of 5 years after exposure to IIV in utero, particularly for seasonal IIVs. Existing studies assessed a range of outcomes and the majority examined exposure to pandemic influenza vaccines. Only 3 studies on seasonal influenza vaccines in children were identified, and these were prone to bias; additional high-quality studies are warranted. Furthermore, given seasonal IIV is recommended in all trimesters of pregnancy and fetal development varies by gestational age, outcomes should be assessed according to gestational age at vaccination. Only 3 studies assessed outcomes by trimester of vaccination, of which 1 study combined second and third trimesters. The number of vaccinated individuals, particularly in the first trimester, was small and consequently limited the statistical power to detect differences between the children in the exposed and unexposed group. Differences in study quality, exposure ascertainment, vaccine type (ie, pandemic or seasonal, adjuvanted or nonadjuvanted, monovalent or trivalent), and study outcomes and outcome ascertainment, made it difficult to compare results across studies and precluded statistical pooling of results. These differences may have also influenced the reliability of findings. For example, diagnoses recorded in medical records and not using a validated standardized clinical assessment could lead to potential outcome misclassification.

Importantly, while the potential confounding influence of maternal age, parity, and pre-existing medical conditions was accounted for in most studies, the study by van Santen et al[33] was the only one that factored for receipt of childhood immunizations as a potential confounding variable by censoring children after receiving their own influenza vaccine.[33] No study factored for receipt of other recommended childhood vaccines. Given that receipt of vaccines during pregnancy may be predictive of childhood vaccination as well as other health behaviors,[44] it is possible that residual bias in the observational studies identified may have influenced findings, especially the observed protective associations. Future studies should aim to account for childhood immunization status as a potential confounding variable.

Finally, there was little geographic variation in the geographic location of studies identified. All included studies were conducted in high-income countries in North America or Europe, and thus these findings may not generalize to children in low and middle-income countries, whose population demographics and risk profiles differ markedly. Research on the safety of influenza vaccination during pregnancy from low and middle-income countries would be useful for guiding future vaccine policies and programs in these settings.

CONCLUSIONS

Maternal influenza vaccination is a growing public health tool for improving the health of mothers and their infants. Despite long-standing recommendations, maternal influenza immunization policies were not widely adopted until the 2009 influenza A/H1N1 pandemic, and, as identified as part of this review, the long-term health effects of in utero exposure of influenza vaccines in children >6 months of age are underinvestigated. We identified relatively few studies in which early childhood health outcomes were evaluated in children aged >6 months of age in maternally vaccinated and unvaccinated children, and the same outcomes were rarely measured in the few existing studies. This made formal meta-analyses impractical. Although our review indicates that exposure to IIV in utero is not associated with adverse health outcomes in childhood, additional epidemiological studies of early childhood health outcomes after maternal influenza vaccination are still needed to address this gap. Future well-

controlled research in which seasonal IIV administered in different trimesters and in different settings is considered is required to provide a stronger evidence-base for the long-term safety of maternal influenza vaccination. Notwithstanding the need for additional research in this area, the results of the studies to-date have not revealed any adverse effect of maternal influenza vaccination on childhood health outcomes during the first 5 years. These findings are reassuring and can help support health care providers and pregnant women in making decisions about influenza vaccination during pregnancy.

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ABBREVIATIONS

A/H1N1: influenza A virus subtype H1N1
aHR: adjusted hazard ratio
aIRR: adjusted incidence rate ratio
aRR: adjusted rate ratio
CI: confidence interval
IIV: inactivated influenza vaccine
ICD: International Classification of Diseases
RCT: randomized controlled trial
VE: vaccine effectiveness

Mr Foo led the development and registration of the original protocol, performed data collection, analysis, and interpretation of findings, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content; Dr Regan conceptualized and designed the study, contributed to the data collection and analysis and interpretation of data, and revised the manuscript critically for important intellectual content; Dr Sarna contributed to the development of the original protocol, contributed to data collection, analysis and interpretation of data, and revised the manuscript critically for important intellectual content; Drs Fell, Moore, and Pereira advised on the development of the original protocol, contributed to the interpretation of results, and revised the manuscript critically for important intellectual content; and all authors have approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work related to the accuracy or integrity of the research.

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REFERENCES

1. Zhou F, Trieu M-C, Davies R, Cox RJ. Improving influenza vaccines: challenges to effective implementation. *Curr Opin Immunol*. 2018;53:88–95
2. Blyth CC, Macartney KK, Hewagama S, et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). *Euro Surveill*. 2016;21(30):25–33
3. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants [published correction appears in *N Engl J Med*. 2009;360(6):648]. *N Engl J Med*. 2008;359(15):1555–1564
4. Macdonald N, Bortolussi R. Protecting young babies from influenza. *Paediatr Child Health*. 2009;14(9):612–617
5. Halasa NB, Gerber MA, Chen Q, Wright PF, Edwards KM. Safety and immunogenicity of trivalent inactivated influenza vaccine in infants. *J Infect Dis*. 2008;197(10):1448–1454
6. World Health Organization. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec*. 2012;87(47):461–476
7. Orije MRP, Maertens K, Corbière V, et al. The effect of maternal antibodies on the cellular immune response after infant vaccination: a review. *Vaccine*. 2020;38(1):20–28
8. Steinhoff MC, Omer SB, Roy E, et al. Influenza immunization in pregnancy–antibody responses in mothers and infants. *N Engl J Med*. 2010;362(17):1644–1646
9. Sperling RS, Engel SM, Wallenstein S, et al. Immunogenicity of trivalent inactivated influenza vaccination received during pregnancy or postpartum. *Obstet Gynecol*. 2012;119(3):631–639
10. Jackson LA, Patel SM, Swamy GK, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. *J Infect Dis*. 2011;204(6):854–863

11. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices-United States, 2018–19 influenza season. *MMWR Recomm Rep*. 2018; 67(3):1–20

12. Silverman N, Beigi R. ACOG committee opinion no. 732: influenza vaccination during pregnancy. *Obstet Gynecol*. 2018; 131(4):e109–e114

13. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. *Influenza Vaccination During Pregnancy (and in Women Planning Pregnancy)*. Melbourne, Australia: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2017

14. Macias AE, Precioso AR, Falsey AR; Global Influenza Initiative. The Global Influenza Initiative recommendations for the vaccination of pregnant women against seasonal influenza. *Influenza Other Respir Viruses*. 2015;9(suppl 1): 31–37

15. Regan AK, Mak DB, Hauck YL, Gibbs R, Tracey L, Effler PV. Trends in seasonal influenza vaccine uptake during pregnancy in Western Australia: implications for midwives. *Women Birth*. 2016;29(5):423–429

16. McCarthy EA, Pollock WE, Tapper L, Sommerville M, McDonald S. Increasing uptake of influenza vaccine by pregnant women post H1N1 pandemic: a longitudinal study in Melbourne, Australia, 2010 to 2014. *BMC Pregnancy Childbirth*. 2015;15(1):53

17. Liu N, Sprague AE, Yasseen AS III, et al. Vaccination patterns in pregnant women during the 2009 H1N1 influenza pandemic: a population-based study in Ontario, Canada. *Can J Public Health*. 2012;103(5):e353–e358

18. Fabry P, Gagneur A, Pasquier J-C. Determinants of A (H1N1) vaccination: cross-sectional study in a population of pregnant women in Quebec. *Vaccine*. 2011;29(9):1824–1829

19. Dabrera G, Zhao H, Andrews N, et al. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. *Euro Surveill*. 2014;19(45):20959

20. Groom HC, Henninger ML, Smith N, et al. Influenza vaccination during pregnancy: influenza seasons 2002–2012, vaccine safety datalink. *Am J Prev Med*. 2016; 50(4):480–488

21. Kennedy ED, Ahluwalia IB, Ding H, Lu P-J, Singleton JA, Bridges CB. Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. *Am J Obstet Gynecol*. 2012;207(suppl 3):S9–S16

22. Kahn KE, Black CL, Ding H, et al. Influenza and tdap vaccination coverage among pregnant women - United States, April 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67(38):1055–1059

23. Lane S, MacDonald NE, Marti M, Dumolard L. Vaccine hesitancy around the globe: analysis of three years of WHO/UNICEF Joint Reporting Form data—2015–2017. *Vaccine*. 2018;36(26): 3861–3867

24. Bratton KN, Wardle MT, Orenstein WA, Omer SB. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. *Clin Infect Dis*. 2015;60(5):e11–e19

25. Nunes MC, Aqil AR, Omer SB, Madhi SA. The effects of influenza vaccination during pregnancy on birth outcomes: a systematic review and meta-analysis. *Am J Perinatol*. 2016;33(11):1104–1114

26. Zhang C, Wang X, Liu D, Zhang L, Sun X. A systematic review and meta-analysis of fetal outcomes following the administration of influenza A/H1N1 vaccination during pregnancy. *Int J Gynaecol Obstet*. 2018;141(2):141–150

27. Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal influenza vaccination and risk for congenital malformations: a systematic review and meta-analysis. *Obstet Gynecol*. 2015; 126(5):1075–1084

28. Jarvis JR, Dorey RB, Warricker FDM, Alwan NA, Jones CE. The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: systematic review and meta-analysis. *Vaccine*. 2020;38(7):1601–1613

29. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264–269, W64

30. Desmeules R, Dorgan M, Campbell S. Acknowledging librarians' contributions to systematic review searching. *J Can Health Libr Assoc*. 2016;37(2)

31. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0*. London, United Kingdom: The Cochrane Collaboration; 2011

32. Wells G, Shea B, O'Connell J. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa, Canada: The Ottawa Hospital; 2014

33. van Santen KL, Bednarczyk RA, Adjaye-Gbewonyo D, Orenstein WA, Davis R, Omer SB. Effectiveness of pneumococcal conjugate vaccine in infants by maternal influenza vaccination status. *Pediatr Infect Dis J*. 2013;32(11):1180–1184

34. Ludvigsson JF, Ström P, Lundholm C, et al. Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design. *BMJ*. 2015;351:h5585

35. van der Maas N, Dijs-Elsinga J, Kemmeren J, van Lier A, Knol M, de Melker H. Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: results on pregnancy outcomes and infant's health: cross-sectional linkage study. *BJOG*. 2016; 123(5):709–717

36. Fell DB, Wilson K, Ducharme R, et al. Infant respiratory outcomes associated with prenatal exposure to maternal 2009 A/H1N1 influenza vaccination. *PLoS One*. 2016;11(8):e0160342

37. Zerbo O, Qian Y, Yoshida C, Fireman BH, Klein NP, Croen LA. Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. *JAMA Pediatr*. 2017; 171(1):e163609

38. Hviid A, Svanström H, Mølgaard-Nielsen D, Lambach P. Association between pandemic influenza A(H1N1) vaccination in pregnancy and early childhood morbidity in offspring. *JAMA Pediatr*. 2017;171(3):239–248

39. Walsh LK, Donelle J, Dodds L, et al. Health outcomes of young children

born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: retrospective cohort study. *BMJ*. 2019;366:l4151

40. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis*. 2010; 51(12):1355–1361
41. Bischoff AL, Følsgaard NV, Vissing NH, Birch S, Brix S, Bisgaard H. Airway mucosal immune-suppression in neonates of mothers receiving A(H1N1)pnd09 vaccination during pregnancy. *Pediatr Infect Dis J*. 2015; 34(1):84–90
42. Wells GA, Shea BOD, Peterson J, Welch V, Losos MTP. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 14, 2019
43. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev*. 2016;10(suppl 1): 29–31
44. Danchin MH, Costa-Pinto J, Attwell K, et al. Vaccine decision-making begins in pregnancy: correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. *Vaccine*. 2018;36(44): 6473–6479

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Appendix C. Study One (Chapter Five): Supplementary Material

Supplementary Table C-1. Summary of search strategy for systematic review of early childhood health outcomes associated with in utero exposure to influenza vaccines.

CINAHL Plus

#	Searches	Results
S1	MH "Influenza, Human"	5,372
S2	MH "Perinatal Care"	3,577
S3	MH "Prenatal Care"	14,635
S4	S2 OR S3	17,961
S5	S1 AND S4	38
S6	MH "Influenza Vaccine"	9,267
S7	MH "Immunization"	21,285
S8	MH "Immunization Programs"	4,979
S9	S7 OR S8	24,999
S10	S1 AND S9	911
S11	S6 OR S10	9,435
S12	MH "Pregnancy"	174,155
S13	"Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*"	258,747
S14	S2 OR S3 OR S12 OR S13	258,747
S15	S11 AND S14	660
S16	("Influenza Vaccin*" OR "Influenza Immuni*") N5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*")	389
S17	S5 OR S15 OR S16	733
S18	"Influenza"	26,492
S19	MH "Respiratory Tract Infections"	7,156
S20	MH "Adverse Drug Event"	10,967
S21	MH "Child Health"	13,757
S22	MH "Morbidity"	9,256
S23	MH "Prenatal Exposure Delayed Effects"	4,599
S24	MH "Treatment Outcomes"	296,343
S25	("Adverse") N2 ("Effect" OR "Event" OR "Outcome*")	47,347
S26	("Child") N2 ("Develop*" OR "Health*" OR "Outcome*")	60,175
S27	"Illness*"	187,907
S28	"Morbid*"	90,317
S29	("P#ediatric") N2 ("Develop*" OR "Health*" OR "Outcome*")	6,737

S30	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	663,443
S31	S17 AND S30	733

Ovid/EMBASE

#	Searches	Results
1	Human/ or "human".mp.	20,676,672
2	"Influenza A (H1N1)"/ or "Influenza A (H3N2)"/ or "Influenza A Virus (A/Puerto Rico/8/1934(H1N1))"/ or "Influenza A Virus (H1N1)"/ or "Influenza A Virus (H3N2)"/ or "Influenza B Virus (B/Jing Fang/76/98)"/ or 2009 H1N1 Influenza/ or Influenza A Virus/ or Influenza A/ or Influenza B Virus/ or Influenza B/ or Influenza C Virus/ or Influenza C/ or Influenza Virus/ or Influenza/ or Pandemic Influenza/ or Seasonal Influenza/ or Swine Influenza Virus/ or Swine Influenza/	89,716
3	1 and 2	71,459
4	Perinatal Care/	13,785
5	Prenatal Care/	36,510
6	4 or 5	49,442
7	3 and 6	199
8	Influenza Vaccination/	15,872
9	Influenza Vaccine/	34,693
10	Swine Influenza Vaccine/	193
11	Immunization/	90,286
12	Vaccination/	130,859
13	Vaccine/	55,971
14	11 or 12 or 13	238,363
15	3 and 14	12,028
16	8 or 9 or 10 or 15	43,472
17	Pregnancy/	569,797
18	Pregnant Woman/	71,374
19	Prenatal Exposure/	23,078
20	("Antenatal" or "Maternal" or "Perinatal" or "Prenatal" or "Pregnan*").mp.	1,185,990
21	4 or 5 or 17 or 18 or 19 or 20	1,185,990
22	16 and 21	2,770
23	(("Influenza Vaccin*" or "Influenza Immuni*") adj5 ("Antenatal" or "Maternal" or "Perinatal" or "Prenatal" or "Pregnan*")).mp.	844
24	7 or 22 or 23	2,852
25	"Influenza".mp.	136,831
26	Respiratory Tract Infection/	54,353
27	Child Health/	24,895

28	"Drug-Related Side Effects and Adverse Reactions"/	150,758
29	Morbidity/	325,757
30	Prenatal Exposure Delayed Effects/	21,784
31	Treatment Outcome/	819,949
32	("Adverse" adj2 ("Effect" or "Event" or "Outcome*")).mp.	225,273
33	("Child" adj2 ("Develop*" or "Health" or "Outcome*")).mp.	128,142
34	"Illness*".mp.	397,836
35	"Morbid*".mp.	687,679
36	("P?ediatric" adj2 ("Develop*" or "Health" or "Outcome*")).mp.	11,216
37	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	2,440,747
38	24 and 37	2,852

Ovid/MEDLINE

#	Searches	Results
1	Influenza, Human/	46,799
2	Perinatal Care/	4,221
3	Prenatal Care/	25,986
4	2 or 3	29,843
5	1 and 4	90
6	Influenza Vaccines/	21,740
7	Vaccination/	77,793
8	Immunization/	49,665
9	Immunization Programs/	10,225
10	7 or 8 or 9	130,208
11	1 and 10	7,299
12	6 or 11	23,400
13	Pregnancy/	848,360
14	("Antenatal" OR "Perinatal" OR "Prenatal" OR "Pregnan*").mp.	1,024,827
15	2 or 3 or 13 or 14	1,024,827
16	12 and 15	1,182
17	(("Influenza Vaccin*" or "Influenza Immuni*") adj5 ("Antenatal" or "Maternal" or "Perinatal" or "Prenatal" or "Pregnan*")).mp.	619
18	5 or 16 or 17	1,359
19	"Influenza".mp.	105,315
20	Respiratory Tract Infections/	37,093
21	Child Health/	2,079
22	"Drug-Related Side Effects and Adverse Reactions"/	30,223
23	Morbidity/	29,000
24	Prenatal Exposure Delayed Effects/	27,470
25	Treatment Outcome/	913,180

26	("Adverse" adj2 ("Effect*" or "Event*" or "Outcome*")).mp.	1,918,588
27	("Child" adj2 ("Develop*" or "Health*" or "Outcome*")).mp.	105,028
28	"Illness*".mp.	509,368
29	"Morbid*".mp.	410,639
30	("P?ediatric" adj2 ("Develop*" or "Health*" or "Outcome*")).mp.	10,893
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	3,486,115
32	18 and 31	1,359

Scopus

#	Searches	Results
#1	TITLE-ABS-KEY (("Influenza Vaccin*" OR "Influenza Immuni*") W/5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*"))	608
#2	(TITLE-ABS-KEY ("Influenza")) AND (TITLE-ABS-KEY (("Vaccin*" OR "Immuni*") W/5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*")))	1,353
#3	#1 OR #2	1,358
#4	TITLE-ABS-KEY (" Influenza ")	146,503
#5	TITLE-ABS-KEY (("Respiratory") W/3 ("Infectio*"))	125,314
#6	TITLE-ABS-KEY (("Adverse") W/2 ("Effect*" OR "Event*" OR "Outcome*"))	592,762
#7	TITLE-ABS-KEY (("Child") W/2 ("Develop*" OR "Health*" OR "Outcome*"))	299,720
#8	TITLE-ABS-KEY ("Illness*")	588,946
#9	TITLE-ABS-KEY ("Morbid*")	561,195
#10	TITLE-ABS-KEY (("P*ediatric") W/2 ("Develop*" OR "Health*" OR "Outcome*"))	17,243
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	2,138,104
#12	#3 AND #11	1,358
#13	#12 AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))	814
#14	#3 AND #11 (2019)	78
	24/07/2019	

Web of Science

#	Searches	Results
#1	(TS=(("Influenza Vaccin*" OR "Influenza Immuni?*") NEAR/5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*"))) OR (TI=(("Influenza Vaccin*" OR "Influenza Immuni?*") NEAR/5 ("Antenatal" OR "Maternal" OR	609

	"Perinatal" OR "Prenatal" OR "Pregnan*")))	
#2	(TS=((("Influenza")) AND (("Vaccin*" OR "Immuni?*") NEAR/5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*")))) OR (TI=((("Influenza")) AND (("Vaccin*" OR "Immuni?*") NEAR/5 ("Antenatal" OR "Maternal" OR "Perinatal" OR "Prenatal" OR "Pregnan*"))))	1,211
#3	#1 OR #2	1,213
#4	TS=("Influenza") OR TI=("Influenza")	103,277
#5	TS=(("Respiratory") NEAR/2 ("Infectio*")) OR TI=(("Respiratory") NEAR/2 ("Infectio*"))	47,155
#6	TS=(("Adverse") NEAR/2 ("Effect*" OR "Event*" OR "Outcome*")) OR TI=(("Adverse") NEAR/2 ("Effect*" OR "Event*" OR "Outcome*"))	380,035
#7	TS=(("Child") NEAR/2 ("Develop*" OR "Health*" OR "Outcome*")) OR TI=(("Child") NEAR/2 ("Develop*" OR "Health*" OR "Outcome*"))	54,909
#8	TS=("Illness*") OR TI=("Illness*")	277,212
#9	TS=("Morbid*") OR TI=("Morbid*")	382,883
#10	TS=(("P?ediatric") NEAR/2 ("Develop*" OR "Health*" OR "Outcome*")) OR TI=(("P?ediatric") NEAR/2 ("Develop*" OR "Health*" OR "Outcome*"))	2,332
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	1,168,998
#12	#3 AND #11	1,213

Supplementary Table C-2. Confounders included in analyses of early childhood health outcomes associated with in utero exposure to influenza vaccines.

