Pertussis and Influenza Vaccination during Pregnancy: Maternal and Neonatal Health Outcomes

`

Hassen Mohammed, BHSc (Hons, First Class)

Discipline of Paediatrics and Reproductive Health

Adelaide School of Medicine

Faculty of Health and Medical Sciences

The University of Adelaide

Australia

Thesis Submitted to the University of Adelaide for fulfilment of the requirement for admission to the degree of Doctor of Philosophy (PhD)

July 2021

TABLE OF CONTENTS

Abstract

Background and objectives

Vaccination during pregnancy can enhance transplacental transfer of protective antibody to the fetus and protect the infant against disease during the first few months of life. Despite the recommendation of maternal influenza and pertussis vaccination to protect pregnant women and their infants against these serious infections, uptake of the vaccines has been suboptimal globally. This thesis aims to determine the most effective interventions used to improve maternal pertussis vaccine uptake, identify psychosocial factors influencing acceptance and uptake of maternal pertussis and seasonal influenza vaccination and evaluate evidence for the safety and benefits of these two routinely recommended vaccines during pregnancy in improving maternal and neonatal health outcomes.

Methods

A systematic review was conducted to identify strategies effective in improving uptake of pertussis vaccine among pregnant women. A prospective cohort study of low risk, nulliparous women with singleton pregnancies were recruited between 2015-2018 at two major maternity hospitals in Adelaide, South Australia, with the primary aim to develop screening tests to identify adverse pregnancy outcomes. Using this multicentre prospective cohort with comprehensive clinical, lifestyle, sociodemographic data, and documented maternal vaccination status, the thesis examined psychosocial predictors of maternal vaccination and evaluated the safety and impact of maternal seasonal influenza and pertussis vaccines on pregnancy and birth outcomes. Poisson regression models were used to identify psychosocial factors influencing acceptance and uptake of the two routinely recommended antenatal vaccines. To evaluate the impact of maternal influenza and pertussis vaccination on health

outcomes for mothers and infants, Cox proportional-hazards and log-binomial models were applied.

Results

The systematic review included six original published studies that reported on interventions to increase uptake of pertussis vaccine among pregnant women. Observational studies showed i) a midwife delivered maternal vaccination program improved uptake of pertussis vaccine during pregnancy from 20% to 90%; ii) implementation of an automated reminder within the electronic medical record improved uptake from 48% to 97%; iii) an increase in maternal pertussis vaccine uptake from 36% to 61% after strategies to increase provider awareness of recommendations were introduced. In contrast, interventions in all three randomised controlled trials (RCTs) (two involved education of pregnant women, one had multi-component interventions) did not demonstrate improvement in the uptake of pertussis vaccination during pregnancy, although two of the RCT studies failed to attain their sample size estimates. Data from the prospective cohort showed that women's willingness to receive the recommended maternal vaccines was high (90%) and independent of psychosocial factors. However, a difference in the actual receipt of pertussis (79%) and seasonal influenza vaccines (48%) during pregnancy was observed. A history of major depressive disorder was the strongest predictor of pertussis (adjusted prevalence ratios, aPR 1.16, 95% CI:1.06–1.26) and influenza vaccination uptake during pregnancy (aPR 1.32; 95% CI: 1.14–1.58). Pregnant women presenting with elevated depressive symptoms were also more likely to receive maternal pertussis vaccination (aPR 1.14, 95% CI:1.00–1.30). In contrast, women with very high-perceived stress levels (aPR 0.87; 95% CI: 0.76–0.99) were less likely to receive maternal pertussis vaccination. Women with mild depressive symptoms (aPR 1.21, 95% CI: 1.00–1.44) and mild anxiety symptoms (aPR 1.21, 95% CI: 0.99–1.48) were more likely to receive influenza vaccine during pregnancy. Data analyses of the prospective cohort found no significant difference in the risk

of adverse pregnancy (spontaneous abortion, chorioamnionitis, gestational hypertension, pre-eclampsia, gestational diabetes, preterm premature rupture of the membranes, spontaneous preterm birth) and birth outcomes (congenital anomalies, small for gestational age births, low birth weight, admission to the neonatal care unit, low Apgar scores and mechanical ventilation) among women who received seasonal influenza or pertussis vaccinations in pregnancy compared with unvaccinated pregnant women. This thesis also presents evidence that maternal influenza vaccination reduces the risk of pre-delivery hospitalisation with influenza-like illness during pregnancy (adjusted hazard ratios, aHR 0.61; 95% CI: 0.39–0.97). Furthermore, the thesis findings suggest a protective effect of maternal seasonal influenza in reducing the rates of low birthweight (aHR 0.46, 95% CI: 0.23–0.94) and small for gestational age births (aHR 0.65, 95% CI: 0.40–1.04) during periods of high influenza activity.

Conclusions

There is limited high quality evidence for interventions to increase uptake of pertussis vaccine among pregnant women. Based on the existing research, incorporating midwife led maternal vaccination programs, increasing healthcare provider awareness of recommendations and implementation of a provider reminder system to target unvaccinated pregnant women are the most effective strategies to improve uptake of pertussis vaccine during pregnancy. The psychosocial predictors of maternal vaccination identified in this thesis can be used in designing effective interventions and maternal vaccination programs. The thesis findings on the safety of maternal pertussis and influenza vaccination and additional potential benefits of influenza vaccine during pregnancy in improving neonatal outcomes can be used to promote antenatal vaccination to expecting mothers and healthcare providers. Furthermore, these findings may aid evidence-based decision making for policy makers in countries considering implementation of universal antenatal seasonal influenza and pertussis vaccination programs.

Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Hassen Mohammed

Signature Date 01 July 2021

Acknowledgments

This thesis has been made possible through the support of many people. I would like to express my sincere gratitude to my supervisor Prof Helen Marshall for her mentorship, guidance, helpful advice and discussion that has made me into a better researcher. I am very grateful to Prof Claire Roberts for allowing me to use her study dataset for my thesis, supervision and providing me feedback during the course of my PhD. I also would like to thank A/Prof Lynne Giles and Dr. Luke Grzeskowiak for joining the supervisory panel 1.5 years ago and generously sharing their valuable statistical and analytical skills. They have been a great value to me in completing my PhD within the time frame. I would also to thank the staff of the Vaccinology and Immunology Research Trials Unit (VIRTU); Michelle Clarke for her supervision during my honours research and inspiring me to pursue a PhD program, Chris Heath for proofreading a number of Chapter during my final stage of thesis writing, Dr. Bing Wang for her continuous support and encouragement and Mark McMillan for providing constructive feedback on the systematic review.

Most importantly, this endeavour would not have been possible without the continual support of my families in Australia and Ethiopia. I am deeply grateful to my parents Ibrahim and Amina, my sisters Hanim and Kulen, my brother Anna and brother in law, Anwar. Thank you for your thoughtful encouragement and numerous prayers throughout this challenging accomplishment. Finally, I would like to thank all my friends who have shown patience and understanding when I needed time to work on the thesis.

List of Publications

Work related to this thesis

Mohammed H, Marshall HS, Roberts CT. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. Protocol for a systematic review. PROSPERO. 2017; CRD42017058178. (Appendix 1)

Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS One. 2019; 14(3): e0214538. (Chapter 4)

Mohammed H, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, Dekker GA, Marshall HS. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study. Vaccine. 2020; 38(17):3358-68. (Chapter 5)

Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. EClinicalMedicine.2020; 26:100522. (Chapter 6)

Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Verburg PE, Dekker G, Marshall HS. Safety of maternal pertussis vaccination on pregnancy and birth outcomes: A prospective cohort study. Vaccine. 2021; 39(2):324-31. (Chapter 7)

Other related work to this thesis published during Candidature

Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS One. 2018;13(6):e0197867 (Ancillary publication- Appendix D)

Other articles produced during candidature

Mohammed H, McMillan M, Marshall HS. Social and behavioral predictors of two-doses 4CMenB vaccine series among adolescents enrolled in a cluster randomized controlled trial in Australia. Human Vaccines & Immunotherapeutics.2021.doi:0.1080/21645515.2021.1953345

Alene KA, Gelaw YA, Fetene DM, Koye DN, Melaku YA… **Mohammed H** et al. COVID-19 in Ethiopia: a geospatial analysis of vulnerability to infection, case severity and death. BMJ Open. 2021; 11(2): e044606.

Gesesew HA, Koye DN, Fetene DM…**Mohammed H** et al. Risk factors for COVID-19 infection, disease severity and related deaths in Africa: a systematic review. BMJ Open. 2021;11(2): e044618. Published 2021 Feb 18. doi:10.1136/bmjopen-2020-044618

Mohammed H, Marshall HS. COVID-19 vaccines during pregnancy. Reproductive Health Australia (RHA) Newsletter June 2021.

Conference Presentations

2020 **Mohammed H**, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. Oral presentation. Robinson Research Institute Virtual Third Thursday Cross-Theme Meeting 2020, Adelaide, Australia.

2019 **Mohammed H**, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, Dekker G, Marshall HS. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women. E-Poster Discussion presented at 37th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) 2019, Ljubljana, Slovenia.

2019 **Mohammed H**, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, Dekker G, Marshall HS. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women. E-Poster presented at Annual Robinson Research Institute Symposium 2019, Adelaide. Australia

2018 **Mohammed H**, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. Oral presentation at the 16th National Immunisation Conference 2018, Adelaide, Australia.

2018 Mohammed H, McMillan, M, Roberts C, M, **Marshall H**. (2018). A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy**.** E-Poster Discussion presented at 36th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) 2018, Malmö, Sweden.

List of Abbreviations

ACT	Adenylate Cyclase Toxin
aHR	Adjusted hazard ratio
AIR	Australian Immunisation Register
aRR	Adjusted relative risk
BMI	Body Mass Index
CALD	Culturally and linguistically diverse
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
dTpa	Diphtheria-Tetanus-acellular pertussis (adult formulation)
DTP	Diphtheria -Tetanus pertussis
DTPa	Diphtheria-Tetanus-acellular pertussis
DTwP	Diphtheria-Tetanus-whole cell pertussis
EPDS	Edinburgh Postnatal Depression Scale
FcR	Fc receptor
FcRn	Neonatal Fc receptor
FHA	Filamentous Hemagglutinin
FIM	Fimbriae
g	grams
GBS	Group B Streptococcus
GP	General practitioner
HA	Hemagglutinin
HREC	Human Research Ethics Committee
H1N1pdm09	2009 H1N1 pandemic influenza A virus
ICD	International statistical classification of diseases
ICU	Intensive care unit
Ig	Immunoglobin
IQR	Interquartile ranges
LBW	Low birth weight
NA	Neuraminidase
NIP	National Immunisation Program

NNDSS	National Notifiable Diseases Surveillance System
PCR	Polymerase Chain Reaction
PSS	Perceived Stress Scale
PT	Pertussis Toxin
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture
RNP	Ribonucleoprotein complex
RSV	Respiratory syncytial virus
SA	Sialic acid
SAPR	South Australian Pregnancy Record
SGA	Small for gestational age
SKAI	Sharing Knowledge About Immunising
STAI	State-Trait Anxiety Inventory
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Chapter 1: Introduction

1.1 Background and Rationale for Research

Pertussis, also known as whooping cough, is a highly contagious infection of the respiratory tract (1). It is caused by *Bordetella pertussis* and has re-emerged globally as a cause of substantial morbidity and mortality in infants, children, and adolescents, despite high immunisation coverage (1). In 2008, the World Health Organization (WHO) estimated around 16 million cases of pertussis and 195,000 child deaths under five years of age annually and global high immunisation pertussis coverage has led to a significant reduction in child deaths in recent years (2-4). However, the morbidity and mortality associated with pertussis infections in young infants particularly within the first three months of life remains substantial (5-9). These first few months are the period when infants are at highest risk for complications and death from pertussis because they are not adequately protected against pertussis until they are old enough to complete the primary three doses immunisation series at six months and build up high levels of protection (10-13). Most young infants with pertussis are infected primarily at the household level (in 75–85% of the cases), with older siblings and adult close contacts the common reservoirs of the bacterium, with new mothers identified as one of the most common sources of infection to newborn infants (14, 15). A meta-analysis of nine studies from high-income countries identified mothers as source of disease transmission in more than 39% (42% in Australia) of cases in infants aged less than six months hospitalised with pertussis infection (15).

Pregnant women are also at increased risk for morbidity and mortality from influenza infection during seasonal and pandemic influenza outbreaks (16-18). Physiological and immunological changes that occur during pregnancy may increase the risk of more severe complications from influenza infections including premature labour, pneumonia, hospitalisation and death in

pregnant women compared to non-pregnant women (19-21). This was particularly evident during the H1N1 influenza pandemic outbreak of 2009–2010 in which the admission rate of pregnant women to an intensive care unit following infection with influenza was significantly higher compared to non-pregnant adults (20, 22). An increased risk of adverse outcomes such as stillbirth (relative risk (RR) from 2.36 to 3.62), preterm birth (RR 2.7 to 5.9) and low birthweight (RR 1.71) is also suggested for neonates born to women affected by influenza during pregnancy, evident in studies conducted during the 2009 H1N1 pandemic (23, 24). However, high-quality evidence from seasonal influenza time periods is lacking (23, 24).

Vaccination against pertussis and influenza during pregnancy has emerged as an effective strategy to protect the mother and provide passive antibodies to the newborn, protecting them in early infancy to reduce the morbidity and mortality associated with these vaccine preventable infections (25, 26). Maternal pertussis vaccination at least seven days before delivery has been shown to prevent up to 91% of pertussis disease in the infants first two months of life (27, 28). Influenza vaccination during pregnancy might also reduce the risk of low birthweight, preterm birth, and stillbirth, but evidence concerning these birth outcomes is conflicting (29-35).

Maternal influenza vaccination was first nationally recommended in the United States (USA) in 2004 for all pregnant women during influenza season regardless of their stage of pregnancy (36) and has been recommended by WHO since 2005 (37). However, most developed countries implemented seasonal influenza vaccination programs for pregnant women following the 2009 H1N1 influenza pandemic outbreak (38-40). In 2011, the USA become the first country to recommend a pertussis-containing (diphtheria-tetanus acellular pertussis) vaccine for pregnant women during the third trimester of pregnancy (41) and this policy has since been adopted by several other industrialised countries such as the United Kingdom (UK) and Australia in response to a pertussis epidemic causing morbidity and mortality in young infants (42-44).

Following the recommendation of maternal pertussis and influenza vaccination from immunisation advisory groups internationally and implementation of government funded maternal vaccination programs for pregnant women in different countries, there has been an increasing trend in the uptake of recommended vaccinations among pregnant women (45). However, influenza vaccine uptake in these countries is well below the Healthy People 2020 target of 80% (46) ranging from about 30% to 50% (47-53). Maternal pertussis vaccine uptake varies between and within countries and has markedly improved, now up to 54% in the USA (47-51, 54-56), 70% in the UK (57), and 75-80% in Australia (52, 53), but uptake in general remains suboptimal. This highlights the importance of developing effective interventions to improve the acceptance and uptake of the recommended maternal pertussis and influenza vaccination to ensure optimum protection for pregnant women and their infants.

Some recent studies have evaluated interventions used to improve maternal influenza and pertussis vaccination uptake in pregnant women (58-62). Most of the interventions predominantly focussed on educational interventions for pregnant women or healthcare providers to improve vaccination uptake among pregnant women (58-62). Some interventions were designed to enhance maternal vaccination coverage by offering free vaccines or at reduced cost for pregnant women (60, 63) while others included multimodal interventions such as implementing standing orders for maternal vaccination at antenatal care settings, increasing vaccine stocks or extending the number of locations to access the vaccine (59, 60). Considering the recommendation of maternal pertussis vaccination is relatively recent, most of these interventions were designed to improve the uptake of seasonal influenza vaccination among pregnant women. Limited data exist on strategies to enhance pertussis vaccination uptake among pregnant women. Given the well-documented benefits of maternal pertussis immunisation in protecting young infants (27, 28), identifying effective strategies or

interventions to enhance pertussis vaccine uptake among pregnant women should be a public health priority.

Previous studies examined determinants of the recommended vaccination uptake among pregnant women and specific aspects of vaccination such as women's perception, knowledge and attitudes towards vaccination in pregnancy (50, 64, 65). There is some evidence on the influence of these assessments on the decision to vaccinate against pertussis and influenza during pregnancy. Furthermore, psychological factors investigated in most studies were primarily specific health beliefs on maternal vaccination and vaccine preventable diseases, often based on the Health Belief Model (a social psychological health behavior change model developed to explain and predict health-related behaviors) – perceived susceptibility to pertussis/influenza, perceived severity to pertussis/influenza, perceived barriers to maternal vaccinations, perceived safety or benefits of vaccination in pregnancy (66, 67). Thus, psychological factors as determinants of maternal vaccination uptake are limited to beliefs, attitudes or perceptions that are directly related to vaccination and diseases during pregnancy. Considering the barriers to maternal vaccination are complex (67), it is important to determine the influence of psychosocial factors such as antenatal depression, stress, anxiety and maternal lifestyle factors on vaccination decision-making during pregnancy, which are poorly addressed by previous studies. Assessment of psychosocial factors might further enhance the understanding of why certain women receive the recommended vaccinations during pregnancy while others do not. Importantly, identifying psychosocial determinants of maternal vaccination uptake will enable comprehensive and pragmatic approach for developing effective interventions to improve the uptake of the recommended pertussis and influenza vaccinations during pregnancy.

One of the most commonly reported reasons for pregnant women not to receive the recommended influenza and pertussis vaccination during pregnancy is concern about its safety

(68-70). An inflammatory response from infection during pregnancy has been shown to increase the risk of fetal injury (71) but no evidence exists that an inflammatory response from a vaccine carries a similar risk. Several systematic reviews have reported no increased adverse pregnancy and birth outcomes following pertussis (72-75) and influenza vaccination during pregnancy (30-35), although the quality of evidence in the underlying studies are low. Most observational research into vaccine safety during pregnancy has been retrospective, due to the relatively cheaper cost, fewer ethical concerns, and difficulty in recruiting pregnant women to randomized controlled trials (RCTs). In most retrospective observational studies, authors have been unable to establish if a pregnancy complication preceded vaccination or account for the time-dependent nature of exposure to vaccination during pregnancy. A robust assessment of the safety of pertussis and influenza vaccination during pregnancy is critical due to population-wide rollouts of vaccines for this group in many countries. In countries where these maternal vaccines are recommended, prospectively designed studies with active follow-up of pregnant women are likely to be the only way to accurately determine the risk or additional potential benefits of maternal influenza vaccination in reducing the risk of delivering low birth weight infants, small for gestational age birth and preterm birth, for which evidence is conflicting (29-35). To address this, prospectively designed studies incorporating statistical approaches suitable for analysing time-dependent associations between maternal vaccine exposure on pregnancy and birth outcomes are warranted.

1.2 Research Questions

The research questions addressed in this thesis as follows:

1. What are the most effective interventions used to improve pertussis vaccination uptake in pregnant women?

2. What psychosocial factors are associated with the willingness and uptake of maternal pertussis and influenza vaccination among pregnant women?

3. Is there any difference in maternal and neonatal outcomes for women who receive seasonal influenza vaccination during pregnancy compared to unvaccinated women?

4. Is there any difference in maternal and birth outcomes for women who received pertussis vaccination during pregnancy compared to unvaccinated women?

1.3 Thesis Outline

This thesis is organised into eight chapters. Chapter 1 contains an introduction, rationale for research and research questions to be addressed in this thesis. Chapter 2 will provide a comprehensive review of the existing literature on pertussis and influenza as well as the current knowledge regarding maternal pertussis and influenza vaccination during pregnancy with gaps in the literature. Chapter 2 will also outline the research aims and specific objectives to be addressed in the thesis. Chapter 3 will describe the methods used to address each of these objectives. Chapter 4 contains a published systematic review, which summarise and evaluate the available evidence on the effectiveness of interventions in improving pertussis vaccination uptake in pregnant women. Chapter 5 presents the results of a prospective cohort which determined psychosocial factors influencing acceptance and uptake of pertussis and influenza vaccination during pregnancy. Chapters 6 and 7 address the safety and impact of maternal seasonal influenza and pertussis immunisation on the health of mothers and their newborn infants, respectively. Finally, Chapter 8 presents summary of the overall findings and implications of the research findings. This thesis contains a combination of written text (Chapters 1-3 and Chapter 8) and peer reviewed journal articles that have been published (Chapters 4,5,6 and 7).

Chapter 2: Literature Review

2.1 Pertussis

2.1.1 *Bordetella Pertussis* Bacterium and Pathogenesis

Pertussis or whooping cough is a highly infectious vaccine preventable respiratory disease that can affect individuals of any age (76). Pertussis is the result of a human acquired infection caused by the gram-negative coccobacillus bacterium known as *Bordetella pertussis* (77). It is a strictly human pathogen with no known animal or environmental reservoir (77). *Bordetella pertussis* expresses virulence factors on the external surface such as filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) assisting the pathogen in the initial colonisation and mediating attachment to the ciliated epithelial cells in the upper respiratory tract of the host. Toxins such as pertussis toxin (PT) and adenylate cyclase toxin (ACT) that assist the bacterium in damaging the epithelial lining are produced by the bacterium (78). ACT also plays a role in evasion and supressing the host innate immune response during infection (78). PT along with other bacterial toxins secreted into the local environment result in destruction of the respiratory tissues, triggering coughs during the early stage of the disease (78, 79). Generally, these virulence factors play a major role in the clinical manifestations of the disease (78, 79).

2.1.2 Transmission, Clinical features and Complications

Bordetella pertussis spread to other people via tiny airborne droplets of an infected person generated from a cough or a sneeze (78). The average incubation period of pertussis is between 7 to 10 days (range 6 to 21 days) preceding the onset of symptoms (77). Acute infection is classically separated into 3 phases: catarrhal, paroxysmal, and convalescent (78). The catarrhal phase (initial 7 to 14 days) is characterised by mild symptoms such as low-grade fever, sneezing and mild cough (80). These features are indistinguishable from other upper respiratory infections making the diagnosis of pertussis challenging in its earliest phase and infected

patients at this phase are considered infectious (80). The paroxysmal stage is characterised by increasing severity and frequency of coughs and lasts between 1 to 6 weeks, but can be as long as 10 weeks. This stage is characterised by prolonged coughs followed by a long inspiratory gasp, which may sound like a "whoop"; hence, the name "whooping cough" is derived (80). Young infants particularly those less than three months of age are at highest risk of several complications from pertussis including apnoea, seizures, encephalopathy post-tussive emesis, and pneumonia and potentially death due to their immature immune and cardiorespiratory systems (81, 82). Adults may also experience complications including bacterial pneumonia, fractured ribs, otitis media and urinary incontinence (83). Convalescent is the last phase characterised by decreasing intensity and frequency of the cough (80). Early treatment with antibiotics such as macrolides can reduce the length of the infection, severity and prevent the spread of the disease (84).

2.1.3 Diagnosis and Reporting

The WHO definition, used for reporting purposes, is "A case diagnosed as pertussis by a physician, or a person with a cough lasting at least two weeks with at least one of the following symptoms: paroxysms (i.e. fits) of coughing, inspiratory "whooping", post-tussive vomiting (i.e. vomiting immediately after coughing) without other apparent cause" (85). According to the National Notifiable Diseases Surveillance System (NNDSS) definition, confirmed cases require either laboratory definitive evidence (''isolation of *Bordetella pertussis* or detection of *B. pertussis* by nucleic acid testing''), or laboratory suggestive evidence (''seroconversion or significant increase in antibody level or fourfold or greater rise in titre to *B. pertussis* in the absence of recent pertussis vaccination; or single high IgA titre to whole cells; or detection of *B. pertussis* antigen by immunofluorescence assay'') combined with clinical evidence (''a coughing illness lasting two more weeks; or paroxysms of coughing or inspiratory whoop or post-tussive vomiting''), or clinical evidence combined with an epidemiological link to a

confirmed case (86). Culture, antigen detection (direct fluorescent antibody), and polymerase chain reaction (PCR) can be used in laboratory confirmation of pertussis infection, but their sensitivity is high only in the early phase of the disease (87). Serologic examination can be conducted to diagnose suspected recent pertussis infection in adolescents and adults (88).

Pertussis is a mandatory notifiable disease in most developed countries like Australia; however, cases are often under-reported particularly in adolescents and adults (89, 90). Studies actively seeking pertussis cases found that passive surveillance statistics significantly under-report the true incidence, depending on the quality of the surveillance system (91, 92). In many developing countries, pertussis is under-reported due to lack of a well-established disease surveillance system and lack of diagnostic tools, which significantly delays pertussis case detection (93).

2.1.4 Epidemiology

Global

A recent model developed in 2017 with WHO data from 2014 estimated 24.1 million pertussis cases and 160,700 pertussis related deaths in children younger than 5 years per year worldwide (94). Of these, 5.1 million (21%) estimated pertussis infections and 85,900 (53%) estimated deaths were in infants < 1 years of age (94). The African region contributed the largest proportions of cases (33%, 7.8 million) and deaths (58%, 92,500) (94). Despite high vaccine coverage, pertussis incident rates have increased in industrialized countries with epidemics occurring in the USA in 2010 and 2012 (95) and in the UK in 2011–2012 (96). The incidence rate of pertussis in the USA between 2005 and 2010 among infants <12 months of age was 117/100,000 person-years, with the highest rate in those aged 2 or 3 months (235/100,000 person-years or 247/100,000 person-years, respectively (97). In 2016, a resurgence of pertussis was also observed in the UK, where the number of reported confirmed pertussis cases was 42% higher than the 4,191 cases reported in 2015 (98).

Australia

Pertussis is a cyclical disease usually occurring every three to four years, linked to demographic differences and different vaccine coverage (99). The most recent epidemic occurring in Australia between 2008 to 2011 (100). Following the introduction of whole-cell pertussis vaccine in the late 1940s, the national pertussis incidence rates in Australia declined sharply (101). The annual pertussis incidence rate during the 1980s ranged from 100 to 800 cases per 100,000 population and increased to between 1,000 and 10,000 during the 1990s (101). During these periods, the pertussis incidence rate among adults was higher than the incidence rate observed among children (101, 102).

Acellular vaccines replaced the whole-cell vaccine for booster doses in 1997 and for all doses in 1999, and 95% coverage with three doses of primary pertussis vaccination series was attained within 4 years (103). Despite high coverage of paediatric and adolescent pertussis vaccination since 2000 (103), the national pertussis incidence rate started to increase in 2008 (104). All eight states and territories in Australia experienced a resurgence of pertussis during an epidemic in 2008-2011 making it is the second most commonly notified vaccine-preventable infectious disease after influenza (104, 105). The notifications rate further increased in 2011 with 38,602 cases (104, 106). During these epidemic periods in Australia, the highest notification rates observed were among infants < 6 months of age (104, 105). South Australia had the highest state notification rate of 1,119.3 per 100,000 for this age group (100).

2.1.5 Burden of Pertussis in young infants

Although pertussis has been preventable by vaccination for many decades, it remains one of the top 10 causes of child and infant mortality (94). Young infants, particularly those too young to have completed the primary three dose immunisation series by six months, are vulnerable to severe morbidity and mortality following pertussis infection (10-13). In the USA, infants aged

<12 months continue to have the highest pertussis notification rate (Figure 1). The risk of pertussis-related death is inversely proportional to infant age, and deaths occur almost exclusively in infants aged < 6 months (5, 7, 107, 108). Overall, 48,909 infant pertussis cases and 255 deaths were reported in the USA from 2000 to 2015 and 39% of these cases were in infants aged < 2 months (109). Between 1993 and 2004, 95% of pertussis-infected neonates who required mechanical ventilation and all of those who died were aged <2 months (7).

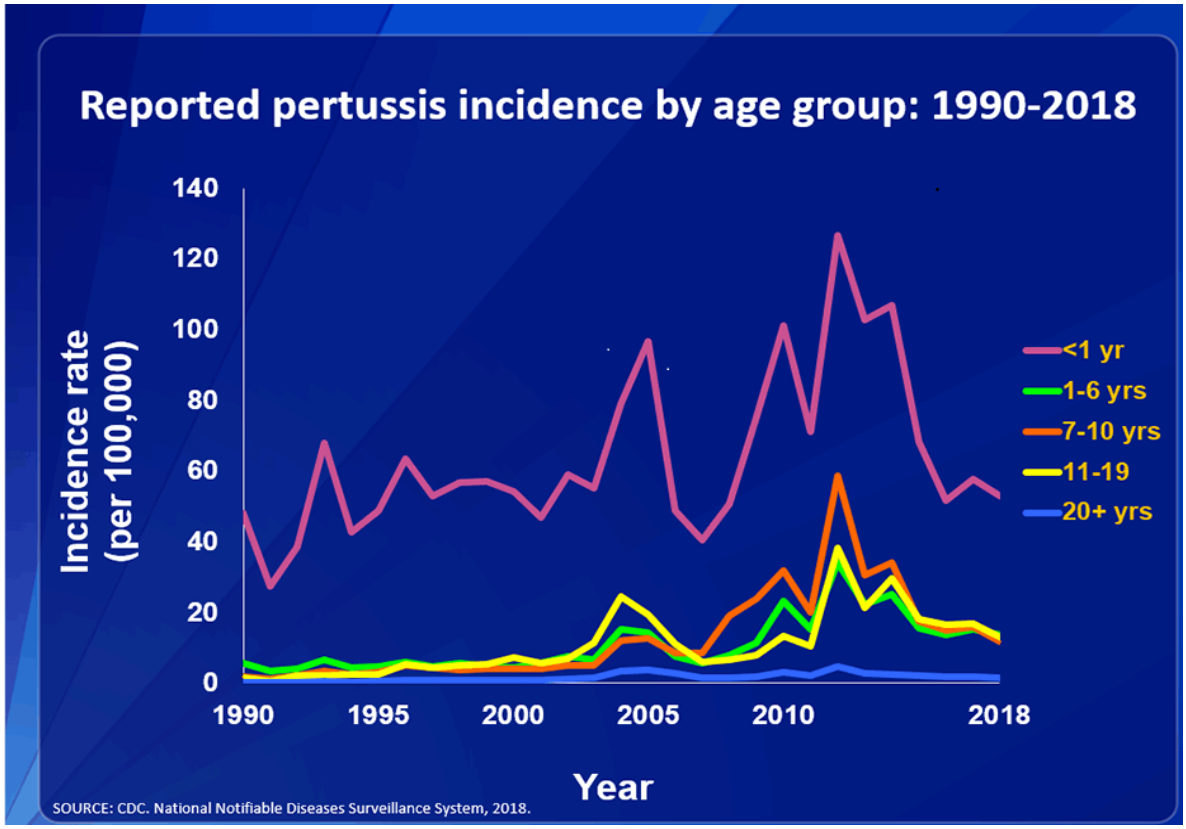


Figure 2.1 Reported pertussis incidence by age group 1990-2018 in USA.
Source: CDC: National Notifiable Disease Surveillance (NNDS) (110).

Among infants <3 months of age with pertussis, as many as 5% acquire secondary bacterial pneumonia, and among infants <6 months of age with pertussis, up to 11.8% acquire secondary bacterial pneumonia, more than double the incidence in older children and adults (111). The burden and trends of pertussis in young infants is also similar in Australia where a recent national report in 2016 for pertussis related hospitalisation was 445 and almost 40% of these

were infants aged <12 months of age. Reported pertussis-related intensive care unit (ICU) admissions, over a 17-year period (between 1997 and 2013) in Australia were 373 (112). Of these cases, 53% occurred during the four years of the recent Australian epidemic 2009–2012 and pertussis related ICU admissions were most likely to occur in infants < 6 weeks of age (42%, n=156) and aged 6 weeks to 4 months (43%, n=160) (Figure 2) (112). The highest incidence of pertussis related hospitalisations and death continued to occur in infants younger than six months of age (101, 102, 113). Aboriginal and Torres Strait Islander infants have the highest pertussis disease burden and severity (114, 115).

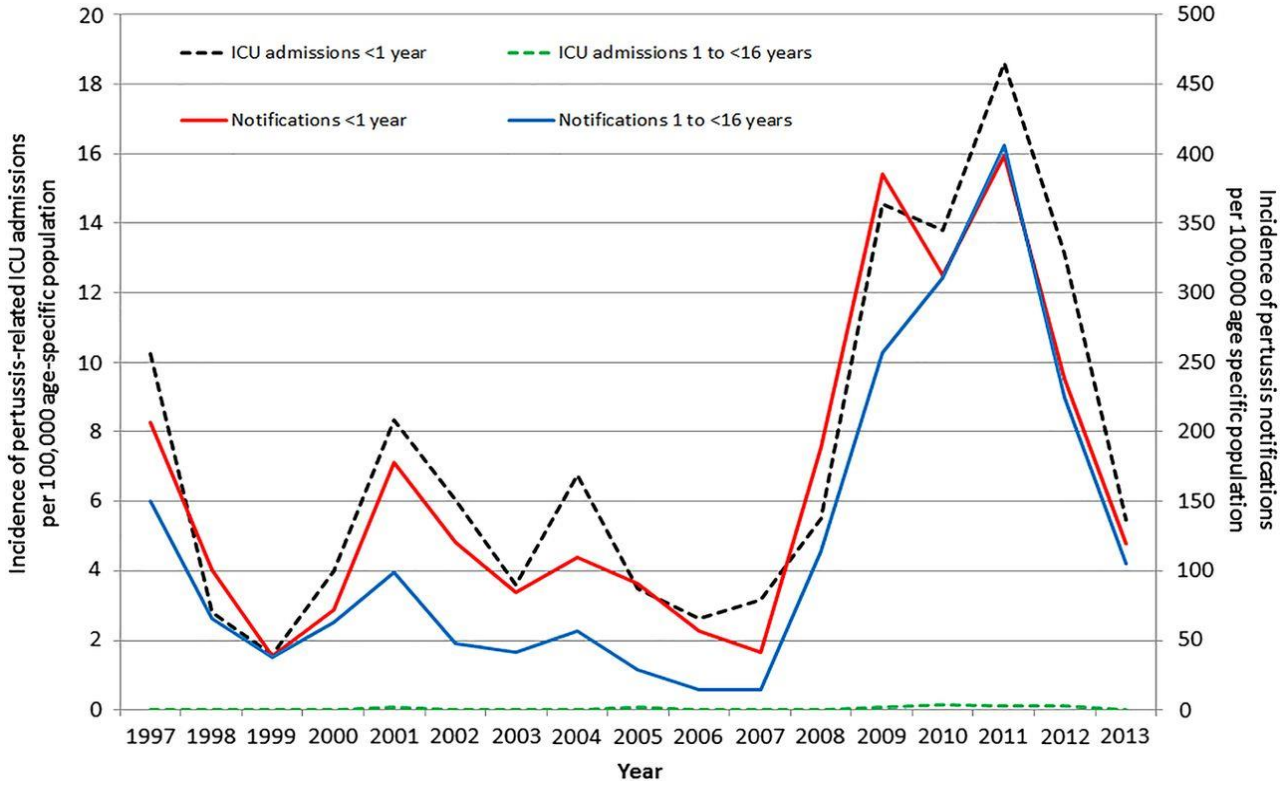


Figure 2.2 Annual cumulative incidence of pertussis-related admissions to ICUs and national notification by age group (<1 year and 1 to <16 years), per 100 000 child-years, Australia, 1997–2013 (112).

A study in England found that among all pertussis-related deaths, 88% of the deaths were in infants < 4 months, and the median age at death was 1.7 months (range: 2 weeks –17 months)

(107). As the number of reported deaths from pertussis in young infants has increased (5), the case fatality ratio has remained constant (116). The average case fatality rate in developed countries is 0.2% (117). However, an analysis of U.S. surveillance data (1990-2009) estimated an age-specific case fatality ratio among infants aged < 1 year to be 0.77%, 4.3 times higher than the overall case fatality ratio (118). Estimates of the case fatality rate for infants <3 months in England averaged 2.5% for 2008-2013 (27).

2.1.6 Prevention of Pertussis through Vaccination

Pertussis has a basic reproduction ratio (R0) of 12-17 (119). This means in a 100% susceptible population on average, each case will infect 12-17 other people during the infectious period (119). Overall, up to 94% of the population must have sustained immunity in order to halt transmission of pertussis infection (119). However, vaccination against pertussis does not result in lifelong immunity (119). This waning immunity makes it virtually impossible to achieve and sustain the required levels of population immunity to eliminate pertussis (117).

A whole-cell pertussis vaccine using dead whole *Bordetella pertussis* organisms was combined with diphtheria and tetanus toxoids (DTwP) in the 1940s (117), and largescale vaccination began in the 1950s (117). Because of concerns about safety and adverse events associated with the whole-cell vaccine, an acellular pertussis vaccine (DTPa) was developed in the 1970s, which used highly purified, selected components of the *Bordetella pertussis* organism. The WHO's Expanded Programme on Immunisation (EPI) has included pertussis vaccine (DTPa) since its introduction in 1974 (117). A three dose primary pertussis immunization series begins at age 6-8 weeks to three months, and is completed by six months, according to WHO's recommendation (117). The EPI schedule used in most developing countries recommends pertussis containing vaccine (DTPa) at 6, 10, and 14 weeks. However, in most industrialized countries, including the USA and Australia, the schedule is given at 2 (can be given from 6

weeks of age), 4 and 6 months (117). Booster doses (dTpa) with substantially lesser amounts of diphtheria toxoid and pertussis antigens than paediatric vaccine (DTPa) are typically given at age 15-18 months and 4-5 years (120).

In the USA in 2017, coverage of children 19-35 months for > 3 doses of DTPa was 94%, and for > 4 doses of DTPa was 83% (121). Similarly, pertussis vaccine coverage among infants at 12 months is reported to be over 90% in Australia (122). According to WHO data in 2014, 86 % of all infants worldwide-received 3 doses of pertussis vaccine (123). WHO estimates that global vaccination against pertussis prevents 687,000 deaths annually (123). However, 22.6 million children under 1 year of age remain incompletely vaccinated against pertussis (124).

A meta-analysis of vaccine effectiveness and efficacy studies showed that acellular pertussis vaccine effectiveness is initially as high as 91% following the primary childhood series and approximately declines at 9.6% annually (125). Initial absolute effectiveness of the vaccine after adolescent boosting is approximately 85% and declines at 11.7% annually (125). Pertussis immunity wanes from 4 to 12 years after the last childhood booster dose of pertussis vaccine (126, 127). This waning immunity leaves older children, adolescents, and adults vulnerable to pertussis infection, and in turn puts unprotected young infants at risk for transmission of disease (128). Despite successful infant pertussis immunisation programs in developed regions such as North America, Europe and Australia, pertussis remains an endemic disease (129). The global resurgence of pertussis could be attributed to several factors, including: the use of better-quality diagnostic methods which result in more case detection, decreasing vaccine coverage in adults, changes in vaccination schedules, shifting in vaccine formulations from whole cell to acellular, waning of immunity in adolescents or *Bordetella pertussis* strain variation (93, 113, 130, 131).

2.1.7 Strategies to Mitigate Pertussis Burden in Young Infants

Young infants typically do not have protective immunity and remain vulnerable to pertussis until they have received all three doses of the primary series of pertussis vaccine (1, 7, 8). Several vaccination strategies for protecting vulnerable young infants from pertussis have been evaluated in recent years, including vaccination of all people in contact with a newborn also known as cocooning, vaccination of pregnant women during pregnancy and immediately postpartum, and vaccinating newborns with a birth dose of pertussis vaccine to provide protection prior to the beginning of the primary series (132). The majority of infant pertussis cases have acquired disease from a family member or close contact (14, 15). Cocooning, which requires immunisation of all family members and close contacts of newborns, has been recommended as a way to protect newborns (133). Cocooning protects infants by preventing disease among their contacts, and thus prevents transmission to the infant (134).

However, full cocoon coverage can be difficult to achieve, and a major disadvantage to cocooning as a protective strategy is that it leaves infants without any endogenous protective antibody until they begin the primary pertussis vaccine series at two months of age (135). Without endogenous protective antibody, infants remain solely dependent on the immunity of those around them for pertussis protection (133). Vaccinating mothers immediately postpartum (after giving birth and before hospital discharge) is another strategy intended to prevent pertussis transmission to young infants (136). However, a major limitation of this strategy is that vaccination that is administered post-delivery leaves a two-week window of risk during which the mother could become infected with pertussis and transmit it to the infant in the first weeks of life because boosted pertussis antibody levels do not peak until two weeks post vaccination (137-139). Recently, maternal pertussis vaccination has emerged as the most effective strategy in preventing morbidity and mortality associated with pertussis in young infants (140). Pertussis vaccination during pregnancy provides indirect protection starting at birth by i) preventing mothers from becoming infected with pertussis and transmitting it to the

infant, ii) passive immunity by way of maternal pertussis antibodies passing by transplacental transfer to the fetus and iii) direct protection from maternal antibodies passing through the breast milk by breastfeeding the newborn (140).

2.2 Influenza

2.2.1 Influenza Virology and Pathogenesis

Influenza is a highly contagious viral infection of the respiratory tract that cause mild to serious morbidity and mortality worldwide (141). Influenza virus is an enveloped, single stranded RNA (ribonucleic acid) genome virus with seven or eight segmented strands of RNA that each contain one or two genes (141). The influenza virus belongs to the family of Orthomyxoviridae and infects both birds and mammals (141). There are four types of influenza viruses: A, B, C and D, which are classified based on antigenic variances in the internal proteins (nucleoprotein (NP) and matrix (M1) protein) (141-143). Influenza A, B and C cause human influenza infection (141-143). Influenza D viruses were recently categorised as a new genus of *Orthomyxoviridae* in 2016, which are known to infect pigs and cattle but not humans (144). Influenza A viruses are categorized by subtypes according to their surface antigens, hemagglutinin (HA) and neuraminidase (NA); whereas influenza B viruses are not categorised, but two distinct lineages of influenza B virus circulate annually: B/Yamagata and B/Victoria (143). All known subtypes of influenza A virus have been isolated from many animal species but wild birds serve as the natural reservoir (141). Only three of the HA subtypes (H1, H2 and H3) and two of the NA subtypes (N1 and N2) have circulated widely in humans this century (141). Influenza B viruses are usually found only in humans and have only one HA and NA subtype (which limits the generation of new strains by reassortment) thus are less likely to cause a pandemic (141). Influenza A and B can cause epidemics, and are clinically indistinguishable. These two types share many common properties, nonetheless all known pandemics, and the worst seasonal epidemics, are caused by type A (141). Influenza C is

believed to be a cause of the common cold and is occasionally associated with bronchitis and pneumonia in adults and children (145).

HA and NA play specific roles in the initiation of influenza virus infection, as well as facilitate the spread of progeny virions to other host epithelial cells (146). The influenza infection starts when viral HA attaches to the sialic acid (SA) residues on the host cell receptor. Following entry into the host cell (cytoplasmic vesicles), influenza virion sheds its envelope, resulting in the release of the genetic material of the virus, ribonucleoprotein complex (RNP) into the host cell cytoplasm which leads to transcription and then translation (147, 148). Virus infected epithelial cells release key cytokines and activation of cytokines leads to the onset of clinical symptoms (147, 148). About 2 to 3 days after infection with the virus, the innate immune system is activated (147, 148).

Influenza viruses go through constant genetic change, which has a significant impact on induced immunity and considerations for vaccine composition (149). There are two types of genetic changes of influenza viruses (149). The first type is minor strain change known as ‘antigenic drift’, which takes place when point mutations and recombination events occur in the viral genome, causing constant emergence of new virus variants (149). Influenza A viruses go through antigenic drift more quickly than influenza B viruses (150). This process is responsible for seasonal influenza epidemics, and requires consideration of adjustment of influenza vaccines each season (149). The second form of major antigenic evolution of influenza strains is known as “antigenic shift”, which occurs among influenza A viruses. Antigenic shift happens less frequently than antigenic drift, and normally arises when novel subtypes of influenza that typically infect only birds or pigs are transmitted to humans (149). This process can result in new or significantly different influenza A viruses, in which there is little or no pre-existing immunity in the human population and is associated with pandemics (149).

2.2.2 Clinical Characteristic and Transmission

Clinical symptoms of human influenza include headache, fever, chills, muscle aches, coughing, congestion and fatigue. Infectivity may start shortly (<24 h) before the onset of the clinical symptoms and usually persists for 3–5 days (149). Serious and fatal outcomes with primary viral and viral-bacterial pneumonia are common in children (151, 152). Complications occur particularly in older patients with chronic disease (153, 154).

Influenza viruses are primarily spread via droplets (particles >5 microns [pm] in diameter) made when an infected person coughs or sneezes (149). As the influenza virus can persist outside of the body, it can also be transmitted by contaminated surfaces (155). Low relative humidity and cold temperatures favour influenza virus transmission because infected individuals shed more virus in colder temperatures and virus particles can remain airborne when relative humidity is low (156). Children are much more infectious than adults and shed virus prior to developing clinical symptoms and until two weeks following infection (157).

2.2.3 Epidemiology

Four influenza pandemics have occurred in the past century (158-160). A novel influenza A (H1N1) virus caused the most recent global pandemic in April 2009, which caused estimated confirmed deaths of 18,500 people globally (161, 162). Following the 2009 pandemic influenza outbreak, there were almost 44,000 confirmed A(H1N1) incidents and 2000 deaths in Australia (163). The WHO estimates that seasonal influenza severely affects between 3-5 million individuals with 260,000 to 650,000 deaths annually (164, 165). A population wide case fatality of seasonal influenza is highest in children, while complications including hospitalisation and mortality occur most frequently in elderly individuals (164, 165). Specific high-risk groups prioritised by WHO for immunisation include pregnant women, the highest priority group, followed by individuals with a compromised immune system and individuals with comorbidities such as pulmonary or cardiac disease (37).

2.2.4 Influenza Vaccination

The best strategy for the prevention and control of influenza is vaccination and it has been recommended and proven to be safe for anyone six months of age and older (165). The two types of influenza vaccines available are i) inactivated influenza vaccines and ii) live attenuated influenza vaccines (165). For several decades, seasonal inactivated influenza vaccines (trivalent vaccines) and live attenuated influenza vaccines were designed to protect against the three most predominant strains in circulation: one A/H3, one A/H1 and one influenza B strain (165). Recently quadrivalent influenza vaccines have been developed to include a second influenza B strain in addition to the strains in trivalent vaccines, and are expected to provide wider protection against influenza B virus infections (165). The inactivated influenza vaccines currently in use are whole virus, split/subvirion and sub unit vaccines that only contain the two highly purified antigens (HA and NA), instead of the whole virus (166). The WHO makes recommendations for two different vaccine formulations every year; one for the Northern, and one for the Southern Hemisphere (167). Annual seasonal inactivated influenza vaccination of people at risk of severe disease is implemented in most high-income countries (166).

The effectiveness of the vaccines that are currently available for influenza depends primarily on the antigenic match between the circulating viruses and the strains included in the vaccine (166). The efficacy of the inactivated vaccine may be influenced by a range of different factors including age, health status and use of concurrent medications, prior vaccination and pre-vaccination antibody titres. In general, 70-80% of healthy individuals between 10-65 years of age obtain a protective immune response after vaccination (168).

2.2.5 Influenza Infection in Pregnant Women and Infants

Several studies have demonstrated that pregnant women are at increased risk for influenza associated morbidity and mortality during both influenza pandemics and seasonal epidemics (169-171). Physiological and immunological changes in pregnancy including: increased heart

rate, stroke volume, and oxygen consumption; diminished lung capacity; increased progesterone and glucocorticoids and a shift in cell-mediated immunity predispose pregnant women to influenza infection complications compared to non-pregnant individuals (172, 173). The underlying mechanism of influenza infection increasing maternal complications has been studied on mice and indicated that altered inflammatory responses following maternal influenza infection can result in increased maternal morbidity, increased risk of preterm birth, fetal growth impairment, and fetal mortality (174).

The burden of influenza illness during pregnancy has been noted in previous pandemics (175, 176). The severity of influenza during pregnancy was first recognized during the 1918 pandemic of 'Spanish Flu' (175). A statistical study of pregnant women during the 1918 pandemic showed that nearly 50% of the 1350 pregnant women infected with influenza were diagnosed with pneumonia and more than 50% of those with pneumonia died, indicating a case fatality rate >25% (175). The burden was also observed during the recent 2009 influenza A pandemic (H1N1), where the median relative risk of pregnant women to be admitted to hospital following influenza infection across 10 high-and middle-income countries was estimated to be almost seven and pregnant women were also twice as more likely to die compared with women of childbearing age in the general population (177). During the 2009 pandemic, the relative risk of pregnant women in Australia to be hospitalised, admitted to intensive care unit and to die as a result of influenza A pandemic (H1N1) infection complications were 5.2, 6.5 and 1.4, respectively (178). Several studies have also shown that pregnant women are also at a higher risk of seasonal influenza-related hospitalisation compared with non-pregnant women, with the greatest increase in risk occurring in the third trimester (171, 179-181). Pregnant women with chronic medical conditions are seven times more likely to require hospitalisation following influenza infections compared with non-pregnant women (180).

The fetus may also suffer adverse outcomes following influenza infection during pregnancy (23, 24, 182-184). This was evident during the 2009 influenza A pandemic (H1N1) infection, where pregnant women who were hospitalised following influenza infection were at increased risk of still birth (23, 24), preterm birth (24, 182) and delivering a small for gestational age infant (185). The severity of influenza illness during pregnancy plays an important role in the impact on fetal health, with more severe illnesses more likely to have adverse impacts (182).

Neonates are susceptible to severe influenza illness due to the immaturity of their immune systems and they have limited antibodies to protect against influenza infection (186). Infants aged <6 months are at increased risk of influenza-associated complications and have the highest risk for being hospitalised (187, 188) and death (186) compared with older children. Globally, 2.9 million cases of influenza associated with Acute Lower Respiratory Infection were estimated among infants aged <12 months (189). During the period 2006–2015 in Australia, particularly in the post 2009 pandemic seasons the highest rates of hospitalisation were in infants under six months of age (100) (Figure 3). Furthermore, the rate of influenza-associated hospitalisation in Indigenous peoples were significantly higher than non-Indigenous peoples across all age bands in Australia but the largest disparity was seen among infants under six months of age (100).

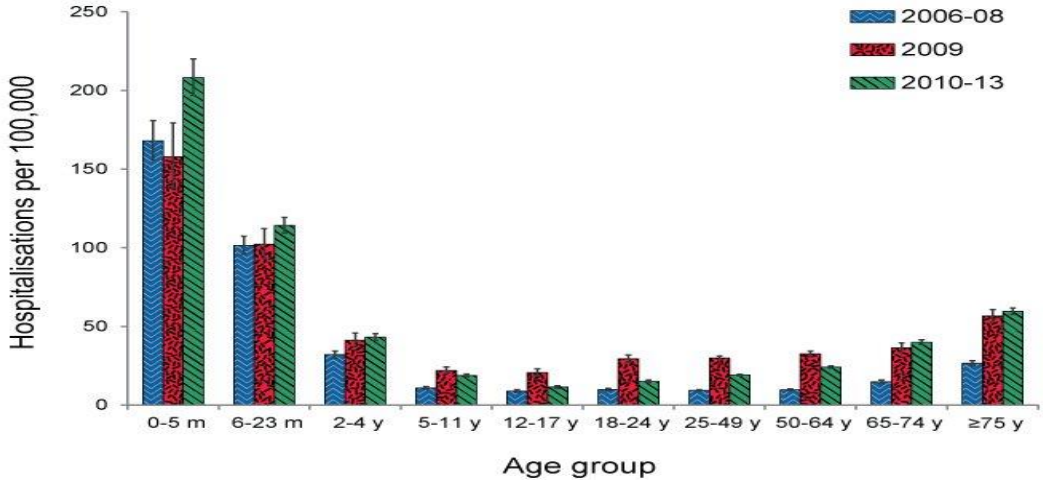


Figure 3: Rate of ICD-coded hospitalisation for influenza (any diagnosis) with 95% confidence intervals, Australia, 2006 to 2013, by age group and time period (100).

In Australia, the burden of influenza continues to occur in infants < 6 months of age, ranging from around 150 hospitalisations per 100,000 population in years of low influenza activity to almost 400 admissions per 100,000 population in years of high activity (190). Among infants < 12 months of age hospitalised with influenza, 35% will require admission to an intensive care unit, and 1 in every 350 dies (191). Because of the immaturity of the newborn immune system, immunisation do not trigger adequate immune response and there is currently no licensed influenza immunisation for infants younger than 6 months (192). However, maternal influenza vaccination has emerged as an effective means to decrease the morbidity and mortality associated with influenza illness in both mothers and their newborns (26).

2.3 Pertussis and Influenza Vaccination during Pregnancy

2.3.1 Mechanism of Maternal Antibody Transfer

The unique position a pregnant woman holds in the protection of the fetus or neonate from infection is via the pathway of vertical transmission, whereby maternally derived antibodies can be transmitted to the fetus through the placenta (IgG) and through breastfeeding (IgG, IgA, IgM) (193, 194). IgG is the only antibody class that is actively transferred from the mother to the fetus across the placenta, with the aid of the neonatal Fc receptor (FcRn), conferring passive immunity and protection against infections to the newborn during the first few months of life (195, 196). Although the transfer of antibodies to the fetus begins around 13 weeks, it is not until the 33rd week that the concentrations of maternal and fetal antibodies are equal and this transfer significantly increases during the third trimester (197). Compared to maternal concentrations, the fetal IgG concentration is higher after 40 weeks gestation (197). The efficiency of the maternal antibody transfer to fetus depends on numerous factors (99). The

structural and functional integrity of the placenta, total IgG concentration in maternal blood, vaccine type, time between vaccination and delivery, and gestational age of fetus at birth all may affect the ability and efficiency of maternally acquired antibodies in the fetus (99). Maternal vaccination boosts the concentration of vaccine-derived antibodies in maternal sera, and as a result, increases the transplacental transfer of maternal antibodies (198). These maternally derived antibodies can offer protection to the infant in the first 6 months of life (26, 198-201).

Maternal vaccination provides the optimal method of protection against severe vaccine preventable disease during early infancy (202, 203). The initial hesitancy in the design and study of vaccine safety in pregnant women has contributed to the delay in recommendation of maternal vaccination as a public health strategy in this high-risk group (204). However, recently the role of immunisation during pregnancy has become a primary focus as a public health strategy, not only for the prevention of maternal and postpartum infection but also for the intent to reduce neonatal and early childhood infections through maximising this unique relationship (204).

2.3.2 Maternal Vaccination as a Public Health Strategy

2.3.2.1 Maternal Pertussis Vaccination

Pertussis vaccination during pregnancy is currently recommended for pregnant women in many high-income countries (205). The initial recommendation for pertussis vaccination of pregnant women was introduced with limited preceding safety studies, but as an alternative strategy in reducing pertussis-related morbidity and mortality in young infants during an epidemic outbreak of pertussis in the UK in 2011 (27). Pertussis vaccination during pregnancy as a public health strategy is based on the recognition that vaccination of infants and children, is not adequate for protecting against the majority of severe pertussis disease and death which predominately occurs in infants <3 months age (27) (206, 207).

In 2006, an animal model study conducted in piglets demonstrated that passively transferred maternal immunity provided protection against infection with *B. pertussis* in newborns of vaccinated sows (208). Although the porcine model used in the study is limited in analysing passive transfer of immunity as there is no transplacental maternal antibodies in swine, it identified the colostrum and milk would be the only source of antibodies (208). However, the authors suggested that pertussis immunisation during pregnancy could be an effective strategy in prevention of young infants against pertussis (208). The effectiveness of maternal pertussis immunisation as a public health strategy in protecting young infants was first demonstrated following implementation of routine antenatal pertussis vaccination of all pregnant women in the middle of a pertussis outbreak in England in 2011 (27).

Following the successful implementation of the maternal pertussis immunisation program, a 91% reduction in pertussis cases was reported in infants younger than 3 months of age born to women who received pertussis vaccine at least 7 days before delivery (27). Maternal pertussis vaccine effectiveness in preventing pertussis in young infants was also demonstrated by a case-control study from the UK, with vaccine effectiveness of 93% (209). A study from the USA showed that administration of acellular maternal pertussis immunisation during the third trimester of pregnancy had a vaccine effectiveness of 78% against pertussis cases with cough in the two-month age group and a 91% effectiveness against hospitalised cases (210). Additionally, a retrospective cohort study demonstrated that infants with confirmed pertussis born to mothers who received pertussis vaccine during pregnancy, were less likely to be admitted to hospital than cases born to women not vaccinated during pregnancy (211). Another case-control study conducted in Australia also demonstrated that pertussis immunisation during pregnancy with a 3-component acellular vaccine (dTap) found a 94% reduction in preventing severe pertussis disease in infants under 6 months of age (212). However, the overall vaccine

effectiveness at preventing mild pertussis cases that did not require admission to hospital was low at 39% (212).

There has been concern that high concentration of maternally derived antibodies could interfere significantly with the infant's own response to pertussis vaccine antigens and other antigens in the primary infant immunisation series (213-215). The studies addressing the presence of maternal derived antibodies interfering with the infant immune response to primary immunisation schedule in early life, yielded conflicting findings (213-215). However, the clinical significance of immunological interference or blunting effect induced by maternal immunisation on infant immune responses needs to be further investigated. The primary aim of reduction in severe disease in infants <3 months of age supports the recommendation of maternal pertussis immunisation to mitigate pertussis related morbidity and mortality in young infants (205). The recommendation to give pertussis vaccination in each pregnancy is based on the assumption that maternal pertussis immunisation would be unlikely to protect infants of subsequent pregnancies (216, 217).

2.3.2.2 Maternal Influenza Vaccination

The recommendation for influenza vaccination of pregnant women in the USA dates back to the 1960s (218). However, it was only following observation of pregnant women being the most severely affected group during the 2009 A/H1N1 pandemic, that greater importance was placed on prioritising pregnant women to receive influenza vaccine at any stage of pregnancy by immunisation advisory groups internationally (38-40). In 2012, the WHO classified pregnant women as a high-risk group for influenza, recommending all pregnant women be vaccinated with inactivated influenza, primarily for their protection, and recommended countries to incorporate antenatal influenza vaccine into their existing routine immunisation programs (219).

The effectiveness of maternal influenza immunisation was conducted in animal models, which demonstrated that inactivated influenza immunisation during pregnancy in mice protected pregnant mice, fetuses and neonates from lethal challenge by influenza virus (220, 221). Furthermore, epidemiological studies have supported the effectiveness of seasonal influenza vaccination in pregnant women in protecting the women and their infants from influenza illness (30, 222-227). Influenza vaccination of pregnant women has been shown to have a protective effect on fetal outcomes including reducing the risk of low birth weight, prematurity and stillbirth, an effect size that might be more evident during pandemic influenza virus circulation than seasonal epidemics (34, 228).

A meta-analysis (34) conducted in 2016 demonstrated that maternal inactivated influenza vaccination was associated with a 13% reduction in risk of delivering preterm and 26% decreased risk of delivering a low birth weight infant. In the meta-analysis (34), maternal A/H1N1 influenza vaccination against the 2009 influenza pandemic was associated with an 8% reduction in risk of delivering a preterm and a 12% lower risk of delivering a low birth weight infant.

Data from three randomized controlled trials (RCTs) also presented conflicting evidence on the protective effect of maternal inactivated influenza vaccination on birth outcomes (199-201). A RCT conducted in Nepal reported a 42-gram higher birth weight in infants born to mothers who received maternal inactivated influenza vaccination and a 15% lower reduced rate of delivering a low birth weight infant (200). However, this effect was neither observed in the RCT conducted in South Africa (201) nor in the RCT conducted in Mali (199). Additionally, a secondary analysis of an earlier RCT conducted in Bangladesh (26) demonstrated a 200-gram higher mean birthweight in infants born during periods of high influenza activity to vaccinated mothers (29).

The two RCTs in South Africa (201) and Nepal (200) found maternal influenza vaccination was neither associated nor protective against preterm birth. However, a secondary analysis of the RCT in Nepal (200) and the RCT in Bangladesh (29) showed a reduction of small for gestational age infants among a subset of infants born during high influenza circulation to vaccinated women. The mixed findings on the potential protective effect of maternal influenza vaccination on birth outcomes from these RCTs raise concern about the validity of observational studies reporting protective effect of maternal influenza vaccination on birth outcomes. For instance, some observational studies have reported protective effects on preterm birth as high as 40% to 70% (229-232). Similarly, a meta-analysis examining the association between maternal influenza vaccination and stillbirth which included seven epidemiological studies, reported a 27% reduced risk of stillbirth and 31% reduction for those women who received the pandemic influenza A/H1N1 vaccine in 2009 (228). However, there was no difference in stillbirth rates observed in the RCT conducted in Nepal (200) or South Africa (201). Although RCTs usually do not have sufficient study periods or population sizes to identify stillbirth, the rates of stillbirth in these settings were 20 per 1000 births with a combined cohort size of more than 5,500 women (200, 201).

The initial RCT from Bangladesh (26) reported a 36% reduction in acute febrile respiratory illness for pregnant women who received maternal inactivated influenza vaccination; findings which were replicated in the subsequent trial in Nepal with a 19% reduction (200). However, the RCTs in South Africa and Mali did not observe efficacy against all-cause influenza-like-illness, but, reported a 50% and 70% significant efficacy against influenza-confirmed (PCR detected) illness in the women respectively (199, 201). Furthermore, all four RCTs (26, 199-201) reported on the efficacy of maternal influenza vaccination in protecting the infants in their first few months of life from influenza. A meta-analysis of these four RCTs yielded an overall vaccine efficacy of 36% in protection of young infants against influenza confirmed illness

following maternal inactivated influenza vaccination (233). The meta-analysis (233) also pooled estimates of influenza-associated hospitalisation in infants following maternal influenza vaccination from four observational studies and found a 72% protective effect in reducing influenza related hospitalisations in infants. However, the four RCTs (26, 199-201) were not designed to evaluate effectiveness of maternal influenza vaccination in reducing influenza related hospitalisation in mothers and infants or examining safety outcomes. Further studies are needed to corroborate the protective effect of maternal influenza vaccination in reducing the risk of influenza related hospitalisation in pregnant women and their infants.