	Maternal characteristics																			Child Characteristics			
First author (year)	Maternal age	Ethnicity	Place of birth	Place of residence	Socioeconomic status	Education	Marital status	Body mass index	Parity	Medical co-morbidities	Pregnancy complications	Multiple gestation/birth	Smoking during pregnancy	Season of conception	Calendar year of conception	Season of birth	Gestational age	Received antenatal care	Medication use	Calendar month/year of birth	Ethnicity	Small-for-gestational age birth	Sex
Pandemic influenza vaccine																							
Bischoff *et al.* (2015)									✓	✓						✓							
Ludvigsson *et al.* (2015)	✓		✓		✓			✓	✓				✓										✓
van der Maas *et al.* (2016)			✓			✓																✓	
Fell *et al.* (2016)	✓			✓	✓				✓	✓	✓	✓	✓				✓			✓			✓
Hviid *et al.* (2017)	✓		✓	✓	✓	✓	✓	✓	✓	✓			✓										
Walsh *et al.* (2019)	✓			✓	✓				✓	✓	✓	✓	✓	✓				✓	✓				
Seasonal influenza vaccine																							
Benowitz et al. (2010)																							
van Santen *et al.* (2013)	✓	✓										✓									✓		✓
Zerbo *et al.* (2017)	✓	✓				✓				✓	✓			✓	✓		✓						✓

Appendix D. Study Two (Chapter Six)

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Longitudinal, population-based cohort study of prenatal influenza vaccination and influenza infection in childhood

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ABSTRACT

Background: Influenza vaccination is recommended to protect mothers and their infants from influenza infection. Few studies have evaluated the health impacts of *in utero* exposure to influenza vaccine among children more than six months of age.

Methods: We used probabilistically linked administrative health records to establish a mother–child cohort to evaluate the risk of influenza and acute respiratory infections associated with maternal influenza vaccination. Outcomes were laboratory-confirmed influenza (LCI) and hospitalization for influenza or acute respiratory infection (ARI). Adjusted hazard ratios (aHRs) accounted for child's Aboriginal status and were weighted by the inverse-probability of treatment.

Results: 14,396 (11.5%) children were born to vaccinated mothers. Maternally vaccinated infants aged < 6 months had lower risk of LCI (aHR: 0.33; 95% CI: 0.13, 0.85), influenza-associated hospitalization (aHR: 0.39; 95% CI: 0.16, 0.94) and ARI-associated hospitalization (aHR: 0.85; 95% CI: 0.77, 0.94) compared to maternally unvaccinated infants. With the exception of an increased risk of LCI among children aged 6 months to < 2 years old following first trimester vaccination (aHR: 2.28; 95% CI: 1.41, 3.69), there were no other differences in the risk of LCI, influenza-associated hospitalization or ARI-associated hospitalization among children aged > 6 months.

Conclusion: Study results show that maternal influenza vaccination is effective in preventing influenza in the first six months and had no impact on respiratory infections after two years of age.

1. Introduction

Influenza causes serious morbidity and mortality through seasonal epidemics each year, particularly in children under the age of five years [1,2]. Although the best preventative tool for influenza is seasonal influenza vaccination [3], there are currently no influenza vaccines licensed for use for infants aged < 6 months [2]. Since maternal antibodies cross the placenta during pregnancy [4], prenatal administration of seasonal inactivated influenza vaccine (IIV) is recommended for pregnant women in many countries, including Australia, at any stage of pregnancy to protect both mothers and their newborns from influenza illness during their first few months of life [2,5].

Several studies have found that maternal influenza vaccination is effective in reducing the risk of laboratory-confirmed influenza (LCI) illness and acute respiratory infections (ARIs) in young infants [6,7]. A systematic review and meta-analysis of four randomized controlled trials and five observational studies reported a lower risk of LCI infection by 48% and lower risk of LCI-associated hospitalizations by 72% among children aged less than six months following maternal influenza vaccination [6]. However, few studies have evaluated the risk of LCI infection beyond six months of age among maternally vaccinated offspring [8]. Maternally-acquired antibodies have been known to "blunt" or dampen primary immune responses to infection or vaccination [9,10]. Although seven studies identified no difference in the risk of acute respiratory infections through five years of age [8], no study has evaluated the risk of LCI after 12 months of age [8].

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0264-410X/

The aim of the present study was to measure the association between *in utero* exposure to seasonal IIV and the occurrence of ARIs, including LCI, from birth to five years of age.

2. Methods

2.1. Study setting

Western Australia (WA) has a resident population of approximately 2.6 million people [11], with approximately 33,000 births in WA each year [12]. In Australia, seasonal IIV during pregnancy has been recommended by the Australian Technical Advisory Group on Immunisation since March 2000 and funded under the National Immunisation Program since January 2010 [5,13]. Influenza virus circulation tends to peak during the winter months (June-August), with less distinct seasonality in the northern areas of the state; seasonal influenza vaccines are typically available in April of each year [14].

2.2. Study design, population, and data sources

We conducted a retrospective, population-based cohort study. The cohort included all singleton, live-born children identified from birth registrations between 1 April 2012 and 1 July 2016 and their mothers (Fig. 1). These mother-infant pairs were probabilistically linked with other population-based administrative health datasets using best practice protocols through the WA Data Linkage Branch [15], including the Midwives Notification System (MNS) [16], WA Antenatal Vaccination Database (WAAVD) [17], WA Notifiable Infectious Diseases Database (WANIDD) [18], Hospital Morbidity Data Collection (HMDC) [19], and death registrations. This study and a waiver of consent was approved by the WA Department of Health (RA#2016.56) and the Curtin University Human Research Ethics Committee (RA#20217–0808).

The MNS is a legally-mandated perinatal data collection of all births ≥ 20 weeks gestation or birthweight of ≥ 400 g (where gestational age is unknown). The MNS includes maternal demographics and health information, obstetric history, date of delivery, gestational age, and birthweight. The WAAVD is a state-wide database, managed by the WA Department of Health, and includes the date of vaccination, vaccine brand and batch number, and the estimated gestation at which vaccinations were administered as reported by their healthcare provider.

WANIDD is a legally-mandated database of notifiable infectious diseases reported to the WA Department of Health. In Australia, LCI is a notifiable disease and WANIDD includes information on the date of specimen collection, laboratory method of confirmation, and virus type/subtype. The HMDC summarizes all episodes of care provided in the state's public and private hospitals. Information details the date of admission and separation, up to 21 diagnosis codes (classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM] codes) [19]. Death registrations include the date and cause of all registered deaths in the state.

2.3. Exposure measurement

Children whose mothers had a record of receipt of prenatal seasonal IIV were considered 'maternally vaccinated'. We estimated the gestational age at vaccination as the number of completed weeks from estimated date of conception to date of vaccination. Trimesters were categorized as: first trimester (0 to ≤ 13 weeks gestation), second trimester (14 to ≤ 27 weeks gestation), and third trimester (≥ 28 weeks gestation). Children of mothers with no vaccination record were considered 'maternally unvaccinated'. Children whose mothers received an influenza vaccine < 2 weeks prior to birth were considered to have 'indeterminate' vaccination status and were excluded from analysis.

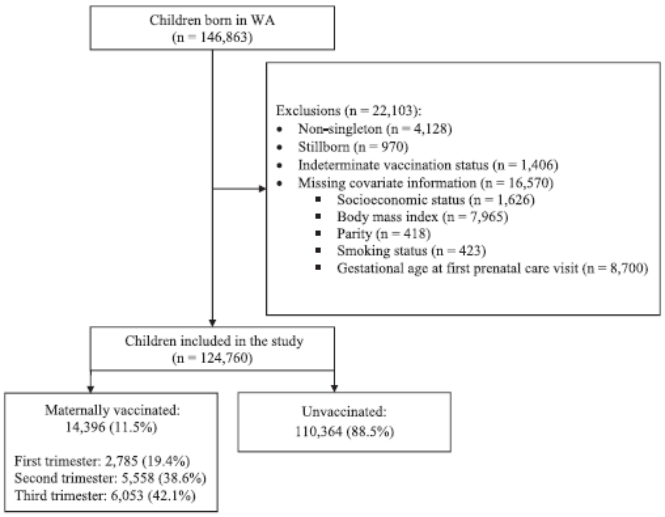

Fig. 1. Flow diagram of study participants included in the cohort.

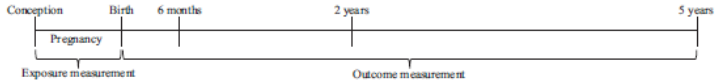

Fig. 2. Timing of exposure measurement and outcome measurement. Exposure: maternal influenza vaccination; outcome: laboratory-confirmed influenza, influenza-associated hospitalization, acute respiratory infection-associated hospitalization, all-cause injury-associated hospitalization, or skin infection-associated hospitalization.

2.4. Outcome measurement

We assessed three primary outcomes: 1) LCI, as reported to WANIDD, 2) influenza-associated hospitalizations, and 3) ARI-associated hospitalizations. We defined influenza-associated hospitalizations and ARI-associated hospitalizations as a hospital admission with a diagnosis code for influenza or an ARI, respectively (Supplemental Table 1). Follow-up data were available up to July 2017. To assess for possible bias in the study results, we included two negative control conditions: 1) all-cause injuries, and 2) skin and soft tissue infections (hereafter referred to as skin infections), using hospital diagnosis codes (Supplemental Table 1). This bias assessment was conducted to evaluate non-causal associations between prenatal exposure to seasonal IIV and the outcomes [20].

2.5. Covariate measurement

Maternal covariates included age at the time of her child's birth ($\leq$ 19, 20–24, 25–29, 30–34 and $\geq$ 35 years), Aboriginal status (Aboriginal, non-Aboriginal), socioeconomic status (quintiles between 1 (most disadvantaged) and 5 (least disadvantaged)), body mass index (BMI), parity (primiparous, one prior birth, $\geq$ 2 prior births), pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking during pregnancy, and gestational age at the first prenatal care visit. Child covariates included Aboriginal status, and season and year of birth. Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage, an area-based measure of relative access to resources for households within the same census collection district [21]. Preterm birth was categorized as: moderate to late preterm (32 to < 37 weeks gestation), very preterm (28 to < 32 weeks gestation), and extremely preterm (< 28 weeks gestation) birth. Small-for-gestational age birth was defined as birthweight < 10th percentile according to Australian national birthweight percentiles by sex and gestational age [22]. All covariates were selected *a priori* because they are known indicators of maternal influenza vaccination [23–28].

2.6. Statistical analyses

Descriptive statistics were calculated to compare demographic and health characteristics between vaccinated and unvaccinated mothers and their children. The odds of vaccination were estimated using univariate logistic regression models. To control for baseline probability of vaccination, we estimated inverse-probability of treatment weights using predicted probabilities derived from a multivariate logistic regression model including all maternal covariates. Standardized mean differences were calculated to assess the balance of maternal covariates between maternally vaccinated and unvaccinated children. Weighted Cox proportional hazard regression models were then used to estimate the hazard ratios (HRs) of study outcomes, comparing maternally vaccinated and unvaccinated children. Adjusted models additionally controlled for the child's Aboriginal status.

Time-at-risk commenced from birth and ended at the earliest of: a) the date the child reached five years of age, b) the last date of available data, c) the date the child died, or d) the date of event (Fig. 2). Children were able to contribute more than one event of interest. Unique episodes of care were considered those with $\geq$ 2 weeks between the date of separation and subsequent admission. A random effect term was incorporated in the model to account for multiple observations within individuals (i.e. more than one event per child). Sub-group analyses compared the risk of study outcomes by trimester of vaccination and specific age groups (< 6 months, 6 months to < 2 years, 2 to < 5 years, 6 months to < 5 years). To assess the potential impact of right truncation and exposure to differential exposure to influenza seasons, we performed a sensitivity analysis restricting to children born between 1 April 2012 and 30 September 2012 which coincides with the first seasonal influenza vaccine availability during the cohort period, fixes the child's age at each influenza season and allows for up to five years of follow-up. Additional sensitivity analyses included similar analyses with LCI restricted to children aged 6 to < 12 months and 1 to < 2 years as the time period where infant immunization would be least common [29]. All analyses were performed in STATA version 15.1 (StataCorp LLC, College Station, Texas, U.S.). Description of the detectable difference of risk of outcome measures between maternally vaccinated and unvaccinated children can be found in Supplemental Table 2.

3. Results

A total of 146,864 births were identified in WA during the study period. Of these, 22,103 (15.0%) records were excluded because the child was a non-singleton (n = 4,128), stillborn (n = 970), had missing covariate information (n = 16,570), or indeterminate vaccination status (n = 1,406). The final cohort included 124,760 singleton, live-born children from 106,206 mothers (Fig. 1). Maternal characteristics were balanced between maternally vaccinated and unvaccinated children (Table 1; Supplemental Fig. 1).

3.1. Maternal influenza vaccination

Of the 124,760 children, 14,396 (11.5%) were maternally vaccinated; 2,785 (19.4%) exposed during the first trimester, 5,558 (38.6%) during the second trimester, and 6,053 (42.1%) during the third trimester. The majority of mothers received influenza vaccine between March and July (n = 12,537; 87.1%). Vaccination was more common among primiparous women, women with pre-existing medical conditions and pregnancy complications, and non-smokers (Table 1). Women of the lowest socioeconomic status (odds ratio [OR]: 0.93; 95% confidence interval [CI]: 0.88–0.98) and mothers of preterm infants had lower odds of vaccination compared to term infants (OR: 0.91; 95% CI: 0.85, 0.98), and women who birthed during winter had the highest odds of being vaccinated as compared to summer (OR: 2.60; 95% CI: 2.46, 2.74).

3.2. Laboratory-confirmed influenza

There were 862 cases of LCI among 852 children aged < 5 years; 670 (77.7%) cases were influenza A virus (sub-type A/H1N1: 252

Table 1
Odds of vaccination by maternal and child characteristics of children born in Western Australia between 1 April 2012 and 1 July 2016 included in the study cohort.

Characteristic	Maternally unvaccinated (N = 110,364) n (%)	Maternally vaccinated (N = 14,396) n (%)	Unadjusted OR (95% CI)
Maternal characteristics			
Age (years):			
≤ 19	3,369 (3.1)	449 (3.1)	**1.13 (1.01–1.26)**
20–24	14,828 (13.4)	1,747 (12.1)	Reference
25–29	31,459 (28.5)	3,978 (27.6)	**1.07 (1.01–1.14)**
30–34	37,706 (34.2)	5,151 (35.8)	**1.16 (1.09–1.23)**
≥ 35	23,002 (20.8)	3,071 (21.3)	**1.13 (1.06–1.21)**
Aboriginal status:			
Aboriginal	5,296 (4.8)	717 (5.0)	1.04 (0.96–1.13)
Non-Aboriginal	105,068 (95.2)	13,679 (95.0)	Reference
Socioeconomic status:[a]			
Quintile 1 (most disadvantaged)	21,181 (19.2)	2,618 (18.2)	**0.93 (0.88–0.98)**
Quintile 2	22,674 (20.5)	3,019 (21.0)	1.00 (0.94–1.05)
Quintile 3	23,256 (21.1)	2,972 (20.6)	0.96 (0.91–1.01)
Quintile 4	22,217 (20.1)	2,979 (20.7)	1.00 (0.95–1.06)
Quintile 5 (least disadvantaged)	21,036 (19.1)	2,808 (19.5)	Reference
Body mass index:			
< 18.5 (underweight)	3,532 (3.2)	450 (3.1)	0.97 (0.87–1.07)
18.5 to < 25 (normal)	54,032 (49.0)	7,114 (49.4)	Reference
25 to < 30 (overweight)	30,720 (27.8)	3,875 (26.9)	0.96 (0.92–1.00)
≥ 30 (obese)	22,080 (20.0)	2,957 (20.5)	1.02 (0.97–1.06)
Parity:			
Primiparous	47,824 (43.3)	6,764 (47.0)	Reference
1 prior birth	38,216 (34.6)	4,958 (34.4)	**0.92 (0.88–0.95)**
≥ 2 prior births	24,324 (22.0)	2,674 (18.6)	**0.78 (0.74–0.81)**
Pre-existing medical conditions:			
Asthma	11,523 (10.4)	1,596 (11.1)	**1.07 (1.01–1.13)**
Essential hypertension	1,417 (1.3)	261 (1.8)	**1.42 (1.24–1.62)**
Pre-existing diabetes mellitus	916 (0.8)	191 (1.3)	**1.61 (1.37–1.88)**
Pregnancy complications:			
Gestational diabetes	11,310 (10.3)	1,688 (11.7)	**1.16 (1.10–1.23)**
Gestational hypertension	5,112 (4.6)	777 (5.4)	**1.17 (1.09–1.27)**
Pre-eclampsia	3,597 (3.3)	543 (3.8)	**1.16 (1.06–1.28)**
Smoked during pregnancy	10,540 (9.6)	1,269 (8.8)	**0.92 (0.86–0.97)**
Trimester of first prenatal care visit:			
First trimester	72,857 (66.0)	*	Reference
Second trimester	32,380 (29.3)	*	**0.82 (0.79–0.85)**
Third trimester	5,053 (4.6)	*	**0.54 (0.49–0.60)**
No prenatal care	74 (0.1)	<5	0.38 (0.14–1.05)
Year of birth:			
2012	19,930 (18.1)	1,304 (9.1)	Reference
2013	25,894 (23.5)	2,909 (20.2)	**1.72 (1.60–1.84)**
2014	26,345 (23.9)	3,205 (22.3)	**1.86 (1.74–1.99)**
2015	24,726 (22.4)	5,148 (35.8)	**3.18 (2.99–3.39)**
2016	13,469 (12.2)	1,830 (12.7)	**2.08 (1.93–2.24)**
Season of birth:			
Summer (Dec-Feb)	27,325 (24.8)	2,186 (15.2)	Reference
Autumn (Mar-May)	31,716 (28.7)	2,291 (15.9)	**0.90 (0.85–0.96)**
Winter (Jun-Aug)	26,062 (23.6)	5,413 (37.6)	**2.60 (2.46–2.74)**
Spring (Sep-Nov)	25,261 (22.9)	4,506 (31.3)	**2.23 (2.11–2.35)**
Child characteristics			
Sex:[b]			
Male	56,822 (51.5)	7,347 (51.0)	Reference
Female	53,539 (48.5)	7,049 (49.0)	1.02 (0.98–1.05)
Aboriginal status:			
Aboriginal	5,779 (5.2)	787 (5.5)	1.05 (0.97–1.13)
Non-Aboriginal	104,585 (94.8)	13,609 (94.5)	Reference
Birth outcomes:			
Preterm birth	7,390 (6.7)	887 (6.2)	**0.91 (0.85–0.98)**
Moderate-to-late preterm	6,587 (6.0)	819 (5.7)	0.95 (0.88–1.02)
Very preterm	520 (0.5)	52 (0.4)	0.76 (0.57–1.01)
Extremely preterm	283 (0.3)	16 (0.1)	**0.43 (0.26–0.71)**
Small-for-gestational age[c]	9,005 (8.2)	1,191 (8.3)	1.02 (0.95–1.08)

Abbreviations: OR, odds ratio; CI, confidence interval.
* In accordance with privacy and confidentiality guidelines by the DLB, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.
[a] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics [21].
[b] The sex of < 5 maternally unvaccinated children was unknown.
[c] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age, 1998–2007 [22].