A post-hoc analysis from the RCT in South Africa demonstrated a 43% lower rate of all-cause pneumonia hospitalisation in infants born to women who received influenza vaccination during pregnancy (234). These data were subsequently corroborated in the Nepal study with a 31% lower rate of severe pneumonia (200), although this was not replicated in the RCT in Mali (200). A pooled analysis across the three studies yielded an overall vaccine efficacy of 20% against all-cause severe pneumonia in infants under six months of age (235). This evidence suggests that maternal influenza vaccination can potentially offer other benefits to both mother and infant. Therefore, monitoring and determining uptake, and evaluating the benefits of maternal influenza vaccination is important.

2.3.3 Uptake of Pertussis and Influenza Vaccination during Pregnancy

Maternal pertussis vaccination was first introduced in the United States in 2011(236) and in the UK in 2012 (237). The Australian Immunisation Handbook was also updated in March 2015 to recommend pertussis vaccination for pregnant women between 28-32 weeks' gestation in the third trimester of every pregnancy (44). Jurisdictional funded pertussis vaccination programs for pregnant women were introduced between August 2014 and June 2015 in all Australian states and territories (44). All jurisdictions deliver pertussis vaccines to pregnant

women via general practitioners, hospital antenatal clinics, immunisation clinics, community health clinic, and obstetricians (238) with a large state-wide promotional campaign targeting healthcare providers and pregnant women (238). Recently in July 2018, the National Immunisation Program (NIP) incorporated pertussis vaccination for all pregnant women during each pregnancy (44).

Since the introduction of maternal pertussis vaccination programs in 2015 in Australia (239), there are no published data on national maternal pertussis vaccine coverage. However, several studies have indicated that it has been suboptimal but improved to 80% in 2019 (52, 63). Similarly, high uptake of pertussis vaccination during pregnancy, up to 70% was achieved in the UK after the antenatal pertussis vaccination program was implemented in response to an increase in neonatal pertussis deaths (57). Similar improved vaccine rates have not been observed in the USA, but rates recently have been estimated to be 54% (56). Although uptake of pertussis vaccination among pregnant women varies and differs between and within countries, there is still room for improvement of vaccination rates to protect young infants from pertussis related morbidity and mortality.

Since 2010 influenza vaccine has been supplied free-of charge for all pregnant women in Australia through the NIP (240). Maternal influenza vaccine uptake in Australia has been low, with estimates ranging from about 10% to 30% (240-246). Although these estimates are usually derived from relatively small sample studies, recent population-based cohort estimates in Australia indicated improved uptake of influenza vaccination up to 35% to 40% in pregnancy (52, 53). Similarly, the uptake of maternal influenza vaccination in other countries has improved significantly during the last several years, following the 2009 influenza pandemic season (247). In the USA during the 2001-2002 epidemic season only 11% of pregnant women had been vaccinated against influenza (247). This was unchanged in 2009 with only 13%, despite the introduction of recommendations for vaccinating pregnant women against seasonal

influenza (247). By 2010 and 2011 the uptake had improved to 40% and 50% respectively (247). Currently, maternal influenza vaccination uptake in the USA has now increased to approximately 50% (248). The uptake of influenza vaccine among pregnant women in most countries is still well below the benchmarks set by Healthy People 2020, which specifies a goal of 80% influenza vaccination for pregnant women (46).

Previous studies have also indicated that uptake of the recommended maternal vaccinations among ethnic minorities, women of culturally and linguistically diverse background (249-251) and Indigenous women (252-254) are suboptimal. Such disparity in maternal vaccination uptake among pregnant women presents a significant risk to the health of these vulnerable women and their newborn infants. Furthermore, most countries including Australia currently lack a coordinated approach to maternal immunisation, with coverage not systematically monitored. It is important to monitor and evaluate the impact of maternal immunisation programs for pregnant women and determine strategies to maximise uptake of the vaccine and design tailored interventions to enhance vaccination coverage for groups with low vaccination rates.

2.3.4 Determinants of Maternal Pertussis and Influenza Vaccination Uptake

There are a number of predictors as well as barriers to achieving high uptake of maternal pertussis and influenza vaccination coverage among pregnant women (66, 67, 255-257). Several systematic reviews have indicated that healthcare provider recommendation is a key driving factor or a major predictor in the decision-making process for pregnant mothers to receive pertussis and influenza vaccines during pregnancy (50, 66, 67, 255-257). Some of the reasons suggested by healthcare providers for not recommending maternal vaccination to their patients included a lack of sufficient data on safety, concerns about the medico-legal risks of

vaccinating pregnant women against pertussis and influenza and the perception that pregnant women would not want to receive the recommend maternal vaccinations (50, 258).

Furthermore, previous studies have suggested that not all women who receive a healthcare provider recommendation are vaccinated, but women who do not receive a recommendation for vaccination are unlikely to be vaccinated (66, 67, 255, 256). Healthcare providers should discuss influenza and pertussis vaccinations with women during pregnancy. Many studies have shown that healthcare provider recommendation is the most important factor to improve maternal vaccine uptake among pregnant women (66, 67, 255, 256, 259). Both healthcare providers and pregnant women should continue to be educated on the importance and safety of the recommended vaccination during pregnancy. In addition to healthcare provider recommendation, other sociodemographic factors previously identified to be associated with uptake across five literature reviews included: maternal age, educational attainment, employment status, socioeconomic status, parity, marital status, ethnic background or race (66, 67, 255-257).

Importantly, the decision to receive the recommended vaccination during pregnancy is, ultimately, an individual decision. Most studies examining individual level determinants of acceptance and uptake of pertussis and influenza during pregnancy focus on women's beliefs, perception, knowledge, and attitudes towards vaccination in pregnancy (50, 64-66, 70, 242, 255, 260-263). The psychological factors investigated in most studies are directly related to health beliefs on maternal vaccination and vaccine preventable diseases and are often based on the Health Belief Model – perceived susceptibility pertussis/influenza, perceived severity to pertussis/influenza, perceived barriers to maternal vaccinations, perceived safety or benefits of vaccination in pregnancy (both for themselves and for their unborn infant) (67). The Health Belief Model is a valuable theoretical or conceptual framework in providing an understanding of factors associated with vaccination behavior during pregnancy (264). Although the Health

Belief Model is derived from psychological and behavioral theories, it is not a suitable framework to examine psychosocial factors associated with disparities in the vaccination uptake among pregnant women.

Considering the barriers to vaccination in pregnancy are complex (67), it is important to determine the influence of other psychosocial factors such as antenatal depression, stress, anxiety and maternal lifestyle factors on vaccination decision-making during pregnancy, which are poorly addressed by previous studies. Pregnant women are seen as responsible for the health of their fetus through regulation of their own behaviours and are pressured to act in a way which meets society's expectations of a good "reproductive citizen" (265). Hence, pregnant women are urged to take part in a healthy maternal lifestyle i.e. avoid smoking and consumption of alcohol, increase intake of multivitamins and folate supplements, avoid becoming stressed, and maintain good health and optimum body weight through diet and exercise (265).

Previous studies revealed that psychosocial factors such as depression, stress, risky maternal healthy behaviours i.e. smoking or binge drinking are associated with suboptimal adherence to standard antenatal care recommendations such as exclusive breastfeeding duration to six months postpartum (266, 267). Thus, it is important to examine whether non-adherence to antenatal vaccination recommendation such as vaccine refusal or hesitancy during pregnancy is associated with the negative effects of anxiety, depression, or stress during pregnancy. Understanding and identifying psychosocial factors in relation to maternal vaccination decision making will enable comprehensive and pragmatic approaches for developing effective interventions to improve the uptake of vaccination during pregnancy.

2.3.5 Interventions to Improve Vaccine Uptake in Pregnancy

The barriers to vaccination in pregnancy are more complicated than the barriers identified for low uptake in childhood immunisation programs (268). Pregnant women have to weigh the benefits and risks not only for themselves, but also for their unborn child. Importantly, new mothers have often advised they are dependent on healthcare provider recommendation for pregnancy related interventions, including vaccination (261).

Some recent studies have evaluated strategies to improve immunisation uptake with pertussis and seasonal influenza vaccination in pregnant women (58-62). Most of the interventions predominantly focussed on educational interventions for pregnant women or healthcare providers to improve pertussis vaccination uptake among pregnant women (58-62). Some interventions were designed to enhance pertussis vaccination coverage by offering vaccines free or at reduced cost for pregnant women (60, 63) while others included bundled antenatal vaccine promotion package such as implementing vaccine standing orders for pregnant women, increasing vaccine stocks or extending number of locations for women to access the vaccine (59, 60).

A systematic review published in 2016 summarised and evaluated strategies used to improve influenza vaccination in pregnancy and suggested the use of vaccination reminders in healthcare systems and educational intervention for pregnant women such as providing an information pamphlet in the antenatal clinic to increase influenza vaccine during pregnancy (51). Most publications describing interventions to improve maternal vaccination relate to influenza vaccine, given the recommendation for pertussis is more recent. There are no systematic or literature reviews published that solely focus on evaluating strategies to improve pertussis vaccination uptake in pregnancy. Considering limited data exist on rigorously evaluated interventions to improve pertussis vaccination uptake among pregnant women,

determining effective interventions to improve pertussis vaccine uptake should be a public health priority.

2.4 Safety of pertussis and influenza vaccination during pregnancy

2.4.1 Safety of maternal pertussis vaccination

Concerns about vaccine safety during pregnancy has been consistently identified as one of the most significant reasons for women not accepting or receiving vaccination during pregnancy (68-70). Efforts to inform expectant mothers and healthcare providers about vaccine safety are essential to continue the momentum of maternal vaccination uptake. Following the introduction of antenatal pertussis vaccination programs in developed countries, several systematic reviews have supported the safety of pertussis or pertussis containing vaccines during pregnancy (72-75).

Several studies reported vaccine reactogenicity among pregnant women following pertussis vaccination with the most frequently reported reactions being injection site reactions (214, 269-272). Although injection site reactions such as pain/tenderness, induration/swelling, itching, and erythema/redness were reported after receipt of maternal pertussis vaccination in most clinical studies, pregnancy was not considered to have increased the rates of these events (214, 269-272). However, moderate to severe injection site pain was more frequent in pregnant than non-pregnant women in two studies (269, 271). Injection site reactions assessed over a week were more common after pertussis vaccination than placebo in one small clinical study (214) but occurred at similar rates over 48 hours in another slightly larger study (273). Furthermore, the rate of fever ranged from 0% to 5.1% in pertussis vaccinated pregnant women but these were usually mild and self-limiting fever and generally well tolerated (214, 231, 269-275). Local and systemic reactions reported among vaccinated pregnant women were not influenced

by repeat exposure to containing tetanus toxoid in pertussis vaccines (269, 276) or by concomitant vaccination with influenza vaccines (231, 272).

Review of passive adverse events following immunization (AEFI) reporting system data have shown there is no concerning maternal or fetal outcomes following pertussis vaccination during pregnancy (275, 277). Both RCTs and observational cohort studies also corroborated the safety of maternal pertussis vaccination, finding no increase in pregnancy or birth complications (274, 278), preterm birth (277, 279), small for gestational birth (277, 279), low birthweight (214, 278, 280), congenital anomalies (280), spontaneous abortion, (280) or stillbirth (278). Three retrospective cohort studies (281-283) reported a small but significant increase in chorioamnionitis for women who had received pertussis vaccination during pregnancy. However, this finding was not replicated in other studies (284-286). A review of the Vaccine Adverse Event Reporting System (VAERS) for all reports of chorioamnionitis showed that the condition is rarely reported following vaccination during pregnancy and 58% of women who report chorioamnionitis had at least one risk factor predisposing them to the condition (286). However, further studies are needed to investigate if there is any biological plausibility of maternal pertussis vaccine causing chorioamnionitis, since this condition is associated with severe short-term and long-term birth complications (287).

2.4.2 Safety of maternal influenza vaccination

Although the initial recommendation for maternal influenza vaccination was based on limited safety, several systematic reviews of RCTs, observational studies, retrospective data linkages, case control studies, and post-licensure vaccine safety studies have reported the safety of influenza vaccination during pregnancy (30-35). Safety data across post-licensure settings have demonstrated the safety of maternal inactivated influenza vaccines on pregnancy and birth outcomes (288, 289). Fewer than 5% report pain or swelling at the injection site and between

1-6% of pregnant women report a fever following seasonal influenza vaccination during pregnancy (272, 290, 291). However, similar rates of local reactions are reported following influenza vaccination by non-pregnant women of the same age, suggesting pregnancy does not elevate the risk of these adverse events (292).

Several studies have shown that influenza vaccination during pregnancy is not associated with increased risk for adverse pregnancy outcomes such as spontaneous abortion (293), gestational diabetes, pre-eclampsia, emergency caesarean delivery (288, 294) or chorioamnionitis (295). Furthermore, many studies corroborated that maternal influenza vaccination is not associated with harmful effects on birth outcomes, including preterm birth (229, 288, 296), small for gestational age births (230, 296-298), congenital anomalies and malformations (230, 288) and stillbirth (228, 299). Several studies have also shown no adverse effects following first trimester administration of influenza vaccine (230, 297, 300). However, a significant increased risk of spontaneous abortion was reported in a case-control study among women who received inactivated influenza vaccination within 28 days before their diagnosis of spontaneous abortion (301). The association was only stronger among women who had also received a A(H1N1) -containing vaccine in the previous influenza season (301). The authors (301) reported the findings could be biased because women who sought care for symptoms foreshadowing spontaneous abortion diagnosis may have had greater opportunity for vaccination in the 28-day exposure window. Compared to the control arm, cases were significantly older, more likely to have a history of two or more previous spontaneous abortions and to have smoked during pregnancy which are known risk factors for spontaneous abortion (302). Another case-control study with a larger sample size found no association between maternal influenza vaccination and spontaneous abortion (303). However, further prospectively designed studies are needed to validate any association between seasonal influenza vaccination and spontaneous abortion.

Following mass vaccination of pregnant women against 2009 influenza A/H1N1, several studies and surveillance initiatives were rapidly initiated (304-308). Among 2.4 million pregnant women in the US vaccinated against 2009 influenza A/H1N1 between 2009 and 2010, there were 294 adverse events submitted to VARES (308). Medical review of these reported events demonstrated that pandemic influenza A/H1N1 vaccine during pregnancy is not associated with adverse pregnancy and birth outcomes (308). Similar to seasonal influenza vaccine, no increased risk of adverse obstetric or birth outcomes were detected following either adjuvanted or non-adjuvanted maternal pandemic influenza vaccination in prospective or retrospective cohort studies (306, 309-312). Overall, numerous systematic reviews and meta-analysis have demonstrated that influenza vaccination at any time during pregnancy is safe for the mother, fetus and newborn (30-35, 228). However, the quality of evidence in the underlying observational studies included in these reviews is low.

2.5 Methodological Issues in Maternal Vaccination Studies

Currently, the effect of maternal pertussis and influenza vaccination on pregnancy and birth outcomes is primarily studied through non-experimental observational studies. This is because RCTs are considered unethical in countries where maternal pertussis and influenza vaccination is recommended and funded for pregnant women. Implementation of further RCTs in many countries including low-and middle-income countries where maternal pertussis or influenza vaccination is not the "standard of care" is challenging. This is due to ethical considerations, limited availability of baseline epidemiologic data on influenza and pertussis disease burden, higher baseline rates of obstetric complications and adverse birth outcomes, lack of local influenza activity surveillance, challenges in recruitment and retention of pregnant women and inconsistency in applying and interpreting assessment methods (e.g. measuring accurate

gestational age) (313).” Given the paucity of RCTs available, observational studies on safety and protective effects of maternal influenza and pertussis vaccination are integral in providing evidence, although they pose some methodological issues. Retrospective observational research has been the mainstay of evidence available for women vaccinated during pregnancy, due to the comparative cost, ethical considerations, and underrepresentation of pregnant women in RCTs. Retrospective observational studies evaluating the effect of maternal pertussis and influenza vaccination are complex due to the multi-factorial risks and causes of pregnancy and birth complications (30-35, 72-75).

Systematic reviews of maternal influenza and pertussis vaccine have highlighted that confounding is a threat to the validity of all observational studies and particularly to retrospective observational studies in examining the effect of vaccination during pregnancy (30-35, 72-75). Many of the large retrospective cohorts examining maternal vaccine safety studies fail to capture important variables that may increase the risk of poor pregnancy or birth outcomes (30-35, 72-75). This is partly due to the use of data gleaned from medical databases or secondary data extracted from computerised medical information that is already coded from a national or state data registry (30-35, 72-75) in many retrospective cohort studies. Several important potential confounders (e.g. gravidity, smoking status, drug use, binge drinking, psychosocial factors) in assessing safety of vaccination during pregnancy are often not collected through medical databases (30-35, 72-75). Therefore, the risk of residual confounding is inherent in the nature of retrospective observational cohort studies into maternal vaccine safety. Furthermore, many observational studies that rely on data extracted from administrative databases do not capture maternal vaccination administered in non-traditional settings (i.e. pharmacist or community health clinics or workplace-administered vaccination). Thus, uptake of maternal vaccinations is likely to be underestimated in such studies. Moreover, most retrospective studies on pertussis and influenza vaccine safety rely on the International

Classification of Diseases (ICD) codes or documentation of influenza or pertussis illness, pregnancy or birth complications from regional or national databases (30, 314). This method of data collection can be susceptible to missing and misclassification of data (30, 314).

Nevertheless, retrospective cohort studies involving large numbers of women are preferable to RCTs in evaluating the impact of maternal vaccination on rare pregnancy and birth outcomes i.e. stillbirth or congenital anomalies. This is because RCTs are not usually statistically powered to evaluate rare pregnancy or birth outcomes. Moreover, placebo-controlled RCTs are highly controlled experiments and they do not replicate the "real-world" circumstances in monitoring health outcomes of pregnant women (315). Therefore, observational cohorts with large representative samples of pregnant women are necessary for complementary investigation of less common adverse pregnancy outcomes, in addition to assessing safety and protective effects of maternal influenza and pertussis vaccination under real-world settings (315).

In observational studies, women with the most favourable risk profile may be more likely to receive the recommended vaccine (315). It would be expected that the women receiving vaccine would be more highly educated, less likely to smoke, have a more optimal pre-pregnancy weight and diet during pregnancy, and be more likely to adhere to prenatal care guidelines (315). Conversely, women with increased risk of obstetric complications or other risk factors for adverse outcomes are more likely to receive influenza vaccination during pregnancy (316), hence increasing the potential for confounding by indication. Therefore, in studies evaluating effect of maternal vaccination on pregnancy and birth outcomes, prospectively designed observational studies are more advantageous over retrospective studies in collecting important potential confounding variables.

The interpretation of maternal influenza vaccine studies has assumed that the same study design and analytic methods used to examine adverse outcomes from vaccination can be directly applied to assessment of potential benefit (i.e., risk ratios greater than 1.0 relating vaccination to adverse pregnancy outcome would suggest harm; risk ratios less than 1.0 would therefore indicate benefit) (315). Although this approach is reasonable, the underlying scenarios for harm and benefit following influenza vaccination are not symmetric (315). This is because a protective effect of maternal influenza vaccination in reducing risk of adverse pregnancy or birth outcomes is potentially mediated by the effectiveness of the maternal influenza vaccine in preventing influenza infection. On this premise, women who received influenza vaccination during pregnancy would be protected from maternal influenza infection, consequently averting potential influenza illness and any adverse effects on their pregnancy that would result from infection.

Since the protective effect of maternal influenza vaccination derives from the sustained reduction in risk of acquiring disease during the influenza season, and vaccination status outside that window would be less pertinent. However, influenza viruses can circulate year-round particularly in tropical regions (317). Assuming the influenza vaccine is usually administered in the pre-influenza season, the period of pregnancy at reduced risk for influenza will depend on the calendar timing of the influenza season in relation to the stage of pregnancy (315). Therefore, it is important to consider the duration of pregnancy length and exposure to a period of widespread influenza circulation in evaluating the protective effect of maternal influenza vaccination on pregnancy and birth outcomes.

Pregnancies must be followed longitudinally since the effect of maternal influenza illness or vaccination on pregnancy or birth outcomes will vary depending on the gestational age at the time of exposure, which introduces the potential for immortal time bias (318, 319). A given woman is “unvaccinated” up to the time of a receipt of vaccine and the time period before

vaccination is considered “immortal” because any adverse event that takes place before a pregnant woman had the opportunity to receive vaccine would result in the event being assigned to the unvaccinated group (319). This bias may lead to inaccurate estimates of the magnitude of effect of maternal immunisation on time-varying outcomes (318-320). Methodologically, using a time-invariant analysis or simply dichotomising a given pregnancy as vaccinated if vaccine was received at some time during the pregnancy or unvaccinated otherwise is insufficient (315). There needs to be a weekly consideration of the pregnancy with regard to vaccination status, the time at risk period prior to adverse pregnancy or birth outcomes, and calendar time of influenza activity and circulating influenza viruses (for maternal influenza vaccination studies). Therefore, it is important to incorporate appropriate time varying analytic methods and confirm receipt of vaccine and date of receipt to calculate the ‘time at risk’ period prior to adverse pregnancy or birth outcomes.

Another methodological challenge with observational studies is that pregnancies are not followed from the time of conception (i.e. first day of the last menstrual period). This causes downward bias in estimation of early pregnancy outcomes such as spontaneous abortion. Such data are said to be left truncated (320). Additionally, including follow-up time during which pregnancies are no longer at risk of some adverse outcomes (e.g. gestation after 37 weeks considered for preterm birth outcomes) can lead to overestimation of any true benefits of maternal vaccination. It is important for observational studies analysing the effect of maternal influenza or pertussis vaccination on birth outcomes to incorporate analytical techniques suitable for time dependent outcomes to minimise these potential biases.

In summary, collecting maternal vaccination status, potential confounding variables, and pregnancy and birth data from medical histories and databases may result in non-differential misclassification bias. This may attenuate the effect of influenza or pertussis vaccine estimates toward the null value, leading to an underestimation of potential risks or overestimation of any

true benefits of maternal vaccination on pregnancy or birth outcomes. In planning retrospective observational studies concerned with evaluating influenza or pertussis vaccine effects on pregnancy or birth outcomes, researchers may consider validating maternal vaccination status and pregnancy or birth outcome data using medical case note review. Importantly, prospective observational studies with active follow-up of pregnant women incorporating methodological approaches suitable for analysing time-dependent associations between maternal vaccine exposure on pregnancy and birth outcomes are warranted.

2.6 Aims and Specific Objectives

Aim 1. To systematically collect and summarise the available evidence on the effectiveness of interventions used to improve pertussis vaccination uptake in pregnant women (Chapter 4) (evaluations of interventions to improve uptake of maternal influenza vaccine has been previously examined and hence not the focus of this thesis).

Objective 1.1 – To identify and describe interventions to increase uptake of pertussis vaccination during pregnancy.

Objective 1.2 – To determine the effectiveness of any identified interventions or strategies to increase uptake of maternal pertussis vaccination.

Objective 1.3 – To identify the most effective interventions used to improve maternal pertussis vaccination and make recommendations based on the available evidence.

Aim 2. To identify psychosocial factors associated with the willingness and uptake of pertussis and influenza vaccination during pregnancy (Chapter 5).

Objective 2.1 – To assess the impact of antenatal depression, anxiety and stress on the willingness and uptake of the recommended pertussis and influenza vaccinations during pregnancy.

Objective 2.2 – To identify sociodemographic and maternal health behaviours associated with the willingness and uptake of the pertussis and influenza vaccination during pregnancy

Aim 3. To investigate the safety and protective effect of seasonal influenza vaccine during pregnancy (Chapter 6).

Objective 3.1 – Measure the rate of adverse pregnancy and birth outcomes among women who received seasonal influenza vaccine during pregnancy compared to unvaccinated women.

Objective 3.2 – Measure the rate of pre-delivery hospitalisations with respiratory illness among women who received seasonal influenza vaccine during pregnancy compared to unvaccinated women.

Objective 3.2 – To evaluate the protective effects of maternal influenza vaccination in improving birth outcomes.

Aim 4. To investigate the safety of pertussis containing (dTpa) vaccine on pregnancy and birth outcomes (Chapter 7).

Objective 4.1 – Measure the rate of adverse pregnancy and birth outcomes among mothers who received pertussis vaccine during pregnancy compared to unvaccinated women.

Chapter 3: Methods

For each of the studies, detailed methods are provided in Chapters 4, 5, 6 and 7. This chapter provides an overview of the methods employed for each study. A systematic review was used for the study in Chapter 4. Quantitative analyses were employed for studies in Chapters 5, 6 and 7, all based on data that were drawn from a prospective cohort study. First, a description of the cohort from which data were drawn for these studies in this thesis is given below.

3.1 Overview of dataset

3.1.1 Screening Tests to predict poor Outcomes of Pregnancy (STOP) cohort

The Screening Tests to predict poor Outcomes of Pregnancy (STOP) study is a prospective, multicentre cohort study of healthy nulliparous women with singleton pregnancy across two major maternity hospitals in Adelaide, South Australia (Lyell McEwin Hospital, Elizabeth Vale; and Women's and Children's Hospital, North Adelaide) from 2015-2018. This is a prospective cohort study of 1364 women. The overarching aim of the STOP study is to developing screening tests to predict the risk of adverse pregnancy outcomes including preeclampsia, gestational diabetes mellitus, small for gestational age birth and spontaneous preterm birth. Women were excluded from participation if they had ≥ 3 miscarriages or ≥ 3 terminations of pregnancy, major fetal anomalies, pre-existing hypertension on medication, Type I or Type II diabetes mellitus, renal disease, systemic lupus erythematosus, anti-phospholipid syndrome, known major uterine anomaly or previous cervical cone biopsy.

At time of recruitment participants interviewed were between 9^{+0} and 16^{+0} weeks' gestation (superscripts denote number of days in addition to weeks of gestation). Extensive baseline information regarding demographics (including maternal age, ethnicity, level of education, household income, socioeconomic index, employment status), family medical and obstetric history, complications during the current pregnancy, BMI, pre-existing conditions, maternal vaccination status and lifestyle questionnaire (including smoking status, intake of alcohol and recreational drugs, micronutrient supplement use, physical exercise) were collected. Participating women also completed the Perceived Stress Scale (PSS-10), (321) to assess perceived stress levels in the past month, the short form of the Spielberger State–Trait Anxiety Inventory (STAI), (322) assessing current anxiety symptoms, and the Edinburgh Postnatal Depression Scale (EPDS), (323) assessing depressive symptoms during pregnancy.

The women were monitored throughout pregnancy, and pregnancy and birth complications were diagnosed using current international guidelines. All women participating in the study were invited to attend a follow-up visit between 31^{+5} and 37^{+2} weeks' gestation. During this follow-up, participants had an interview regarding current pregnancy issues, medication use, and maternal vaccination status. Following delivery, a research midwife verified final maternal vaccination status by reviewing the South Australian Pregnancy Record (SAPR) (the primary hand-held antenatal medical record in South Australia) and interviewing women. Clinical measurements, pregnancy outcomes, neonatal outcomes data were collected and managed using REDCap (Research Electronic Data Capture) (324, 325). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (324, 325).

3.2 Study Designs and Methods used in the Thesis

3.2.1 Aim 1 - Interventions to improve uptake of maternal pertussis vaccination

A systematic review was used to identify strategies or interventions that were effective in improving uptake of pertussis vaccine among pregnant women. The details of the methodology of the systematic review, which followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (326) were pre-specified in a published protocol in the international prospective register of systematic reviews (PROSPERO, ID CRD42017058178), presented in Appendix A. The methods are also summarised in the systematic review publication, presented in Chapter 4.

3.2.2 Aim 2 - Psychosocial predictors of maternal vaccine uptake

Data from the STOP cohort were drawn to identify psychosocial predictors of pertussis and influenza vaccine uptake among pregnant women. A Poisson regression model was the most appropriate model to determine psychosocial factors influencing acceptance and uptake of pertussis and influenza vaccines during pregnancy. This is because when the incidence of an outcome of interest is common in the population of interest (i.e. > 10%), the estimated odds ratio (OR) derived from the logistic regression is a poor approximation of the prevalence ratio (PR) (327). In this situation, the OR tends to overestimate the strength of the association when the outcome is common (i.e. vaccine uptake, as in this study) (328). As vaccination uptakes increase, ORs become increasingly less reliable estimates of the PR. In this situation, use of ORs are potentially misleading for readers or policy makers, who may inappropriately interpret ORs and PRs as being interchangeable. Additionally, in this study fitting the Poisson regression model allowed the incorporation of the natural logarithm of the total time of each woman's pregnancy in gestational weeks as an offset term in the model, thereby accounting for the relative opportunity each woman had to receive influenza vaccination during pregnancy.

3.2.3 Aim 3 - Safety and benefits of seasonal influenza vaccination during pregnancy

Data from the STOP cohort were used to evaluate the safety and impact of maternal seasonal influenza vaccination on pregnancy and birth outcomes. Time-dependent analyses were conducted. Cox proportional-hazards models with gestational age in weeks as the underlying time scale were used to derive hazard ratios (HRs) that compared the hazard rates for time-sensitive outcomes such as spontaneous abortion (Objective 3.1), hospital admissions during pregnancy with influenza-like illness (Objective 3.2) and preterm birth (Objective 3.3) between vaccinated and unvaccinated women. Maternal influenza vaccination status was coded as a time-dependent exposure variable. In this approach, each woman may contribute unvaccinated and vaccinated time in any risk set. Vaccinated women contributed unvaccinated exposure time up until their gestational time of vaccination. Any pregnancy or birth events of interest

occurring prior to vaccination was designated as occurring in unvaccinated time period. Log-binomial models were also used in this study to estimate risk ratios (RR) and adjusted risk ratios (aRR) comparing risk of late onset or early postpartum adverse pregnancy outcomes or time-independent perinatal outcomes. Finally, a linear regression model was applied to compare the difference in mean gestational age at delivery and mean birthweight by maternal vaccination status. Details of these analyses and the findings are described in Chapter 6.

3.2.4 Aim 4 - Safety of pertussis vaccination during pregnancy

Data were drawn from the prospective STOP cohort to evaluate the safety of pertussis vaccine during pregnancy. The methodological approach that was applied to address Aim 3 was also used to address Aim 4. Cox proportional-hazards models and log-binomial models were fit to quantify the associations between maternal pertussis vaccination status and pregnancy and birth outcomes. The analyses and findings are explained in more detail in Chapter 7.

3.3 Ethics

Written informed consent was obtained from all women. Personal identifying information in the STOP study database was eliminated to ensure that confidentiality of all patients' records was maintained. The STOP study protocol was approved by the Women's and Children's Health Network Human Research Ethics Committee Adelaide, Australia (HREC/14/WCHN/90), dated 16/10/2014 (329).

Chapter 4: A systematic Review of Interventions to Improve Uptake of Pertussis vaccination in Pregnancy

4.1 Publication

Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS One. 2019;14(3): e0214538.

Statement of Authorship

Title of Paper	A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS One. 2019;14(3): e0214538.

Principal Author

Name of Principal Author (Candidate)	Hassen Mohammed		
Contribution to the Paper	Conceived and designed the study, developed and published the protocol, conducted database searches, retrieved papers and assessed each paper for their eligibility, extracted, analysed and interpreted data, performed quality assessment, prepared the first and final draft of the manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mark McMillan		
Contribution to the Paper	Extracted, analysed and interpreted data, performed quality assessment, reviewed and edited the manuscript		
Signature		Date	15/9/2020
Name of Co-Author	Prof. Claire Roberts		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	17/9/20
Name of Co-Author	Prof. Helen Marshall		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	15/09/2020

PLOS ONE

RESEARCH ARTICLE

A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy

Hassen Mohammed[1,2]*, **Mark McMillan**[1,2], **Claire T. Roberts**[1], **Helen S. Marshall**[1,2,3]

1 Adelaide Medical School and Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia, **2** Vaccinology and Immunology Research Trials Unit (VIRTU), Women's and Children's Hospital, North Adelaide, South Australia, Australia, **3** School of Public Health, University of Adelaide, Adelaide, South Australia, Australia

* hassen.mohammed@adelaide.edu.au

Citation: Mohammed H, McMillan M, Roberts CT, Marshall HS (2019) A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS ONE 14(3): e0214538. https://doi.org/10.1371/journal.pone.0214538

Editor: Ray Borrow, Public Health England, UNITED KINGDOM

Received: November 23, 2018

Accepted: March 14, 2019

Published: March 28, 2019

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: Research grants from vaccine manufacturers GSK and Sanofi Pasteur for investigator-led research have been provided to the institution at which Dr. Marshall and Mr. McMillan are employees. Dr. Roberts and Mohammed did not report any potential conflicts of interest. This

Abstract

Background

Maternal pertussis vaccination has been introduced in several countries to prevent pertussis morbidity and mortality in infants too young to be vaccinated. Our review aimed to systematically collect and summarize the available evidence on the effectiveness of interventions used to improve pertussis vaccination uptake in pregnant women.

Methods

We conducted a systematic search of MEDLINE/PubMed, PMC and CINAHL. Before and after studies and those with a concurrent control group were considered for inclusion. Standardized effect sizes were described as the ratio of the odds to be vaccinated in the intervention group compared with the standard care group and absolute benefit increase (ABI) were calculated.

Results

Six studies were included in the review, of which three were randomized controlled trials (RCTs). Strategies to improve uptake were focused on healthcare providers, pregnant women, or enhancing vaccine access. Healthcare provider interventions included provider reminder, education, feedback and standing orders. Interventions directed at pregnant women focused solely on education. Observational studies showed: (1) the provision of maternal pertussis vaccination by midwives at the place of antenatal care has improved uptake of pertussis vaccine during pregnancy from 20% to 90%; (2) introduction of an automated reminder within the electronic medical record was associated with an improvement in the pertussis immunization rate from 48% to 97%; (3) an increase in prenatal pertussis vaccine uptake from 36% to 61% after strategies to increase provider awareness of recommendations were introduced. In contrast to these findings, interventions in all three RCTs (2 involved education of pregnant women, 1 had multi-component interventions) did not demonstrate improved vaccination uptake.

does not alter our adherence to PLOS ONE policies on sharing data and materials.

Conclusions

Based on the existing research, we recommend incorporating midwife delivered maternal immunization programs at antenatal clinics, use of a provider reminder system to target unvaccinated pregnant women and include maternal pertussis immunization as part of standard antenatal care.

Introduction

There has been a global resurgence in pertussis in recent years, particularly in the US, the UK and Australia, with the highest rates of hospitalization and death in young infants, mainly those less than 2 months of age, prior to the recommended age for vaccination [1–6]. Infection of young infants occurs primarily at the household level with new mothers identified as the most common sources [7, 8]. Maternal pertussis immunization protects infants through passive and active transfer of maternal antibodies that protect the infant until the primary immunization series commences in infants at 6–8 weeks of age [9–11]. The highest level of protection is not achieved in infants until they have received 3 doses at 6 months of age [12]. Pertussis vaccination in pregnancy at least 7 days before delivery can prevent up to 91% of pertussis disease in infants age <3 months [11]. In 2011, the US became the first country to recommend that health care personnel administer pertussis vaccine to pregnant women [13] and many countries have recently adopted this policy in an attempt to reduce the burden of pertussis in young infants [14]. Despite the recommendation of maternal pertussis vaccination from immunization advisory groups internationally [13–15], uptake remains suboptimal [16–19]. The barriers to vaccination in pregnancy are more complicated than the barriers identified for low uptake in childhood immunization programs [20].

Some recent studies have evaluated the effectiveness of strategies in improving maternal immunization uptake, which predominantly focussed on educational interventions for pregnant women or healthcare providers while others included a multi-component intervention package [21–25]. A systematic review has been recently published to identify effective strategies in improving the uptake of vaccination in pregnancy in high-income countries [26]. However, the review [26] was aimed to make recommendations to an English setting and the majority of the published articles (18/22) identified in the review evaluated the effectiveness of strategies in improving seasonal influenza vaccination uptake in pregnancy. Limited data exist on rigorously evaluated interventions to improve pertussis immunization uptake among pregnant women. Given the well-documented benefits of maternal pertussis immunization in protecting very young infants, determining effective strategies to improve pertussis vaccine uptake during pregnancy should be a public health priority. This is the first review aimed to systematically collect and summarize the available evidence on the effectiveness of interventions in improving pertussis vaccination uptake in pregnant women. The protocol for this review is published in PROSPERO International prospective register of systematic reviews—CRD42017058178.

Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see S1 Table) [27].

Search strategy

The search strategy included the following electronic databases:—PubMed, PMC, Medline, Cochrane Library, CINAHL and ClinicalTrials.gov. Other sources include conference proceedings—World Society for Paediatric Infectious Diseases (WSPID) and European Society for Paediatric Infectious Diseases (ESPID). Specific search terms suitable to the individual databases were developed. These search terms included combinations of Medical Subject Headings (Messi)/Emtree and text words contained in the title and abstract (see S2 Table).

Eligibility criteria

Our systematic review includes all original studies that reported on interventions to improve pertussis uptake during pregnancy. Some countries recommending pertussis vaccination during pregnancy are using combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) or with inactivated polio vaccine (Tdap-IPV) in their programs. Hence, studies comparing pertussis vaccination uptake in pregnancy combined with or without other antigens either pre-post introduction of intervention or a concurrent control group during the same observation period were considered. The primary outcome measured was pertussis vaccination uptake during pregnancy, with confirmation in electronic medical records or self-reported data (Table 1).

Study selection

Two independent reviewers (HM and MM) completed initial screening based on titles and abstracts of potentially relevant studies. If the articles reported interventions to improve pertussis vaccination uptake during pregnancy, the reviewers performed a more detailed subsequent assessment by looking at the full text. The reference lists considered for inclusion were searched for additional studies that might have been missed in the database search. Disagreements about the inclusion or exclusion of studies were resolved through consensus discussions among reviewers.

Data analysis

The primary measures extracted were percentage changes in uptake of pertussis vaccination during pregnancy from standard care group to intervention group. Standardized effect sizes were described as the ratio of the odds to be vaccinated in the intervention group compared with the standard care group and absolute benefit increase (ABI) with 95% confidence

Table 1. The inclusion and exclusion criteria used during the screening process.

Criteria	Included
Study design	• Studies comparing pertussis vaccine uptake among pregnant women who were exposed to an intervention vs. standard care • Observational studies • Randomised controlled trials • Interventions that include pertussis as a compound of the immunization i.e. Tdap or Tdap-IPV
Population	Pregnant women
Outcomes	Pertussis vaccination uptake during pregnancy (Standard care vs. intervention group)
Publication date	Up to January 2019
Language	Studies published in English

https://doi.org/10.1371/journal.pone.0214538.t001

intervals (CI), were calculated. In studies with concurrent comparison groups, the overall change in pertussis vaccination uptake was calculated by using the difference in vaccine uptake change observed in the intervention and comparison groups. In studies without a concurrent comparison group, the absolute percentage change was calculated from measurements of pertussis vaccination uptake during pregnancy in pre- and post-intervention. Additionally, a list of all confounders adjusted for in the data analysis was reported. To strengthen the generalisability of our review results, we used the intervention classification guidelines adopted from the Task Force on Community Preventive Services [28].

1. Provider-focused interventions
2. Pregnant woman-focused interventions
3. Interventions to enhance maternal pertussis vaccination access

Our review did not conduct meta-analysis because of the broad heterogeneity in study design and types of interventions used to improve pertussis vaccination uptake during pregnancy.

Data quality assessment

Two independent reviewers (HM and MM) assessed the quality of the included studies. The Cochrane Collaboration method was used for the risk of bias assessment of randomized controlled trials (RCTs) [29]. The risk of bias was assessed in six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. A 'risk of bias summary' displaying the quality assessment of all included RCT studies was generated. For each outcome, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were also used to evaluate the quality of the RCT studies [30]. The GRADE criteria were used along with the Cochrane Collaboration tool because these criteria, take into account assessment of three additional domains: consistency, directness, and precision of the results in addition to the risk of bias. Randomized trials began as high-quality evidence but were rated down if trials demonstrated limitations (see S3 Table). The Joanna Briggs Institute (JBI) critical appraisal tools were used to assess the quality of experimental studies without random allocation (observational studies) (see S4 Table) [31].

Results

Search results

The initial search generated 3542 published studies. After removing duplicates, screening titles and abstracts of the remaining 1935 studies, 16 studies were identified for full text review (Fig 1). Of these, we excluded 10 papers because they did not include an intervention component (n = 4), eligible population (n = 3), outcome of interest (n = 1) or did not have a standard care group for comparison (n = 2) (see S5 Table). Six studies that met the selection criteria were included. No additional studies were obtained from the reference lists of the included studies.

Study characteristics

The six included studies were published between 2015 and 2017. Five studies were conducted in the United States (US) [23–25, 32, 33] and one study was conducted in Australia [34]. The sample sizes varied from 106 to 10,600 participants. Pregnant women were recruited from public maternity hospitals, tertiary hospitals, antenatal clinics, university hospitals and a multi-specialty medical organization.

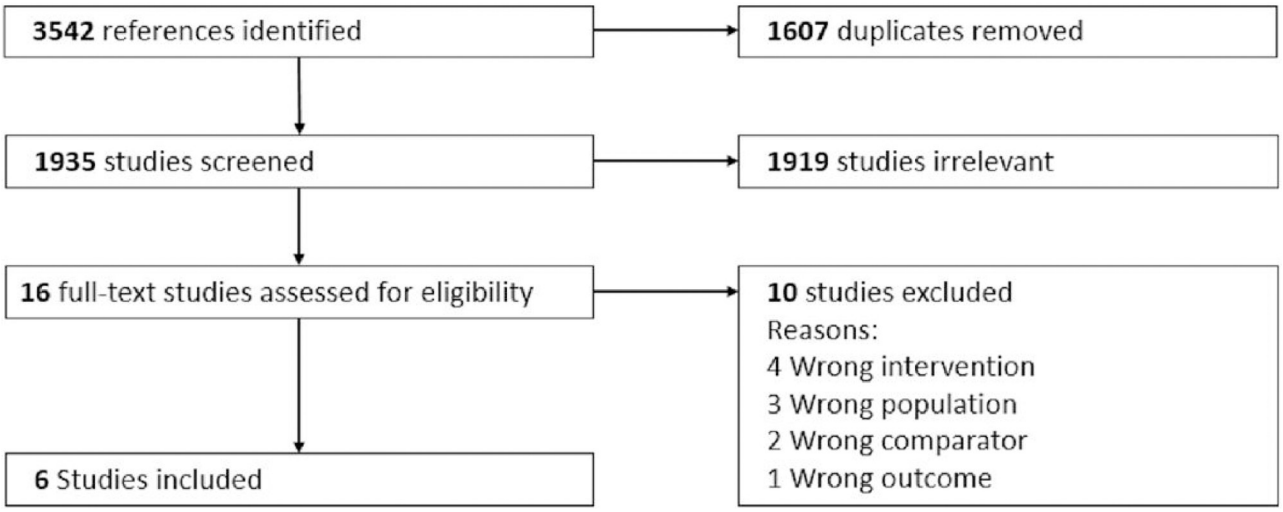


Fig 1. Flow diagram of the process and results of study selection.

https://doi.org/10.1371/journal.pone.0214538.g001

The studies investigated a variety of interventions; two studies used provider-based interventions only [25, 32], two studies used pregnant woman-focused interventions only [24, 33] and two studies incorporated provider-focused interventions, pregnant woman-focused interventions, as well as interventions to enhance maternal pertussis vaccination access (Table 2) [23, 34]. Standard care varied and included pre-intervention routine prenatal care [23, 24, 32, 34], routinely offered pertussis vaccination only during the postpartum period [25] and standard Vaccine Information Statements (VISs) produced by the Centers for Disease Control and Prevention (CDC) [33].

Critical appraisal

Randomized controlled trials. The evidence quality of the two RCTs were rated "moderate" [23, 32] and "low" [24]. In two studies, the proportion of missing outcomes likely resulted in bias of the effect estimates [23, 24]. Self-report was the primary method used to judge if a pertussis vaccine was administered in two of the RCTs [23, 24]. In Chamberlain et al. [23] there was a higher proportion of self-reported vaccination in the intervention group compared to the standard care group, which may have introduced bias. Kris et al. [24] assessed the

Table 2. Strategies used to improve pertussis vaccination uptake among pregnant women.

Included studies	Interventions for health care providers				Pregnant women focussed intervention	Interventions to enhance vaccination access	
	Provider reminder/ recall	Provider Education	Standing orders	Provider feedback	Pregnant women education	Extend service location	Increase stock
Kriss [24]					√		
Payakachat [33]					√		
Chamberlain [23]		√		√	√	√	√
Morgan [25]	√		√				
Healey [32]	√	√	√				
Mohammed [34]		√	√		√		√

https://doi.org/10.1371/journal.pone.0214538.t002

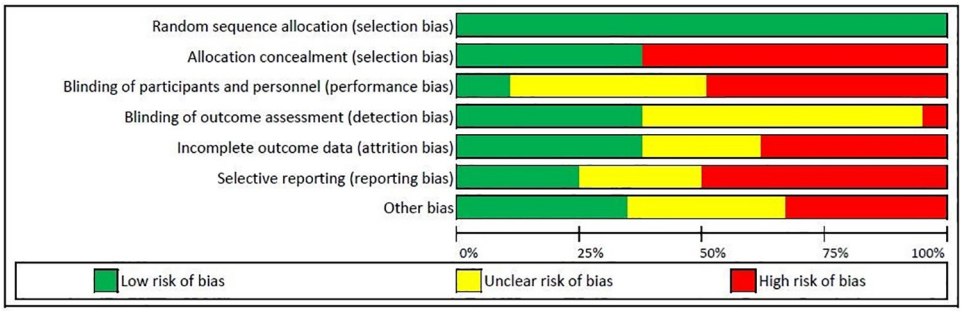


Fig 2. Risk of bias in included RCT studies.

https://doi.org/10.1371/journal.pone.0214538.g002

outcome via self-report during a follow-up survey which could introduce recall bias (Supplementary File).

Two of the RCT studies [23, 24] did not have a sufficient number of participants in both arms to achieve 80% power to detect effects caused by the interventions while only one of the RCT studies met the required sample size [33]. One RCT targeted minority women who were African American women [24]. One of the RCT [33] studies was conducted in only one public hospital and the majority of participants were from low socioeconomic backgrounds and had poor health literacy. Hence, these findings may not be representative of other pregnant women in different US regions [33]. The risk of bias of all RCTs is summarized in Fig 2.

Observational studies. For all observational studies, interventions were introduced with the aim to improve the uptake of pertussis vaccines among pregnant women. These were assessed using electronic medical records [25, 32] or self-reported data [34]. Two studies [25, 34] included pregnant women who were recruited prior to the recommendation as the standard care groups and the intervention groups included women recruited after the change in the pertussis vaccination recommendations. Hence, observed improvement in vaccination rates could also be attributed to the change in national recommendations in these studies [25, 34]. These observational studies are likely to result in chronology bias and an overestimation of the effect of an intervention. Adjustment for confounding was performed in two of the observational studies (Table 3) [23, 34]. However, not all of the observational studies have considered potential confounders influencing vaccination uptake during pregnancy in their adjusted analysis such as maternal age, parity, primary language, ethnicity, socioeconomic factors, educational level and marital status.

Effect of various interventions in increasing pertussis vaccine uptake

Provider-focused interventions. Two retrospective cohort studies [25, 32] implemented intervention solely on provider-focused interventions while one RCT study used multi intervention components that targeted both HCPs and pregnant women [23]. One of the retrospective studies involved delivering an electronic reminder "best practice alert" within the medical record system by alerting HCPs to offer maternal pertussis vaccination to their pregnant patients [25]. Post-implementation of best practice alert, uptake of pertussis vaccine during pregnancy was significantly improved to 97% compared with 48% of postpartum pertussis vaccination uptake prior to the program. The computed absolute benefit increase (ABI) of the intervention was 49% (95% CI 48% to 50%) (Table 3). Healy et al. [32] evaluated an American College of Obstetricians and Gynaecologists (ACOG) tool kit that aimed to improve HCPs' awareness of the recommendation to vaccinate pregnant women with pertussis vaccines. The uptake of pertussis vaccine among pregnant women was significantly improved after the

Table 3. Absolute benefit increase and 95% confidence intervals of each intervention.

Author	Study design, period and methods	Participants and setting	Uptake of maternal Tdap vaccine (n, %)	Absolute benefit increase, ABI (95% CI)	Confounders adjusted for
A. Pregnant women focused intervention programs					
Payakachat [33]	**RCT**:	Academic medical centre Arkansas, USA	**Standard care**	**0.03** (-0.07, 0.15)	None
	May–August 2014		65/144 (45%)		
	Standard care:				
	Vaccine information statement (sVIS)		**Intervention**		
			66/135 (49%)		
	Intervention:				
	Plain language version (mVIS)				
Kriss [24]	**RCT**:	Pregnant African American women in 4 antenatal clinics in metropolitan Atlanta, USA	**Standard care**	**Intervention 1**	None
	January 30-April 3, 2013.		2/34 (6%)during pregnancy	**0.00** (-0.13,0.15)	
	Follow up: after delivery		4/34 (12%) postpartum	**Intervention 2**	
	Standard care:		**Intervention 1 (Video)**	**0.00** (-0.13, 0.16)	
	Routine prenatal care		2/31 (6%) during pregnancy	**Postpartum**	
	Intervention:		7/31 (23%) Postpartum	**Intervention 1**	
	1. Messaging video		**Intervention 2 (iBook)**	**0.10** (-0.07,0.29)	
	2. Messaging iBook		2/30 (7%) during pregnancy	**Intervention 2**	
			13/30 (43%) postpartum	**0.31** (0.09, 0.50)	
B. Healthcare provider focused intervention programs					
Morgan [25]	**Retrospective study**	Pregnant women from Parkland Hospital, USA	**Standard care**	**0.49** (0.48,0.50)	None
	Standard care: Routinely offered Tdap during the postpartum period. Historical control, Jan 2012 to May 2013		5,064/10,600 (48%)		
			Intervention		
			9,879/10,201 (97%)		
	Intervention A best-practice alert, June 2013 to July 2014				
Healey [32]	**Retrospective study**	Women delivering at Texas Children's Hospital, USA	**Standard care**	**0.25** (0.11,0.37)	None
	Standard care: Routine antenatal care. Historical control April to Sept 2013		(36%)[a]		
			Intervention:		
	Intervention: ACOG "toolkit" Physicians information through email and regular meetings. Sep 2013 to Jun 2014		(61%)[a]		
			N = 6577		
C. Interventions with bundled components					
Mohammed [34]	**Observational prospective study**	Pregnant women attending a territory obstetric hospital in Adelaide, Australia	**Standard care**	**0.70** (0.50, 0.82)	Age, parity, country of birth, provider recommendation
	November 2014 and July 2016		5/25 (20%)		
	Standard care: Routine antenatal care		**Intervention**		
			140/155 (90%)		
	Intervention: A midwife delivered immunization program				

(*Continued*)

Table 3. (Continued)

Author	Study design, period and methods	Participants and setting	Uptake of maternal Tdap vaccine (n, %)	Absolute benefit increase, ABI (95% CI)	Confounders adjusted for
Chamberlain [23]	**A cluster RCT**	Pregnant women from obstetric practices in Georgia, USA	**Standard care**	**0.04** (-0.02,0.12)	Adjusted for clustered study design and intention to receive the vaccine before delivery
	December 2012–April 2013		13/151 (9%)		
	Standard care Routine antenatal care				
			Intervention		
	Intervention Vaccine Champions, provider-to-patient talking points, educational brochures, posters, lapel buttons & iPads loaded with tutorials		19/140 (14%)		

[a] The authors did not state the number of vaccinated women pre-and post-intervention

https://doi.org/10.1371/journal.pone.0214538.t003

release of the ACOG tool kit in the tertiary care centre. The ABI generated from this study was 25% (95% CI 11% to 37%) (Table 3).

Pregnant woman-focused interventions. Two RCT studies [24, 33] evaluated the sole effect of pregnant women-focused interventions alone while three studies also incorporated other intervention components [23, 25, 34]. Kris et al. [24] assessed the effect of two Elaboration Likelihood Model (ELM) based vaccine educational interventions—an affective messaging video and a cognitive messaging iBook intervention among pregnant African American women [24]. Only 6% and 7% received the pertussis vaccination during pregnancy in the iBook and video groups, respectively. Sample sizes were too small to obtain meaningful estimates in the improvement of pertussis vaccination during pregnancy. However, of the two interventions, the iBook was significantly associated with uptake of the postpartum pertussis vaccination compared with women in the control group (Table 3). Payakchat et al. [33] conducted a prospective study among pregnant women who were randomized to receive either the standard CDC pertussis vaccine information statement (sVIS) or a modified version (mVIS). There was no significant differences in the pertussis vaccination uptake during pregnancy between the sVIS and mVIS groups. The computed ABI for the study was 3% (95% CI -7% to 15%) (Table 3).

Interventions to enhance access to pertussis vaccination. Our review found no studies that implemented interventions solely focused on enhancing access to the pertussis immunization during pregnancy. However, two of the reviewed studies included strategies to enhance vaccine access along with two of the classified intervention types: pregnant woman-focused and provider-focused strategies [23, 34]. One of the studies was a cluster-randomized trial [23] while the other was a prospective observational study [34].

Bundled interventions. The reviewed studies included only two intervention components as part of bundled interventions [23, 34]. Chamberlain et al. [23] introduced multi-component antenatal vaccine promotion package among 11 obstetric practices in Georgia. Each intervention obstetric practice was instructed to hand out iPads pre-loaded with lessons demonstrating the importance of maternal immunization to obstetric patients in examination rooms. Chamberlin et al. [23] also evaluated the use of identification of a vaccine champion and assessed whether stocking of influenza and pertussis vaccines in obstetric practices could improve vaccine uptake during pregnancy. Women who received pertussis vaccination during pregnancy were significantly more likely to have been enrolled from a practice stocking pertussis vaccines

than women who did not receive a pertussis vaccine during pregnancy (78% vs 51%; $p < 0.01$). Overall, antenatal pertussis vaccination uptake was higher in the bundled intervention group than the control group, although improvements were not significant (RR 1.58, 95% CI 0.81, 3.07) [23].

Mohammed et al. [34] aimed to estimate maternal vaccine uptake pre-post introduction of a midwife delivered maternal immunization program at a territory obstetric hospital, South Australia. The midwife vaccine delivery program in South Australia equipped midwives with knowledge and skills to engage with pregnant women on the topic of maternal immunization and administer pertussis immunizations to pregnant women [35]. The adjusted odds of women receiving pertussis vaccination during pregnancy were significantly higher after the implementation of the midwife delivered program compared with women who delivered babies prior to the program (AOR 21.1, 95% CI 6.14–72.9; $p<0.001$) [33]. The calculated ABI for this study was 70% (95% CI 50% to 82%).

Discussion

Given the well-documented benefits of maternal pertussis immunization in protecting young infants, our review findings are relevant to HCPs and public health policy makers, to guide the establishment of effective maternal pertussis immunization programs. Our review identified six studies evaluating the effectiveness of interventions that promote pertussis vaccination in pregnant women. These studies primarily focused on interventions targeting either HCPs or pregnant women. Our review included three RCTs and three observational studies. RCTs are the most rigorous scientific method for appraising the effectiveness of health care interventions [36]. The interventions in all the three RCTs included in this review did not demonstrate a significant improvement in the uptake of pertussis vaccination during pregnancy, although two studies failed to attain their sample size estimates.

The three observational studies in our review have reported statistically significant absolute increases in the vaccination rate of at least 25% [25, 32, 34]. Mohammed et al. [34] demonstrated provision of pertussis vaccination by midwives at the place of antenatal service was strongly associated with increased pertussis vaccination uptake during pregnancy. The program enables registered midwives to administer vaccination during pregnancy using a standing medication order, without seeking permission from a referring medical doctor [34]. Previous studies suggested that administering maternal immunizations through standard antenatal care by midwives could improve vaccination uptake among pregnant women [37, 38]. However, the relatively small sample size of the reviewed study could be a limitation to the study findings [34].

Previous studies have shown the implementation of a "best practice alert" with in the electronic medical record is associated with improved uptake of influenza vaccines in several high-risk groups [39–41] which supports our reviewed observational study findings in pregnant women [25]. Installing an automated reminder within electronic medical records in an antenatal care setting may encourage health care provider–patient discussions on the safety, efficacy, and necessity of pertussis vaccination during pregnancy. The use of the best-practice alert would also enable prenatal care providers to administer the vaccine at a moment when the pregnant women can act immediately with a minimum of additional time, effort or cost.

The finding of one of the reviewed observational studies [32] is also consistent with earlier research that multiple educational interventions to improve provider awareness has improved vaccine uptake among pregnant women in antenatal care settings [38, 39, 42]. Several studies have also reported that recommendation from maternity care providers is the most important

factor in improving vaccination uptake during pregnancy [43–49]. Many of the barriers cited for pregnant women often apply to HCPs as well, including lack of knowledge about the benefits of maternal vaccinations [50–54]. Pregnant women's misperceptions about the risk of the disease, effectiveness and safety of vaccination during pregnancy are the main barriers to the delivery of vaccinations during pregnancy [55–58]. Hence, overcoming pregnant women and HCP barriers play a major role in improving pertussis vaccination uptake among pregnant women.

Two of the studies assessing the sole effect of pregnant woman-focused interventions were RCTs and found no significant effect of pregnant woman-focused educational interventions [24, 33]. Although, these studies have shown a positive effect of educational interventions on improving pertussis vaccination uptake among pregnant women, they did not significantly improve uptake of pertussis vaccination during pregnancy. It could be argued that interventions solely focussed on educating pregnant women on the benefits of vaccines might not be an effective strategy. Moniz et al. [59] argued that the content of the message in educational interventions might influence its effectiveness and further studies assessing messaging would be of value. There is a need for high-quality patient education highlighting the role of maternal pertussis vaccination in preventing severe pertussis infection in very young infants. Educational materials on maternal pertussis immunization should also be easily readable and accessible to women from culturally and linguistically diverse backgrounds. There is also a need for studies in other countries and low resource settings as it is likely that interventions will need to be cognisant of cultural considerations. In addition, understanding the psychological and social factors influencing women's decisions to accept vaccines during pregnancy could help in designing strong maternal immunization programs.

Limitations

Although our review tried to standardize intervention into distinct classifications to enhance their comparability, some studies included interventions of more than one classification, which complicated comparability between interventions. Some of the studies were not adequately powered and were susceptible to bias and thus may only provide indirect evidence of effectiveness. Vaccination behaviour influences the self-report and explains a tendency to overestimate vaccination coverage in self-reporting compared to the electronic medical record [60]. Hence, the reviewed studies with self-reported vaccination are likely biased toward overestimating the intervention's effect. Moreover, none of the reviewed studies takes into account the impact of contemporaneous vaccination for influenza as a predictor of pertussis vaccination uptake. In other words, participants could be more likely to be vaccinated for pertussis during the time of year when HCPs were also recommending vaccination for influenza particularly during the flu season. Furthermore, recommended national changes in timing of maternal pertussis vaccination from postpartum to antepartum may have introduced bias in comparison of vaccination coverage between standard care and intervention groups in some of the observational studies. In addition, most of the reviewed studies were done in the US and the difference in access to the antenatal health care system among countries limits the generalizability of the results internationally.

Overall, the certainty of the findings in this review are low. To improve the certainty of evidence more RCTs are required. In situations where only observational designs are feasible, consideration of how best to limit potential bias is paramount. Before and after studies should use at least three data points before and after the implementation of the intervention, and adjust for secular trend in the analysis [61].

Conclusions

The best available evidence suggests that to improve maternal pertussis vaccination to protect young infants, HCPs should inform all pregnant women about the importance of pertussis vaccination during pregnancy, incorporate midwife delivered maternal immunization program at antenatal clinics, use provider reminder systems to target unimmunized pregnant women, and include maternal pertussis immunization as part of standard antenatal care.

Supporting information

S1 Table. PRISMA checklist.
(PDF)

S2 Table. Database search strategies.
(PDF)

S3 Table. Quality assessment of the reviewed randomized controlled trials.
(PDF)

S4 Table. Quality assessment of the reviewed observational studies.
(PDF)

S5 Table. Characteristics of the excluded studies.
(PDF)

Author Contributions

Conceptualization: Hassen Mohammed, Mark McMillan, Claire T. Roberts, Helen S. Marshall.

Formal analysis: Hassen Mohammed, Mark McMillan.

Methodology: Hassen Mohammed, Mark McMillan, Helen S. Marshall.

Supervision: Claire T. Roberts, Helen S. Marshall.

Validation: Helen S. Marshall.

Writing – original draft: Hassen Mohammed.

Writing – review & editing: Hassen Mohammed, Mark McMillan, Claire T. Roberts, Helen S. Marshall.