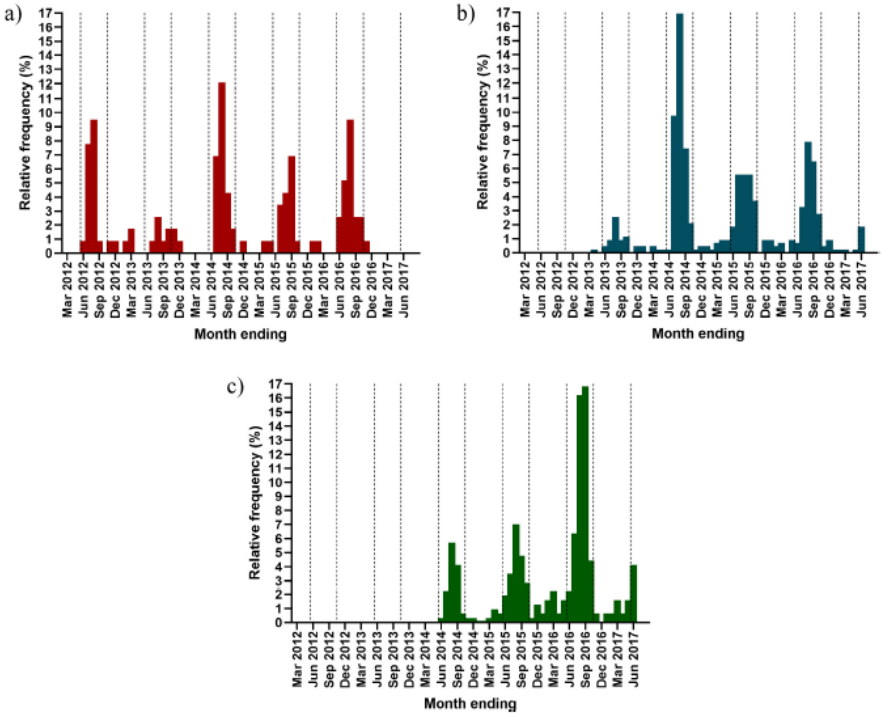

Fig. 3. Monthly rate of laboratory-confirmed influenza notifications, by age sub-group and month/year: a) children aged 0 to < 6 months, b) children aged 6 months to < 2 years, or c) children aged 2 to < 5 years–Western Australia, 1 April 2012–1 July 2017. Note: dashed lines indicate influenza seasons (Jun-Oct).

(29.2%); sub-type A/H3N2: 267 (31.0%); A/unsubtyped: 151 (17.5%)) and 192 (22.3%) were influenza B virus. One hundred and sixteen cases (13.5%) occurred in the first six months of life, 431 (50.0%) between 6 months and 2 years, and 315 (36.5%) between 2 and 5 years (Fig. 3). Two hundred and forty-three cases (28.2%) occurred among children born in 2012, 264 (30.6%) in 2013, 203 (23.5%) in 2014, 114 (13.2%) in 2015, and 38 (4.4%) in 2016.

We observed no difference in the risk of LCI between maternally vaccinated and maternally unvaccinated children from birth to 5 years of age (aHR: 1.10; 95% CI: 0.88, 1.38) (Table 2). Among infants aged < 6 months, we observed a lower risk of LCI associated with maternal influenza vaccination (aHR: 0.32; 95% CI: 0.12, 0.84) (Table 2). There were insufficient numbers to generate estimates by trimester of vaccination.

Among children aged 6 months to < 2 years, there was no difference in the risk of LCI between maternally vaccinated and maternally unvaccinated children (aHR: 1.33; 95% CI: 1.00, 1.76). However, an increased risk was observed among children of mothers vaccinated during the first trimester (aHR: 2.28; 95% CI: 1.41, 3.69). No associations were observed following maternal vaccination in later trimesters (Table 2). Sensitivity analyses restricting to children aged 6 to < 12 months (aHR: 2.70; 95% CI: 1.40, 5.98) and 1 to < 2 years (aHR: 2.00; 95% CI: 1.05, 3.80) similarly identified a higher risk of LCI following maternal vaccination during the first trimester (Supplemental Table 3). Among children aged 2 to < 5 years, no association was observed with maternal influenza vaccination (aHR: 1.14; 95% CI: 0.76, 1.71) (Table 2).

3.3. Influenza-associated hospitalization

A total of 360 influenza-associated hospitalizations were identified in 352 children aged < 5 years, of which 243 (67.5%) were associated with a LCI notification record. Similar to LCI, we observed no association between influenza-associated hospitalization and maternal influenza vaccination among children from birth to age 5 years (aHR: 0.91; 95% CI: 0.62, 1.33) (Table 3). Maternally vaccinated infants aged < 6 months had a lower risk of influenza-associated hospitalization compared to maternally unvaccinated infants (aHR: 0.38; 95% CI: 0.16, 0.91) (Table 3).

Among children aged 6 months to < 2 years and 2 to < 5 years, there was no difference in the risk of influenza-associated hospitalization between maternally vaccinated and maternally unvaccinated children (aHR: 1.09; 95% CI: 0.67, 1.78 and aHR: 1.40; 95% CI: 0.65, 3.01, respectively) (Table 3).

Table 2
Risk of laboratory-confirmed influenza infection associated with prenatal exposure to seasonal inactivated influenza vaccine among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	759 (0.7)	93 (0.6)	28 (1.0)	34 (0.6)	31 (0.5)
Cases, n (%)	768 (0.7)	94 (0.7)	29 (1.0)	34 (0.6)	31 (0.5)
Unweighted HR (95% CI)	1 [Reference]	1.08 (0.87–1.35)	**1.71 (1.17–2.51)**	0.96 (0.68–1.35)	0.91 (0.63–1.30)
Weighted aHR (95% CI)[a]	1 [Reference]	1.10 (0.88–1.39)	**1.80 (1.21–2.68)**	0.97 (0.67–1.39)	0.91 (0.62–1.33)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	111 (0.1)	5 (0)	<5	<5	<5
Cases, n (%)	111 (0.1)	5 (0)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	**0.35 (0.14–0.85)**	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	**0.32 (0.12–0.84)**	-	-	-
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	368 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Cases, n (%)	370 (0.3)	61 (0.4)	19 (0.7)	23 (0.4)	19 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.31 (1.00–1.72)	**2.13 (1.34–3.37)**	1.23 (0.81–1.88)	1.00 (0.63–1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	1.33 (1.00–1.76)	**2.28 (1.41–3.69)**	1.20 (0.78–1.86)	1.00 (0.61–1.64)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	284 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Cases, n (%)	287 (0.3)	28 (0.3)	8 (0.4)	11 (0.3)	9 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.09 (0.74–1.60)	1.54 (0.76–3.11)	0.97 (0.53–1.78)	0.98 (0.51–1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.14 (0.76–1.71)	1.52 (0.72–3.17)	1.05 (0.55–1.99)	1.04 (0.52–2.07)
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	648 (0.6)	88 (0.6)	26 (0.9)	34 (0.6)	28 (0.5)
Cases, n (%)	657 (0.6)	89 (0.6)	27 (1.0)	34 (0.6)	28 (0.5)
Unweighted HR (95% CI)	1 [Reference]	1.23 (0.98–1.54)	**1.91 (1.29–2.84)**	1.13 (0.80–1.60)	1.00 (0.68–1.46)
Weighted aHR (95% CI)[a]	1 [Reference]	1.24 (0.98–1.57)	**1.96 (1.29–2.97)**	1.13 (0.79–1.63)	1.01 (0.68–1.51)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; –, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Laboratory-confirmed influenza cases obtained from notification records reported to WANIDD.
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

3.4. Acute respiratory infection-associated hospitalization

A total of 18,643 ARI-associated hospitalizations were identified in 13,638 children < 5 years of age, 5,394 in children aged < 6 months, 9,776 in children aged 6 months to < 2 years, and 3,495 in children aged 2 to < 5 years. The distribution of ARIs is presented in Supplemental Table 1.

There was no association between ARI-associated hospitalization and maternal influenza vaccination among children from birth to 5 years of age (aHR: 0.94; 95% CI: 0.88, 1.01) (Table 4). Maternally vaccinated infants aged < 6 months had a lower risk of an ARI-associated hospitalization compared to maternally unvaccinated infants (aHR: 0.85; 95% CI: 0.77, 0.94); maternal vaccination during the first and second trimester were associated with a lower risk of ARI-associated hospitalization (aHR: 0.67; 95% CI: 0.50, 0.88 and aHR: 0.79; 95% CI: 0.67, 0.93, respectively). This was not observed for maternal vaccination during the third trimester (aHR: 1.00; 95% CI: 0.87, 1.14). We observed no associations between maternal influenza vaccination and ARI-associated hospitalizations in other age groups (Table 4).

3.5. Bias assessment

There were 4,162 hospitalizations for all-cause injuries in 3,975 children and 1,687 hospitalizations for skin infections in 1,559 children aged < 5 years. We observed no difference in the risk of all-cause injury-hospitalization or skin infection-associated hospitalization between maternally vaccinated and maternally unvaccinated children from birth to 5 years of age by trimester of vaccination or age sub-group (Supplemental Table 4; Supplemental Table 5).

3.6. Sensitivity analysis

Of the 13,834 children born between 1 April 2012 and 30 September 2012, 789 (5.7%) were maternally vaccinated; 5 (0.6%) exposed during the first trimester, 315 (39.9%) during the second trimester, and 469 (59.4%) during the third trimester. We observed no difference in the risk of LCI or hospitalization for influenza, acute respiratory infections, all-cause injuries and skin infections between maternally vaccinated and maternally unvaccinated children aged < 5 years and 6 months to < 5 years (Supplemental Table 6).

4. Discussion

In this large, population-based cohort study of 124,760 children, we observed a lower risk of LCI, ARI-associated hospitalization, and influenza-associated hospitalization following seasonal IIV during pregnancy among infants aged < 6 months. No consistent differences in risks for children aged > 6 months were observed by maternal vaccination status. These findings suggest maternal vaccination is effective in preventing influenza in young infants, and

Table 3
Risk of influenza hospitalization associated with prenatal exposure to seasonal inactivated influenza vaccination among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	318 (0.3)	34 (0.2)	7 (0.3)	12 (0.2)	15 (0.2)
Cases, n (%)	325 (0.3)	35 (0.2)	7 (0.3)	13 (0.2)	15 (0.2)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.63–1.28)	0.92 (0.43–1.95)	0.83 (0.46–1.50)	0.95 (0.56–1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.62–1.33)	1.29 (0.58–2.85)	0.80 (0.43–1.48)	0.85 (0.49–1.47)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	106 (0.1)	6 (0)	<5	<5	5 (0.1)
Cases, n (%)	108 (0.1)	6 (0)	<5	<5	5 (0.1)
Unweighted HR (95% CI)	1 [Reference]	**0.43 (0.19–0.97)**	-	-	0.84 (0.34–2.07)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.38 (0.16–0.91)**	-	-	0.68 (0.26–1.73)
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	145 (0.1)	20 (0.1)	<5	10 (0.2)	8 (0.1)
Cases, n (%)	146 (0.1)	21 (0.1)	<5	11 (0.2)	8 (0.1)
Unweighted HR (95% CI)	1 [Reference]	1.13 (0.70–1.82)	-	1.49 (0.77–2.89)	1.05 (0.52–2.15)
Weighted aHR (95% CI)[a]	1 [Reference]	1.09 (0.67–1.78)	-	1.36 (0.70–2.65)	0.96 (0.47–1.99)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	69 (0.1)	8 (0.1)	<5	<5	<5
Cases, n (%)	71 (0.1)	8 (0.1)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	1.23 (0.59–2.56)	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.40 (0.65–3.01)	-	-	-
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	212 (0.2)	28 (0.2)	6 (0.2)	12 (0.2)	10 (0.2)
Cases, n (%)	217 (0.2)	29 (0.2)	6 (0.2)	13 (0.2)	10 (0.2)
Unweighted HR (95% CI)	1 [Reference]	1.16 (0.78–1.73)	1.23 (0.54–2.78)	1.26 (0.69–2.30)	1.01 (0.54–1.91)
Weighted aHR (95% CI)[a]	1 [Reference]	1.18 (0.77–1.80)	1.67 (0.69–4.01)	1.20 (0.64–2.23)	0.94 (0.48–1.83)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Influenza-associated hospitalization obtained from ICD-10-AM codes: J09-J11, found in the principal and additional diagnosis fields of hospital inpatient records (Supplemental Table 1).
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

does not impact the susceptibility to respiratory infections through early childhood.

We did observe a two-fold increase in the risk of LCI associated with maternal influenza vaccination when administered during the first trimester of pregnancy. The first six months of life is an important window for priming the immune system, and the influence of maternal immunization beyond passive immunity is not well-understood [30]. The presence of maternal antibodies from other maternal vaccines has been shown to inhibit the development of children's primary antibody response [31], including blunted response to pertussis, *Haemophilus influenzae B* and pneumococcal vaccines [32]. It is not currently known whether this is also the case with seasonal influenza vaccines. It is possible that although maternally vaccinated infants are protected by maternal antibodies early in life, once these antibodies wane around 2–3 months after birth, this may leave a temporary window of susceptibility [30]. This may explain the temporary increased risk of LCI infection among children aged 6 months to < 2 years whose mothers were vaccinated in first trimester. A Danish cohort of children whose mothers received pandemic influenza vaccine during the first trimester of pregnancy observed down-regulation of key immune mediators in airway mucosal cells, suggesting a compromised local immune defence [33]. This effect was enhanced the earlier in the pregnancy the mothers received vaccination. While this down-regulation was observed in neonates and the study was not powered to examine the immune response later in infancy, it may be hypothesized that the boosted adaptive immune response in vaccinated mothers was responsible for down-regulation of the fetal immune system in this study. Whether this down-regulation is temporary, has lasting effects, or is also the case with seasonal vaccines is unknown and requires further examination.

Despite this, there are other explanations for these results, and this finding requires further evaluation. First, sensitivity analyses restricting the influence of truncation and exposure to different influenza seasons did not suggest an increased risk of LCI for children 6 months to < 5 years of age. However, our cohort was too small to perform analyses specific to first trimester exposure. Second, we were unable to measure receipt of influenza vaccines during childhood in this cohort and it is possible that vaccination rates in maternally vaccinated children varied to rates in maternally unvaccinated children [34]; however, sensitivity analyses restricted to the time period when childhood influenza vaccination is unlikely showed similar results, suggesting this was not a strong factor in our results. Another possibility is that residual confounding influenced our results. Although we did not identify associations in our negative control analysis, and we attempted to restrict the influence of health-seeking behavior using inverse-probability treatment weighting, we cannot entirely exclude the possible influence of confounding in our results.

The main strengths of our study include the availability of a large, population-based birth cohort and the use of record linkage to incorporate detailed information on birth, perinatal, and health

Table 4
Risk of acute respiratory infection hospitalization associated with prenatal exposure to seasonal inactivated influenza vaccination among children < 5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged < 5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	12,193 (11.0)	1,445 (10.0)	255 (9.2)	579 (10.4)	611 (10.1)
Cases, n (%)	16,706 (15.1)	1,937 (13.5)	356 (12.8)	785 (14.1)	796 (13.2)
Unweighted HR (95% CI)	1 [Reference]	0.96 (0.90–1.02)	0.90 (0.78–1.04)	0.96 (0.87–1.06)	0.97 (0.89–1.07)
Weighted aHR (95% CI)[a]	1 [Reference]	0.94 (0.88–1.01)	0.88 (0.75–1.02)	0.97 (0.87–1.07)	0.95 (0.86–1.05)
Children aged < 6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	4,434 (4.0)	506 (3.5)	70 (2.5)	180 (3.2)	256 (4.2)
Cases, n (%)	4,838 (4.4)	556 (3.9)	83 (3.0)	193 (3.5)	280 (4.6)
Unweighted HR (95% CI)	1 [Reference]	**0.88 (0.80–0.97)**	**0.68 (0.53–0.88)**	**0.79 (0.68–0.92)**	1.05 (0.93–1.20)
Weighted aHR (95% CI)[a]	1 [Reference]	**0.85 (0.77–0.94)**	**0.67 (0.50–0.88)**	**0.79 (0.67–0.93)**	1.00 (0.87–1.14)
Children aged 6 months to < 2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	6,775 (6.2)	842 (5.9)	170 (6.1)	351 (6.3)	321 (5.3)
Cases, n (%)	8,702 (7.9)	1,074 (7.5)	218 (7.8)	446 (8.0)	410 (6.8)
Unweighted HR (95% CI)	1 [Reference]	0.97 (0.89–1.05)	1.02 (0.86–1.21)	1.00 (0.89–1.13)	0.91 (0.80–1.03)
Weighted aHR (95% CI)[a]	1 [Reference]	0.97 (0.90–1.06)	0.99 (0.83–1.18)	1.03 (0.91–1.16)	0.91 (0.80–1.04)
Children aged 2 to < 5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	2,570 (3.0)	252 (2.8)	46 (2.5)	116 (3.3)	90 (2.6)
Cases, n (%)	3,186 (3.7)	309 (3.5)	56 (3.0)	147 (4.1)	106 (3.0)
Unweighted HR (95% CI)	1 [Reference]	1.06 (0.92–1.22)	0.93 (0.68–1.29)	1.13 (0.92–1.39)	1.03 (0.83–1.29)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.87–1.17)	0.90 (0.65–1.24)	1.06 (0.85–1.32)	1.01 (0.80–1.27)
Children aged 6 months to < 5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	8,678 (7.9)	1,028 (7.2)	199 (7.2)	437 (7.9)	392 (6.5)
Cases, n (%)	11,883 (10.8)	1,383 (9.6)	274 (9.9)	593 (10.7)	516 (8.5)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.92–1.07)	1.00 (0.85–1.18)	1.03 (0.92–1.16)	0.93 (0.83–1.05)
Weighted aHR (95% CI)[a]	1 [Reference]	0.98 (0.91–1.06)	0.97 (0.82–1.14)	1.04 (0.92–1.16)	0.93 (0.83–1.05)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).
Acute respiratory infection-associated hospitalization obtained from ICD-10-AM codes: B34, J05, J06, J09-J11, J12-J18, J20, J21, J22, found in the principal and additional diagnosis fields of hospital inpatient records (Supplemental Table 1).
[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

care information. With the exception of antenatal vaccination registers, these registers are nationally mandated and provide data to the Australian Institute of Health and Welfare, and the quality is considered to be high [35]. Record linkage has been well established in WA since 1995 [36]. The MNS is also estimated to capture 99% of all births in WA [16]. Furthermore, through the use of WANIDD data, we were able to assess laboratory-confirmed outcomes with high specificity [37], rather than influenza identified through diagnostic codes alone which have been shown to under-report the incidence of influenza admissions [38].

The study had some limitations: firstly, the inability to measure childhood influenza vaccination, which is a potential confounder and effect modifier. Despite this, childhood influenza vaccine coverage was low (< 10%) during our study period [29], indicating this was unlikely to have significantly influenced our results. It is possible that childhood vaccination is associated with maternal vaccination, and if this is the case, our analyses accounting for confounding maternal factors may have by proxy adjusted for some influence of childhood vaccination as a confounder. Secondly, maternal vaccination status was captured by medical reports from immunization providers. Although the immunizations identified by this system are likely to reflect accurate medical information, it is possible that immunization capture was incomplete [17]. Thirdly, the use of LCI as an endpoint is a strength of our study, however, there may be some outcome misclassification, in cases where a child was not tested for influenza. For this reason, we included additional endpoints considering diagnostic coding. Finally, despite the large cohort size in our study, some outcomes were suppressed when stratifying by trimester of vaccination due to < 5 cases, and post-hoc power analysis suggests some associations may not have been detected.

5. Conclusion

Few studies have evaluated the effects of seasonal IIV during pregnancy on acute respiratory infectious outcomes beyond infancy and into early childhood. As maternal vaccination programs continue to expand globally, it will become increasingly important to understand the comprehensive impact of prenatal exposure to vaccines on child health, particularly the immune signature of the child [39]. Overall, our findings suggest maternal influenza vaccination prevented influenza in young infants aged < 6 months and was not associated with long-term differences in the risk of acute respiratory infections among children aged < 5 years. However, there was a suggested increase in the risk of LCI among children aged 6 months to < 2 years following maternal influenza vaccination during the first trimester. This observed association could be due to residual confounding, differential exposure to influenza seasons, and/or the absence of vaccination information beyond six months of age implying that these results should be interpreted cautiously. Regardless, we believe our results

support current vaccine policies and practices prioritizing influenza immunization during pregnancy to protect young infants from influenza infection, and suggests the need for additional studies to further evaluate longer term health outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

D.F., M.S., and A.K.R. performed all data management. D.F. performed all analysis and led the writing of the first draft of the manuscript. A.K.R., M.S., G.P., and H.C.M. contributed to the study design, interpretation of data and writing of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.11.084.

References

[1] Zhou F, Trieu M-C, Davies R, Cox RJ. Improving influenza vaccines: challenges to effective implementation. Curr Opin Immunol. 2018;53:88–95.
[2] World Health Organization. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Rec. 2012;87:461-76.
[3] Kachikis A, Eckert LO, Englund J. Who's the Target: Mother or Baby? Viral Immunol. 2018;31(2):184–94.
[4] Kay AW, Blish CA. Immunogenicity and Clinical Efficacy of Influenza Vaccination In Pregnancy. Front Immunol. 2015;6:289.
[5] Australian Technical Advisory Group on Immunisation. The Australian Immunisation Handbook: 10th Edition. Canberra, Australia: Australian Government: Department of Health; 2013.
[6] Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: A systematic review and meta-analysis. Hum Vaccin Immunother. 2018;14(3):758–66.
[7] Regan AK, Klerk Nd, Moore HC, Omer SB, Shellam G, Effler PV. Effectiveness of seasonal trivalent influenza vaccination against hospital-attended acute respiratory infections in pregnant women: A retrospective cohort study. Vaccine. 2016;34(32):3649–56.
[8] Foo DYP, Sarna M, Pereira G, Moore HC, Fell DB, Regan AK. Early Childhood Health Outcomes Following In Utero Exposure to Influenza Vaccines: A Systematic Review. Pediatrics 2020;146(2):e20200375. https://doi.org/10.1542/peds.2020-0375.
[9] Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol. 2014;5.
[10] Glezen W. Effect of maternal antibodies on the infant immune response. Vaccine. 2003;21(24):3389–92.
[11] Australian Bureau of Statistics. 3301.0 - Births, Australia, 2016. 2017.
[12] Australian Bureau of Statistics. Births, summary, by state. 2018.
[13] National Centre for Immunisation Research and Surveillance. Significant events in influenza vaccination practice in Australia. 2020.
[14] Australian Government: Department of Health. Clinical update: 2020 seasonal influenza vaccines – early advice for vaccination providers. 2020.
[15] Holman CDJ, Bass JA, Rosman DL, Smith MB, Semmens JB, Glasson EJ, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. Aust Health Rev. 2008;32(4):766. https://doi.org/10.1071/AH080766.
[16] Gee V, Dawes V. Validation study of the Western Australian Midwives' Notification System 1992. Perth, WA: Western Australia Department of Health; 1994.
[17] Regan AK, Mak DB, Moore HC, Tracey L, Saker R, Jones C, et al. Surveillance of antenatal influenza vaccination: validity of current systems and recommendations for improvement. BMC Public Health 2015;15(1). https://doi.org/10.1186/s12889-015-2234-z.
[18] Communicable Disease Control Directorate. Guide to interpreting notifiable infections disease data for Western Australia. In: Health Do, editor.: Western Australia Department of Health; 2016.
[19] Department of Health Western Australia. Hospital Morbidity Data System. Reference Manual Part A: Contacts, Hospital Responsibilities, Data Element Definitions. 2017.
[20] Lipsitch M, Tchetgen ET, Cohen T. Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. Epidemiology 2010;21:383–8.
[21] Australian Bureau of Statistics. 2033.0.55.001 - Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2016. 2018.
[22] Dobbins TA, Sullivan EA, Roberts CL, Simpson JM. Australian national birthweight percentiles by sex and gestational age, 1998–2007. Med J Aust 2012;197(5):291–4.
[23] Lindley MC, Kahn KE, Bardenheier BH, D'Angelo DV, Dawood FS, Fink RV, et al. Vital Signs: Burden and Prevention of Influenza and Pertussis Among Pregnant Women and Infants - United States. MMWR Morb Mortal Wkly Rep 2019;68(40):885–92.
[24] 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;18:416.
[25] Lutz CS, Carr W, Cohn A, Rodriguez L. Understanding barriers and predictors of maternal immunization: Identifying gaps through an exploratory literature review. Vaccine 2018;36(49):7445–55.
[26] Kahn KE, Black CL, Ding H, Williams WW, Lu P-J, Fiebelkorn AP, et al. Influenza and Tdap Vaccination Coverage Among Pregnant Women — United States, April 2018. MMWR Morb Mortal Wkly Rep 2018;67(38):1055–9.
[27] Barber A, Muscoplat MH, Fedorowicz A. Coverage with Tetanus, Diphtheria, and Acellular Pertussis Vaccine and Influenza Vaccine Among Pregnant Women — Minnesota, March 2013–December 2014. MMWR Morb Mortal Wkly Rep 2017;66(02):56–9.
[28] Yuen CYS, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women – A systematic review. Vaccine. 2014;32:4602-13.
[29] Blyth CC, Macartney KK, Hewagama S, Senenayake S, Friedman ND, Simpson G, et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). Euro Surveill. 2016;21:30301.
[30] Marchant A, Sadarangani M, Garand M, Dauby N, Verhasselt V, Pereira L, et al. Maternal immunisation: collaborating with mother nature. Lancet Infect Dis 2017;17(7):e197–208.
[31] Orije MRP, Maertens K, Corbière V, Wanlapakorn N, Van Damme P, Leuridan E, et al. The effect of maternal antibodies on the cellular immune response after infant vaccination: A review. Vaccine 2020;38(1):20–8.
[32] Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E. Pneumococcal Immune Response in Infants Whose Mothers Received Tetanus, Diphtheria and Acellular Pertussis Vaccination During Pregnancy. Pediatr Infect Dis J 2017;36:1186–92.

[33] Bischoff AL, Følsgaard NV, Vissing NH, Birch S, Brix S, Bisgaard H. Airway Mucosal Immune-suppression in Neonates of Mothers Receiving A(H1N1) pnd09 Vaccination During Pregnancy. Pediatr Infect Dis J 2015;34:84–90.
[34] Danchin MH, Costa-Pinto J, Attwell K, Willaby H, Wiley K, Hoq M, et al. Vaccine decision-making begins in pregnancy: Correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. Vaccine 2018;36(44):6473–9.
[35] Australian Government: Australian Institute of Health and Welfare. Metadata standards. 2019.
[36] Western Australian Data Linkage Branch. About the Data Linkage Branch.
[37] Lim FJ, Blyth CC, Levy A, Fathima P, de Klerk N, Giele C, et al. Using record linkage to validate notification and laboratory data for a more accurate assessment of notifiable infectious diseases. BMC Med Inform Decis Mak 2017;17(1). https://doi.org/10.1186/s12911-017-0484-7.
[38] Government of Western Australia. Surveillance Case Definitions for Notifiable Infectious Diseases and Related Conditions in Western Australia. 2020.
[39] Munoz FM, Long SS. The Safety of Maternal Influenza Vaccination and Infant Health Outcomes. Pediatrics. 2020;146:e2020006916.

Appendix E. Study Two (Chapter Six): Supplementary Material

Supplementary Table E-1. ICD-10-AM diagnosis codes for hospital-attended influenza infections, all-cause acute respiratory infections, all-cause injuries, and skin infections.

Outcome	ICD-10-AM code*	N
Influenza admission	J09-J11	360
All-cause acute respiratory infection admission:	All below:	18,643
Viral infection of unspecified site	B34	6,314
Croup	J05	1,160
Unspecified upper respiratory infection	J06	3,060
Influenza	J09-J11	340
Pneumonia	J12-J18	1,663
Bronchitis	J20	111
Bronchiolitis	J21	5,785
Unspecified lower respiratory tract infection	J22	1,276
Negative control condition 1: all-cause injury admission	S00-S99	4,162
Negative control condition 2: skin and soft tissue infection admission	L00-L09	1,687

*Diagnosis codes were based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification. Principal and all additional diagnosis fields were used to classify outcomes.

Supplementary Table E-2. Post-hoc power analysis of detectable differences in risk of outcomes among children <5 years of age, by trimester of vaccination.

Condition	Number of outcomes:	% of unexposed with outcome	Detectable alternative[a] 90% power Lower	90% power Upper	80% power Lower	80% power Upper
Exposed to seasonal influenza vaccine during any trimester						
Laboratory-confirmed influenza	862	0.69%	0.680	1.370	0.717	1.313
Acute respiratory infection-associated hospitalisation	18,643	11.05%	0.920	1.083	0.930	1.071
Influenza-associated hospitalisation	360	0.29%	0.526	1.593	0.576	1.497
All-cause injury-associated hospitalisation	4,162	3.24%	0.848	1.162	0.867	1.139
Skin infection-associated hospitalisation	1,687	1.27%	0.760	1.267	0.789	1.227
Exposed to seasonal influenza vaccine during the first trimester						
Laboratory-confirmed influenza	797	0.69%	0.369	1.854	0.424	1.706
Acute respiratory infection-associated hospitalisation	17,062	11.05%	0.829	1.182	0.851	1.156
Influenza-associated hospitalisation	332	0.29%	0.132	2.411	0.177	2.142
All-cause injury-associated hospitalisation	3,832	3.24%	0.683	1.362	0.720	1.306
Skin infection-associated hospitalisation	1,549	1.27%	0.513	1.607	0.562	1.507
Exposed to seasonal influenza vaccine during the second trimester						
Laboratory-confirmed influenza	802	0.69%	0.524	1.592	0.573	1.495
Acute respiratory infection-associated hospitalisation	17,491	11.05%	0.876	1.129	0.892	1.111
Influenza-associated hospitalisation	338	0.29%	0.316	1.963	0.372	1.793
All-cause injury-associated hospitalisation	3,912	3.24%	0.768	1.255	0.796	1.217
Skin infection-associated hospitalisation	1,576	1.27%	0.638	1.424	0.679	1.357
Exposed to seasonal influenza vaccine during the third trimester						
Laboratory-confirmed influenza	799	0.69%	0.541	1.566	0.589	1.474
Acute respiratory infection-associated hospitalisation	17,502	11.05%	0.881	1.124	0.897	1.106
Influenza-associated hospitalisation	340	0.29%	0.337	1.920	0.393	1.759
All-cause injury-associated hospitalisation	3,910	3.24%	0.777	1.245	0.804	1.208
Skin infection-associated hospitalisation	1,598	1.27%	0.651	1.406	0.691	1.343

[a] Significance level: α = 5%.

Supplementary Table E-3. Risk of laboratory-confirmed influenza infection associated with prenatal exposure to seasonal inactivated influenza vaccine among children aged 6 months to 1 year and 1 to <2 years, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
Children aged 6 to <12 months					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	117 (0.1)	22 (0.2)	8 (0.3)	11 (0.2)	<5
Cases, n (%)	117 (0.1)	22 (0.2)	8 (0.3)	11 (0.2)	<5
Unweighted HR (95% CI)	1 [Reference]	1.44 (0.91-2.27)	**2.71 (1.33-5.55)**	**1.87 (1.01-3.46)**	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.52 (0.96-2.42)	**2.70 (1.40-5.98)**	1.85 (0.96-3.43)	-
Children aged 1 to <2 years					
N	110,067	14,340	2,773	5,547	6,020
No. of children with event(s), n	251 (0.2)	39 (0.3)	11 (0.4)	12 (0.2)	16 (0.3)
Cases, n (%)	253 (0.2)	39 (0.3)	11 (0.4)	12 (0.2)	16 (0.3)
Unweighted HR (95% CI)	1 [Reference]	1.25 (0.89-1.75)	**1.84 (1.01-3.37)**	0.94 (0.53-1.68)	1.28 (0.77-2.12)
Weighted aHR (95% CI)[a]	1 [Reference]	1.24 (0.87-1.77)	**2.00 (1.05-3.80)**	0.93 (0.51-1.70)	1.20 (0.70-2.07)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

Laboratory-confirmed influenza cases obtained from notification records reported to WANIDD.

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

Supplementary Table E-4. Risk of all-cause injury hospitalisation associated with prenatal exposure to seasonal inactivated influenza vaccination among children <5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged <5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	3,572 (3.2)	403 (2.8)	85 (3.1)	160 (2.9)	158 (2.6)
Cases, n (%)	3,746 (3.4)	416 (2.9)	86 (3.1)	166 (3.0)	164 (2.7)
Unweighted HR (95% CI)	1 [Reference]	1.01 (0.91-1.12)	1.08 (0.87-1.33)	0.97 (0.83-1.14)	1.02 (0.87-1.20)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.89-1.11)	1.08 (0.86-1.35)	0.95 (0.80-1.12)	1.01 (0.85-1.21)
Children aged <6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	407 (0.4)	54 (0.4)	9 (0.3)	23 (0.4)	22 (0.4)
Cases, n (%)	414 (0.4)	55 (0.4)	9 (0.3)	23 (0.4)	23 (0.4)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.77-1.36)	0.86 (0.45-1.67)	1.10 (0.72-1.68)	1.01 (0.65-1.57)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.67-1.22)	0.75 (0.38-1.47)	1.01 (0.64-1.59)	0.89 (0.57-1.39)
Children aged 6 months to <2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	1,579 (1.4)	213 (1.5)	43 (1.5)	83 (1.5)	87 (1.4)
Cases, n (%)	1,619 (1.5)	217 (1.5)	44 (1.6)	84 (1.5)	89 (1.5)
Unweighted HR (95% CI)	1 [Reference]	1.07 (0.92-1.23)	1.13 (0.83-1.53)	1.02 (0.82-1.27)	1.08 (0.87-1.34)
Weighted aHR (95% CI)[a]	1 [Reference]	1.07 (0.92-1.24)	1.17 (0.86-1.61)	1.00 (0.79-1.27)	1.09 (0.86-1.37)
Children aged 2 to <5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	1,660 (1.9)	144 (1.6)	34 (1.8)	58 (1.6)	52 (1.5)
Cases, n (%)	1,713 (2.0)	145 (1.6)	34 (1.8)	59 (1.7)	52 (1.5)
Unweighted HR (95% CI)	1 [Reference]	0.95 (0.80-1.12)	1.12 (0.80-1.56)	0.87 (0.67-1.13)	0.95 (0.72-1.24)
Weighted aHR (95% CI)[a]	1 [Reference]	0.95 (0.80-1.14)	1.10 (0.78-1.56)	0.88 (0.67-1.16)	0.97 (0.72-1.31)
Children aged 6 months to <5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	3,193 (2.9)	351 (2.4)	76 (2.7)	138 (2.5)	137 (2.3)
Cases, n (%)	3,332 (3.0)	361 (2.5)	77 (2.8)	143 (2.6)	141 (2.3)

Unweighted HR (95% CI)	1 [Reference]	1.01 (0.90-1.13)	1.11 (0.89-1.39)	0.95 (0.80-1.13)	1.02 (0.86-1.22)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.90-1.13)	1.12 (0.89-1.42)	0.94 (0.79-1.13)	1.03 (0.85-1.24)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All-cause injury-associated hospitalisation obtained from ICD-10-AM codes: S00-S09, S10-S19, S20-S29, S30-S39, S40-S49, S50-S59, S60-S69, S70-S79, S80-S89, S90-S99, found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table E-1**).

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

Supplementary Table E-5. Risk of skin and soft tissue infection hospitalisation associated with prenatal exposure to seasonal inactivated influenza vaccination among children <5 years of age, by trimester of vaccination and age sub-group.