References

1. Munoz FM. Pertussis in infants, children, and adolescents: diagnosis, treatment, and prevention. Semin Pediatr Infect Dis. 2006; 17 (1):14–9. https://doi.org/10.1053/j.spid.2005.11.005 PMID: 16522501
2. Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J. 2003; 22 (7):628–34. https://doi.org/10.1097/01.inf.0000073266.30728.0e PMID: 12867839
3. Smith C, Vyas H. Early infantile pertussis; increasingly prevalent and potentially fatal. Eur J Pediatr. 2000; 159 (12):898–900. PMID: 11131347
4. Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. Pediatrics. 2008; 121(3):484–92. https://doi.org/10.1542/peds.2007-1393 PMID: 18310196
5. Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995-2005—trends by region and age group. Communicable diseases intelligence quarterly report. 2007; 31:205–15. PMID: 17724997

6. Crowcroft N, Andrews N, Rooney C, Brisson M, Miller E. Deaths from pertussis are underestimated in England. Archives of Disease in Childhood. 2002; 86(5):336–8. https://doi.org/10.1136/adc.86.5.336 PMID: 11970924
7. Baptista PN, Magalhaes VS, Rodrigues LC. The role of adults in household outbreaks of pertussis. Int J Infect Dis. 2010; 14(2):e111–4. https://doi.org/10.1016/j.ijid.2009.03.026 PMID: 19559636
8. Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013; 31(4):618–25. https://doi.org/10.1016/j.vaccine.2012.11.052 PMID: 23200883
9. Mooi FR, de Greeff SC. The case for maternal vaccination against pertussis. Lancet Infect Dis. 2007; 7(9):614–24. https://doi.org/10.1016/S1473-3099(07)70113-5 PMID: 17537674
10. Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol. 2011; 204(4):334 e1–5
11. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. The Lancet. 384 (9953):1521–8.
12. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics. 2014; 133(3):e513–9. https://doi.org/10.1542/peds.2013-3181 PMID: 24515514
13. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR—Morbidity & Mortality Weekly Report. 2013; 62 (7):131–5.
14. World Health Organization. Pertussis vaccines: WHO position paper–September 2015. Wkly Epidemiol Rec. 2015; 90:433–458. PMID: 26320265
15. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health, Canberra; 2018. immunisationhandbook.health.gov.au. Accessed March 15, 2018.
16. Deverall EJ, Gilmore B, Illing S, Peiris-John R. Pertussis vaccination uptake in pregnancy: lessons to be learned from an integrated healthcare approach. N Z Med J. 2018; 131(1473):42–7. PMID: 29649195
17. Laenen J, Roelants M, Devlieger R, Vandermeulen C. Influenza and pertussis vaccination coverage in pregnant women. Vaccine. 2015; 33(18):2125–31. https://doi.org/10.1016/j.vaccine.2015.03.020 PMID: 25796339
18. 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(2):56–9. https://doi.org/10.15585/mmwr.mm6602a4 PMID: 28103212
19. Housey M, Zhang F, Miller C, Lyon-Callo S, McFadden J, Garcia E, et al. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid—Michigan, 2011–2013. MMWR Morb Mortal Wkly Rep. 2014; 63(38):839–42. PMID: 25254561
20. Pearce A, Marshall H, Bedford H, Lynch J. Barriers to childhood immunisation: Findings from the Longitudinal Study of Australian Children. Vaccine 2015; 33(29):3377–83 https://doi.org/10.1016/j.vaccine.2015.04.089 PMID: 26003493
21. Chamberlain AT, Seib K, Ault KA, Rosenberg ES, Frew PM, Cortes M, et al. Impact of a multi-component antenatal vaccine promotion package on improving knowledge, attitudes and beliefs about influenza and Tdap vaccination during pregnancy. Hum Vaccin Immunother. 2016; 12(8):2017–24. https://doi.org/10.1080/21645515.2015.1127489 PMID: 27082036
22. Mazzoni SE, Brewer SE, Pyrzanowski JL, Durfee MJ, Dickinson LM, Barnard JG, et al. Effect of a multimodal intervention on immunization rates in obstetrics and gynecology clinics. Am J Obstet Gynecol. 2016; 214(5):617 e1–7.
23. Chamberlain AT, Seib K, Ault KA, Rosenberg ES, Frew PM, Cortes M, et al. Improving influenza and Tdap vaccination during pregnancy: A cluster-randomized trial of a multi-component antenatal vaccine promotion package in late influenza season. Vaccine. 2015; 33(30):3571–9. https://doi.org/10.1016/j.vaccine.2015.05.048 PMID: 26044495
24. Kriss JL, Frew PM, Cortes M, Malik FA, Chamberlain AT, Seib K, et al. Evaluation of two vaccine education interventions to improve pertussis vaccination among pregnant African American women: A randomized controlled trial. Vaccine. 2017; 35:1551–8. https://doi.org/10.1016/j.vaccine.2017.01.037 PMID: 28216190
25. Morgan JL, Baggari SR, Chung W, Ritch J, McIntire DD, Sheffield JS. Association of a Best-Practice Alert and Prenatal Administration With Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular

Pertussis Vaccination Rates. Obstet Gynecol. 2015; 126(2):333–7. https://doi.org/10.1097/AOG.0000000000000975 PMID: 26241423

26. Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review. Vaccine. 2018; 36(20):2751–9. https://doi.org/10.1016/j.vaccine.2018.04.013 PMID: 29661584

27. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PG. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. Ann Intern Med. 2009; 151(4):264–9. PMID: 19622511

28. Briss PA, Rodewald LE, Hinman AR, Shefer AM, Strikas RA, Bernier RR, et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults12. Am J Prev Med. 2000; 18:97–140.

29. Higgins JPT, Sally G, editors. Cochrane Handbook for Systematic Reviews ofInterventions Version 5.1.0 [updated March 2011]. 2011. http://handbook.cochrane.org/. Accessed February 25, 2018.

30. Balshem H, Helfand M, Schünemann H, Oxman A, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4):501–6.

31. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. https://reviewersmanual.joannabriggs.org/. Accessed April 2, 2018.

32. Healy CM, Ng N, Taylor RS, Rench MA, Swaim LS. Tetanus and diphtheria toxoids and acellular pertussis vaccine uptake during pregnancy in a metropolitan tertiary care center. Vaccine. 2015; 33(38):4983–7. https://doi.org/10.1016/j.vaccine.2015.07.018 PMID: 26192356

33. Payakachat N, Hadden KB, Ragland D. Promoting Tdap immunization in pregnancy: Associations between maternal perceptions and vaccination rates. Vaccine. 2016; 34(1):179–86. https://doi.org/10.1016/j.vaccine.2015.09.062 PMID: 26428452

34. Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS One. 2018; 13(6):e0197867. https://doi.org/10.1371/journal.pone.0197867 PMID: 29902184

35. SA Health. Understanding Vaccines for Midwives-vaccination requirements during pregnancy and early childhood Adelaide: Goverment of South Australia; 2012. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/professional+development/immunisation+provider+training+and+education/understanding+vaccines+for+midwives-vaccination+requirements+during+pregnancy+and+early+childhood. Accessed April 2, 2018.

36. Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005; 90(8):840–4. https://doi.org/10.1136/adc.2004.058222 PMID: 16040885

37. Robbins SC, Leask J, Hayles EH, Sinn JK. Midwife attitudes: an important determinant of maternal postpartum pertussis booster vaccination. Vaccine. 2011; 29(4):5591–4.

38. MacDougall DM, Halperin SA. Improving rates of maternal immunization: Challenges and opportunities. Hum Vaccin Immunother. 2016; 12(4):857–65. https://doi.org/10.1080/21645515.2015.1101524 PMID: 26552807

39. Klatt TE, Hopp E. Effect of a best-practice alert on the rate of influenza vaccination of pregnant women. Obstet Gynecol. 2012; 119(2):301–5.

40. Ledwich LJ, Harrington TM, Ayoub WT, Sartorius JA, Newman ED. Improved influenza and pneumococcal vaccination in rheumatology patients taking immunosuppressants using an electronic health record best practice alert. Arthritis Rheum. 2009; 61(11):1505–10. PMID: 19877088

41. Fiks AG, Hunter KF, Localio AR, Grundmeier RW, Bryant-Stephens T, Luberti AA, et al. Impact of electronic health record-based alerts on influenza vaccination for children with asthma. Pediatrics. 2009; 124(1):159–69. https://doi.org/10.1542/peds.2008-2823 PMID: 19564296

42. Wallis DH, Chin JL, Sur DK, Lee MY. Increasing rates of influenza vaccination during pregnancy: a multisite interventional study. J Am Board Fam Med. 2006; 19(4):345–9. PMID: 16809648

43. Webb H, Street J, Marshall H. Incorporating immunizations into routine obstetric care to facilitate Health Care Practitioners in implementing maternal immunization recommendations. Hum Vaccin Immunother. 2014;(10):1114–21.

44. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015; 33:6420–9. https://doi.org/10.1016/j.vaccine.2015.08.046 PMID: 26320417

45. Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake of influenza vaccine by pregnant women: a cross-sectional survey. Med J Aust. 2013; 198(7):373–5. PMID: 23581957

46. Ding H, Santibanez TA, Jamieson DJ, Weinbaum CM, Euler GL, Grohskopf LA, et al. Influenza vaccination coverage among pregnant women–National 2009 H1N1 Flu Survey (NHFS). Am J Obstet Gynecol. 2011; 204(6):S96–S106.

47. Bonville CA, Cibula DA, Domachowske JB, Suryadevara M. Vaccine attitudes and practices among obstetric providers in New York State following the recommendation for pertussis vaccination during pregnancy. Hum Vaccin Immunother. 2015; 11(3):713–8. https://doi.org/10.1080/21645515.2015.1011999 PMID: 25714987

48. Link-Gelles R, Chamberlain AT, Schulkin J, Ault K, Whitney E, Seib K, et al. Missed opportunities: a national survey of obstetricians about attitudes on maternal and infant immunization. Maternal and child health journal. 2012; 16(9):1743–7. https://doi.org/10.1007/s10995-011-0936-0 PMID: 22198260

49. Gauld NJ, Braganza CS, Babalola OO, Huynh TT, Hook SM. Reasons for use and non-use of the pertussis vaccine during pregnancy: an interview study. J Prim Health Care. 2016; 8(4):344–50. https://doi.org/10.1071/HC15049 PMID: 29530159

50. Boyd CA, Gazmararian JA, Thompson WW. Knowledge, attitudes, and behaviors of low-income women considered high priority for receiving the novel influenza A (H1N1) vaccine. Maternal and child health journal. 2013; 17(5):852–61. https://doi.org/10.1007/s10995-012-1063-2 PMID: 22729697

51. Kharbanda EO, Vargas CY, Castaño PM, Lara M, Andres R, Stockwell MS. Exploring pregnant women's views on influenza vaccination and educational text messages. Prev Med 2011; 52(1):75–7. https://doi.org/10.1016/j.ypmed.2010.10.009 PMID: 21047526

52. Shavell VI, Moniz MH, Gonik B, Beigi RH. Influenza immunization in pregnancy: Overcoming patient and health care provider barriers. Am J Obstetr Gynecol 2012; 207(3 Suppl):S67–74.

53. Vitek WS, Akers A, Meyn LA, Switzer GE, Lee BY, Beigi RH. Vaccine eligibility and acceptance among ambulatory obstetric and gynecologic patients. Vaccine 2011; 29(11):2024–8. https://doi.org/10.1016/j.vaccine.2011.01.026 PMID: 21272604

54. Leddy MA, Anderson BL, Power ML, Gall S, Gonik B, Schulkin J. Changes in and current status of obstetrician-gynecologists' knowledge, attitudes, and practice regarding immunization. Obstet Gynecol Surv 2009; 64(12):823–9. https://doi.org/10.1097/OGX.0b013e3181c4bbb7 PMID: 19939296

55. Broughton DE, Beigi RH, Switzer GE, Raker CA, Anderson BL. Obstetric health care workers' attitudes and beliefs regarding influenza vaccination in pregnancy. Obstet Gynecol 2009; 114(5):981–7. https://doi.org/10.1097/AOG.0b013e3181bd89c2 PMID: 20168097

56. Power ML, Leddy MA, Anderson BL, Gall SA, Gonik B, Schulkin J. Obstetrician-gynecologists' practices and perceived knowledge regarding immunization. Am J Prev Med 2009; 37(3):231–4. https://doi.org/10.1016/j.amepre.2009.05.019 PMID: 19596538

57. Wu P, Griffin MR, Richardson A, Gabbe SG, Gambrell MA, Hartert TV. Influenza vaccination during pregnancy: opinions and practices of obstetricians in an urban community. South Med J 2006; 99(8):823–8. https://doi.org/10.1097/01.smj.0000231262.88558.8e PMID: 16929876

58. Ishola DA Jr, Permalloo N, Cordery RJ, Anderson SR. Midwives' influenza vaccine uptake and their views on vaccination of pregnant women. J Public Health (Oxf) 2013; 35(4):570–7.

59. Moniz MH, Hasley S, Meyn LA, Beigi RH. Improving influenza vaccination rates in pregnancy through text messaging: a randomized controlled trial. Obstet Gynecol. 2013; 121(4):734–40. https://doi.org/10.1097/AOG.0b013e31828642b1 PMID: 23635672

60. Llupia A, Garcia-Basteiro AL, Mena G, Rios J, Puig J, Bayas JM, et al. Vaccination behaviour influences self-report of influenza vaccination status: a cross-sectional study among health care workers. PLoS One. 2012; 7(7):e39496. https://doi.org/10.1371/journal.pone.0039496 PMID: 22808039

61. Polus S, Pieper D, Burns J, Fretheim A, Ramsay C, Higgins JPT, et al. Heterogeneity in application, design, and analysis characteristics was found for controlled before-after and interrupted time series studies included in Cochrane reviews. J Clin Epidemiol. 2017; 91:56–69. https://doi.org/10.1016/j.jclinepi.2017.07.008 PMID: 28750849

Chapter 5: Psychosocial Determinants of Pertussis and Influenza vaccine uptake in pregnant women: A Prospective Cohort Study

5.1 Publication

Mohammed H, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, Dekker GA, Marshall HS. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study. Vaccine. 2020;38 (17):3358-68.

Statement of Authorship

Title of Paper	Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Mohammed H, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, Dekker GA, Marshall HS. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study. Vaccine. 2020;38(17):3358-68.

Principal Author

Name of Principal Author (Candidate)	Hassen Mohammed		
Contribution to the Paper	Conceived and designed the study, performed data analysis, interpretation of the findings, prepared the first and final draft of the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2020

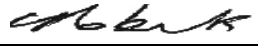
Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Prof. Claire Roberts		
Contribution to the Paper	Conceived and designed the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	17/9/20

Name of Co-Author	Dr Luke Grzeskowiak		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, provided methodological guidance and reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	A/Prof. Lynne Giles		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, provided methodological guidance, assisted HM in data analysis, reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	Dr Shalem Leemaqz		
Contribution to the Paper	Assisted in study design and reviewed the manuscript		
Signature		Date	17 SEP 2020
Name of Co-Author	Julia Dalton		
Contribution to the Paper	Assisted in study design and reviewed the manuscript		
Signature		Date	17/9/2020
Name of Co-Author	Prof Gustaaf Dekker		
Contribution to the Paper	Assisted in study design and reviewed the manuscript		
Signature		Date	17/09/2020
Name of Co-Author	Prof Helen Marshall		
Contribution to the Paper	Conceived and designed the study, supervised development of work, helped in data interpretation, reviewed and edited the manuscript		
Signature		Date	15/09/2020

Vaccine 38 (2020) 3358–3368

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study

Hassen Mohammed [a,b], Claire T. Roberts [b], Luke E. Grzeskowiak [b], Lynne Giles [b], Shalem Leemaqz [b], Julia Dalton [b], Gustaaf Dekker [c], Helen S. Marshall [a,b,*]

[a] Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, Adelaide, South Australia, Australia
[b] Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia
[c] Northern Campus Women's and Children's Division, Lyell McEwin Hospital, The University of Adelaide, Elizabeth Vale, South Australia, Australia

ARTICLE INFO

Article history:
Received 19 September 2019
Received in revised form 3 February 2020
Accepted 7 February 2020
Available online 16 February 2020

Keywords:
Maternal immunization
Pertussis
Influenza
Psychosocial factors
Provider recommendation

ABSTRACT

Objective: To identify the psychosocial factors influencing women's uptake and willingness to receive pertussis and influenza vaccine during pregnancy.
Methods: The study population comprised 1364 healthy nulliparous pregnant women who participated in a prospective cohort study at two obstetric hospitals in South Australia between 2015 and 2017. Information on women's vaccination status, sociodemographic, lifestyle and psychological state were collected at 9–16 weeks' gestation and medical case notes were checked post-delivery to verify the reported vaccination status. Poisson regression models were used to estimate the crude and adjusted prevalence ratios (aPRs) to identify psychosocial factors influencing uptake of vaccination during pregnancy.
Results: Willingness to receive the recommended maternal vaccines was high (90%). Overall, 79% and 48% received maternal pertussis and influenza vaccines respectively. There was no evidence to support the influence of psychosocial factors on women's willingness to receive immunization during pregnancy. High levels of anxiety (aPR 0.98, 95% CI: 0.87–1.09) was not associated with uptake of maternal pertussis vaccine. However, elevated depressive symptoms (aPR 1.14, 95% CI: 1.00–1.30) and very high-perceived stress during pregnancy were significantly associated with receipt of pertussis vaccination (aPR 0.87; 95% CI 0.76–0.99). Women with mild depressive symptoms (aPR 1.21, 95% CI 1.00–1.44) and mild anxiety symptoms (aPR 1.21, 95% CI: 0.99–1.48) were more likely to receive influenza vaccine during pregnancy. A history of major depressive disorder was independently associated with receipt of pertussis (aPR 1.16, 95% CI 1.06–1.26) and influenza vaccination during pregnancy (aPR 1.32; 95% CI 1.14–1.58).
Conclusion: Regardless of psychosocial factors, most women reported a positive willingness to receive the recommended vaccinations during pregnancy. However, psychosocial factors influenced the uptake of pertussis and influenza vaccines during pregnancy. Psychosocial factors should be taken into consideration in designing interventions and implementation of maternal pertussis and influenza immunization programs.

1. Introduction

Pregnant women are at increased risk of morbidity and death from influenza infection particularly during seasonal and pandemic influenza outbreaks [1–3]. Newborn infants born to mothers with influenza during pregnancy are also at increased risk of adverse birth outcomes such as preterm birth and low birthweight [4]. Similarly, *Bordetella pertussis* infections pose the highest risk for pertussis-related complications and death in infants too young to be fully protected by routine childhood immunization schedules [5,6]. Vaccination of pregnant women against influenza and pertussis has now been shown to be effective in not only protecting the mother but also the newborn via transfer of transplacental antibodies [7,8]. Maternal pertussis vaccination can provide more than 90% protection against pertussis disease in infants under 3 months of age [9,10]. Maternal influenza vaccination has been

* Corresponding author at: Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, 72 King William Road, North Adelaide 5006, South Australia, Australia.
E-mail addresses: hassen.mohammed@adelaide.edu.au (H. Mohammed), claire.roberts@adelaide.edu.au (C.T. Roberts), luke.grzeskowiak@adelaide.edu.au (L.E. Grzeskowiak), lynne.giles@adelaide.edu.au (L. Giles), shalem.leemaqz@adelaide.edu.au (S. Leemaqz), julia.dalton@adelaide.edu.au (J. Dalton), gustaaf.dekker@adelaide.edu.au (G. Dekker), helen.marshall@adelaide.edu.au (H.S. Marshall).

https://doi.org/10.1016/j.vaccine.2020.02.020
0264-410X/

shown to decrease the risk of influenza and its complications among pregnant women and prevent up to 91% of influenza related hospital admissions in infants under 6 months of age [11,12]. Substantial evidence supports the safety of influenza and pertussis vaccination in pregnancy, with no serious adverse pregnancy or neonatal outcomes related to maternal vaccination [13,14]. Despite the recommendation of maternal pertussis and influenza vaccination from immunization advisory groups internationally, uptake of the vaccines has been low [15–17].

Pregnant women's low perceptions of disease severity and concerns about the safety of maternal vaccination are barriers to the delivery of vaccinations during pregnancy [18,19]. Previous literature investigated determinants of pertussis and influenza vaccination uptake during pregnancy and specific aspects of vaccination such as women's perception, knowledge and attitudes towards vaccination in pregnancy [20–22]. There is some evidence on the influence of these assessments on the decision to vaccinate against influenza and pertussis during pregnancy. However, the association between maternal vaccination uptake and antenatal depression, anxiety, stress, and maternal lifestyle factors are poorly addressed by previous studies. Research about prenatal psychosocial factors might further enhance the understanding of why certain women receive the recommended vaccinations during pregnancy while others do not. This is the first study aimed to investigate the influence of psychosocial factors on uptake and willingness to receive pertussis and influenza vaccines during pregnancy.

2. Material and methods

2.1. Sample and study design

The current study draws on data collected as part of a prospective cohort study (STOP), which aims to develop screening tests to identify adverse pregnancy outcomes. Healthy nulliparous women were recruited in pregnancy at two major public maternity hospitals in metropolitan Adelaide (Lyell McEwin Hospital, in the Northern suburbs of Adelaide, in a low socio-economic area and at the Women's and Children's Hospital, the primary tertiary maternity hospital for complex care with approximately 5000 births per year) between March 2015 and December 2017. Women with a singleton pregnancy attending their first antenatal clinic between 9 + 0 and 16 + 0 weeks' gestation were eligible to participate. Women were excluded if they were considered to be at high risk of preeclampsia, small for gestational age (SGA) birth, spontaneous preterm birth or had previously experienced three or more miscarriages. Participants were followed prospectively, with pregnancy outcome data collected by research midwives.

Pregnancies ending before 28 weeks' gestation were excluded in our final analyses of psychosocial factors influencing maternal pertussis vaccination because pertussis vaccine was recommended to be administered between 28 and 32 weeks of pregnancy at the time of the study. Women who only received seasonal influenza vaccination within 6 months prior to their conception were excluded from our final analyses of psychosocial factors influencing maternal influenza vaccination because they had a shorter window of opportunity to receive a seasonal influenza vaccine during their pregnancy. Assigning these women to the "unvaccinated during pregnancy" reference group would likely bias the results as vaccination receipt in the preceding influenza season has been associated with positive perceptions regarding maternal vaccination [18,21].

2.2. Main outcome measures

The primary outcome was the proportion of women immunized against pertussis and influenza during pregnancy. The secondary outcome was women's willingness to receive the recommended vaccines during pregnancy. Women's willingness to receive the prenatal vaccines and vaccination status were collected by a research midwife during the first study visit at 9–16 weeks' gestation. Pregnant women were asked to confirm if they had been vaccinated against pertussis and influenza during pregnancy at the 32–36 weeks' gestation. If the vaccines were administered, the date or gestational week of administration were recorded. Following delivery, the vaccination status of the women was checked against their medical case notes to verify the reported vaccination status. A woman was considered vaccinated if there was written documentation of receipt of vaccines in the patient's hand held antenatal care record or medical notes. A woman was considered to have been unvaccinated if she could not recall receipt of vaccination and/or there was no documentation.

2.3. Psychosocial factors

Participating women completed sociodemographic and lifestyle questionnaires at their first STOP visit, which included information on education, occupation, employment, ethnicity, exercise, smoking status, intake of alcohol and recreational drugs, psychological history and current psychological state. During the interview, women completed the Perceived Stress Scale (PSS-10) [23], to assess perceived stress levels in the past month, the short form of the Spielberger State–Trait Anxiety Inventory (STAI) [24], assessing current anxiety symptoms, and the Edinburgh Postnatal Depression Scale (EPDS) [25], assessing depressive symptoms during pregnancy.

Scores for psychological measurements were calculated after reverse keying positive items and summation of scores. For all psychological measures, higher scores represent lower mental wellbeing. For the purposes of the present study, we categorized the psychological measures for improved interpretation of the results. The depression scale was converted using three clinical cut-off values to indicate unlikely to have antenatal depression (EPDS score 0–9), increased risk of depression in the next 6–12 months (EPDS score 10–12) and very likely depressed (EPDS score > 13) [25]. As there are no standardized cut-off values for the Perceived Stress Scale (PSS-10) and the State-Trait Anxiety Inventory (STAI), they were converted into five categories to indicate low (<25th percentile), mild (25th to <50th percentile), moderate (50th to <75th percentile), high (75th to <90th percentile) and very high (>90th percentile) scores. Participant's psychosocial risk status was also determined using the Antenatal Risk Questionnaire (ANRQ) [26]. Our study used a recommended clinically useful cut-off score of 23 or more on ANRQ [26] or the presence of any of the weighted critical factors i.e. a history of depression or psychiatric diagnosis to identify women at high mental health risk group. This enabled a comparison of the influence of different levels of prenatal stress, anxiety, depression and prenatal mental health on a woman's decision to vaccinate against pertussis and influenza during her pregnancy.

2.4. Statistical analyses

Differences in baseline characteristics between vaccinated and unvaccinated women were examined using the Chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables. Poisson regression models were used to estimate both the crude and mutually adjusted prevalence ratios (aPRs) and their corresponding 95% confidence intervals to determine psychosocial factors associated with uptake of maternal pertussis and influenza vaccination during pregnancy. We chose a Poisson model with robust errors as the appropriate analysis model, because it is usually preferable to model and estimate prevalence ratios instead of

odds ratios in cohort studies when the prevalence of the outcome are not rare (i.e. vaccination uptake is common among pregnant women) and due to convergence issues with log binomial models [27].

In the mutually adjusted models, we included all covariates (i.e. maternal age, educational level, employment status, country of birth, marital status, Indigenous status and season of delivery) that were known potential confounders associated with vaccination uptake in pregnancy based on published literature [18,21,28]. Potential psychosocial and periconceptional lifestyle predictors of vaccination uptake in pregnancy (i.e. prenatal stress, anxiety and depression, history of depression, smoking and illicit drug use, multivitamin use and physical exercise) previously shown to be associated with adherence to other prenatal care recommendations [29–31] were also included in the final adjusted models.

Although the influenza vaccine can be given at any time during pregnancy, women who had miscarriages or terminations before 20 weeks' gestation would have a shorter window of opportunity to receive influenza vaccine during pregnancy compared with women who had successful full-term pregnancies. To account for the relative opportunity each woman had to receive influenza vaccination during pregnancy, the natural logarithm of the total time of a pregnancy in gestational weeks up to miscarriage, termination, stillbirth, or delivery was included in the final adjusted model as an offset term. All statistical analyses were performed using Stata version 15 (Stata Corp, College Station, Texas, USA).

3. Results

During the study period between 2015 and 2018, 1364 nulliparous pregnant women with singleton pregnancies were recruited to the STOP study. Of the final 1364 women, 12 women who withdrew access to their medical records, 3 women with no medical case notes and 3 women who were lost to follow up were excluded from our final analyses. After excluding 83 women who had only received influenza vaccination within 6 months before they become pregnant, information from the remaining 1263 participating women with examined vaccination status against their medical case notes were included in our analyses of psychosocial factors influencing influenza vaccination uptake during pregnancy (Fig. 1). The overall percentage of women vaccinated against influenza during pregnancy was 47.9% (95% CI: 45.2–50.7%; n = 605). After excluding 50 pregnancies that ended earlier than 28 weeks' gestation, 1296 pregnancies were included in our analyses of psychosocial factors influencing uptake of pertussis vaccination during pregnancy (Fig. 1). Of these 1296 women, 1024 (79.0%; 95% CI: 76.8–81.2%) received pertussis vaccination during pregnancy. Overall, 44% (n = 556) of the women received both recommended maternal vaccines.

The mean age of the women at recruitment was 26.0 ± 5.0 years (range: 15–45 years old). The mean gestational age at delivery was 39.2 ± 1.9 weeks. Baseline characteristics are presented in Table 1. During the first study visit at 9–16 weeks' gestation, 90% of the women (n = 1227) reported willingness to receive the recommended vaccines during pregnancy. Willingness to get vaccinated during pregnancy at the first study visit was lower among unemployed women (aPR, 0.91; 95% CI 0.86–0.97) and women with diploma/certificate (compared with university graduates) (aPR, 0.94; 95% CI 0.89–0.99) (Table 2). Women who had been vaccinated against influenza (PR, 2.51; 95% CI 1.72–3.67) and pertussis (PR, 1.15; 95% CI 1.01–1.31) during pregnancy were significantly more likely to have reported willingness to accept the recommended vaccines in pregnancy at baseline compared to those who had not been vaccinated.

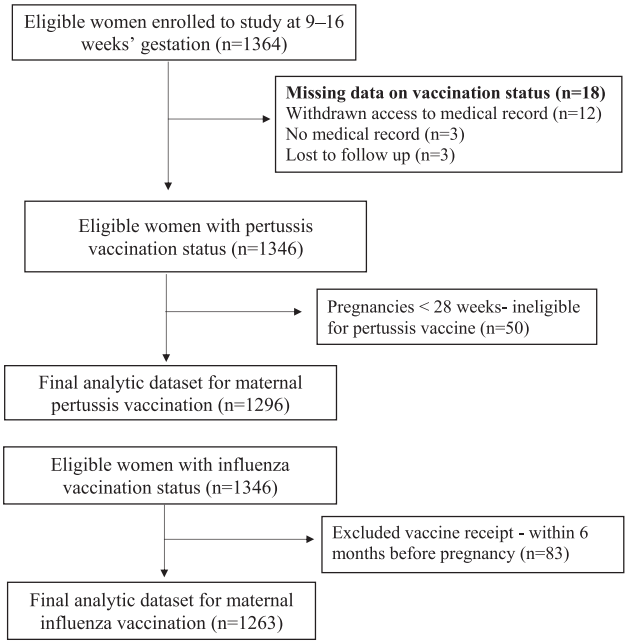


Fig. 1. Flowchart of recruited participants.

Maternal influenza vaccination uptake was higher for pregnancies ending in winter or spring (Fig. 2). Uptake of influenza vaccine during pregnancy significantly increased from 40.2% in the 2015–16 influenza season to 51.7% in the 2017–2018 influenza season (P < 0.01). Receipt of maternal influenza vaccine was lowest for women whose estimated birth season was in autumn (26.6%) (Fig. 2) and women who conceived during winter (24.2%). The proportion of women vaccinated against pertussis was relatively stable over time. However, the highest uptake of pertussis and influenza vaccines was recorded when the women's estimated month of birth is in August (late winter) (Fig. 2). The uptake of pertussis vaccine during pregnancy increased from 76.8% in 2015 to 80.5% in 2016, decreasing slightly to 78.4% in 2017.

3.1. Antenatal depression

Of the 1364 women, 112 (8.2%) screened positive on the EPDS (scored ≥ 13). Most of the women (1133, 83%) had scores suggestive of low depressive symptoms (0–9) while some women (106, 7.8%) had scores indicating mild depressive symptoms (10–12) (Table 1). Women with a prior history of major depression were almost 8 times more likely to screen positive for antenatal depression symptoms (EPDS scores ≥13) (PR 7.90; 95% CI 5.11–12.20) and 3 times more likely to have mild maternal depressive symptoms (PR 3.30; 95% CI 2.19–4.97) compared to those who had no history of depression. Of the women who screened positive on the EPDS, 89% of them reported in the highest quintile of perceived stress. Women who screened positive were more likely to be single (PR 3.87; 95% CI 2.20–6.80), obese (PR 1.47; 95 CI 1.17–1.84), younger (PR 3.26; 95% CI 1.83–5.81), less educated (PR 2.50; 95% CI 1.33–4.70), unemployed (PR 2.40; 95% CI 1.66–3.47), from the lowest socioeconomic status group (PR 1.87; 95% CI 1.09–3.27) and illicit drug users (PR 2.36; 95% CI 1.41–3.93).

Women who screened positive for antenatal depression were significantly more likely to receive pertussis vaccination during pregnancy compared with women who had a score of low maternal depressive symptoms (aPR 1.14; 95% CI 1.00–1.30) (Table 3). However, there was no evidence to support an association between high depressive symptoms scores in early pregnancy and receipt of maternal influenza vaccine (aPR 0.99; 95% CI 0.77–1.28). Pregnant

Table 1
Maternal characteristics of enrolled pregnant women, 2015 to 2018.