Age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First	Second	Third
All children aged <5 years					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	1,397 (1.3)	162 (1.1)	30 (1.1)	56 (1.0)	76 (1.3)
Cases, n (%)	1,518 (1.4)	169 (1.2)	31 (1.1)	58 (1.0)	80 (1.3)
Unweighted HR (95% CI)	1 [Reference]	0.95 (0.81-1.12)	0.90 (0.63-1.30)	0.81 (0.61-1.06)	1.13 (0.89-1.43)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.82-1.20)	0.98 (0.67-1.42)	0.79 (0.59-1.06)	1.21 (0.91-1.61)
Children aged <6 months					
N	110,364	14,396	2,785	5,558	6,053
No. of children with event(s), n	419 (0.4)	49 (0.3)	10 (0.4)	16 (0.3)	23 (0.4)
Cases, n (%)	427 (0.4)	49 (0.3)	10 (0.4)	16 (0.3)	23 (0.4)
Unweighted HR (95% CI)	1 [Reference]	0.88 (0.65-1.18)	0.93 (0.50-1.74)	0.74 (0.45-1.22)	0.98 (0.65-1.49)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.67-1.24)	1.05 (0.55-2.02)	0.76 (0.45-1.27)	0.98 (0.62-1.52)
Children aged 6 months to <2 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	613 (0.6)	73 (0.5)	12 (0.4)	28 (0.5)	33 (0.5)
Cases, n (%)	661 (0.6)	77 (0.5)	12 (0.4)	29 (0.5)	36 (0.6)
Unweighted HR (95% CI)	1 [Reference]	0.92 (0.72-1.18)	0.75 (0.42-1.32)	0.86 (0.59-1.26)	1.06 (0.73-1.54)
Weighted aHR (95% CI)[a]	1 [Reference]	0.98 (0.71-1.34)	0.76 (0.42-1.39)	0.80 (0.53-1.22)	1.26 (0.76-2.08)
Children aged 2 to <5 years					
N	85,224	8,904	1,855	3,552	3,497
No. of children with event(s), n	414 (0.5)	42 (0.5)	9 (0.5)	12 (0.3)	21 (0.6)
Cases, n (%)	431 (0.5)	43 (0.5)	9 (0.5)	13 (0.4)	21 (0.6)
Unweighted HR (95% CI)	1 [Reference]	1.12 (0.81-1.55)	1.19 (0.62-2.31)	0.77 (0.43-1.39)	1.51 (0.98-2.34)
Weighted aHR (95% CI)[a]	1 [Reference]	1.08 (0.78-1.49)	1.23 (0.64-2.36)	0.80 (0.43-1.48)	1.34 (0.86-2.09)
Children aged 6 months to <5 years					
N	110,158	14,373	2,778	5,551	6,044
No. of children with event(s), n	1,004 (0.9)	114 (0.8)	20 (0.7)	40 (0.7)	54 (0.9)
Cases, n (%)	1,091 (1.0)	120 (0.8)	21 (0.8)	42 (0.8)	57 (0.9)

Unweighted HR (95% CI)	1 [Reference]	0.99 (0.81-1.20)	0.89 (0.57-1.40)	0.83 (0.60-1.15)	1.20 (0.90-1.59)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.81-1.28)	0.94 (0.59-1.49)	0.80 (0.57-1.14)	1.29 (0.92-1.81)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

Skin infection-associated hospitalisation obtained from ICD-10-AM codes: L00-L09, found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table E-1**).

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

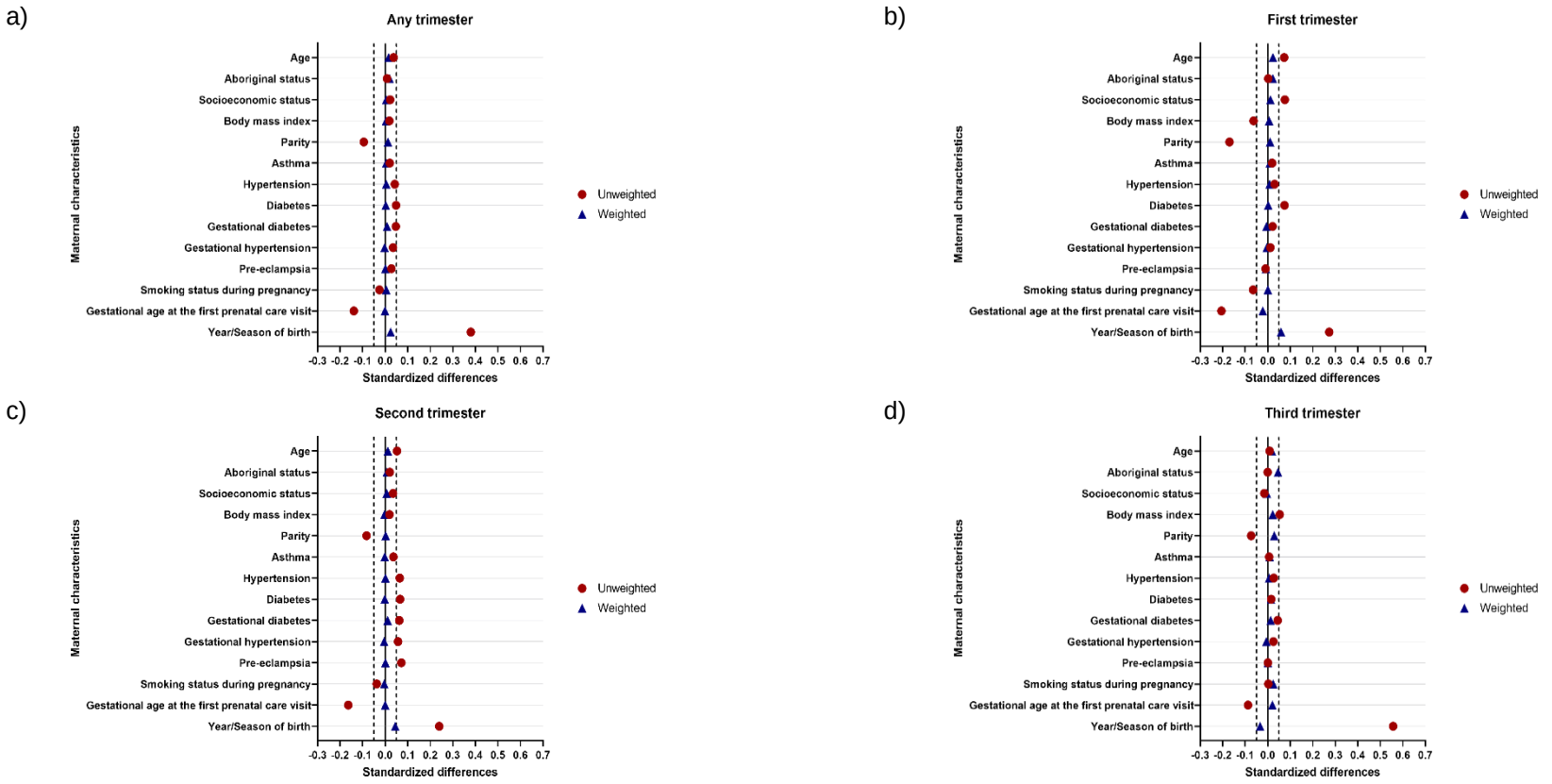
Supplementary Table E-6. Risk of laboratory-confirmed influenza infection and hospitalisation for influenza, acute respiratory infections, all-cause injuries and skin infections associated with prenatal exposure to seasonal inactivated influenza vaccine among children aged <5 years born between 1 April 2012 and 30 September 2012, by trimester of vaccination and age sub-group.

Outcome and age sub-group	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy
Laboratory-confirmed influenza		
All children aged <5 years		
N	13,053	789
No. of children with event(s), n	158 (1.2)	9 (1.1)
Cases, n (%)	163 (1.2)	9 (1.1)
Unweighted HR (95% CI)	1 [Reference]	0.92 (0.47-1.79)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.46-1.80)
Children aged 6 months to <5 years		
N	13,025	787
No. of children with event(s), n	135 (1.0)	9 (1.1)
Cases, n (%)	140 (1.1)	9 (1.1)
Unweighted HR (95% CI)	1 [Reference]	1.07 (0.55-2.09)
Weighted aHR (95% CI)[a]	1 [Reference]	1.06 (0.54-2.11)
Influenza-associated hospitalisation		
All children aged <5 years		
N	13,053	789
No. of children with event(s), n	59 (0.5)	<5
Cases, n (%)	60 (0.5)	<5
Unweighted HR (95% CI)	1 [Reference]	-
Weighted aHR (95% CI)[a]	1 [Reference]	-
Children aged 6 months to <5 years		
N	13,025	787
No. of children with event(s), n	35 (0.3)	<5
Cases, n (%)	36 (0.3)	<5
Unweighted HR (95% CI)	1 [Reference]	-
Weighted aHR (95% CI)[a]	1 [Reference]	-
Acute respiratory infection-associated hospitalisation		
All children aged <5 years		
N	13,053	789
No. of children with event(s), n	1,685 (12.9)	117 (14.8)
Cases, n (%)	2,338 (17.9)	175 (22.2)
Unweighted HR (95% CI)	1 [Reference]	**1.24 (1.01-1.53)**
Weighted aHR (95% CI)[a]	1 [Reference]	1.15 (0.93-1.42)
Children aged 6 months to <5 years		
N	13,025	787
No. of children with event(s), n	1,244 (9.6)	94 (11.9)
Cases, n (%)	1,707 (13.1)	141 (17.9)
Unweighted HR (95% CI)	1 [Reference]	**1.37 (1.09-1.73)**
Weighted aHR (95% CI)[a]	1 [Reference]	1.26 (1.00-1.59)
All-cause injury-associated hospitalisation		
All children aged <5 years		
N	13,053	789
No. of children with event(s), n	684 (5.2)	36 (4.6)
Cases, n (%)	721 (5.5)	37 (4.7)
Unweighted HR (95% CI)	1 [Reference]	0.85 (0.61-1.19)
Weighted aHR (95% CI)[a]	1 [Reference]	0.88 (0.62-1.24)
Children aged 6 months to <5 years		
N	13,025	787
No. of children with event(s), n	650 (5.0)	35 (4.4)
Cases, n (%)	681 (5.2)	36 (4.6)
Unweighted HR (95% CI)	1 [Reference]	0.88 (0.63-1.23)
Weighted aHR (95% CI)[a]	1 [Reference]	0.89 (0.63-1.27)

Skin infection-associated hospitalisation		
All children aged <5 years		
N	13,053	789
No. of children with event(s), n	217 (1.7)	18 (2.3)
Cases, n (%)	247 (1.9)	21 (2.7)
Unweighted HR (95% CI)	1 [Reference]	1.42 (0.85-2.38)
Weighted aHR (95% CI)[a]	1 [Reference]	1.25 (0.73-2.16)
Children aged 6 months to <5 years		
N	13,025	787
No. of children with event(s), n	167 (1.3)	18 (2.3)
Cases, n (%)	194 (1.5)	21 (2.7)
Unweighted HR (95% CI)	1 [Reference]	**1.81 (1.07-3.05)**
Weighted aHR (95% CI)[a]	1 [Reference]	1.56 (0.90-2.72)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes). Laboratory-confirmed influenza cases obtained from notification records reported to WANIDD. Hospitalisation for influenza, acute respiratory infections, all-cause injuries and skin infections were obtained from ICD-10-AM codes (**Supplementary Table E-1**).

[a] Hazard ratios weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, BMI, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.



Supplementary Figure E-1. Balance of standardised differences of maternal covariates before and after inverse-probability treatment weighting, by trimester of vaccination: children of mothers a) vaccinated during any trimester, b) vaccinated during the first trimester, c) vaccinated during the second trimester, or d) vaccinated during the third trimester.
Note: dashed lines indicate 5% standardised mean difference.

Appendix F. Study Three (Chapter Seven): Supplementary Material

Supplementary Table F-1. ICD-10-AM diagnosis codes used to identify allergic or autoimmune diseases, and all-cause injuries, and frequency of outcomes by data source.

Outcome	ICD-10-AM or Symptom Code	Both data sources[a,b] (n)	Hospital inpatient admission (HMDC)[a] (n)	Emergency department episode (EDDC)[b] (n)
Allergic or autoimmune diseases	Composite of all codes listed below:	8,568	3,819	6,074
Allergic diseases		8,416	3,674	6,017
Allergic rhinitis	J30, J45.0	148	35	114
Asthma and wheezing	J45, J46, SQA00*, SQAA0*, R06.2, CH000*	3,757	3,078	1,519
Asthma	J45, J46, SQA00*, SQAA0*	1,556	637	1,276
Wheezing	R06.2, CH000*	2,906	2,732	290
Hypersensitivity pneumonitis due to organic dust	J67	0	0	0
Allergic gastroenteritis	K52.2	82	82	0
Atopic dermatitis	L20	270	51	224
Allergic dermatitis	L23	713	19	694
Urticaria	L50	2,994	229	2,848
Anaphylaxis	T78.0, T78.2, T78.4, T80.5, T88.1, T88.6, T88.7	1,157	294	1,041
Angioneurotic oedema	T78.3	121	21	105
Autoimmune diseases		174	160	61
Idiopathic thrombocytopenic purpura	D69.3	33	**	<5
Diabetes mellitus	E10-14	54	48	51
Addison’s disease	E27.1	<5	<5	0
Multiple sclerosis	G35	0	0	0
Vasculitis	I77.6, L95, M30.1-M30.2, M31.1-M31.2, M31.4-M31.9	9	**	<5
Ulcerative colitis and Crohn's disease	K50-K51	7	**	<5

Inflammatory liver diseases	K75	9	5	5
Coeliac disease	K90.0	40	40	0
Reactive arthropathy	M02.9	0	0	0
Juvenile arthritis	M08	21	21	0
Dermatopolymyositis	M33	0	0	0
Sjögren's disease	M35.0	0	0	0
Lupus	L93, M32	0	0	0
Localized connective tissue disorders	L94	0	0	0
Negative control condition: all-cause injury admission	Composite of all codes listed below:	21,730	3,528	20,898
Head	S01-S09	14,466	2,347	13,786
Neck	S11-S19	200	30	179
Thorax	S21-S29	106	53	64
Abdomen, lower back, lumbar spine and pelvis	S31-S39	365	63	315
Shoulder and upper arm	S41-S49	1,005	172	932
Elbow and forearm	S51-S59	3,481	189	3,407
Wrist and hand	S61-S69	1,868	473	1,759
Hip and thigh	S71-S79	254	122	240
Knee and lower leg	S81-S89	1,120	99	1,077
Ankle and foot	S91-S99	1,541	154	1,478
Multiple site	ABD*	0	-	0
Chest	ABE*	0	-	0
Head	ABF*	0	-	0
Limb	ABG*	0	-	0
Burn	ABH*	0	-	0
Laceration	ABI*	0	-	0
Facial	ABJ*	0	-	0
Eye	ABK*	0	-	0
Bite	ABL*	0	-	0
Sexual	ABM*	0	-	0
Insect bite	ABN*	0	-	0
Nil	ABO*	0	-	0

Abbreviations: EDDC, Emergency Department Data Collection; HMDC, Hospital Morbidity Data Collection; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

[a] Principal and all additional diagnoses fields were used to classify outcomes.

[b] Principal diagnosis fields, and symptom fields were used to classify outcomes.

* Symptom code used if principal diagnosis field is missing (EDDC only).

** In accordance with privacy and confidentiality guidelines by the WA Data Linkage Branch, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.

Supplementary Table F-2. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age who were born at term (>37 weeks gestational age), by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 102,974)	Exposed to seasonal influenza vaccine during pregnancy (N = 13,509)	Trimester of vaccine exposure		
			First trimester (N = 2,600)	Second trimester (N = 5,117)	Third trimester (N = 5,792)
Allergic or autoimmune disease					
Cases, n (%)	6,955 (6.8)	841 (6.2)	155 (6.0)	361 (7.1)	325 (5.6)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.97 to 1.12)	0.99 (0.85 to 1.16)	1.12 (1.00 to 1.24)	1.00 (0.90 to 1.12)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.95 to 1.11)	0.96 (0.81 to 1.14)	1.10 (0.98 to 1.23)	0.99 (0.88 to 1.12)
Allergic disease					
Cases, n (%)	6,835 (6.6)	829 (6.1)	153 (5.9)	357 (7.0)	319 (5.5)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.97 to 1.13)	1.00 (0.85 to 1.17)	**1.12 (1.01 to 1.25)**	1.00 (0.89 to 1.12)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.95 to 1.11)	0.97 (0.82 to 1.15)	1.10 (0.99 to 1.24)	0.99 (0.87 to 1.11)
Asthma diagnosis or wheezing					
Cases, n (%)	2,977 (2.9)	338 (2.5)	60 (2.3)	145 (2.8)	133 (2.3)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.91 to 1.14)	0.92 (0.72 to 1.17)	1.07 (0.91 to 1.25)	1.00 (0.84 to 1.18)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.89 to 1.13)	0.92 (0.71 to 1.19)	1.07 (0.91 to 1.26)	0.97 (0.81 to 1.15)
Asthma diagnosis only[b]					
Cases, n (%)	1,266 (1.2)	113 (0.8)	26 (1.0)	52 (1.0)	35 (0.6)
Unweighted HR (95% CI)	1 [Reference]	0.86 (0.71 to 1.05)	1.02 (0.69 to 1.50)	0.95 (0.72 to 1.26)	**0.69 (0.50 to 0.97)**
Weighted aHR (95% CI)[a]	1 [Reference]	0.84 (0.69 to 1.03)	0.95 (0.63 to 1.42)	0.95 (0.71 to 1.26)	**0.68 (0.48 to 0.96)**
Anaphylaxis					
Cases, n (%)	955 (0.9)	104 (0.8)	28 (1.1)	44 (0.9)	32 (0.6)
Unweighted HR (95% CI)	1 [Reference]	0.94 (0.77 to 1.15)	1.32 (0.90 to 1.92)	1.00 (0.74 to 1.35)	0.71 (0.50 to 1.01)
Weighted aHR (95% CI)[a]	1 [Reference]	0.84 (0.68 to 1.04)	1.14 (0.77 to 1.69)	0.92 (0.67 to 1.27)	**0.62 (0.43 to 0.91)**
Autoimmune disease					
Cases, n (%)	137 (0.1)	14 (0.1)	<5	6 (0.1)	6 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.96 (0.55 to 1.67)	-	1.00 (0.44 to 2.27)	1.05 (0.46 to 2.37)
Weighted aHR (95% CI)[a]	1 [Reference]	0.97 (0.55 to 1.71)	-	1.04 (0.44 to 2.49)	1.07 (0.47 to 2.47)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

Supplementary Table F-3. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age who were born preterm (<37 weeks gestational age), by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 7,390)	Exposed to seasonal influenza vaccine during pregnancy (N = 887)	Trimester of vaccine exposure		
			First trimester (N = 185)	Second trimester (N = 441)	Third trimester (N = 261)
Allergic or autoimmune disease					
Cases, n (%)	700 (9.5)	72 (8.1)	16 (8.6)	34 (7.7)	22 (8.4)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.71 to 1.14)	0.97 (0.59 to 1.59)	0.82 (0.58 to 1.15)	1.02 (0.67 to 1.55)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.70 to 1.17)	0.99 (0.59 to 1.67)	0.81 (0.56 to 1.16)	1.03 (0.66 to 1.61)
Allergic disease					
Cases, n (%)	683 (9.2)	70 (7.9)	15 (8.1)	34 (7.7)	21 (8.0)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.70 to 1.15)	0.92 (0.55 to 1.54)	0.84 (0.59 to 1.18)	1.00 (0.65 to 1.53)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.70 to 1.17)	0.95 (0.56 to 1.63)	0.83 (0.58 to 1.19)	1.02 (0.65 to 1.61)
Asthma diagnosis or wheezing					
Cases, n (%)	398 (5.4)	44 (5.0)	8 (4.3)	24 (5.4)	12 (4.6)
Unweighted HR (95% CI)	1 [Reference]	0.98 (0.72 to 1.34)	0.84 (0.42 to 1.68)	1.02 (0.67 to 1.53)	1.01 (0.57 to 1.79)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.71 to 1.38)	0.89 (0.43 to 1.83)	1.05 (0.68 to 1.62)	0.96 (0.52 to 1.76)
Asthma diagnosis only[b]					
Cases, n (%)	159 (2.2)	18 (2.0)	<5	9 (2.0)	5 (1.9)
Unweighted HR (95% CI)	1 [Reference]	1.06 (0.65 to 1.72)	-	0.99 (0.51 to 1.94)	1.13 (0.47 to 2.76)
Weighted aHR (95% CI)[a]	1 [Reference]	1.12 (0.67 to 1.88)	-	1.07 (0.53 to 2.16)	1.10 (0.41 to 2.95)
Anaphylaxis					
Cases, n (%)	88 (1.2)	10 (1.1)	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.54 to 1.99)	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.51 to 1.97)	-	-	-
Autoimmune disease					
Cases, n (%)	21 (0.3)	<5	<5	<5	<5
Unweighted HR (95% CI)	1 [Reference]	-	-	-	-
Weighted aHR (95% CI)[a]	1 [Reference]	-	-	-	-