Variable	Level	Raw data N = 1364	%
Maternal age	15–19	136	10.0
	20–24	412	30.2
	25–29	483	35.4
	>30	333	24.4
Born in Australia	Yes	1116	81.8
	No	248	18.2
Ethnicity	Caucasian	1126	82.5
	Aboriginal/Torres Strait Islander	25	1.9
	Others	213	15.6
Marital status	Married	527	38.6
	Cohabiting/living with a partner	686	50.3
	Single/separated/ widowed	151	11.1
Educational attainment	≤Secondary school qualification	593	43.5
	Diploma/certificate	484	35.5
	Bachelor's or higher degree	283	20.7
	Missing values	4	0.3
Household annual income in AUD	<40,000	322	23.6
	40,001–70,000	300	22.0
	70,001–105,000	352	25.8
	>105,001	352	27.5
	Missing values	15	1.1
Employment Status	Full/part-time work	1115	81.7
	Unemployed	242	17.7
	Missing values	7	0.6
The Antenatal Risk Questionnaire (ANRQ)	Low (0–22)	773	56.6
	High (≥23)	578	42.3
	Missing values	13	0.9
Likelihood of depression (EPDS) at 9–16 weeks' gestation	Unlikely to have depression (0–9)	1133	83.0
	Increased risk of depression (10–12)	106	7.8
	Very likely depressed (≥13)	112	8.2
	Missing values	13	0.9
Smoking status at 9–16 weeks' gestation	Non-smoker	1078	79.0
	Quit during pregnancy	148	10.8
	Current smoker	130	9.5
	Missing values	8	0.5
Illicit drug use during 1st trimester/pre-pregnancy[a]	No	1286	94.3
	Yes	78	5.7
Recruiting center	The Lyell McEwin Hospital	1301	95.4
	The Women's and Children's Hospital (WCH)	63	4.6

[a] Use of Binge alcohol ≥ 6 drinks per session, Marijuana, Cocaine/crack, Cigars, Amphetamines, Substance P/crystal meth, XTC, Opiates, Hallucinogens, Herbal highs, E-cigarettes, Shisha (or hookah).

women who had scores of mild depressive symptoms in early pregnancy were significantly more likely to receive influenza vaccination during pregnancy (aPR 1.21; 95% CI 1.00–1.44) (Table 4). Pregnant women with a history of major depressive disorder were significantly more likely to receive both maternal pertussis (aPR 1.16; 95% CI 1.06–1.26) and influenza vaccination (aPR 1.32; 95% CI 1.14–1.58) (Tables 3 and 4).

3.2. Antenatal psychosocial risk status

Of the 1364 women, 578 (42.3%) were classified as being at moderate to high risk for poor perinatal mental health outcomes. Women identified as 'high risk' were significantly more likely to be unemployed (PR 1.38; 95% CI 1.21–1.58), single (compared with married women) (PR 1.94; 95% CI 1.61–2.34) asthmatic patients (PR 1.36; 95% CI 1.18–1.57) and in the low household income group (PR 1.58; 95% CI 1.33–1.89). Given that the ANRQ includes current mood as a risk, women at high-risk were significantly more likely to screen positive on the EPDS (scored 13 points or higher) (PR 2.71; 95% CI 2.35–3.13) and significantly more likely to report in the highest quintile of the anxiety score (>90th percentile) (PR 2.03; 95% CI 1.70–2.44). However, there was no evidence to support correlation between pertussis and influenza uptake during pregnancy and antenatal psychosocial risk status (Tables 3 and 4).

3.3. Perceived stress

The median score of the pregnant women on perceived stress scale was 13 (IQR: 8–17). The likelihood of receiving the pertussis vaccine for women with very high-perceived stress levels was significantly lower compared to women with low perceived stress (aPR 0.87; 95% CI 0.76–0.99) at the first visit. However, there was little evidence of an association between influenza vaccination uptake during pregnancy and perceived stress score at the first study visit (Table 4).

3.4. Anxiety

The median score of the women on State-Trait Anxiety Inventory (STAI-6) was 9 (IQR: 7–12). The skewness statistic for STAI scores was 0.84 indicating a positively skewed distribution. Relatively few women presented with moderate anxiety scores. Women with moderate levels of state or trait anxiety were more likely to receive pertussis (aPR 1.08; 95% CI 0.98–1.18) and influenza vaccine (aPR 1.21; 95% CI 0.99–1.48) during pregnancy compared with those women who scored low levels of state or trait anxiety. The lowest proportion of pertussis and influenza vaccine uptake was among women who scored in the highest quintile of anxiety (>90th percentile). However, there was no evidence to support an association between elevated anxiety scores measured at 9–16 weeks' gestation and low pertussis and influenza vaccination uptake during pregnancy (Tables 3 and 4).

3.5. Sociodemographic factors

The adjusted model (Table 3) suggests social factors such as being younger than 25 years of age, born outside of Australia, being in a defacto relationship (compared with married women) and being unemployed were associated with low pertussis vaccination uptake during pregnancy. For influenza uptake, women aged 20–24 (compared with women aged >30) and being unemployed were significantly associated with low influenza vaccination uptake during pregnancy after adjusting with all variables in the model (Table 4). Pertussis and influenza vaccine uptake during pregnancy was lowest among women with secondary school qualification or lower level but these associations were not significant in the final adjusted model (Tables 3 and 4).

3.6. Maternal health behaviors

Pregnant women who did not use multivitamin and mineral supplements pre-conception or during pregnancy were significantly less likely to have received both pertussis (aPR 0.88; 95% CI 0.81–0.96) and influenza vaccination during pregnancy (aPR 0.77; 95% CI 0.64–0.93). Women who were physically inactive were less likely to receive maternal pertussis vaccine (aPR 0.95; 95% CI 0.87–1.03) compared to women who actively engaged in regular moderate-intensity exercises. Smoking or illicit drug use

Table 2
Factors associated with willingness to receive vaccination during pregnancy.

Variable	Willing to get vaccinated n/N[a] (%) 1227/1342[b] (91.4)	Prevalence ratio (PR) (95% CI)	P-value	Adjusted PR[c] (95%CI)	P-value
Perceived stress score (PSS)					
Low	258/281 (91.8)	Reference			
Mild	252/275 (91.6)	0.99 (0.94,1.04)	0.939	1.00 (0.95,1.05)	0.905
Moderate	224/246 (91.0)	0.99 (0.94,1.04)	0.757	0.98 (0.93,1.04)	0.645
High	253/278 (91.0)	0.99 (0.94,1.04)	0.733	0.97 (0.92,1.04)	0.510
Very High	235/257 (91.4)	0.99 (0.94,1.04)	0.875	0.97 (0.90,1.04)	0.943
Anxiety score (STAI)					
Low	323/349 (92.5)	Reference			
Mild	289/327 (88.3)	0.95 (0.90,1.00)	0.067	0.96 (0.91,1.01)	0.151
Moderate	114/124 (91.9)	0.99 (0.93,1.05)	0.828	1.00 (0.94,1.07)	0.858
High	285/304 (93.7)	1.01 (0.97,1.05)	0.544	1.01 (0.96,1.06)	0.472
Very High	191/211 (90.5)	0.97 (0.92,1.03)	0.411	0.98 (0.92,1.04)	0.592
Depression score (EPDS)					
Unlikely to have depression (0-9)	1020/1116 (91.4)	Reference			
Increased risk of depression (10-12)	100/105 (95.2)	1.04 (0.99,1.09)	0.082	1.02 (0.97,1.08)	0.292
Very likely depressed (≥13)	95/109 (87.1)	0.95 (0.88,1.02)	0.210	0.93 (0.86,1.01)	0.127
Previous history of depression					
No history of depression	883/974 (90.6)	Reference			
History of depression	167/179 (93.3)	1.02 (0.98,1.07)	0.203	1.01 (0.96,1.06)	0.636
History of major/clinical depression	177/189 (93.6)	1.03 (0.98,1.07)	0.132	1.10 (0.96,1.06)	0.571
ANRQ					
Low (0–22)	684/762 (89.7)	Reference			
High (≥23)	531/568 (93.4)	1.04 (1.00,1.07)	**0.014**	1.03 (0.99,1.10)	0.106
Moderate exercise early pregnancy					
≥4 per week	145/156 (92.9)	Reference			
1–3 per week	596/641 (92.9)	1.00 (0.95,1.04)	0.989	1.00 (0.95,1.04)	0.992
Never	478/537 (89.0)	0.95 (0.90,1.00)	0.106	0.96 (0.91,1.02)	0.252
Smoking status at 9–16 weeks'					
Non-Smoker	976/1065 (91.6)	Reference			
Quit during pregnancy	135/145 (93.1)	1.01 (0.96,1.06)	0.518	1.01 (0.96,1.06)	0.687
Current smoker	115/130 (88.4)	0.96 (0.90,1.02)	0.284	0.96 (0.90,1.04)	0.389
Illicit drug use during 1st trimester/pre-pregnancy					
No	1155/1266 (91.2)	Reference			
Yes	72/76(94.7)	1.03 (0.98,1.09)	0.185	1.03 (0.97,1.10)	0.250
Multivitamin use					
Pre-conception and 1st trimester	283/303 (93.4)	Reference			
1st trimester	651/718 (90.6)	0.97 (0.93,1.00)	0.126	0.97 (0.93,1.01)	0.173
None	285/313 (91.0)	0.97 (0.93,1.02)	0.277	0.98 (0.93,1.03)	0.491
Maternal age group					
>30	295/325 (90.7)	Reference			
25–29	437/475 (92.0)	1.01 (0.97,1.05)	0.545	1.01 (0.96,1.06)	0.528
20–24	371/407 (91.1)	1.00 (0.95,1.05)	0.857	1.00 (0.95,1.06)	0.755
15–19	124/135 (91.8)	1.01 (0.95,1.07)	0.704	1.03 (0.97,1.11)	0.277
Born in Australia					
Yes	994/1074 (92.5)	Reference			
No	209/243 (86.0)	0.92 (0.88,0.97)	**0.006**	0.94 (0.88,1.00)	0.084
Indigenous status					
Not Indigenous	1203/1317 (91.3)	Reference			
Indigenous	24/25 (96.0)	1.05 (0.96,1.14)	0.233	1.03 (0.95,1.12)	0.365
Marital status					
Married	492/515 (89.7)	Reference			
Cohabiting/living with a partner	629/679 (92.6)	1.02 (1.00,1.05)	0.082	1.03 (0.99,1.08)	0.113
Single/separated/widowed	136/148 (91.8)	1.02 (0.96,1.08)	0.401	1.04 (0.97,1.11)	0.249
Education level					
Bachelor's or higher degree	254/276 (92.0)	Reference			
Diploma/certificate	434/477 (90.9)	0.98 (0.94,1.03)	0.618	0.94 (0.90,0.99)	**0.048**
≤Secondary school qualification	538/588 (91.5)	0.99 (0.95,1.04)	0.789	0.96 (0.91,1.02)	0.263
Employment Status					
Full/part-time work	1015/1097 (92.5)	Reference			
Unemployed	207/240 (86.2)	0.93 (0.88,0.98)	**0.001**	0.91 (0.86,0.97)	**0.004**

Table 2 (*continued*)

Variable	Willing to get vaccinated n/N[a] (%) 1227/1342[b] (91.4)	Prevalence ratio (PR) (95% CI)	P-value	Adjusted PR[c] (95%CI)	P-value
Estimated season of delivery					
Summer	313/351 (89.1)	Reference			
Autumn	330//360 (91.6)	1.02 (0.97,1.07)	0.260	1.01 (0.96,1.06)	0.555
Winter	315/334 (94.3)	1.05 (1.01,1.10)	**0.015**	1.04 (0.99,1.09)	0.054
Spring	269/297 (90.5)	1.01 (0.96,1.06)	0.566	1.01 (0.96,1.07)	0.559

Bold values denote statistical significance at the p < 0.05 level.
[a] Weighted n in cohort.
[b] Missing data (n = 22, participants were excluded from the analysis because they did not provide answer).
[c] Mutually adjusted.

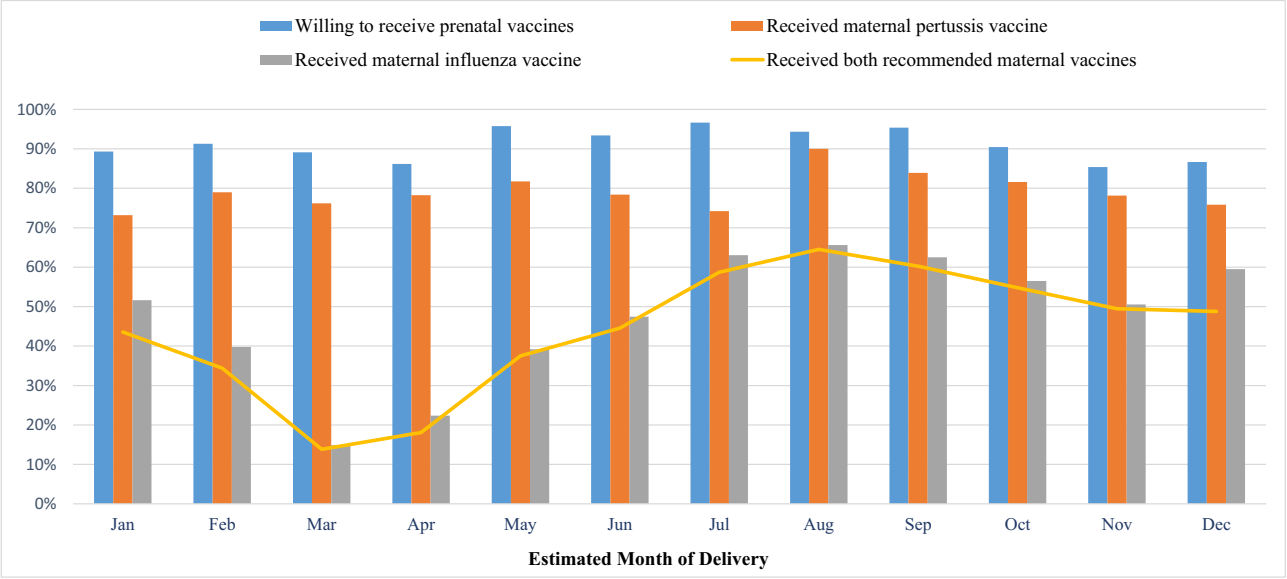


Fig. 2. Willingness to receive maternal vaccinations and pertussis and influenza vaccination uptake in pregnant women at two obstetric hospitals in South Australia, by expected birth month. Note: The monthly denominator reported was the number of pregnant women with an estimated date of delivery (EDD) in that month. The monthly numerator was the number of women identified in the denominator defined above who received the recommended vaccines during their pregnancy or were willing to receive the prenatal vaccines.

during pregnancy were also associated with lower uptake of both vaccines during pregnancy but these associations were not significant in the final adjusted model (Tables 3 and 4).

4. Discussion

The study found that 79% of women received a pertussis vaccine during pregnancy which is higher coverage than other high-income countries with a national maternal pertussis immunization programs such as the United States of America (54% in 2018) [32] and the United Kingdom (68% in 2018) [33]. Following the introduction of government funded antenatal pertussis immunization programs in all Australian states over the previous few years, uptake of maternal pertussis immunization has increased in Australia [34,35]. The uptake of influenza vaccine among pregnant women in our cohort was 48%, still well below the benchmarks set by Healthy People 2020, which specifies a goal of 80% influenza vaccination for pregnant women [36]. The lower uptake of influenza vaccine during pregnancy compared to pertussis vaccine in our study could be because most women perceive influenza as a disease affecting the mother, rather than a threat to their infant, as for pertussis. Evidence indicates that women are more concerned about potential risks to their infant's health than their own [37].

Our findings suggest that women whose pregnancies started in winter with estimated birth season in autumn had the lowest influenza vaccine uptake during pregnancy. This may have serious adverse consequences particularly for pregnant women at high risk of developing complications from influenza when the influenza season is unpredictable. In Australia, the influenza season is generally from May to October, peaking in the winter month of August. However, during the 2018–2019 influenza season, most Australian states experienced a high increase in influenza-like illness notifications from March 2019, while South Australia had already experienced a peak in influenza notifications in Autumn (early April) [38]. Hence, it is possible for a pregnant woman to be severely affected by influenza infections at any time of the year and immunization providers need to offer influenza vaccination at any stage of pregnancy, year round.

The study investigated psychosocial factors that influence uptake of pertussis and influenza vaccination uptake during pregnancy. We hypothesized that non-adherence to maternal healthy behaviors such as vaccine refusal or hesitancy during pregnancy might be associated with the negative effects of anxiety, depression, or stress during pregnancy. Interestingly, our results indicate that women's willingness to receive the recommended prenatal vaccines was high and independent of psychosocial factors but we observed a difference in the actual vaccination uptake during pregnancy. Although, willingness to receive the recommended

Table 3
Factors associated with the uptake of pertussis vaccination during pregnancy.

Variable	Vaccinated n/N (%)[a] 1024/1296 (79.0)	Prevalence ratio (PR) (95% CI)	P- value	Adjusted aPR[b] (95%CI)	P-value
Perceived stress score (PSS)					
Low	217/267 (81.2)	Reference			
Mild	212/263 (80.6)	0.99 (0.91,1.07)	0.846	0.98 (0.91,1.07)	0.800
Moderate	200/244 (81.9)	1.00 (0.92,1.09)	0.840	0.98 (0.90,1.07)	0.703
High	209/269 (77.7)	0.95 (0.87,1.04)	0.306	0.94 (0.85,1.04)	0.272
Very High	181/245 (73.8)	0.90 (0.82,0.99)	**0.047**	0.87 (0.76,0.99)	**0.039**
Anxiety score (STAI)					
Low	275/339 (81.1)	Reference			
Mild	252/325 (77.5)	0.95 (0.88,1.03)	0.291	1.00 (0.92,1.08)	0.979
Moderate	92/109 (84.4)	1.04 (0.94,1.14)	0.587	1.08 (0.98,1.18)	0.085
High	232/293 (79.1)	0.97 (0.90,1.05)	0.976	1.02 (0.94,1.11)	0.538
Very High	151/199 (75.8)	0.93 (0.85,1.02)	0.162	0.98 (0.87,1.09)	0.748
Depression score (EPDS)					
Unlikely to have depression (0-9)	8541078 (79.2)	Reference			
Increased risk of depression (10-12)	74/99 (74.7)	0.94 (0.83,1.06)	0.337	0.97 (0.86,1.10)	0.738
Very likely depressed (≥13)	87/107 (81.3)	1.02 (0.93,1.12)	0.595	1.14 (1.00,1.30)	**0.035**
Previous history of depression					
No history of depression	737/949 (77.6)	Reference			
History of depression	131/170 (77.0)	0.99 (0.90,1.08)	0.864	1.06 (0.96,1.18)	0.210
History of major/clinical depression	156/177 (88.1)	1.13 (1.06,1.20)	**0.001**	1.16 (1.06,1.26)	**0.001**
ANRQ					
Low (0–22)	581/739 (78.6)	Reference			
High (≥23)	433/544 (79.6)	1.01 (0.95,1.07)	0.670	0.98 (0.91,1.07)	0.781
Moderate exercise early pregnancy					
≥4 per week	127/149 (85.2)	Reference			
1–3 per week	495/620 (79.8)	0.93 (0.86,1.01)	0.099	0.94 (0.87,1.02)	0.181
Never	395/517 (76.4)	0.89 (0.82,0.97)	**0.009**	0.95 (0.87,1.03)	0.252
Smoking status at 9–16 weeks'					
Non-Smoker	819/1025 (79.9)	Reference			
Quit during pregnancy	113/141 (80.1)	1.00 (0.91,1.09)	0.947	1.04 (0.95,1.14)	0.322
Current smoker	87/123 (70.7)	0.88 (0.78,0.99)	**0.043**	0.96 (0.90,1.03)	0.588
Illicit drug use during 1st trimester/pre-pregnancy					
No	973/1219 (79.8)	Reference			
Yes	51/77 (66.2)	0.82 (0.70,0.97)	**0.024**	0.91 (0.77,1.06)	0.254
Multivitamin use					
Pre-conception and 1st trimester	249/289 (86.1)	Reference			
1st trimester	549/689 (79.6)	0.92 (0.87,0.98)	**0.010**	0.96 (0.91,1.02)	0.301
None	220/311 (70.7)	0.82 (0.75,0.89)	**0.001**	0.88 (0.81,0.96)	**0.007**
Maternal age group					
>30	258/310 (83.2)	Reference			
25–29	391/464 (84.2)	1.01 (0.95,1.07)	0.702	0.99 (0.93,1.06)	0.958
20–24	289/390 (74.1)	0.89 (0.82,0.96)	**0.003**	0.90 (0.83,0.98)	**0.020**
15–19	86/132 (65.1)	0.78 (0.68,0.89)	**0.001**	0.86 (0.74,0.99)	**0.040**
Born in Australia					
Yes	8521065 (80.0)	Reference			
No	172/231 (74.4)	0.93 (0.85,1.00)	0.084	0.91 (0.84,1.00)	0.066
Indigenous status					
Not Indigenous	1009/1272 (79.3)	Reference			
Indigenous	15/24 (62.5)	0.78 (0.57,1.07)	0.133	0.87 (0.65,1.16)	0.360
Marital status					
Married	425/507 (83.8)	Reference			
Cohabiting/living with a partner	490/641 (76.4)	0.91 (0.86 ,0.96)	**0.002**	0.93 (0.87.0.99)	**0.037**
Single/separated/widowed	109/148 (73.6)	0.87 (0.79 ,0.97)	**0.014**	0.96 (0.86,1.08)	0.582
Education level					
Bachelor's or higher degree	218/265 (82.6)	Reference			
Diploma/certificate	366/461 (79.3)	0.96 (0.89,1.03)	0.338	1.04 (0.95,1.13)	0.342
≤Secondary school qualification	438/566 (77.3)	0.94 (0.87,1.01)	0.094	0.98 (0.90,1.06)	0.658
Employment Status					
Full/part-time work	864/1059 (81.5)	Reference			
Unemployed	157//231 (67.9)	0.83 (0.75,0.91)	**0.001**	0.90 (0.81,0.99)	0.050
Estimated season of delivery					
Summer	257/339 (75.8)	Reference			
Autumn	273/346 (78.9)	1.04 (0.95,1.12)	0.355	1.07 (0.99,1.16)	0.084
Winter	259/322 (80.4)	1.08 (0.97,1.15)	0.151	1.06 (0.97,1.15)	0.143
Spring	234 288 (81.2)	1.07 (0.98,1.16)	0.097	1.09 (1.00,1.18)	**0.042**

Bold values denote statistical significance at the $p < 0.05$ level.
[a] Weighted n in cohort.
[b] Mutually adjusted.

Table 4
Factors associated with the uptake of influenza vaccination during pregnancy.

Variable	Vaccinated n/N (%)[a] 605/1263 (47.9)	Prevalence ratio (PR) (95% CI)	P-value	Adjusted PR[b] (95%CI)	P-value
Perceived stress score (PSS)					
Low	121/261 (46.3)	Reference			
Mild	126/259 (48.6)	1.04 (0.87,1.25)	0.602	1.02 (0.85,1.22)	0.818
Moderate	110/229 (48.0)	1.03 (0.85,1.24)	0.711	0.96 (0.79,1.16)	0.684
High	137/269 (50.9)	1.09 (0.92,1.30)	0.294	1.07 (0.87,1.24)	0.503
Very High	109/238 (45.8)	0.98 (0.81,1.19)	0.900	1.07 (0.88,1.33)	0.549
Anxiety score (STAI)					
Low	153/328 (46.6)	Reference			
Mild	147/308 (47.7)	1.02 (0.86,1.20)	0.785	1.03 (0.87,1.21)	0.681
Moderate	61/112 (54.4)	1.16 (0.95,1.43)	0.139	1.21 (0.99,1.48)	0.061
High	143/287 (49.8)	1.06 (0.90,1.25)	0.431	1.05 (0.89,1.25)	0.508
Very High	86/199 (43.2)	0.92 (0.76,1.12)	0.477	0.85 (0.68,1.07)	0.186
Depression score (EPDS)					
Unlikely to have depression (0-9)	501/1056 (47.4)	Reference			
Increased risk of depression (10-12)	55/93 (59.1)	1.24 (1.09,1.49)	**0.017**	1.21 (1.00,1.44)	**0.040**
Very likely depressed (≥13)	45/104 (43.2)	0.91 (0.72,1.14)	0.431	0.99 (0.77,1.28)	0.985
Previous history of depression					
No history of depression	429/923 (46.4)	Reference			
History of depression	76/166 (45.7)	0.98 (0.82,1.17)	0.869	1.11 (0.90,1.35)	0.309
History of major/clinical depression	100/174 (57.4)	1.23 (1.06,1.43)	**0.004**	1.32 (1.14,1.58)	**0.002**
ANRQ					
Low (0–22)	338/717 (47.1)	Reference			
High (≥23)	262/535 (48.9)	1.03 (0.92,1.16)	0.520	0.99 (0.85,1.16)	0.958
Moderate exercise early pregnancy					
≥4 per week	81/150 (54.0)	Reference			
1–3 per week	283/586 (48.2)	0.89 (0.75,1.05)	0.198	0.89 (0.76,1.05)	0.191
Never	238/518 (45.9)	0.85 (0.71,1.01)	0.070	0.90 (0.76,1.07)	0.276
Smoking status at 9–16 weeks'					
Non-Smoker	493/994 (49.6)	Reference			
Quit during pregnancy	67/140 (47.8)	0.96 (0.80,1.15)	0.704	1.07 (0.90,1.28)	0.414
Current smoker	43/121 (35.5)	0.71 (0.55,0.91)	**0.008**	0.92 (0.72,1.16)	0.500
Illicit drug use during 1st trimester/pre-pregnancy					
No	576/1188(48.4)	Reference			
Yes	29/75 (38.6)	0.79 (0.59,1.06)	0.128	0.94 (0.70,1.26)	0.705
Multivitamin use					
Pre-conception and 1st trimester	157/275 (57.0)	Reference			
1st trimester	326/676 (48.2)	0.81 (0.72,0.91)	**0.001**	0.95 (0.83,1.09)	0.490
None	118/305 (38.6)	0.67 (0.57,0.79)	**0.001**	0.77 (0.64,0.93)	**0.008**
Maternal age group					
>30	164/297 (55.2))	Reference			
25–29	234/449 (52.1)	0.94 (0.82,1.08)	0.403	0.95 (0.83,1.09)	0.538
20–24	157/390 (40.2)	0.72 (0.62,0.85)	**0.001**	0.81 (0.69,0.97)	**0.022**
15–19	50/127 (39.3)	0.71 (0.56,0.90)	**0.006**	0.90 (0.68,1.18)	0.456
Born in Australia					
Yes	491/1032 (47.5)	Reference			
No	114/231 (49.3)	1.03 (0.89,1.19)	0.622	0.96 (0.81,1.14)	0.676
Indigenous status					
Not Indigenous	598/1240 (48.2)	Reference			
Indigenous	7/23 (30.4)	0.63 (0.33,1.17)	0.146	0.95 (0.52,1.75)	0.888
Marital status					
Married	270/490 (55.1)	Reference			
Cohabiting/living with a partner	277/630 (43.9)	0.79 (0.70,0.89)	**0.001**	0.87 (0.76,0.99)	**0.046**
Single/separated/widowed	58/143 (40.5)	0.73 (0.59,0.61)	**0.005**	0.86 (0.68,1.09)	0.222
Education level					
Bachelor's or higher degree	143/248 (57.6)	Reference			
Diploma/certificate	214/450 (47.5)	0.82 (0.71,0.95)	**0.009**	0.87 (0.73,1.02)	0.103
≤Secondary school qualification	247/561 (44.0)	0.76 (0.66,0.87)	**0.001**	0.92 (0.77,1.09)	0.355
Employment Status					
Full/part-time work	524/1034 (50.6)	Reference			
Unemployed	78/223 (34.9)	0.69 (0.57,0.83)	**0.001**	0.78 (0.64,0.95)	**0.014**
Estimated season of delivery					
Summer	173/338 (51.1)	Reference			
Autumn	82/308 (26.2)	0.52 (0.42,0.64)	**0.001**	0.55 (0.44,0.67)	**0.001**
Winter	184/322 (57.1)	1.11 (0.96,1.28)	0.125	1.09 (0.95,1.25)	0.200
Spring	166/294 (56.4)	1.10 (0.95,1.27)	0.184	1.10 (0.95,1.28)	0.185

Bold values denote statistical significance at the $p < 0.05$ level.
[a] Weighted n in cohort.
[b] Mutually adjusted.

vaccines in pregnancy was a significant predictor of the actual receipt of both maternal vaccines, only just over half of the women who were interested in receiving the vaccines had actually been vaccinated against influenza during their pregnancy.

Previous studies suggest that most pregnant women are willing to be vaccinated following recommendation from their health care provider [39,40]. However, women's willingness to receive the recommended vaccinations in pregnancy does not necessarily lead to actual vaccination. Expectant mothers' decision-making to receive vaccination in pregnancy is complex and involves emotional, antenatal health system/institutional, and socio-cultural factors as much as cognitive factors [41]. Incorporation of an automated reminder within electronic medical records in an antenatal care setting so as to aid healthcare providers in identifying women needing immunization was found to be an effective intervention in improving maternal vaccinations uptake by following up women and verifying their actual behavior after their verbal response [42]. This strategy would enable providers to administer the vaccine at a moment when the pregnant women can act immediately with a minimum of additional time, effort or cost [42]. Hence, addressing system-level barriers and understanding psychosocial factors influencing women's uptake of pertussis and influenza vaccination during pregnancy could assist in improving maternal immunization programs.

Contrary to what we expected, a history of clinical depression was the strongest independent predictor of both influenza and pertussis vaccination uptake during pregnancy. Moreover, screening positive for antenatal depression in our findings was associated with uptake of pertussis vaccine uptake in pregnancy. Women with a past history of a severe mental health condition require comprehensive mental health assessment before conception or in the prenatal period and additional support [43]. The South Australian Perinatal Practice Guideline [43] endorsed the use of the EPDS as part of a universally-delivered psychosocial assessment for women receiving maternity care in the public health care system. A score of 13 or more merits possible referral for specialized assessment or at least re-application of the EPDS within two to four weeks for women experiencing mild maternal depressive symptoms [43].

Women with a history of clinical depression or experiencing severe symptoms of antenatal depression are more likely to have more encounters with health services including being referred to perinatal mental health services that include specialized psychiatric and mental health midwife services [44]. Additionally, women with a history of severe depression in our study were receiving antidepressant medication and may already be under the care of a psychiatrist and/or a general practitioner (GP) as decisions about continuing use of antidepressant during pregnancy need to be discussed [45]. Current antenatal mild depressive symptoms was also a predictor of influenza vaccination during pregnancy due to the possibility that women with an EPDS score between 10 and 12 are referred to their GP for mental health reassessment within two to four weeks [43]. It is plausible that frequent antenatal midwife services or GP visits for women with mental health issues may have provided more opportunities for maternal vaccination. Previous studies have shown that GP led care was associated with high uptake of influenza vaccination during pregnancy [35,46].

The present study suggests women with a very high level of perceived stress score were less likely to be vaccinated against pertussis. There is evidence that high-perceived stress in pregnant women is associated with engaging in unhealthy behaviors during pregnancy and infrequent antenatal visits [29,47]. This may explain why elevated perceived stress in early pregnancy is associated with low receipt of pertussis vaccine during pregnancy. The current study also demonstrated that the lowest influenza and pertussis vaccine uptake was among women who reported a very high anxiety score in early pregnancy. It is possible that women with high anxiety symptoms are more likely to be concerned about the safety of vaccination during pregnancy with safety concerns known to be one of the barriers to vaccination during pregnancy [18]. Moderate anxiety score was a predictor of pertussis and influenza vaccination uptake during pregnancy. However, this should be interpreted with caution as the anxiety scores in our study were positively skewed and relatively few women presented with moderate anxiety scores.