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

Supplementary Table F-4. Risk of inpatient admission (only) for allergic or autoimmune disease associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Allergic or autoimmune disease					
Cases, n (%)	3,431 (3.1)	388 (2.7)	71 (2.5)	165 (3.0)	152 (2.5)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.89 to 1.10)	0.93 (0.73 to 1.17)	1.01 (0.87 to 1.19)	1.00 (0.85 to 1.18)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.89 to 1.11)	0.93 (0.72 to 1.19)	1.02 (0.87 to 1.21)	0.99 (0.84 to 1.18)
Allergic disease					
Cases, n (%)	3,298 (3.0)	375 (2.6)	68 (2.4)	161 (2.9)	146 (2.4)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.89 to 1.11)	0.92 (0.72 to 1.17)	1.03 (0.88 to 1.20)	1.00 (0.84 to 1.18)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.89 to 1.11)	0.92 (0.71 to 1.20)	1.04 (0.88 to 1.23)	0.99 (0.83 to 1.18)
Asthma diagnosis or wheezing					
Cases, n (%)	2,759 (2.5)	319 (2.2)	57 (2.0)	139 (2.5)	123 (2.0)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.91 to 1.15)	0.93 (0.71 to 1.21)	1.06 (0.90 to 1.26)	1.02 (0.85 to 1.22)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.90 to 1.15)	0.95 (0.72 to 1.26)	1.07 (0.89 to 1.28)	1.00 (0.83 to 1.21)
Asthma diagnosis only[b]					
Cases, n (%)	584 (0.5)	53 (0.4)	12 (0.4)	26 (0.5)	15 (0.2)
Unweighted HR (95% CI)	1 [Reference]	0.89 (0.67 to 1.18)	1.03 (0.58 to 1.83)	1.02 (0.69 to 1.52)	0.67 (0.40 to 1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	0.87 (0.65 to 1.17)	1.07 (0.58 to 1.96)	1.03 (0.68 to 1.54)	0.61 (0.36 to 1.05)
Anaphylaxis					
Cases, n (%)	268 (0.2)	26 (0.2)	9 (0.3)	7 (0.1)	10 (0.2)
Unweighted HR (95% CI)	1 [Reference]	0.82 (0.55 to 1.23)	1.46 (0.75 to 2.84)	0.55 (0.26 to 1.16)	0.80 (0.42 to 1.50)
Weighted aHR (95% CI)[a]	1 [Reference]	0.79 (0.52 to 1.21)	1.59 (0.80 to 3.15)	0.54 (0.24 to 1.20)	0.67 (0.35 to 1.28)
Autoimmune disease					
Cases, n (%)	145 (0.1)	15 (0.1)	<5	6 (0.1)	6 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.97 (0.57 to 1.65)	-	0.92 (0.41 to 2.09)	1.01 (0.44 to 2.29)
Weighted aHR (95% CI)[a]	1 [Reference]	0.97 (0.56 to 1.69)	-	0.97 (0.41 to 2.31)	1.04 (0.45 to 2.39)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

Supplementary Table F-5. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among children between 6 months and <5 years of age, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,158)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,373)	Trimester of vaccine exposure		
			First trimester (N = 2,778)	Second trimester (N = 5,551)	Third trimester (N = 6,044)
Allergic or autoimmune disease					
Cases, n (%)	6,898 (6.3)	811 (5.6)	155 (5.6)	350 (6.3)	306 (5.1)
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.96 to 1.11)	1.02 (0.87 to 1.19)	1.08 (0.97 to 1.20)	1.00 (0.89 to 1.12)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.94 to 1.10)	1.00 (0.84 to 1.18)	1.07 (0.95 to 1.19)	0.98 (0.87 to 1.10)
Allergic disease					
Cases, n (%)	6,771 (6.1)	799 (5.6)	152 (5.5)	348 (6.3)	299 (4.9)
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.96 to 1.12)	1.01 (0.86 to 1.19)	1.09 (0.98 to 1.22)	0.99 (0.88 to 1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	1.02 (0.94 to 1.10)	1.00 (0.84 to 1.18)	1.08 (0.96 to 1.21)	0.97 (0.86 to 1.10)
Asthma diagnosis or wheezing					
Cases, n (%)	3,325 (3)	379 (2.6)	68 (2.4)	167 (3.0)	144 (2.4)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.92 to 1.14)	0.93 (0.73 to 1.19)	1.07 (0.92 to 1.25)	1.01 (0.85 to 1.19)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.90 to 1.13)	0.93 (0.72 to 1.21)	1.07 (0.91 to 1.26)	0.98 (0.82 to 1.17)
Asthma diagnosis only[b]					
Cases, n (%)	1,412 (1.3)	131 (0.9)	30 (1.1)	61 (1.1)	40 (0.7)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.75 to 1.07)	1.05 (0.73 to 1.50)	0.98 (0.76 to 1.27)	0.73 (0.53 to 1.00)
Weighted aHR (95% CI)[a]	1 [Reference]	0.88 (0.73 to 1.07)	1.00 (0.68 to 1.46)	0.99 (0.75 to 1.29)	**0.71 (0.51 to 0.99)**
Anaphylaxis					
Cases, n (%)	880 (0.8)	96 (0.7)	25 (0.9)	39 (0.7)	32 (0.5)
Unweighted HR (95% CI)	1 [Reference]	0.97 (0.79 to 1.20)	1.31 (0.88 to 1.95)	0.96 (0.70 to 1.33)	0.82 (0.58 to 1.17)
Weighted aHR (95% CI)[a]	1 [Reference]	0.84 (0.68 to 1.05)	1.15 (0.76 to 1.74)	0.86 (0.62 to 1.21)	**0.68 (0.47 to 0.99)**
Autoimmune disease					
Cases, n (%)	144 (0.1)	14 (0.1)	<5	<5	7 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.93 (0.54 to 1.61)	-	-	1.22 (0.57 to 2.61)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.52 to 1.61)	-	-	1.17 (0.54 to 2.55)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

Supplementary Table F-6. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among one randomly selected child per mother, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 93,799)	Exposed to seasonal influenza vaccine during pregnancy (N = 12,407)	Trimester of vaccine exposure		
			First trimester (N = 2,397)	Second trimester (N = 4,798)	Third trimester (N = 5,212)
Allergic or autoimmune disease					
Cases, n (%)	6,512 (6.9)	800 (6.4)	156 (6.5)	341 (7.1)	303 (5.8)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.97 to 1.13)	1.05 (0.90 to 1.23)	1.09 (0.98 to 1.22)	1.00 (0.89 to 1.13)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.95 to 1.11)	1.02 (0.86 to 1.21)	1.07 (0.95 to 1.20)	1.00 (0.88 to 1.13)
Allergic disease					
Cases, n (%)	6,395 (6.8)	789 (6.4)	154 (6.4)	337 (7.0)	298 (5.7)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.98 to 1.13)	1.05 (0.90 to 1.24)	1.10 (0.98 to 1.22)	1.00 (0.89 to 1.13)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.96 to 1.12)	1.03 (0.87 to 1.22)	1.07 (0.96 to 1.21)	1.00 (0.88 to 1.13)
Asthma diagnosis or wheezing					
Cases, n (%)	2,892 (3.1)	334 (2.7)	64 (2.7)	140 (2.9)	130 (2.5)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.91 to 1.14)	0.99 (0.77 to 1.27)	1.02 (0.86 to 1.20)	1.03 (0.86 to 1.23)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.89 to 1.13)	0.98 (0.75 to 1.28)	1.02 (0.85 to 1.22)	1.01 (0.84 to 1.22)
Asthma diagnosis only[b]					
Cases, n (%)	1,225 (1.3)	116 (0.9)	28 (1.2)	51 (1.1)	37 (0.7)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.74 to 1.09)	1.10 (0.76 to 1.6)	0.93 (0.70 to 1.23)	0.76 (0.55 to 1.06)
Weighted aHR (95% CI)[a]	1 [Reference]	0.88 (0.72 to 1.07)	1.01 (0.68 to 1.49)	0.93 (0.69 to 1.25)	0.74 (0.53 to 1.05)
Anaphylaxis					
Cases, n (%)	862 (0.9)	100 (0.8)	26 (1.1)	43 (0.9)	31 (0.6)
Unweighted HR (95% CI)	1 [Reference]	1.00 (0.81 to 1.22)	1.33 (0.90 to 1.97)	1.05 (0.78 to 1.43)	0.77 (0.54 to 1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	0.89 (0.72 to 1.11)	1.19 (0.79 to 1.79)	0.96 (0.69 to 1.32)	0.68 (0.47 to 1.00)
Autoimmune disease					
Cases, n (%)	136 (0.1)	13 (0.1)	<5	6 (0.1)	5 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.88 (0.50 to 1.56)	-	0.97 (0.43 to 2.20)	0.88 (0.36 to 2.15)
Weighted aHR (95% CI)[a]	1 [Reference]	0.86 (0.47 to 1.56)	-	1.02 (0.43 to 2.45)	0.84 (0.33 to 2.14)

Abbreviations: CI, confidence interval; HR, crude hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

Supplementary Table F-7. Risk of allergic or autoimmune diseases associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age matched by year and month of birth, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Allergic or autoimmune disease					
Cases, n (%)	7,655 (6.9)	913 (6.3)	171 (6.1)	395 (7.1)	347 (5.7)
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.97 to 1.12)	0.96 (0.83 to 1.12)	1.11 (1.00 to 1.23)	1.01 (0.91 to 1.13)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.96 to 1.11)	0.97 (0.83 to 1.14)	1.10 (0.99 to 1.22)	1.00 (0.89 to 1.13)
Allergic disease					
Cases, n (%)	7,518 (6.8)	899 (6.2)	168 (6.0)	391 (7.0)	340 (5.6)
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.97 to 1.12)	0.96 (0.82 to 1.12)	1.12 (1.01 to 1.24)	1.01 (0.90 to 1.13)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.96 to 1.11)	0.96 (0.82 to 1.13)	1.11 (1.00 to 1.23)	1.00 (0.89 to 1.13)
Asthma diagnosis or wheezing					
Cases, n (%)	3,375 (3.1)	382 (2.7)	68 (2.4)	169 (3.0)	145 (2.4)
Unweighted HR (95% CI)	1 [Reference]	0.92 (0.77 to 1.11)	1.07 (0.74 to 1.54)	1.02 (0.79 to 1.33)	0.74 (0.53 to 1.03)
Weighted aHR (95% CI)[a]	1 [Reference]	0.93 (0.77 to 1.13)	1.13 (0.77 to 1.66)	0.98 (0.76 to 1.28)	0.76 (0.54 to 1.07)
Asthma diagnosis only[b]					
Cases, n (%)	1,425 (1.3)	131 (0.9)	30 (1.1)	61 (1.1)	40 (0.7)
Unweighted HR (95% CI)	1 [Reference]	1.03 (0.93 to 1.15)	0.89 (0.70 to 1.13)	1.11 (0.95 to 1.30)	1.04 (0.87 to 1.24)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.92 to 1.15)	0.92 (0.72 to 1.18)	1.11 (0.95 to 1.31)	1.00 (0.84 to 1.20)
Anaphylaxis					
Cases, n (%)	1,043 (0.9)	114 (0.8)	30 (1.1)	48 (0.9)	36 (0.6)
Unweighted HR (95% CI)	1 [Reference]	0.90 (0.74 to 1.10)	1.18 (0.82 to 1.71)	0.92 (0.69 to 1.24)	0.72 (0.51 to 1.01)
Weighted aHR (95% CI)[a]	1 [Reference]	0.89 (0.73 to 1.10)	1.17 (0.81 to 1.70)	0.90 (0.67 to 1.22)	**0.69 (0.49 to 0.97)**
Autoimmune disease					
Cases, n (%)	158 (0.1)	16 (0.1)	<5	6 (0.1)	7 (0.1)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.58 to 1.68)	-	0.82 (0.35 to 1.90)	1.16 (0.53 to 2.55)
Weighted aHR (95% CI)[a]	1 [Reference]	0.96 (0.57 to 1.64)	-	0.83 (0.34 to 2.02)	1.08 (0.51 to 2.29)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, models were additionally adjusted for child's Aboriginal status.

[b] Sensitivity analysis restricting the definition of asthma to the presence of a diagnosis code of asthma alone (i.e., J45-J46).

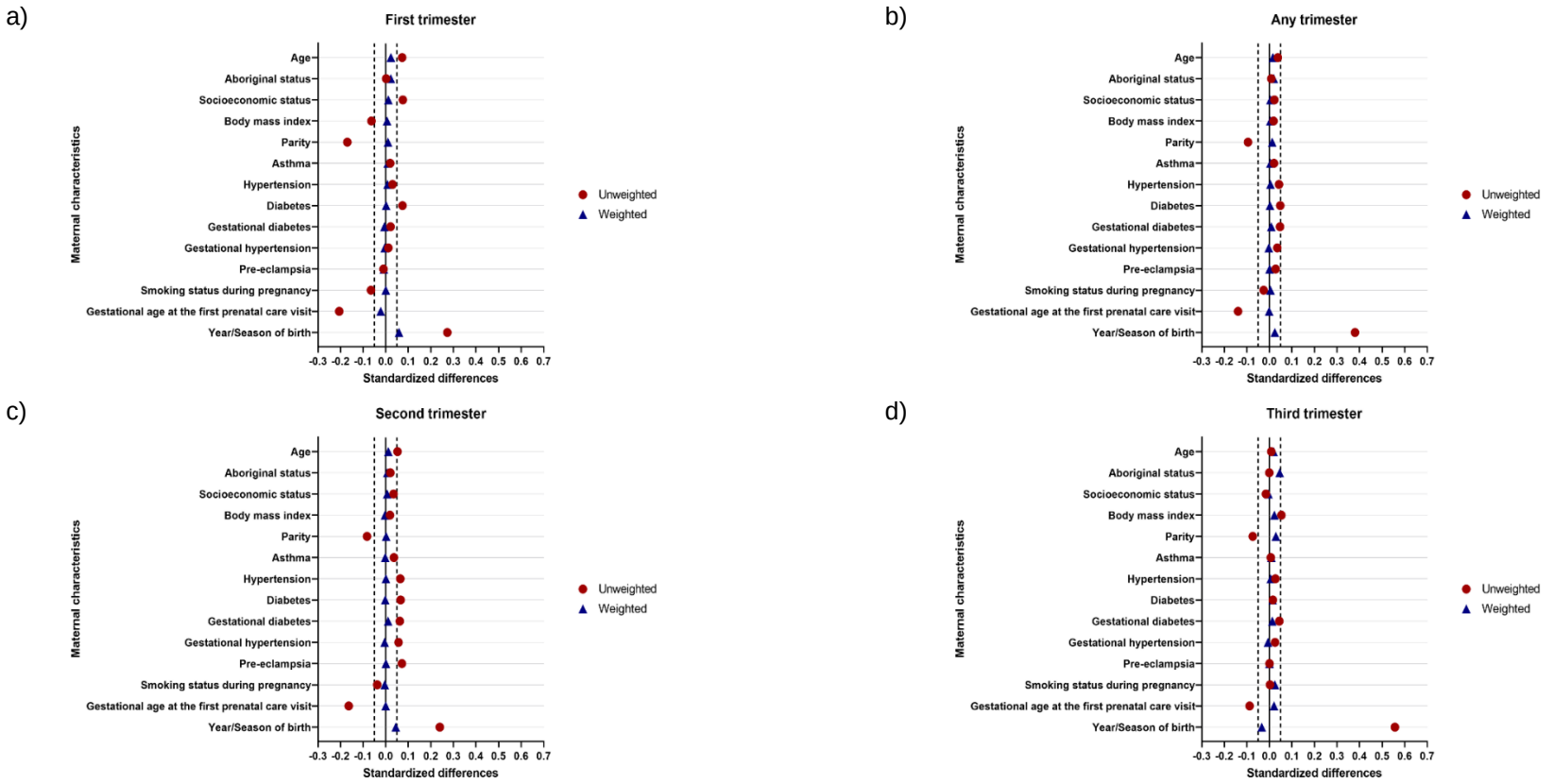
Supplementary Table F-8. Risk of all-cause injury associated with prenatal exposure to seasonal inactivated influenza vaccination among children <5 years of age, by trimester of prenatal vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Hospital inpatient admissions and emergency department presentations					
Cases, n (%)	19,452 (17.6)	2,278 (15.8)	446 (16.0)	966 (17.4)	866 (14.3)
Unweighted HR (95% CI)	1 [Reference]	**1.06 (1.02 to 1.11)**	1.07 (0.98 to 1.18)	**1.08 (1.01 to 1.15)**	1.04 (0.97 to 1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	1.04 (0.99 to 1.11)	1.05 (0.95 to 1.16)	1.05 (0.99 to 1.13)	1.02 (0.94 to 1.09)
Hospital inpatient admissions only					
Cases, n (%)	3,173 (2.9)	355 (2.5)	74 (2.7)	138 (2.5)	143 (2.4)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.92 to 1.14)	1.10 (0.88 to 1.39)	0.95 (0.80 to 1.13)	1.06 (0.90 to 1.25)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.90 to 1.14)	1.11 (0.87 to 1.41)	0.93 (0.78 to 1.12)	1.05 (0.87 to 1.27)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All-cause injury was identified from the ICD-10-AM codes: S01-S09, S11-S19, S21-S29, S31-S39, S41-S49, S51-S59, S61-S69, S71-S79, S81-S89, S91-S99, found in the principal and additional diagnosis fields of hospital inpatient records and/or emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table F-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, gestational age at first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.



Supplementary Figure F-1. Balance of standardised differences of maternal covariates before and after inverse-probability treatment weighting, by trimester of vaccination: children of mothers a) vaccinated during any trimester, b) vaccinated during the first trimester, c) vaccinated during the second trimester, or d) vaccinated during the third trimester.

Note: dashed lines indicate 5% standardised mean difference.

Appendix G. Study Four (Chapter Eight): Supplementary Material

Supplementary Table G-1. ICD-10-AM diagnosis codes used to identify neurodevelopmental disorders, and all-cause injuries, and frequency of outcomes by data source.