In the current study, women who used multivitamin/supplements routinely in the preconception period were more likely to receive both pertussis and influenza vaccination during pregnancy. Previous research has shown that women with planned pregnancies are more likely to use multivitamin/supplements before becoming pregnant [30]. Our findings also suggest that women who engaged in moderate exercise were more likely to receive pertussis vaccination during pregnancy. These results are consistent with previous studies that demonstrated women who engage in periconceptional health-promoting behaviors or who plan their pregnancies are more likely to follow other recommended health behaviors during pregnancy and personally feel more responsible for the health of their unborn baby [31,48].

Consistent with previous findings, our study has indicated maternal sociodemographic characteristics such as lower educational attainment or unemployment are associated with low uptake of influenza vaccination during pregnancy [18,21,28]. Our results are also consistent with previous studies that demonstrated an association between younger maternal age and low uptake of pertussis and influenza vaccination during pregnancy [35,21]. Improving access to maternal vaccines for first-time young mothers needs consideration. Uptake of maternal pertussis vaccine was also lower among women born overseas. Educational materials on the importance of maternal vaccination should be easily readable and accessible to culturally and linguistically diverse women in several languages. Receipt of the recommended vaccines by Indigenous Australian women was lower than non-Indigenous women; the uptake difference was not statistically significant but more research is needed to understand and reduce this disparity.

This study has some limitations. The participants in the cohort were healthy nulliparous women and 95% of them were recruited through the Lyell McEwin Hospital, one of the most socioeconomically disadvantaged urban areas in Australia. Hence, the estimated vaccine uptake and prenatal psychosocial factors may differ for women receiving antenatal care through private obstetric care providers and multiparous women in Australia. Although vaccination status was checked against patients' medical records, providers without access to medical records could have administered vaccinations not captured in patients' medical records (i.e. pharmacist or workplace-administered vaccination). Thus, uptake of the vaccines during pregnancy may have been underestimated.

5. Conclusion

Regardless of prenatal psychosocial factors, our findings suggest that most expectant mothers are willing to vaccinate against pertussis and influenza vaccination during pregnancy. However, we found that psychosocial factors influenced the uptake of pertussis and influenza vaccines during pregnancy. This highlights that addressing health care provider–patient barriers and provider cognizance of psychosocial factors is important in improving vaccination uptake during pregnancy. Interventions that improve maternal vaccination uptake in women with psychological stressors should be designed and implemented in maternal immunization programs. Mental health midwives or nurses are well

positioned to recommend vaccines to pregnant women while undertaking psychosocial assessment in conjunction with screening for antenatal depression and anxiety.

Author contributions

HM performed data analyses and prepared the first and final drafts of the manuscript under direct supervision of HSM, CTR, LEG and LCG. CTR, GD, SL and JD designed and implemented the STOP study. All named authors were involved in critically reviewing the content, and have approved the final version for publication.

CRediT authorship contribution statement

Hassen Mohammed: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Claire T. Roberts:** Conceptualization, Supervision, Writing - review & editing. **Luke E. Grzeskowiak:** Conceptualization, Supervision, Writing - review & editing. **Lynne Giles:** Methodology, Supervision, Writing - review & editing. **Shalem Leemaqz:** Writing - review & editing. **Julia Dalton:** Writing - review & editing. **Gustaaf Dekker:** Writing - review & editing. **Helen S. Marshall:** Conceptualization, Supervision, Writing - review & editing.

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.

Acknowledgments

The Screening Tests to predict poor Outcomes of Pregnancy (STOP) study was funded by the University of Adelaide. The authors would like to thank all of the women who participated in the STOP study, Samantha Pahl and Suzette Coat for their assistance with recruitment and data collection.

References

[1] Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006;12:1638–43.
[2] Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012;207:S3–8.
[3] Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. Int J Womens Health 2014;6:681–9.
[4] McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol 2011;204:S54–7.
[5] Munoz FM. Pertussis in infants, children, and adolescents: diagnosis, treatment, and prevention. Semin Pediatr Infect Dis 2006;17:14–9.
[6] Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995–2005–trends by region and age group. Commun Dis Intell Quart Rep 2007;31:205–15.
[7] Blanchard-Rohner G, Siegrist CA. Vaccination during pregnancy to protect infants against influenza: why and why not?. Vaccine 2011;29:7542–50.
[8] Reuman PD, Ayoub EM, Small PA. Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J 1987;6:398–403.
[9] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. The Lancet 2014;384:1521–8.
[10] Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. Clin Infect Dis 2015;60:333–7.
[11] 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;51:1355–61.
[12] Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371:918–31.
[13] McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of tetanus, diphtheria, and pertussis vaccination during pregnancy: a systematic review. Obstet Gynecol 2017;129:560–73.
[14] McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine 2015;33:2108–17.
[15] Laenen J, Roelants M, Devlieger R, Vandermeulen C. Influenza and pertussis vaccination coverage in pregnant women. Vaccine 2015;33:2125–31.
[16] Koepke R, Kahn D, Petit AB, Schauer SL, Hopfensperger DJ, Conway JH, et al. Pertussis and influenza vaccination among insured pregnant women – Wisconsin, 2013–2014. MMWR Morb Mortal Wkly Rep 2015;64:746–50.
[17] 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;66:56–9.
[18] Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: a literature review. Vaccine 2015;33:6420–9.
[19] MacDougall DM, Halperin BA, Langley JM, McNeil SA, MacKinnon-Cameron D, Li L, et al. Knowledge, attitudes, beliefs, and behaviors of pregnant women approached to participate in a Tdap maternal immunization randomized, controlled trial. Hum Vaccin Immunother 2016;12:879–85.
[20] Weinstein ND, Kwitel A, McCaul KD, Magnan RE, Gerrard M, Gibbons FX. Risk perceptions: assessment and relationship to influenza vaccination. Health Psychol 2007;26:146–51.
[21] Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women – a systematic review. Vaccine 2014;32:4602–13.
[22] Wilcox CR, Calvert A, Metz J, Kilich E, MacLeod R, Beadon K, et al. Determinants of influenza and pertussis vaccination uptake in pregnancy: a multi-centre questionnaire study of pregnant women and healthcare professionals. Pediatr Infect Dis J 2018.
[23] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385–96.
[24] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31(Pt 3):301–6.
[25] Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale. Br J Psychiatry 1987;150:782–6.
[26] Austin MP, Colton J, Priest S, Reilly N, Hadzi-Pavlovic D. The antenatal risk questionnaire (ANRQ): acceptability and use for psychosocial risk assessment in the maternity setting. Women Birth 2013;26:17–25.
[27] Barros AJD, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol 2003;3:21-.
[28] Myers KL. Predictors of maternal vaccination in the United States: an integrative review of the literature. Vaccine 2016;34:3942–9.
[29] Omidvar S, Faramarzi M, Hajian-Tilak K, Nasiri Amiri F. Associations of psychosocial factors with pregnancy healthy life styles. PLoS ONE 2018;13:e0191723.
[30] Barrett G, Shawe J, Howden B, Patel D, Ojukwu O, Pandya P, et al. Why do women invest in pre-pregnancy health and care? A qualitative investigation with women attending maternity services. BMC Pregnancy Childbirth 2015;15:236-.
[31] Haslam C, Lawrence W, Haefeli K. Intention to breastfeed and other important health-related behaviour and beliefs during pregnancy. Fam Pract 2003;20:528–30.
[32] Kahn KE, Black CL, Ding H, Williams WW, Lu PJ, Fiebelkorn AP, et al. Influenza and Tdap vaccination coverage among pregnant women – United States, April 2018. MMWR Morb Mortal Wkly Rep 2018;67:1055–9.
[33] Public Health England. Pertussis vaccination programme for pregnant women update: vaccine coverage in England, April to June 2018; 2018.
[34] Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS ONE 2018;13:e0197867.
[35] Rowe SL, Perrett KP, Morey R, Stephens N, Cowie BC, Nolan TM, et al. Influenza and pertussis vaccination of women during pregnancy in Victoria, 2015–2017. Med J Aust 2019;210:454–62.
[36] Healthy People 2020 objectives for influenza vaccination among pregnant women. Healthy People 2020; 2019.
[37] Wiley KE, Cooper SC, Wood N, Leask J. Understanding pregnant women's attitudes and behavior toward influenza and pertussis vaccination. Qual Health Res 2015;25:360–70.
[38] Australian Goverment Department of Health. Australian influenza surveillance report and activity updates – 2019. In: Influenza (Flu), editor. Australia; 2019.
[39] Silverman NS, Greif A. Influenza vaccination during pregnancy: Patients' and physicians' attitudes. J Reprod Med Obstetrician Gynecol 2001;46:989–94.
[40] Tong A, Biringer A, Ofner-Agostini M, Upshur R, McGeer A. A cross-sectional study of maternity care providers' and women's knowledge, attitudes, and behaviours towards influenza vaccination during pregnancy. J Obstetr Gynaecol Canada 2008;30:404–10.
[41] Moniz MH, Beigi RH. Maternal immunization: Clinical experiences, challenges, and opportunities in vaccine acceptance. Hum Vaccin Immunother 2014;10:2562–70.
[42] Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS ONE 2019;14:e0214538.

[43] Department for Health and Ageing. South Australian perinatal practice guideline, anxiety and depression in the perinatal period; 2017. Available from https://www.sahealth.sa.gov.au/wps/wcm/connect/c7c0ccf9-b704-4411-9b47-fbf777ac0829/Anxiety+and+Depression+in+the+Perinatal+Period_PPG_v1_0.pdf?MOD=AJPER ES&CACHEID=ROOTWORKSPACE-c7c0ccf9-b704-4411-9b47-fbf777ac0829-mTXCinG [cited 2020 Jan 11].
[44] Buist A. Perinatal mental health Identifying problems and managing medications. Aust Fam Physician 2014;43:182–5.
[45] Austin MP. Psychosocial assessment and management of depression and anxiety in pregnancy. Key aspects of antenatal care for general practice. Aust Fam Physician 2003;32:119–26.
[46] Taksdal S, Mak D, Joyce S, Tomlin S, Carcione D, Armstrong P, et al. Predictors of uptake of influenza vaccination A survey of pregnant women in Western Australia. Aust Fam Physician 2013;42:582–6.
[47] Shishehgar S, Mahmoodi A, Dolatian M, Mahmoodi Z, Bakhtiary M, Alavi Majd H. The relationship of social support and quality of life with the level of stress in pregnant women using the PATH model. Iran Red Crescent Med J 2013;15:560–5.
[48] Williams L, Zapata LB, D'Angelo DV, Harrison L, Morrow B. Associations between preconception counseling and maternal behaviors before and during pregnancy. Matern Child Health J 2012;16:1854–61.

Chapter 6: Safety and Protective Effects of Maternal Influenza Vaccination on Pregnancy and Birth outcomes: A Prospective Cohort study

6.1 Publication

Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. EClinicalMedicine.2020; 26:100522.

Statement of Authorship

Title of Paper	Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. EClinicalMedicine.2020; 26:100522.

Principal Author

Name of Principal Author (Candidate)	Hassen Mohammed		
Contribution to the Paper	Conceived and designed the study, performed data analysis, interpretation of the findings prepared the first and final draft of the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Prof. Claire Roberts		
Contribution to the Paper	Conceived and designed the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	17/9/20

Name of Co-Author	Dr Luke Grzeskowiak		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, provided methodological guidance, assisted HM in data analysis, reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	A/Prof. Lynne Giles		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, provided methodological guidance, instructed and assisted HM in data analysis, reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	Prof Gustaaf Dekker		
Contribution to the Paper	Reviewed and edited the manuscript		
Signature		Date	17/09/2020
Name of Co-Author	Prof Helen Marshall		
Contribution to the Paper	Conceived and designed the study, supervised development of work, interpretation of the findings, reviewed and edited the manuscript		
Signature		Date	15/09/2020

EClinicalMedicine 26 (2020) 100522

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study

Hassen Mohammed[a,b,c], Claire T. Roberts[b,c,d], Luke E. Grzeskowiak[b,c,e], Lynne C. Giles[b,f], Gustaaf A. Dekker[b,c,g], Helen S. Marshall[a,b,c,f,*]

[a] Vaccinology and Immunology Research Trials Unit, Women's and Children's Health Network, Adelaide, South Australia, Australia
[b] Robinson Research Institute, The University of Adelaide, Adelaide, South Australia, Australia
[c] Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
[d] College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia
[e] SA Pharmacy, Flinders Medical Centre, SA Health, Bedford Park, Adelaide, Australia
[f] School of Public Health, The University of Adelaide, Adelaide, South Australia, Australia
[g] Women's and Children's Division, Lyell McEwin Hospital, Elizabeth Vale, South Australia, Australia

ARTICLE INFO

Article History:
Received 7 June 2020
Revised 29 July 2020
Accepted 11 August 2020
Available online 9 September 2020

ABSTRACT

Background: Our study aimed to assess the safety and protective effect of maternal influenza vaccination on pregnancy and birth outcomes.
Methods: The study population comprised 1253 healthy nulliparous pregnant women in South Australia between 2015 and 2018. Participants were followed prospectively, with vaccination status (confirmed by medical records), pregnancy, and birth outcome data collected by midwives. Adjusted relative risks (aRRs) and adjusted hazard ratios (aHRs) were estimated accounting for time-varying vaccine exposure and temporal nature of each outcome.
Findings: Maternal influenza vaccination (48%, 603 of 1253) reduced the risk for pre-delivery hospitalisation with influenza like illness (aHR 0•61; 95% CI 0•39, 0•97). Maternal influenza vaccination was not associated with spontaneous abortion (aHR 0•42, 95% CI 0•12, 1•45), chorioamnionitis (aRR 0•78, 95% CI, 0•32, 1•88), gestational hypertension (aHR 0•78, 95% CI 0•47, 1•29), pre-eclampsia (aHR 0.84, 95% CI 0•54, 1•27), gestational diabetes (aHR 1•16, 95% CI 0•82, 1•66) nor preterm birth (aHR 0•94, 95% CI 0•59, 1•49). No associations between antenatal influenza vaccination and congenital anomalies, admission to the neonatal care unit, low Apgar scores, and mechanical ventilation were observed. Results were not materially changed after adjustment for pertussis vaccination. We observed a protective effect of maternal influenza vaccination on low birth weight (aHR 0•46, 95% CI 0•23, 0•94) and a marginal protective effect on small for gestational age births (aHR 0•65, 95% CI 0•40, 1•04) during periods of high influenza activity.
Interpretation: These results support the safety of maternal influenza vaccination and suggest a protective effect in reducing the rates of low birthweight and small for gestational age births.
Funding: There was no funding for this study.

1. Introduction

Pregnant women are vulnerable to serious complications from influenza including preterm labour, pneumonia, hospitalisation and death, particularly during seasonal and pandemic influenza outbreaks [1,2]. Newborns whose mothers had influenza during pregnancy are also at increased risk of adverse outcomes such as preterm birth and low birthweight [3,4]. Maternal influenza vaccination protects mothers against influenza infection and their offspring by transplacental antibody transfer from mother to foetus conferring passive immunity until the first influenza vaccination from age six months [5,6]. Influenza vaccination during pregnancy might also reduce the risk of low birthweight, preterm birth, and stillbirth but evidence concerning these birth outcomes is conflicting [7–13]. Despite recommendations for maternal influenza vaccination, uptake during pregnancy remains suboptimal globally [14].

A major challenge for achieving high uptake of influenza vaccination during pregnancy relates to relatively limited published evidence of vaccine safety for pregnant women and their foetus [8–12].

* Corresponding author at: Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, 72 King William Road, North Adelaide 5006, South Australia, Australia.
E-mail address: helen.marshall@adelaide.edu.au (H.S. Marshall).

https://doi.org/10.1016/j.eclinm.2020.100522

Research in context panel

Evidence before this study

We searched PubMed for English language studies published until March 31, 2020, with no start date restriction, with the terms "influenza", "influenza vaccine", "maternal influenza vaccination", maternal influenza immunisation", "humans" and "pregnancy". The World Health Organization (WHO) considers pregnant women as a priority group for seasonal inactivated influenza vaccination due to their vulnerability to influenza infection and its resulting morbidities. Previous studies have shown that inactivated influenza vaccine during pregnancy is safe and provides passive antibodies to the infant, as well as clinical protection for both mother and infant < 6 months of age against influenza infections and influenza-related hospitalisations. Despite the recommendation of maternal influenza vaccination from immunisation advisory groups internationally including WHO, it has not been implemented in most low-resource countries, and even in high income countries where it is incorporated into standard antenatal care, vaccination uptake is often suboptimal. While the body of literature regarding the safety of influenza vaccination during pregnancy is mounting, there are relatively few prospectively designed or clinical trials that include pregnant women. In high income countries where maternal influenza vaccination is recommended, prospectively designed studies with advanced statistical approaches are likely to be the only way to comprehensively assess the safety of influenza immunisation during pregnancy and its important potential protective effects in reducing low birth weight, small for gestational age birth and preterm birth, for which evidence is conflicting.

Added value of this study

This prospective cohort of healthy pregnant women, with confirmed vaccination status and accurate pregnancy and infant outcome data used robust nuanced time-to-event analyses. The study showed that influenza vaccination during pregnancy is not associated with adverse pregnancy, foetal or birth outcomes. This study also presents evidence that inactivated influenza vaccination decreases the risk of pre-delivery hospitalisation with maternal influenza-like illness by 39% and reduces the risk of low birthweight and small for gestational age births during periods of high influenza activity.

Implications of all the available evidence

These findings provide further reassurance to women and health care providers about the safety of inactivated influenza vaccination during pregnancy. Importantly, our results provide evidence in support of maternal influenza vaccination **reducing** low birth weight and small for gestational age births during periods of widespread influenza activity. These findings need to be replicated in other countries as it is plausible that the impact of maternal influenza vaccine on these birth outcomes may vary with the underlying local influenza epidemiology and demographic characteristics. Our findings could be pivotal for countries weighing the additional benefits of implementing maternal influenza immunisation programs. This may be particularly important for low income countries where the rates of low birthweight and small for gestational age births are very high, and known to be strong risk factors for neonatal and early childhood morbidity and in which health systems have poor capacity to mitigate short and long-term effects.

A review of factors influencing acceptance of antenatal vaccination indicated that access issues and safety concerns are major barriers to uptake [15]. An inflammatory response from infection during pregnancy has been shown to increase the risk of foetal injury [16] but no evidence exists that an inflammatory response from a vaccine carries a similar risk. A robust assessment of the safety of influenza vaccination during pregnancy is critical due to population-wide rollouts of vaccines for this group. A number of systematic reviews have reported pregnancy and birth safety outcomes following influenza vaccination in pregnancy [8–13].

Most observational research into vaccine safety and efficacy during pregnancy has been retrospective, due to the relatively cheaper cost, fewer ethical concerns, and difficulty in recruiting pregnant women to randomized controlled trials (RCTs). Whilst providing timely reporting, this approach has limitations. In most retrospective studies, authors have been unable to establish if a pregnancy complication preceded vaccination nor account for the time-dependant nature of exposure to vaccination during pregnancy. In countries where maternal influenza vaccination is recommended, prospectively designed studies are likely to be the only way to accurately determine the true risk or potential benefits of maternal vaccination beyond prevention of influenza for pregnant women and their infants. Our study aimed to prospectively assess maternal and birth outcomes following inactivated influenza vaccination during pregnancy, while also taking into account the most comprehensive set of potential confounding variables considered to date.

2. Methods

2.1. Study design and participants

The current study draws on data collected as part of a prospective cohort study (STOP), which aims to develop screening tests to identify adverse pregnancy outcomes. Healthy nulliparous women were recruited in pregnancy at two major maternity hospitals, the Lyell McEwin Hospital, the tertiary hospital serving the low socio-economic community in Adelaide's Northern suburbs and the Women's and Children's Hospital, the primary tertiary maternity hospital for complex care, accounting for around 50% of the 16,000 annual births in metropolitan Adelaide, South Australia. Between March 2015 and December 2017, nulliparous women with a singleton pregnancy attending their first antenatal clinic between 9^{+0} and 16^{+0} weeks' gestation were enroled. Women were excluded if they were considered already at high risk of pregnancy complications at screening (i.e. experienced three or more previous miscarriages or with pre-existing hypertension or diabetes). Participants were followed prospectively, with vaccination, pregnancy, and birth outcome data collected by research midwives. Written informed consent was obtained from all participants included in the STOP study. The original STOP study protocol was approved by the Human Research Ethics Committee of the Women's and Children's Hospital Adelaide Australia (HREC/14/WCHN/90), registered at Australian New Zealand Clinical Trials Registry, ACTRN12614000985684.

2.2. Exposure

The exposure of interest was trivalent inactivated influenza vaccination during pregnancy, defined as a vaccine received between the first day (date) of the last menstrual period and the end of pregnancy. A research midwife interviewed and collected maternal vaccination status of the women during their first study visit at 9–16 weeks' gestation and during their second study visit interview at 32–36 weeks' gestation. Vaccination date and gestation of administration were recorded. Following delivery, a research midwife interviewed the

participants and verified final vaccination status by reviewing medical case notes and Pregnancy-Hand-Held-Record to confirm the reported vaccination status. Pregnancy-Hand-Held-Records are the main medical record of pregnancy care in South Australia and are reviewed and updated at antenatal appointments.

2.3. Outcomes

Pregnancy outcomes assessed were pre-delivery admission due to influenza-like illness, spontaneous abortion after inclusion in the STOP study, gestational diabetes, gestational hypertension, pre-eclampsia, severe pre-eclampsia, chorioamnionitis, premature rupture of membranes, spontaneous preterm birth, preterm birth and stillbirth. Birth outcomes included congenital anomalies, small for gestational age (SGA), low birthweight ($<$ 2500 g) (LBW), low birthweight at term ($\geq$ 37 weeks' gestation), Apgar scores at 1 and 5 min, neonatal care unit admissions, respiratory distress and mechanical ventilation.

Pregnancy and birth complications were diagnosed using the Brighton Collaboration consensus list of terms, and international guidelines. Gestational hypertension was defined as (peripheral) hypertension [systolic BP (SBP) $\geq$ 140 mmHg or diastolic BP (DBP) $\geq$ 90 mmHg] after 20 weeks of gestation in previously normotensive women. Pre-eclampsia was defined as gestational hypertension with proteinuria (24 h urinary protein $\geq$ 300 mg or spot urine protein: creatinine ratio $\geq$ 30 mg/mmol creatinine or urine dipstick protein $\geq$ 2+) or any multi-organ complication of pre-eclampsia. Severe pre-eclampsia was defined as pre-eclampsia with one or more of the following clinical features: BP of $\geq$ 160/110 mmHg or hypertension requiring intravenous therapy with an antihypertensive agent or magnesium sulphate after 20 weeks of gestation. Preterm birth was defined as any birth before 37 and after 20 completed weeks of gestation. SGA was defined as neonates with a birthweight below the $<$10th percentile customized for maternal factors such as maternal height, booking weight, ethnicity and gestational age at delivery. The estimated date of delivery was calculated from a certain last menstrual period (LMP) date and was only adjusted if either (1) a scan performed at $<$ 16 weeks of gestation found a difference of $\geq$7 days between the scan gestation and that calculated by the LMP or (2) on 20-week scan a difference of $\geq$ 10 days was found between the scan gestation and that calculated from the LMP. If the LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery.

2.4. Covariates

During the first study visit at 9–16 weeks' gestation, information was obtained regarding baseline socio-demographic, lifestyle and clinical characteristics such as age, ethnicity, level of education, household income, employment, exercise, smoking, supplement use, intake of alcohol and recreational drugs, medical and obstetric history, and complications during the current pregnancy. Participating women also completed the Perceived Stress Scale (PSS-10), to assess perceived stress levels in the past month, the short form of the Spielberger State–Trait Anxiety Inventory (STAI), assessing current anxiety symptoms, and the Edinburgh Postnatal Depression Scale (EPDS), assessing depressive symptoms during pregnancy.

2.5. Statistical methods

Demographic, lifestyle and clinical characteristics of participants were summarized descriptively, by influenza vaccination exposure during pregnancy. Continuous variables were summarized as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate, while counts and percentages were used to summarize categorical variables. To investigate if there was an association between influenza vaccination status and each of the outcome variables, we initially conducted independent samples t-tests or Mann-Whitney U tests, as appropriate, for continuous variables and chi-square tests of association for binary and categorical variables.

The timing for vaccination exposures and time at risk windows were calculated for each time sensitive pregnancy and birth outcome accounting for the temporal nature of each outcome of interest. For example, women were at risk for preterm birth from 20 weeks until 36^{+6} weeks of gestation. Cox proportional-hazards models with gestational age in weeks as the underlying time metric were used to derive hazard ratios (HRs) that compared the hazard rates for time-sensitive outcomes such as spontaneous abortion or preterm birth between vaccinated and unvaccinated women. Vaccination status was treated as a time-varying exposure in these models, in that each vaccinated woman's pregnancy was decomposed into an unvaccinated exposure period and a vaccinated exposure period. In sensitivity analyses, we estimated HRs and adjusted HRs of time-dependant pregnancy or birth outcomes by trimester of influenza vaccination during pregnancy. To assess the impact of the intensity of influenza activity on the association between maternal influenza vaccination and key birth outcomes, we also stratified analyses by the level of influenza activity at time of delivery using the South Australian Influenza Surveillance Report [17] based on the percentage of laboratory confirmed influenza during the study period 2015–2018. We identified high activity periods as having rates of laboratory confirmed influenza of at least 10% for at least 3 of 4 consecutive weeks. Low influenza activity period was defined as the first week during which the positive rate was lower than 10% and remained at that level for at least four consecutive weeks. On this basis, "high influenza activity" periods were identified for 01 June – 31 October 2015, 01 July – 31 December 2016, 01 June – 30 November 2017 and 31 August – 31 October 2018. The delivery months of the vaccinated women were classified into "high" and "low" influenza activity to compare key birth outcomes of infants born to vaccinated mothers during high/low influenza activity with births occurring at any time to unvaccinated women.

We used log-binomial models to estimate risk ratios (RR) and adjusted risk ratios (aRR) comparing risk of late onset or early postpartum adverse pregnancy outcomes and adverse birth outcomes including congenital anomalies, low Apgar score, admission to neonatal unit, respiratory distress syndrome and mechanical ventilation in infants of vaccinated and unvaccinated mothers. Finally, we used a multivariable linear regression model to predict the difference in mean gestational age at delivery and mean birthweight by vaccination status. For all multivariable (i.e. adjusted) models, annual household income, level of education, ethnicity, maternal health risk factors (age, gravidity, alcohol intake, recreational drug use, smoking, pre-pregnancy body mass index (BMI)), use of micronutrient supplements, asthma and current psychological states were amongst the variables selected as potential confounders based on evidence in the literature [8–11] guided by directed acyclic graphs. Additional sensitivity analyses were conducted in all multivariable models to evaluate whether the effects of maternal influenza vaccination on pregnancy and birth outcomes were maintained after adjustment for pertussis vaccination in third trimester. As pertussis vaccination was also recommended in pregnancy from 28 to 32 weeks' gestation in Australia, in our linear regression analyses, we restricted the cohort to women whose pregnancies reached at least 32 weeks' gestation to allow for all women to have had the opportunity to receive the pertussis vaccine. Missing covariate values are reported in the baseline table where relevant. The amount of missing data is minimal ranging between 0•1% (estimated season of delivery data) to 2•3% (STAI data), and therefore all available data were used in the analyses of all pre-specified outcomes. For all analyses, a p value $<$ 0•05 was considered statistically significant. Data were recorded in a REDCap [18, 19]

online database and all statistical analyses were conducted using Stata version 15 (Stata Corp, College Station, Texas, USA).

Role of Funding Source: Not applicable

3. Results

Of 1364 pregnant women enroled, 12 withdrew access to their medical records, three had no medical case notes and three were lost to follow up or delivered elsewhere (n = 10); all 28 were excluded from our final analyses. So as not to confound any observed associations, we excluded 83 women who had influenza vaccination prior to pregnancy. Our final cohort consisted of 1253 women (Fig. 1). Key variables of interest did not differ between women included and excluded from our study (supplementary material p 1). At recruitment, mean maternal age of nulliparous women was 25•9 years (SD 5•0) (range: 15–45 years) and median gestational age was 11•4 weeks (IQR 9•1–12•8) with 82•2% (1031 of 1253) presenting for their first antenatal care visit in the first trimester of pregnancy.

The overall uptake of influenza vaccination was 48•1% (603 of 1253); of the vaccinated women, 24•0% (n = 145) were vaccinated in first trimester, 20•2% (n = 122) in second trimester, and 55•7% (n = 336) in third trimester. Both influenza and pertussis vaccinations occurred in 555 of 1253 (44•2%) pregnancies. Unvaccinated women were more likely to be younger, Aboriginal and/or Torres Strait Islander, in lowest household income group, smoke cigarettes, use illicit drugs, physically inactive, have lower educational attainment and less likely to take micronutrient supplements pre-conception or during pregnancy, and give birth during Autumn compared with vaccinated pregnant women (Table 1).

3.1. Pregnancy outcomes

Of the 1253 women, 34 (2•7) had spontaneous abortions < 20 weeks' gestation, seven had terminations (0•5%), six had stillbirths (0•4%), and 1201 (95•8%) delivered a live infant (five missing values). The mean gestational age at delivery was 39•2 weeks (SD 2•0 weeks). Overall, 95 of 1253 (7•5%) women were admitted to hospital due to influenza like illness during pregnancy; mostly in the third (93 of 95) trimesters of pregnancy. The time-dependant Cox proportional hazards regression model shows that women vaccinated at any time during pregnancy had a significant lower risk of pre-delivery hospitalisation with influenza like illness compared to unvaccinated women (aHR 0•61; 95% CI 0•39, 0•97) (Table 2). After accounting for the assumption that immunologic protection after influenza vaccination requires 2 weeks for full effect, the estimated aHR remained unchanged (supplementary material p 2). The observed protective effect of maternal influenza vaccination in reducing hospitalisation due to influenza like illness was stronger for those vaccinated in second trimester (aHR 0•09; 95% CI 0•01, 0•71) and those who delivered during periods of high influenza activity (aHR 0•51; 95% CI 0•27, 0•95) (Table 3).

There was no association with spontaneous abortion for women who were vaccinated for influenza prior to 20 weeks' gestation (aHR 0•42, 95% CI 0•12, 1•45) (Table 2). Our Cox model shows that influenza vaccination during pregnancy was not associated with maternal hypertensive disorders including gestational hypertension (aHR 0•78, 95% CI 0•47, 1•29), pre-eclampsia (aHR 0•84, 95% CI 0•54, 1•27) or severe pre-eclampsia (aHR 0•65, 95% CI 0•26, 1•64) (Table 2). Additional adjustment for maternal pertussis vaccination as a time-varying covariate yielded similar results for hypertensive disorders (supplementary material p 2). In the log-binomial models, there was no association between risk of chorioamnionitis and influenza vaccination during pregnancy (aRR 0•78, 95% CI, 0•32, 1•88) (Table 4).