Outcome	ICD-10-AM or Symptom Code	Both data sources[a,b] (n)	Hospital inpatient admission (HMDC)[a] (n)	Emergency department episode (EDDC)[b] (n)
Neurodevelopmental disorder	Composite of all codes listed below:	6,642	5,126	2,715
Mental or behavioural disorder				
Organic, including symptomatic, mental disorders	F00-F09	70	17	54
Mental and behavioural disorders due to psychotic substance use	F10-F19	43	23	20
Schizophrenia, schizotypal and delusional disorders	F20-F29	0	0	0
Mood (affective) disorders	F30-F39	0	0	0
Neurotic, stress-related and somatoform disorders	F40-F48	38	7	31
Behavioural syndromes associated with physiological development	F50-F59	8	<5	<5
Disorders of adult personality and behaviours	F60-F69	<5	<5	0
Intellectual disability	F70-F79	<5	<5	0
Disorders of psychological development	F80-F89	187	176	14
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F90-F98	113	33	81
Unspecified mental disorder	F99	<5	0	<5
Neurologic disorder				
Inflammatory disease of the central nervous system	G00-G09	174	119	73
Systematic atrophies primarily affecting the central nervous system	G10-G14	14	14	0

Extrapyramidal and movement disorders	G20-G26	165	*	<5
Other degenerative diseases of the central nervous system	G30-G32	<5	<5	0
Demyelinating diseases of the central nervous system	G35-G37	<5	<5	0
Episodic and paroxysmal disorders	G40-G47	3,929	3,476	623
Seizure disorder	G40-G41; R56	2,730	1,377	2,359
Epilepsy and status epileptus	G40-G41	642	204	577
Convulsions, not elsewhere classified	R56	2,507	1,282	2,005
Nerve, nerve root and plexus disorders	G50-G59	35	27	13
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	7	*	<5
Diseases of myoneural junction and muscle	G70-G73	20	*	<5
Cerebral palsy and other paralytic syndromes	G80-G83	110	108	7
Other disorders of the nervous system	G90-G99	228	180	63
Negative control condition: all-cause injury admission	Composite of all codes listed below:	21,730	3,528	20,898
Head	S01-S09	14,466	2,347	13,789
Neck	S11-S19	200	30	179
Thorax	S21-S29	106	53	64
Abdomen, lower back, lumbar spine and pelvis	S31-S39	365	63	315
Shoulder and upper arm	S41-S49	1,005	172	932
Elbow and forearm	S51-S59	3,481	189	3,407
Wrist and hand	S61-S69	1,868	473	1,759
Hip and thigh	S71-S79	254	122	240
Knee and lower leg	S81-S89	1,120	99	1,077
Ankle and foot	S91-S99	1,541	154	1,478
Multiple site	ABD**	0	-	0
Chest	ABE**	0	-	0
Head	ABF**	0	-	0
Limb	ABG**	0	-	0
Burn	ABH**	0	-	0
Laceration	ABI**	0	-	0
Facial	ABJ**	0	-	0
Eye	ABK**	0	-	0
Bite	ABL**	0	-	0
Sexual	ABM**	0	-	0
Insect bite	ABM**	0	-	0
Nil	ABO**	0	-	0

Abbreviations: EDDC, Emergency Department Data Collection; HMDC, Hospital Morbidity Data Collection; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.
[a] Principal and 20 additional diagnoses fields were used to classify outcomes.
[b] Principal diagnosis fields, and symptom fields were used to classify outcomes.
* In accordance with privacy and confidentiality guidelines by the WA Data Linkage Branch, secondary suppression was used to prevent suppressed cells (<5) from being recalculated through subtraction.
** Symptom code used if principal diagnosis field is missing (EDDC only).

Supplementary Table G-2. Post-hoc power analysis of detectable differences in risk of outcomes among children <5 years of age, by trimester of vaccination.

Condition	Number of outcomes	% of unexposed with outcome	Detectable alternative[a] 90% power Lower	90% power Upper	80% power Lower	80% power Upper
Exposed to seasonal influenza vaccine during any trimester						
Neurodevelopmental disorder	6,642	5.40	0.883	1.123	0.898	1.106
Mental or behavioural disorder	454	0.37	0.575	1.518	0.621	1.436
Neurologic disorder	6,335	5.15	0.880	1.126	0.895	1.108
Seizure disorder	2,730	2.21	0.816	1.199	0.839	1.170
All-cause injury	21,730	17.63	0.939	1.063	0.947	1.054
Exposed to seasonal influenza vaccine during the first trimester						
Neurodevelopmental disorder	6,097	5.40	0.753	1.273	0.783	1.232
Mental or behavioural disorder	413	0.37	0.200	2.223	0.251	1.996
Neurologic disorder	5,817	5.15	0.747	1.280	0.777	1.238
Seizure disorder	2,486	2.21	0.621	1.447	0.662	1.376
All-cause injury	19,898	17.63	0.869	1.137	0.885	1.118
Exposed to seasonal influenza vaccine during the second trimester						
Neurodevelopmental disorder	6,253	5.40	0.820	1.193	0.843	1.165
Mental or behavioural disorder	23	0.37	0.379	1.838	0.435	1.694
Neurologic disorder	5,964	5.15	0.816	1.198	0.839	1.169
Seizure disorder	2,567	2.21	0.721	1.314	0.754	1.266
All-cause injury	20,418	17.63	0.905	1.098	0.918	1.084
Exposed to seasonal influenza vaccine during the third trimester						
Neurodevelopmental disorder	6,222	5.40	0.827	1.185	0.849	1.158
Mental or behavioural disorder	18	0.37	0.400	1.801	0.455	1.664
Neurologic disorder	5,932	5.15	0.823	1.190	0.845	1.162
Seizure disorder	2,559	2.21	0.732	1.301	0.764	1.255
All-cause injury	20,318	17.63	0.909	1.094	0.921	1.081

[a] Significance level: α = 5%.

Supplementary Table G-3. Risk of neurodevelopmental disorders associated with maternal influenza vaccination among children <5 years of age who were born at term or later (>37 weeks gestational age), by trimester of vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 102,974)	Exposed to seasonal influenza vaccine during pregnancy (N = 13,509)	Trimester of vaccine exposure		
			First trimester (N = 2,600)	Second trimester (N = 5,117)	Third trimester (N = 5,792)
Neurodevelopmental disorder					
Cases, n (%)	5,323 (5.2)	606 (4.5)	120 (4.6)	244 (4.8)	242 (4.2)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.94-1.11)	1.05 (0.87-1.26)	1.01 (0.89-1.15)	1.02 (0.90-1.16)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.92-1.10)	1.02 (0.84-1.23)	1.01 (0.88-1.15)	0.99 (0.87-1.14)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.01 (0.91-1.12)	1.02 (0.81-1.28)	1.01 (0.86-1.18)	0.99 (0.85-1.17)
Mental or *behavioural disorder*					
Cases, n (%)	349 (0.3)	38 (0.3)	6 (0.2)	15 (0.3)	17 (0.3)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.71-1.39)	0.81 (0.36-1.82)	0.97 (0.58-1.62)	1.10 (0.68-1.79)
Weighted aHR (95% CI)[a]	1 [Reference]	0.99 (0.69-1.44)	0.79 (0.33-1.89)	1.02 (0.58-1.80)	1.07 (0.61-1.86)
Weighted aHR (98% CI)[ab]	1 [Reference]	0.99 (0.64-1.54)	0.79 (0.28-2.22)	1.02 (0.52-2.00)	1.07 (0.55-2.06)
Neurologic disorder					
Cases, n (%)	5,083 (4.9)	580 (4.3)	116 (4.5)	235 (4.6)	229 (4.0)
Unweighted HR (95% CI)	1 [Reference]	1.03 (0.94-1.12)	1.06 (0.88-1.28)	1.02 (0.9-1.16)	1.02 (0.89-1.16)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.92-1.11)	1.03 (0.85-1.25)	1.02 (0.89-1.17)	0.99 (0.86-1.13)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.01 (0.91-1.12)	1.03 (0.82-1.29)	1.02 (0.86-1.20)	0.99 (0.83-1.16)
Seizure disorder					
Cases, n (%)	2,184 (2.1)	258 (1.9)	39 (1.5)	106 (2.1)	113 (2.0)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.87-1.12)	0.77 (0.56-1.05)	1.01 (0.83-1.23)	1.07 (0.88-1.29)
Weighted aHR (95% CI)[a]	1 [Reference]	1.00 (0.87-1.15)	0.72 (0.51-1.00)	1.08 (0.88-1.33)	1.04 (0.85-1.27)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.00 (0.85-1.18)	0.72 (0.48-1.06)	1.08 (0.85-1.38)	1.04 (0.82-1.32)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table G-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.
[b] Adjusted models accounted for multiple comparisons using Bonferroni-corrected confidence intervals.

Supplementary Table G-4. Risk of neurodevelopmental disorders associated with maternal influenza vaccination among children <5 years of age who were born preterm (<37 weeks gestational age), by trimester of vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 7,390)	Exposed to seasonal influenza vaccine during pregnancy (N = 887)	Trimester of vaccine exposure		
			First trimester (N = 185)	Second trimester (N = 441)	Third trimester (N = 261)
Neurodevelopmental disorder					
Cases, n (%)	642 (8.7)	71 (8.0)	12 (6.5)	44 (10.0)	15 (5.7)
Unweighted HR (95% CI)	1 [Reference]	0.99 (0.77-1.27)	0.79 (0.44-1.39)	1.19 (0.88-1.62)	0.77 (0.46-1.28)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.70-1.19)	0.69 (0.39-1.24)	1.1 (0.79-1.53)	0.73 (0.41-1.29)
Weighted aHR (98% CI)[ab]	1 [Reference]	0.91 (0.67-1.25)	0.69 (0.35-1.39)	1.1 (0.75-1.63)	0.73 (0.37-1.44)
Mental or *behavioural disorder*					
Cases, n (%)	58 (0.8)	9 (1.0)	<5	8 (1.8)	<5
Unweighted HR (95% CI)	1 [Reference]	1.42 (0.71-2.87)	-	**2.43 (1.16-5.08)**	-
Weighted aHR (95% CI)[a]	1 [Reference]	1.08 (0.51-2.26)	-	1.90 (0.87-4.14)	-
Weighted aHR (98% CI)[ab]	1 [Reference]	1.08 (0.45-2.59)	-	1.90 (0.76-4.78)	-
Neurologic disorder					
Cases, n (%)	606 (8.2)	66 (7.4)	12 (6.5)	40 (9.1)	14 (5.4)
Unweighted HR (95% CI)	1 [Reference]	0.98 (0.76-1.26)	0.83 (0.47-1.47)	1.15 (0.83-1.58)	0.76 (0.45-1.29)
Weighted aHR (95% CI)[a]	1 [Reference]	0.91 (0.69-1.19)	0.74 (0.41-1.33)	1.06 (0.75-1.50)	0.74 (0.41-1.34)
Weighted aHR (98% CI)[ab]	1 [Reference]	0.91 (0.65-1.25)	0.74 (0.37-1.48)	1.06 (0.70-1.60)	0.74 (0.37-1.49)
Seizure disorder					
Cases, n (%)	257 (3.5)	31 (3.5)	6 (3.2)	20 (4.5)	5 (1.9)
Unweighted HR (95% CI)	1 [Reference]	1.05 (0.72-1.52)	0.96 (0.43-2.15)	1.31 (0.83-2.07)	0.61 (0.25-1.49)
Weighted aHR (95% CI)[a]	1 [Reference]	0.93 (0.62-1.38)	0.84 (0.37-1.91)	1.21 (0.74-1.98)	0.48 (0.19-1.21)
Weighted aHR (98% CI)[ab]	1 [Reference]	0.93 (0.58-1.49)	0.84 (0.32-2.23)	1.21 (0.67-2.17)	0.48 (0.16-1.44)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient records (**Supplementary Table G-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.
[b] Adjusted models accounted for multiple comparisons using Bonferroni-corrected confidence intervals.

Supplementary Table G-5. Risk of inpatient admission (only) for neurodevelopmental disorders associated maternal influenza vaccination among children <5 years of age, by trimester of vaccination.

	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Neurodevelopmental disorder					
Cases, n (%)	4,605 (4.2)	521 (3.6)	116 (4.2)	219 (3.9)	186 (3.1)
Unweighted HR (95% CI)	1 [Reference]	1.04 (0.95-1.14)	1.19 (0.99-1.43)	1.05 (0.91-1.20)	0.95 (0.82-1.10)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.92-1.11)	1.13 (0.93-1.37)	1.02 (0.89-1.18)	0.93 (0.80-1.09)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.01 (0.90-1.13)	1.13 (0.90-1.42)	1.02 (0.86-1.21)	0.93 (0.78-1.12)
Mental or *behavioural disorder*					
Cases, n (%)	230 (0.2)	28 (0.2)	<5	14 (0.3)	10 (0.2)
Unweighted HR (95% CI)	1 [Reference]	1.14 (0.77-1.68)	-	1.36 (0.79-2.33)	1.05 (0.55-1.98)
Weighted aHR (95% CI)[a]	1 [Reference]	1.06 (0.68-1.64)	-	1.17 (0.65-2.10)	1.10 (0.53-2.31)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.06 (0.63-1.78)	-	1.17 (0.59-2.34)	1.10 (0.46-2.65)
Neurologic disorder					
Cases, n (%)	4,462 (4.0)	503 (3.5)	113 (4.1)	210 (3.8)	180 (3.0)
Unweighted HR (95% CI)	1 [Reference]	1.03 (0.94-1.14)	1.20 (0.99-1.45)	1.04 (0.90-1.19)	0.95 (0.82-1.10)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.92-1.11)	1.14 (0.94-1.38)	1.02 (0.88-1.18)	0.93 (0.79-1.08)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.01 (0.90-1.13)	1.14 (0.90-1.43)	1.02 (0.86-1.21)	0.93 (0.77-1.12)
Seizure disorder					
Cases, n (%)	1,227 (1.1)	150 (1.0)	26 (0.9)	63 (1.1)	61 (1.0)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.86-1.21)	0.91 (0.61-1.34)	1.05 (0.82-1.35)	1.04 (0.81-1.35)
Weighted aHR (95% CI)[a]	1 [Reference]	1.03 (0.86-1.23)	0.80 (0.53-1.19)	1.14 (0.87-1.50)	1.01 (0.77-1.33)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.03 (0.83-1.28)	0.80 (0.49-1.28)	1.14 (0.83-1.57)	1.01 (0.73-1.40)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient records (**Supplementary Table G-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.
[b] Adjusted models accounted for multiple comparisons using Bonferroni-corrected confidence intervals.

Supplementary Table G-6. Risk of all-cause injury associated maternal influenza vaccination among children <5 years of age, by trimester of vaccination.

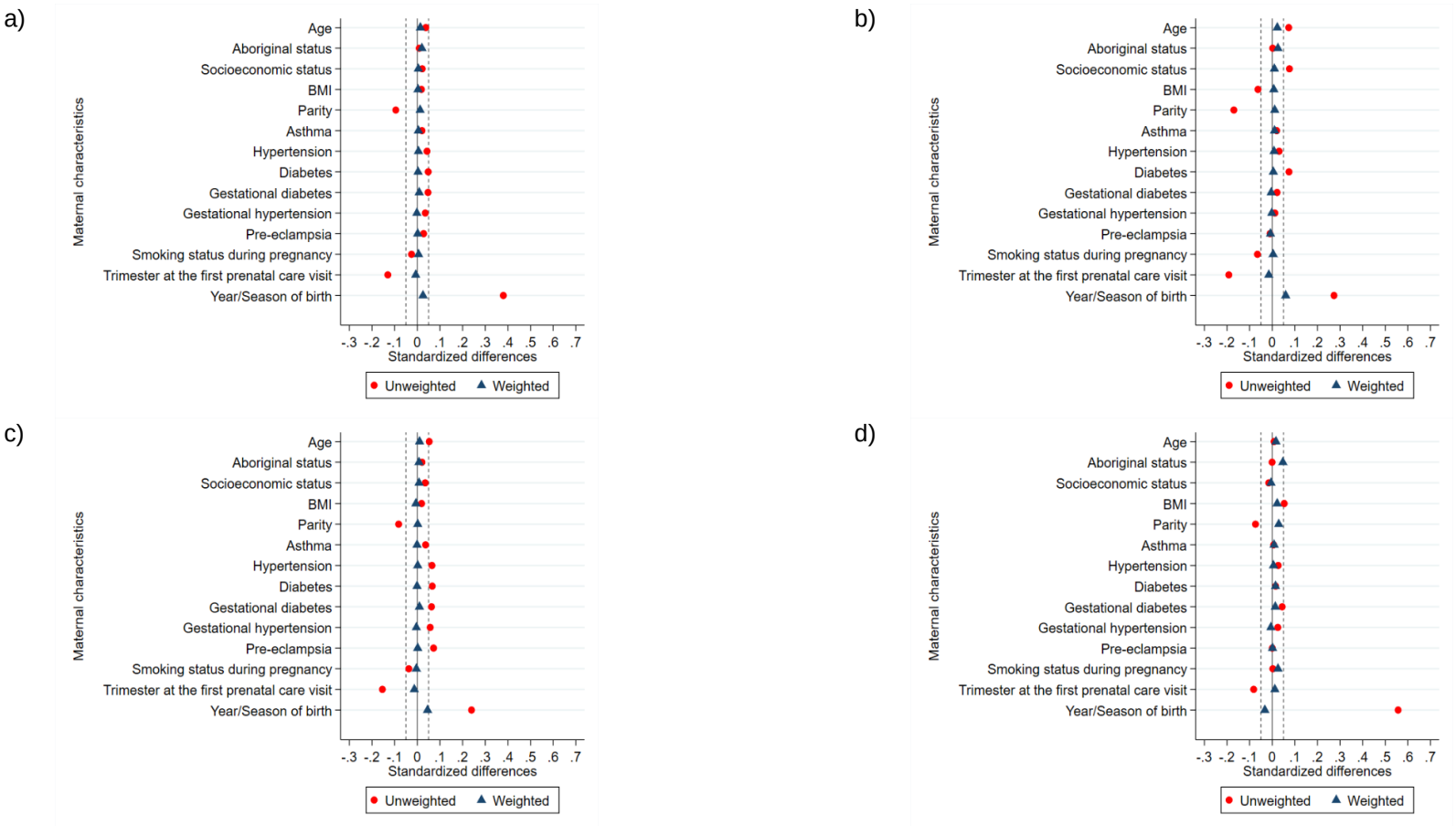
	Unexposed to seasonal influenza vaccine during pregnancy (N = 110,364)	Exposed to seasonal influenza vaccine during pregnancy (N = 14,396)	Trimester of vaccine exposure		
			First trimester (N = 2,785)	Second trimester (N = 5,558)	Third trimester (N = 6,053)
Hospital inpatient admissions and emergency department presentations					
Cases, n (%)	19,452 (17.6)	2,278 (15.8)	446 (16.0)	966 (17.4)	866 (14.3)
Unweighted HR (95% CI)	1 [Reference]	**1.06 (1.02-1.11)**	1.07 (0.98-1.18)	**1.08 (1.01-1.15)**	1.04 (0.97-1.11)
Weighted aHR (95% CI)[a]	1 [Reference]	1.04 (0.99-1.09)	1.05 (0.95-1.16)	1.05 (0.99-1.13)	1.02 (0.94-1.09)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.04 (0.98-1.10)	1.05 (0.94-1.18)	1.05 (0.97-1.14)	1.02 (0.93-1.11)
Hospital inpatient admissions only					
Cases, n (%)	3,173 (2.9)	355 (2.5)	74 (2.7)	138 (2.5)	143 (2.4)
Unweighted HR (95% CI)	1 [Reference]	1.02 (0.92-1.14)	1.10 (0.88-1.39)	0.95 (0.80-1.13)	1.06 (0.90-1.25)
Weighted aHR (95% CI)[a]	1 [Reference]	1.01 (0.90-1.14)	1.11 (0.87-1.41)	0.93 (0.78-1.12)	1.05 (0.87-1.27)
Weighted aHR (98% CI)[ab]	1 [Reference]	1.01 (0.88-1.16)	1.11 (0.83-1.48)	0.93 (0.75-1.16)	1.05 (0.84-1.31)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

All-cause injury was identified from the ICD-10-AM codes: S01-S09, S11-S19, S21-S29, S31-S39, S41-S49, S51-S59, S61-S69, S71-S79, S81-S89, S91-S99, found in the principal and 20 additional diagnosis fields of hospital inpatient records and/or emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (**Supplementary Table G-1**).

[a] Hazard ratios were weighted by inverse-probability of treatment factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth; models were additionally adjusted for child's Aboriginal status.

[b] Adjusted models accounted for multiple comparisons using Bonferroni-corrected confidence intervals.



Supplementary Figure G-1. Balance of maternal covariates before and after inverse-probability treatment weighting, by trimester of vaccination: children of mothers a) vaccinated during any trimester, b) vaccinated during the first trimester, c) vaccinated during the second trimester, or d) vaccinated during the third trimester.
Note: dashed lines indicates 5% standardised mean difference.

Appendix H. Study Five (Chapter Nine): Supplementary Material

Supplementary Table H-1. Post-hoc power analysis of detectable differences in the risk of child mortality for children <5 years of age, by trimester of vaccination.

Trimester of exposure to seasonal influenza vaccine	Children of unvaccinated mothers (n = 155,582)	Children of vaccinated mothers (n = 35,665)	Detectable alternative[a] 90% power		90% power	
	Number of child deaths		Lower	Upper	Lower	Upper
Any trimester	413	73	0.889	1.117	0.903	1.101
First trimester	413	14	0.757	1.269	0.786	1.229
Second trimester	413	24	0.823	1.190	0.846	1.163
Third trimester	413	31	0.841	1.170	0.861	1.146

[a] Significance level: α = 5%.

Supplementary Table H-2. Maternal and child characteristics for children born in Western Australia between 1 December 2012 and 31 December 2017.

Characteristic	Children of unvaccinated mothers (n = 155,582) n (%)	Children of vaccinated mothers (n = 35,665) n (%)
Maternal characteristics		
Age (years)		
≤19	4,639 (3.0)	1,011 (2.8)
20-24	20,812 (13.4)	4,334 (12.2)
25-29	44,176 (28.4)	9,961 (27.9)
30-34	53,056 (34.1)	12,901 (36.2)
≥35	32,899 (21.2)	7,458 (20.9)
Aboriginal status:[a]		
Aboriginal	8,118 (5.2)	1,819 (5.1)
Non-Aboriginal	147,464 (94.8)	33,846 (94.9)
Socioeconomic status:[b,c]		
Quintile 1 (most disadvantaged)	30,421 (19.6)	6,570 (18.4)
Quintile 2	31,583 (20.3)	7,281 (20.4)
Quintile 3	33,319 (21.4)	7,637 (21.4)
Quintile 4	31,251 (20.1)	7,347 (20.6)
Quintile 5 (least disadvantaged)	29,008 (18.6)	6,830 (19.2)
Body mass index:		
<18.5 (underweight)	4,642 (3.2)	1,074 (3.1)
18.5 to <25 (normal)	71,175 (48.3)	17,094 (49.1)
25 to <30 (overweight)	41,410 (28.1)	9,558 (27.5)
≥30 (obese)	30,087 (20.4)	7,059 (20.3)
Parity:[d]		
Primiparous	65,185 (41.9)	16,684 (46.8)
1 prior birth	54,561 (35.1)	12,425 (34.8)
≥2 prior births	35,836 (23.0)	6,556 (18.4)
Pre-existing medical conditions:		
Asthma	15,518 (10.0)	3,522 (9.9)
Essential hypertension	2,622 (1.7)	1,088 (3.1)
Diabetes mellitus	1,402 (0.9)	516 (1.5)
Pregnancy complications:		
Gestational diabetes	15,598 (10.0)	4,026 (11.3)
Gestational hypertension	6,909 (4.4)	1,664 (4.7)
Pre-eclampsia	4,971 (3.2)	1,170 (3.3)

Smoked during pregnancy	15,228 (9.8)	2,882 (8.1)
Trimester of first prenatal care visit:[e]		
First trimester	102,095 (65.6)	25,069 (70.3)
Second trimester	45,697 (29.4)	9,584 (26.9)
Third trimester	7,504 (4.8)	1,004 (2.8)
No prenatal care	286 (0.2)	8 (0.0)
Year of birth:		
2012	22,844 (14.7)	1,552 (4.4)
2013	29,458 (18.9)	3,410 (9.6)
2014	29,827 (19.2)	3,771 (10.6)
2015	27,444 (17.6)	5,982 (16.8)
2016	24,339 (15.6)	9,974 (28.0)
2017	21,670 (13.9)	10,976 (30.8)
Season of birth:		
Summer (Dec-Feb)	37,897 (24.4)	5,813 (16.3)
Autumn (Mar-May)	43,329 (27.9)	4,900 (13.7)
Winter (Jun-Aug)	37,327 (24.0)	12,117 (34.0)
Spring (Sep-Nov)	37,029 (23.8)	12,835 (36.0)
Child characteristics		
Sex:[f]		
Male	80,085 (51.5)	18,317 (51.4)
Female	75,494 (48.5)	17,346 (48.6)
Aboriginal status:[a]		
Aboriginal	8,788 (5.7)	1,991 (5.6)
Non-Aboriginal	146,794 (94.4)	33,674 (94.4)
Birth outcomes:		
Preterm birth	10,868 (7.0)	2,262 (6.4)
Moderate-to-late preterm	9,572 (6.2)	2,100 (5.9)
Very preterm	845 (0.6)	122 (0.3)
Extremely preterm	451 (0.3)	40 (0.1)
Small-for-gestational age[g]	12,522 (8.1)	2,902 (8.2)

Abbreviations: CI, confidence interval.

[a] Includes Aboriginal and/or Torres Strait Islander.

[b] Socioeconomic status was based on the Socioeconomic Index for Areas (SEIFA) measure of relative socioeconomic advantage and disadvantage developed by the Australian Bureau of Statistics.

[c] The socioeconomic status of 2,798 (1.5%) children was imputed due to missing data.

[d] The parity of 962 (7.0%) children was imputed due to missing data.

[e] The trimester at the first prenatal care visit of 11,919 (6.2%) children was imputed due to missing data.

[f] The sex of <5 children of vaccinated and unvaccinated mothers was unknown.

[g] Small-for-gestational age was based on the Australian national birthweight percentiles by sex and gestational age.

Supplementary Table H-3. Risk of child mortality associated with maternal influenza vaccination among children aged <5 years of age born between 1 April 2012 and 31 December 2017, by trimester of vaccination and age sub-group.

	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First trimester	Second trimester	Third trimester
Children aged 0 to <5 years					
N	155,582	35,665	5,989	12,140	15,353
Cases, n (%)	413 (0.3)	73 (0.2)	14 (0.2)	24 (0.2)	31 (1.4)
HR	1 [Reference]	0.85 (0.65-1.12)	0.94 (0.54-1.66)	0.80 (0.51-1.25)	0.83 (0.56-1.22)
aHR (95% CI)[a]	1 [Reference]	0.89 (0.68-1.17)	1.01 (0.58-1.77)	0.84 (0.54-1.31)	0.85 (0.58-1.24)
Children aged 1 month to <5 years					
N	155,367	35,629	5,980	12,127	15,342
Cases, n (%)	198 (0.1)	37 (0.1)	5 (0.1)	11 (0.1)	20 (0.9)
HR	1 [Reference]	1.04 (0.71-1.52)	0.78 (0.31-1.95)	0.89 (0.46-1.71)	1.29 (0.78-2.14)
aHR (95% CI)[a]	1 [Reference]	1.08 (0.74-1.58)	0.87 (0.35-2.16)	0.94 (0.49-1.81)	1.30 (0.79-2.14)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio.

[a] Hazard ratios were pooled from the 20 imputed datasets and were adjusted for maternal covariates, including Aboriginal and/or Torres Strait Islander status, socioeconomic status, pre-existing medical conditions (asthma, hypertension, diabetes mellitus), and trimester at the first prenatal care visit.

Supplementary Table H-4. Risk of child mortality associated with maternal influenza vaccination among children aged <5 years of age born between 1 April 2012 and 31 December 2017, excluding children of mothers with indeterminate vaccination status, by trimester of vaccination and age-sub-group.

	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First trimester	Second trimester	Third trimester
Children aged 0 to <5 years					
N	155,582	34,276	5,989	12,124	13,981
Cases, n (%)	413 (0.3)	65 (0.2)	14 (0.2)	21 (0.2)	27 (1.2)
HR	1 [Reference]	0.78 (0.59-1.04)	0.94 (0.54-1.66)	0.69 (0.43-1.11)	0.80 (0.53-1.21)
aHR (95% CI)[a]	1 [Reference]	0.82 (0.62-1.09)	1.01 (0.58-1.77)	0.73 (0.45-1.16)	0.83 (0.55-1.25)
Children aged 1 month to <5 years					
N	155,367	34,244	5,980	12,113	13,971
Cases, n (%)	198 (0.1)	33 (0.1)	5 (0.1)	10 (0.1)	17 (0.8)
HR	1 [Reference]	0.96 (0.64-1.43)	0.78 (0.31-1.95)	0.81 (0.41-1.60)	1.23 (0.71-2.11)
aHR (95% CI)[a]	1 [Reference]	1.02 (0.69-1.52)	0.87 (0.35-2.16)	0.85 (0.43-1.69)	1.27 (0.75-2.17)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio.

[a] Hazard ratios were pooled from the 20 imputed datasets and were adjusted for maternal covariates including, Aboriginal and/or Torres Strait Islander status, socioeconomic status, pre-existing medical conditions (asthma, hypertension, diabetes mellitus), and trimester at the first prenatal care visit.

Supplementary Table H-5. Risk of child mortality associated with maternal influenza vaccination among children aged <5 years of age born between 1 December 2012 and 31 December 2017, by trimester of vaccination and age sub-group.

	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First trimester	Second trimester	Third trimester
Children aged 0 to <5 years					
N	135,232	34,268	5,896	11,521	14,669
Cases, n (%)	351 (0.3)	67 (0.2)	12 (0.2)	21 (0.2)	30 (1.4)
HR	1 [Reference]	0.82 (0.62-1.09)	0.81 (0.45-1.48)	0.74 (0.46-1.20)	0.86 (0.58-1.29)
aHR (95% CI)[a]	1 [Reference]	0.87 (0.65-1.15)	0.87 (0.48-1.58)	0.78 (0.49-1.26)	0.90 (0.60-1.33)
Children aged 1 month to <5 years					
N	135,038	34,233	5,888	11,508	14,658
Cases, n (%)	157 (0.1)	32 (0.1)	<5	8 (0.1)	19 (0.9)
HR	1 [Reference]	0.96 (0.64-1.44)	-	0.70 (0.33-1.49)	1.39 (0.82-2.37)
aHR (95% CI)[a]	1 [Reference]	1.04 (0.69-1.56)	-	0.76 (0.36-1.61)	1.46 (0.87-2.47)

Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

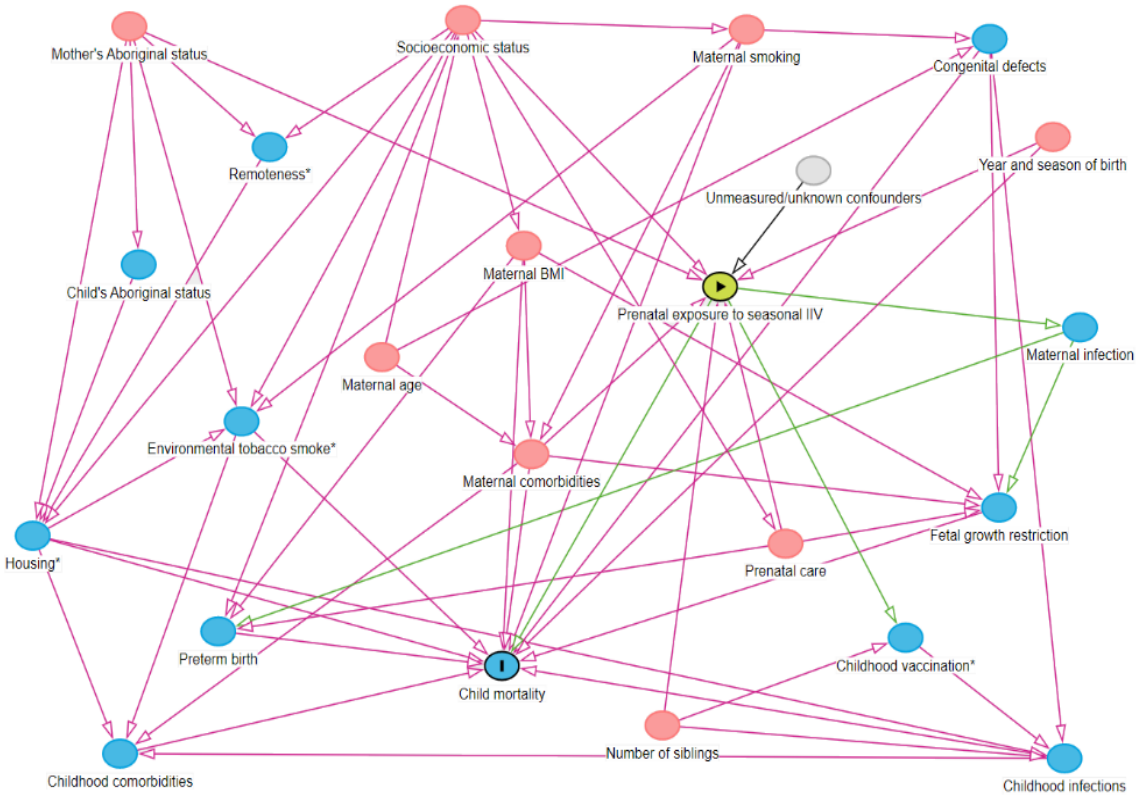
[a] Hazard ratios were pooled from the 20 imputed datasets and were adjusted for maternal covariates including, Aboriginal and/or Torres Strait Islander status, socioeconomic status, pre-existing medical conditions (asthma, hypertension, diabetes mellitus), and trimester at the first prenatal care visit.

Supplementary Table H-6. Risk of child mortality associated with maternal influenza vaccination among children aged <5 years of age born between 1 December 2012 and 31 December 2017, excluding children of mothers with indeterminate vaccination status, by trimester of vaccination and age-sub-group.

	Unexposed to seasonal influenza vaccine during pregnancy	Exposed to seasonal influenza vaccine during pregnancy	Trimester of vaccine exposure		
			First trimester	Second trimester	Third trimester
Children aged 0 to <5 years					
N	135,232	33,031	5,896	11,510	13,444
Cases, n (%)	351 (0.3)	60 (0.2)	12 (0.2)	18 (0.2)	27 (1.2)
HR	1 [Reference]	0.76 (0.56-1.02)	0.81 (0.45-1.48)	0.63 (0.38-1.04)	0.86 (0.56-1.31)
aHR (95% CI)[a]	1 [Reference]	0.80 (0.59-1.08)	0.87 (0.48-1.58)	0.66 (0.40-1.09)	0.90 (0.59-1.37)
Children aged 1 month to <5 years					
N	135,038	33,000	5,888	11,499	13,434
Cases, n (%)	157 (0.1)	29 (0.1)	<5	7 (0.1)	17 (0.8)
HR	1 [Reference]	0.90 (0.59-1.38)	-	0.61 (0.27-1.35)	1.39 (0.79-2.44)
aHR (95% CI)[a]	1 [Reference]	0.99 (0.65-1.52)	-	0.66 (0.30-1.47)	1.49 (0.85-2.61)

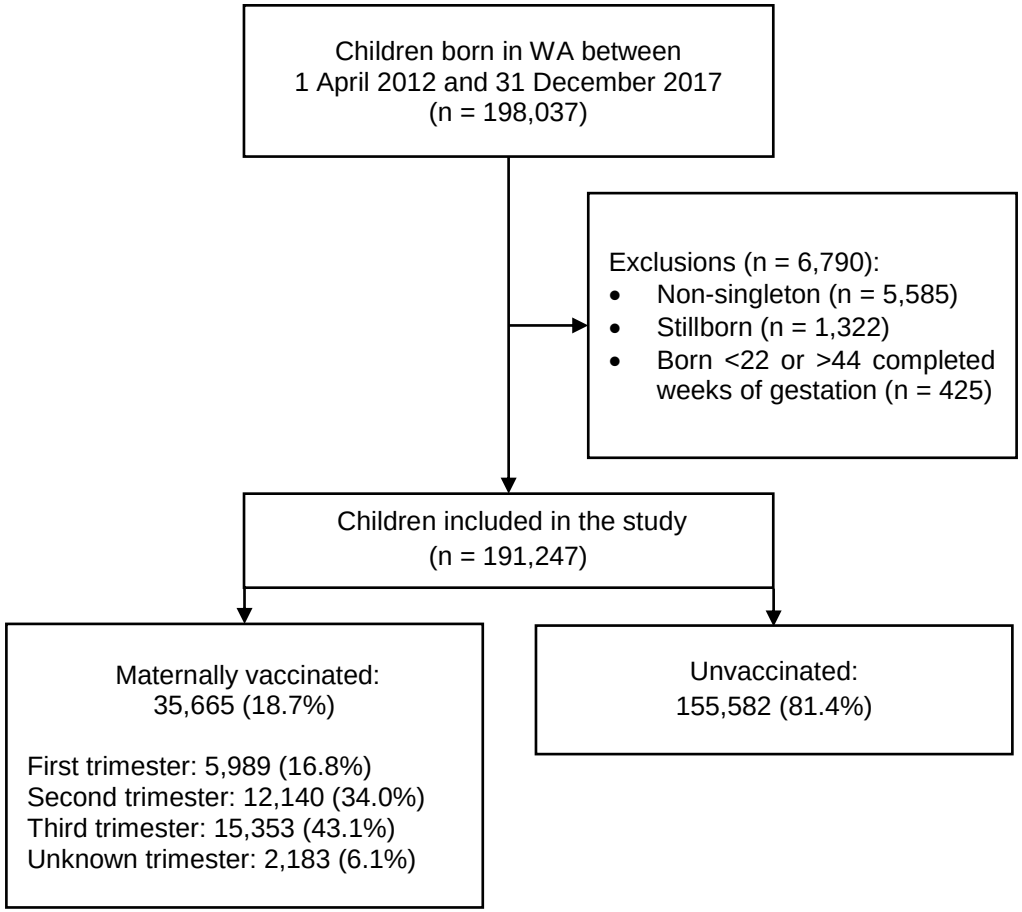
Abbreviations: CI, confidence interval; HR, unadjusted hazard ratio; aHR, adjusted hazard ratio; -, indeterminate (a stable estimate could not be generated due to the low number of outcomes).

[a] Hazard ratios were pooled from the 20 imputed datasets and were adjusted for maternal covariates including, Aboriginal and/or Torres Strait Islander status, socioeconomic status, pre-existing medical conditions (asthma, hypertension, diabetes mellitus), and trimester at the first prenatal care visit.



Supplementary Figure H-1. Directed acyclic graph of relationship between maternal influenza vaccination and child mortality.
Exposure: prenatal exposure to seasonal IIV (i.e., inactivated influenza vaccine); outcome: child mortality; blue node: ancestor of outcome; red node: ancestor of exposure and outcome; grey node: unobserved/unknown (latent) confounders; green arrow: causal paths; red arrow: biasing paths; black arrow: relationship unclear. The minimal sufficient adjustment set for estimating the total effect of prenatal exposure to seasonal IIV on child mortality are: maternal comorbidities, mother's Aboriginal and/or Torres Strait Islander status, number of siblings, prenatal care, socioeconomic status, year and season of birth.

*Data not available for remoteness, environmental tobacco smoking, housing and childhood vaccination.



Supplementary Figure H-2. Flow diagram of study participants included in the cohort.