After adjusting for covariates, women vaccinated for influenza during pregnancy had on average 1•8 days longer gestation at delivery than unvaccinated women (Table 2). Restricting the analysis to pregnancies reaching at least 32 weeks' gestation followed by

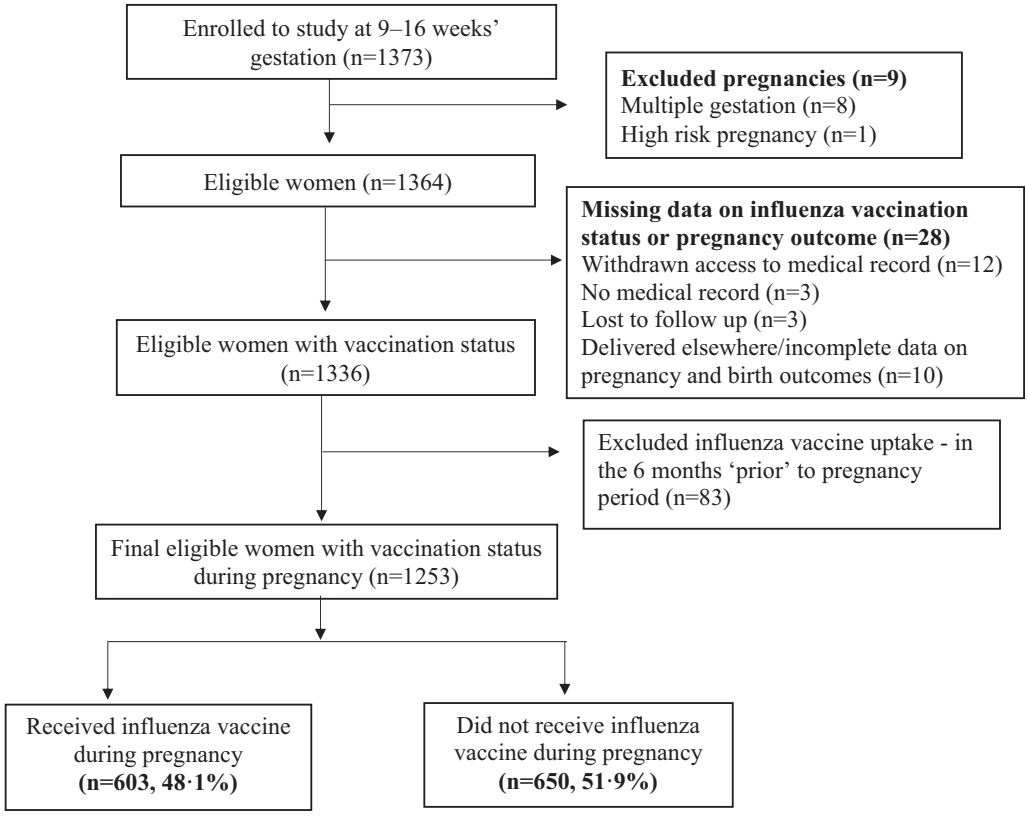


Fig. 1. Participants flow diagram.

Table 1
Maternal characteristics of vaccinated and unvaccinated pregnant women who delivered at two obstetric hospitals in South Australia, 2015 to 2018 (*N* = 1253).

Variable	Vaccinated women *N* = 603, n (%)	Unvaccinated women *N* = 650, n (%)
Maternal age (years)		
15–19	50 (8•2)	76 (11•6)
20–24	157 (26•0)	232 (35•6)
25–29	233 (38•6)	212 (32•6)
>30	163 (27•0)	130 (20•0)
Race/ethnicity		
Caucasian	492 (81•5)	542 (83•3)
Aboriginal/TSI	7 (1•1)	16 (2•4)
Others	104 (17•2)	92 (14•1)
Household annual income in AUD		
<40,000	118 (19•5)	184 (28•3)
40,001–70,000	125 (20•7)	157 (24•1)
70,001–105,000	165 (27•3)	153 (23•5)
>105,001	190 (31•5)	146 (22•4)
Missing	5 (0•8)	10 (1•5)
Maternal education		
≤ Secondary school qualification	245 (40•6)	311 (47•8)
Diploma/certificate	215 (35•7)	234 (36•0)
Bachelor's or higher degree	142 (23•5)	102 (15•6)
Missing	1 (0•1)	3 (0•4)
Smoking status at 9–16 weeks' gestation		
Current smoker	43 (7•1)	78 (12•0)
Quit during pregnancy	67 (11•1)	71 (10•9)
Non-smoker	491 (81•4)	495 (76•1)
Missing	2 (0•3)	6 (0•9)
Illicit drug use during 1st trimester/pre-pregnancy	29 (4•8)	46 (7•0)
Multivitamin and mineral supplements use		
Pre-conception and 1st trimester	157 (26•0)	116 (17•8)
1st trimester	326 (54•0)	345 (53•0)
None	116 (19•2)	186 (28•6)
Missing	4 (0•6)	3 (0•4)
Moderate exercise during 1st trimester/pre-pregnancy		
≥ 4 per week	82 (13•6)	68 (10•4)
1–3 per week	281 (46•6)	300 (46•1)
Never	237 (39•3)	276 (42•4)
Missing	3 (0•5)	6 (0•9)
Gravidity >1	165 (27•3)	185 (28•4)
Pre-pregnancy asthma	78 (12•9)	90 (13•8)
Pre-pregnancy BMI (kg/m2)		
<18•5 (Under)	11 (1•8)	15 (2•1)
18•5–24 (Normal)	237 (39•3)	255 (39•2)
25–29•9 (Overweight)	168 (27•8)	181 (27•8)
≥ 30 (Obese)	187 (31•0)	199 (30•6)
Psychological measures at 9–16 weeks' gestation		
Edinburgh Perinatal Depression Scale (EPDS) scores, mean (SD)	5•5 ± 4•4	5•4 ± 4•6
State and trait anxiety (STAI) scores, mean (SD)	33•4 ± 11•0	33•5 ± 11•1
Perceived stress scale (PSS) scores, mean (SD	13•0 ± 6•4	12•9 ± 6•6
Missing	19 (1.5)	19 (1.5)
Influenza vaccine timing		NA
1st trimester	145 (24•0)	
2nd trimester	122 (20•2)	
3rd trimester	336 (55•7)	
Gestational week of vaccine administration, mean (SD)	23•0 ± 10•5	NA
Received pertussis vaccination during pregnancy	555 (92•0)	398 (61•2)
Estimated season of delivery		
Summer	171 (28•3)	163 (25•0)
Autumn	82 (13•6)	224 (34•4)
Winter	184 (30•5)	135 (20•7)
Spring	166 (27•5)	127 (19•5)
Missing	0 (0)	1 (0•1)

Data are mean (SD) or n (%). SD= standard deviations. AUD=Australian dollars. BMI=body-mass-index.

adjustment for maternal pertussis vaccination showed that any differences in gestational age at birth between unvaccinated and vaccinated mothers were negligible (supplementary material p 2). Overall, 7•3% (89 of 1207) of pregnancies resulted in preterm birth. There was no difference in stillbirth between vaccinated (*n* = 3) and unvaccinated women (*n* = 3). Our time-dependant analysis showed no association between influenza vaccination through to 37 weeks' gestation and preterm birth (aHR 0•94, 95% CI 0•59, 1•49), preterm premature rupture of the membranes (aHR 0•85, 95% CI 0•44, 1•63), and spontaneous preterm birth (aHR 0•74, 95% CI 0•41, 1•33) (Table 2). Maternal influenza vaccination showed a modest reduction in the hazard of spontaneous preterm birth during periods of lower influenza virus circulation but the confidence intervals were wide and included one (aHR 0•52, 95% CI 0•24, 1•13) (supplementary material p 3).

3.2. Birth outcomes

Maternal influenza vaccination was protective against delivering LBW term infants in our Cox proportional hazard regression analyses

Table 2
Crude and adjusted hazard ratios for time-based pregnancy and birth outcomes by maternal influenza vaccination status at two obstetric hospitals in South Australia 2015–2018.

Variables	Total	Unvaccinated N (%)	Vaccinated N (%)	Crude HR* (95% CI)	p-value	Adjusted † aHR (95% CI)	p-value
Pre-delivery hospitalisation due to influenza like illness ‡	95/1253 (7•5)	60/650 (9•2)	35/603 (5•8)	0•58 (0•37, 0•91)	0•018	0•61 (0•39, 0•97)	0•038
Spontaneous abortion §	34/1253 (2•7)	31/650 (4•7)	3/603 (0•5)	0•66 (0•20, 2•19)	0•507	0•42 (0•12, 1•45)	0•171
Gestational hypertension ‖	81/1205 (6•7)	41/606 (6•7)	40/599 (6•6)	0•80 (0•49, 1•31)	0•391	0•78 (0•47, 1•29)	0•343
Pre-eclampsia ‖	111/1205 (9•2)	58/606 (9•5)	53/599 (8•8)	0•85 (0•58, 1•26)	0•445	0•84 (0•54, 1•27)	0•417
Severe pre-eclampsia ‖	28/1204 (2•3)	14/606 (2•3)	14 /598 (2•3)	0•86 (0•37, 1•96)	0•725	0•65 (0•26, 1•64)	0•368
Gestational diabetes ¶	190/1207 (15•7)	85/608 (13•9)	105/599 (17•5)	1•33 (0•95, 1•84)	0•088	1•16 (0•82, 1•66)	0•383
Preterm premature rupture of the membranes **	47/1207 (3•8)	27/608 (4•4)	20/599 (3•3)	0•82 (0•43, 1•56)	0•561	0•85 (0•44, 1•63)	0•634
Preterm birth **	89/1207 (7•3)	49/608 (8•0)	40/599 (6•6)	0•94 (0•60, 1•47)	0•802	0•94 (0•59, 1•49)	0•817
Spontaneous preterm birth **	59/1207 (4•8)	36/608(5•9)	23/599 (3•8)	0•71 (0•40, 1•26)	0•253	0•74 (0•41, 1•33)	0•323
LBW (<2500 g) ††	80/1205 (6•6)	49/606 (8•0)	31/599 (5•1)	0•70 (0•42, 1•14)	0•158	0•71 (0•43, 1•19)	0•202
LBW at term (<2500 g)††, ‡‡	29/1116 (2•6)	20/557 (3•5)	9 /559 (1•6)	0•43 (0•18, 0•99)	0•048	0•38 (0•16, 0•89)	0•027
SGA ††	144/1207 (11•9)	83 /608(13•6)	61/599 (10•1)	0•77 (0•54, 1•09)	0•152	0•84 (0•58, 1•20)	0•346
				Difference in means (vaccinated-unvaccinated)		**Difference in adjusted means (vaccinated -unvaccinated)**	
Mean birth weight ††, g (95% CI)	3334•9 ± 557	3301•8 ± 610	3368•4 ± 498	63•7 (0•09, 127•0)	0•050	58•8 (- 4•2, 121•7)	0•067
Mean gestational age at delivery, weeks (95% CI)	39•2 ± 2•0	39•1 ± 2•3	39•4 ± 1•6	0•26 (0•04, 0•49)	0•019	0•27 (0•04, 0•49)	0•019

CI=confidence interval. HR=hazard ratios. LBW=low birthweight. SGA=small for gestational age.
* HR results compared outcome variable in vaccinated group to reference (unvaccinated).
† Adjustments were made for maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal. Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery.
‡ Women admitted to hospital with influenza/ respiratory tract infection were censored at their admission date.
§ The time metric for spontaneous abortion analysis was the first week of gestation up to the event (week of last available pregnancy data or week 20 of gestation; whichever occurred first).
‖ For hypertensive disorders analysis, women who were vaccinated at or after the gestational age at diagnosis (≥ 20 weeks' gestation) and pregnancies ending prior to 20 weeks of gestation were censored.
¶ Women who were vaccinated at or after the gestational age at diagnosis of gestational diabetes mellitus (median gestational age at screening was 27•8 (IQR, 26•5–29) weeks) were censored.
** Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of preterm birth.
†† Additionally adjusted for infant's sex.
‡‡ Low birthweight at term (<2500 g and ≥ 37 completed weeks' gestation at birth).

(aHR 0•38, 95% CI 0•16, 0•89) (Table 2). This effect persisted following additional adjustment for maternal pertussis vaccination (aHR 0•38, 95% CI 0•15, 0•94) (supplementary material p 2). An even greater protective effect of influenza vaccination against delivering a LBW infant at term (aHR 0•20, 95% CI 0•04, 0•87) and LBW in either preterm or term infants (aHR 0•46, 95% CI 0•23, 0•94) was observed during periods of high influenza activity (Table 3). There was no evidence of increased risk of LBW associated with receipt of inactivated influenza vaccine during any trimester of pregnancy (Table 3). First trimester influenza vaccination had no effect on risk of congenital anomalies (aRR 0•33, 95% CI 0•04, 2•73) (Table 4). Overall, 510 (42•2%) of 1207 infants were born during high influenza activity across three Australian influenza seasons 2015–2018. The infants born to vaccinated mothers were estimated to be 59 g heavier than infants born to unvaccinated mothers (58•8 g, 95% CI −4•2 g, 121•7 g) but the confidence intervals were wide and included zero (Table 2). This association was attenuated (18•3 g, 95% CI − 42•2 g, 79•0 g) after adjustment for maternal pertussis vaccination (supplementary material p 2).

Our study found no increased risk for SGA delivery after influenza vaccination during pregnancy (aHR 0•84, 95% CI 0•58, 1•20) (Table 2). Maternal influenza vaccination was associated with a marginal reduction in risk of SGA births during periods of high influenza activity (aHR 0•65, 95% CI 0•40, 1•04). Influenza vaccination in third trimester was associated with a 39% reduction in risk of SGA birth regardless of the level of influenza activity (aHR 0•61, 95% CI 0•38, 0•98) (Table 3). However, these protective effects on SGA were slightly attenuated after adjustment for pertussis vaccination (supplementary material p 3). There was no association between maternal influenza vaccination and adverse infant outcomes including low Apgar scores at 1 and 5 min, admission to the neonatal care unit, mechanical ventilation, and respiratory distress syndrome (Table 4).

4. Discussion

In robust nuanced analyses that account for timing of maternal influenza vaccination and the time risk of adverse pregnancy outcomes, we show maternal influenza vaccination is safe in a prospective cohort of healthy pregnant women, with confirmed vaccination history and accurate, pregnancy and infant outcome data. There was no evidence of associations between influenza vaccination administered at any time in pregnancy and adverse pregnancy or foetal outcomes including spontaneous abortion, congenital anomalies, shortened gestation, gestational diabetes, chorioamnionitis or gestational hypertensive disorders, consistent with the literature [8–12]. In addition to reassuring safety of maternal influenza vaccination, our study found influenza vaccination during pregnancy reduced a pregnant woman's risk of pre-delivery hospitalisation with influenza like illness by around 39%. This protective effect was most pronounced for those women who delivered during periods of high influenza activity, consistent with previous studies [20, 21]. Across the three influenza seasons 2015–2018 in South Australia, influenza A (H3N2) was the dominant circulating virus followed by influenza B [17].

In contrast to our findings, a recent Bayesian meta-analysis of 28 cohort studies showed maternal influenza vaccination protects against preterm birth [13]. However, the pooled summary estimates [13] did not find any association when the preterm birth analysis included 2 randomized placebo-controlled studies (RCTs) and 2 case-control studies. The two RCTs [22, 23] investigating maternal influenza vaccine efficacy and safety in South Africa and Nepal, respectively, found that vaccination was not associated with preterm birth. However, the RCT in Nepal showed a reduction of LBW [23] and another RCT [7] conducted in Bangladesh demonstrated a reduction of SGA amongst a subset of infants born during peak influenza

Table 3
Crude and adjusted hazard ratios for pre-delivery hospitalisation due to influenza like illness and key adverse birth outcomes stratified by trimester of influenza vaccination and influenza activity.

Variables	Unvaccinated N (%)	Vaccinated N (%)	Crude HR* (95% CI)	p-value	Adjusted† aHR (95% CI)	p-value
Pre-delivery hospitalisation due to influenza like illness	60/650 (9•2)	35/603 (5•8)	0•58 (0•37, 0•91)	0•018	0•61 (0•39, 0•97)	0•038
1st trimester			0•43 (0•18, 0•99)	0•049	0•46 (0•19, 1•09)	0•080
2nd trimester			0•09 (0•01, 0•68)	0•019	0•09 (0•01, 0•72)	0•023
3rd trimester			0•70 (0•43, 1•13)	0•149	0•73 (0•44, 1•22)	0•244
Low influenza activity			0•58 (0•33, 0•99)	0•049	0•60 (0•35, 1•05)	0•079
High influenza activity			0•47 (0•26, 0•85)	0•013	0•53 (0•29, 0•96)	0•039
Preterm birth†	49/608 (8•0)	40/599 (6•6)	0•94 (0•60, 1•47)	0•802	0•94 (0•59, 1•49)	0•817
1st trimester			0•46 (0•18, 1•16)	0•111	0•50 (0•19, 1•28)	0•151
2nd trimester			0•91 (0•43, 1•93)	0•811	0•90 (0•41, 1•94)	0•793
3rd trimester			0•79 (0•47, 1•33)	0•384	0•75 (0•43, 1•29)	0•304
Low influenza activity			0•61 (0•33, 1•12)	0•112	0•61 (0•33, 1•12)	0•113
High influenza activity			0•85 (0•50, 1•45)	0•571	0•89 (0•52, 1•53)	0•696
Spontaneous preterm birth ‡	36/608(5•9)	23/599 (3•8)	0•71 (0•40, 1•26)	0•253	0•74 (0•41, 1•33)	0•323
1st trimester			0•37 (0•11, 1•22)	0•104	0•41 (0•12, 1•37)	0•149
2nd trimester			0•61 (0•21, 1•73)	0•361	0•61 (0•21, 1•76)	0•364
3rd trimester			0•61 (0•31, 1•18)	0•147	0•63 (0•32, 1•25)	0•193
Low influenza activity			0•53 (0•25, 1•11)	0•096	0•55 (0•26, 1•17)	0•123
High influenza activity			0•58 (0•28, 1•17)	0•131	0•60 (0•29, 1•26)	0•180
LBW (<2500 g)§	49/606 (8•0)	31/599 (5•1)	0•70 (0•42, 1•14)	0•158	0•71 (0•43, 1•19)	0•202
1st trimester			0•56 (0•24, 1•35)	0•206	0•54 (0•23, 1•29)	0•168
2nd trimester			0•47 (0•16, 1•30)	0•161	0•41 (0•14, 1•16)	0•096
3rd trimester			0•57 (0•32, 1•03)	0•065	0•63 (0•34, 1•15)	0•138
Low influenza activity			0•66 (0•37, 1•19)	0•171	0•63 (0•34, 1•14)	0•170
High influenza activity			0•43 (0•22, 0•86)	0•018	0•46 (0•23, 0•94)	0•033
LBW at term	20/557 (3•5)	9 /559 (1•6)	0•43 (0•18,1•09)	0•048	0•38 (0•16, 0•89)	0•027
(<2500 g)§,‖,¶			0•61 (0•24, 1•54)	0•303	0•48 (0•18, 1•36)	0•132
Low influenza activity			0•20 (0•05, 0•89)	0•035	0•20 (0•04, 0•87)	0•032
High influenza activity						
SGA§	83 /608 (13•6)	61/599 (10•1)	0•77 (0•55, 1•09)	0•152	0•84 (0•58, 1•20)	0•346
1st trimester			1•15 (0•71, 1•86)	0•549	1•22 (0•74, 2•02)	0•347
2nd trimester			0•79 (0•42, 1•49)	0•476	0•79 (0•41, 1•50)	0•483
3rd trimester			0•57 (0•36, 0•89)	0•014	0•61 (0•38, 0•98)	0•044
Low influenza activity			0•88 (0•59, 1•32)	0•596	0•92 (0•61, 1•39)	0•708
High influenza activity			0•60 (0•37, 0•95)	0•030	0•65 (0•40, 1•04)	0•079

CI=confidence interval. HR=hazard ratios. LBW=low birthweight. SGA=small for gestational age.

* HR results compared outcome variable in vaccinated group to reference (unvaccinated).

† Adjustments were made for maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery.

‡ Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of having a preterm birth.

§ Additionally adjusted for infant's sex.

‖ Low birthweight at term (<2500 g and ≥ 37 completed weeks' gestation at birth).

¶ Analysis by trimester of influenza vaccination was not performed because a small number of mothers who delivered LBW at term babies received the vaccine prior to their third trimester (n = 1 during 1st trimester, n = 1 during 2nd trimester).

circulation to influenza-vaccinated women. We also found that vaccinated mothers were less likely to deliver LBW and SGA infants during periods of high influenza activity. Decreased risk for LBW and SGA during peak influenza season amongst vaccinated mothers could be attributed to decreased risk of influenza infection during pregnancy following maternal influenza vaccination. Differing from our study

Table 4
Pregnancy and birth outcomes following influenza vaccination in pregnancy at two obstetric hospitals in South Australia 2015−2018.

Pregnancy outcomes	Total	Unvaccinated N (%)	Vaccinated N (%)	Risk Ratios RR (95% CI)	p-value	Adjusted* aRR (95% CI)	p-value
Chorioamnionitis and/or funisitis	25/1207 (2•0)	15/608 (2•4)	10/599 (1•6)	0•65 (0•28, 1•49)	0•316	0•78 (0•32, 1•88)	0•581
Postpartum haemorrhage	113/1205 (9•3)	62/606 (10•2)	51/599 (8•5)	0•79 (0•55, 1•14)	0•215	0•72 (0•49, 1•06)	0•099
Caesarean delivery (Vs Vaginal)†	349/1205 (28•9)	176/606 (29•0)	173/599 (28•8)	1•01 (0•93, 1•08)	0•758	0•91 (0•75, 1•09)	0•326
Birth outcomes							
Congenital anomalies‡	23/1207 (1•9)	21/1066 (1•8)	2/141 (1•4)	0•31 (0•04, 2•33)	0•256	0•33 (0•04, 2•73)	0•311
Low Apgar at 1 min (<7)	151/1201 (12•5)	72/603 (11•9)	79/598 (13•2)	1•13 (0•83, 1•53)	0•433	1•11 (0•81, 1•52)	0•490
Low Apgar at 5-min (<7)	31/1203 (2•5)	16/604 (2•6)	15/599 (2•5)	0•93 (0•44, 1•97)	0•874	0•84 (0•39, 1•81)	0•670
Admitted to Neonatal unit§	282/1207 (23•3)	140/608 (23•0)	142/599 (23•7)	0•98 (0•80, 1•22)	0•780	1•04 (0•84, 1•28)	0•693
Respiratory distress syndrome	14/1207 (1•1)	10/608 (1•6)	4/599 (0•6)	0•40 (0•12, 1•26)	0•120	0•46 (0•14, 1•52)	0•208
Mechanical ventilation	51/1207 (4•2)	30/608 (4•9)	21/599 (3•5)	0•72 (0•41, 1•26)	0•258	0•74 (0•42, 1•31)	0•313

* Pregnancy outcomes were adjusted for maternal age, ethnicity, total years of full time education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery• Birth outcomes were additionally adjusted for infant's sex.

† Poisson regression model was used because the log binomial model failed to converge.

‡ For congenital anomalies analysis, the exposure time window comprised the first trimester and women vaccinated after first trimester were classified as unvaccinated.

§ Reasons for admission: Preterm, Respiratory distress Infection, Feeding problem, Hypoglycaemia, Drug withdrawal, SGA, Birth asphyxia, congenital abnormality, Phototherapy and Cyanosis.

findings, a secondary analysis of the RCT in Nepal [24], which was the only trial powered to detect difference in birth weight has found that maternal influenza vaccination significantly increased mean birthweight by 42 g. Birth weight is an important indicator of an infant's vulnerability to the risk of childhood illness and chances of survival and the health burden of babies born SGA or LBW is very high in low income countries [25]. Reduction of these adverse birth outcomes following maternal influenza vaccination would be an important achievement, particularly in tropical regions, where influenza circulates year-round.

Consistent with previous studies, [26, 27] we demonstrated that newborns whose mothers were vaccinated for influenza in pregnancy were not more likely to experience any adverse outcomes, including admission to the neonatal care unit, respiratory distress, low Apgar scores nor need for mechanical ventilation at birth compared with neonates born to unvaccinated women. A protective effect of maternal influenza vaccination on preventing either influenza or influenza-related complications in infants up to 6 months old [28, 29] provides important additional evidence that women should be offered influenza vaccination during pregnancy, irrespective of time of year.

Our study has a number of strengths and some potential limitations. The major strength is the prospective cohort design that recruited a large number of nulliparous women with singleton pregnancies at low risk for obstetric complications at two major maternity hospitals, reducing potential confounding by indication. Such bias could have occurred if women with known comorbidities and/or high-risk factors were more likely to receive the influenza vaccine during pregnancy and have a higher baseline risk of adverse pregnancy outcomes than healthy women leading to an underestimation of vaccine safety. The opposite effect (i.e. an overestimate of the size of the protective effect of maternal vaccination) due to a 'healthy vaccinee bias' could also have occurred. Vaccinated women in our study were more likely to engage in healthy lifestyles i.e. pregnancy micronutrient supplementation, exercise regularly and were less likely to smoke or use illicit drugs in pregnancy than unvaccinated women. The analysis framework used herein adjusted for putative risk factors, including psychosocial factors, to mitigate the impact of any 'healthy vaccinee bias' on our findings.

Our use of Cox proportional-hazards models accounting for time-varying vaccine exposure within pregnancy, minimized the introduction of immortal time bias in our data [30]. The potential for this bias arises because the opportunity for vaccination increases the longer a woman remains pregnant and free of adverse foetal outcomes. The fact that the pregnancies were not followed from the beginning (i.e. first day of the last menstrual period), causes downward bias in estimation of spontaneous abortion. Such data are said to be left truncated. Additionally, including follow-up time during which pregnancies are no longer at risk of some adverse outcomes (e.g. gestation after 37 weeks' considered for preterm birth outcomes) can lead to overestimation of any true benefits of maternal vaccination but our analysis strategy minimized the risk of these biases occurring. One potential limitation that we could not take into account is that vaccine administered in non-traditional settings (i.e. pharmacist or community or workplace-administered vaccination) might not be recorded in women's Pregnancy-Hand-Held-Records. Thus, uptake of vaccination during pregnancy may have been underestimated. However, this is unlikely as women were interviewed by a research midwife at several time points including post-delivery to confirm final vaccination status. Another limitation in our study is the inability to distinguish pre-delivery hospital admission due to laboratory-confirmed influenza infections from influenza-like illness. However, these limitations are likely to have negligible effects on our study findings.

Evidence from previous influenza pandemics, and seasonal influenza demonstrates that pregnant women and their infants are at high risk of severe influenza-related complications [1, 2]. Our robust study analysis demonstrated that maternal influenza vaccination reduced pregnant women's risk of pre-delivery hospitalisation with influenza like illness. Furthermore, our study provides a unique prospective assessment of the safety of an inactivated influenza vaccine amongst pregnant women providing reassurance for health providers and pregnant women. Importantly, although numerous factors may contribute, we show positive impacts on key birth outcomes that inordinately occur in low-middle income countries with long term consequences for offspring health and impacts on low capacity health systems.

Data statement

The datasets generated and/or analysed during the current study are available upon reasonable request to Prof. Claire Roberts (claire.roberts@adelaide.edu.au) and subject to regulatory approvals.

Declaration of Competing Interest

HSM has been an investigator on clinical trials funded by pharmaceutical companies including Pfizer, GSK Sanofi-Pasteur, Novartis. Her institution receives funding for Investigator led research. HSM receives no personal payments from Industry. The remaining authors have no conflicts of interest to declare.

Funding

No funding source directly supported the work in this manuscript.

Acknowledgments

The STOP Study was funded by a University of Adelaide Grant awarded to CTR. CTR was supported by a Lloyd Cox Professorial Research Fellowship from the University of Adelaide and is currently supported by an Australian National Health and Medical Research Council (NHMRC) Investigator Grant (GNT1174971) and a Matthew Flinders Fellowship from Flinders University.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100522.

References

[1] Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. Vaccine 2017;35(4):521–8.
[2] Creanga AA, Johnson TF, Graitcer SB, Hartman LK, Al-Samarrai T, Schwarz AG, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol 2010;115(4):717–26.
[3] McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol 2011;204(6 Suppl 1):S54–7.
[4] Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012;207(3):S3–8.
[5] Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis 1993;168(3):647–56.
[6] Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359(15):1555–64.
[7] Steinhoff MC, Omer SB, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ 2012;184(6):645–53.
[8] McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine 2015;33(18):2108–17.
[9] Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother 2019;15(3):687–99.

[10] Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: a systematic review and Bayesian meta-analysis. PLoS ONE 2019;14(8) e0220910-e.
[11] Fell DB, Platt RW, Lanes A, Wilson K, Kaufman JS, Basso O, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG 2015;122(1):17–26.
[12] 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):1104–14.
[13] Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: a systematic review and Bayesian meta-analysis. PLoS ONE 2019;14(8):e0220910.
[14] Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - a systematic review. Vaccine 2014;32(36):4602–13.
[15] Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: a literature review. Vaccine 2015;33(47):6420–9.
[16] Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev 2007;65(12 Pt 2):S194–202.
[17] The Communicable Disease Control Branch (CDCB). Influenza in South Australia: surveillance of notifiable conditions2020.
[18] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
[19] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
[20] Regan AK, Klerk N, 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.
[21] Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010-2016. Clin Infect Dis 2019;68(9):1444–53.
[22] Madhi SA, Nunes MC, Cutland CL. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(24):2340.
[23] Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. The Lancet Infectious Diseases 2017;17(9):981–9.
[24] Kozuki N, Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, et al. Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal. Int J Gynaecol Obstet 2018;140(1):65–72.
[25] Lee ACC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health 2013;1(1):e26–36.
[26] Zerbo O, Modaressi S, Chan B, Goddard K, Lewis N, Bok K, et al. No association between influenza vaccination during pregnancy and adverse birth outcomes. Vaccine 2017;35(24):3186–90.
[27] 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):709–17.
[28] Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359(15):1555–64.
[29] Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Arch Pediatr Adolesc Med 2011;165(2):104–11.
[30] Hutcheon JA, Savitz DA. Invited commentary: influenza, influenza immunization, and pregnancy-it's about time. Am J Epidemiol 2016;184(3):187–91.

Chapter 7: Safety of Maternal Pertussis Vaccination on Pregnancy and Birth outcomes: A Prospective Cohort Study

7.1 Publication

Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Verburg PE, Dekker G, Marshall HS. Safety of maternal pertussis vaccination on pregnancy and birth outcomes: A prospective cohort study. Vaccine. 2021; 39(2):324-31.

Statement of Authorship

Title of Paper	Safety of maternal pertussis vaccination on pregnancy and birth outcomes: A prospective cohort study.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Verburg PE, Dekker GA, Marshall HS. Safety of maternal pertussis vaccination on pregnancy and birth outcomes: A prospective cohort study. Under review in Vaccine.

Principal Author

Name of Principal Author (Candidate)	Hassen Mohammed		
Contribution to the Paper	Conceived and designed the study, performed data analysis and interpreted data, prepared the first and final draft of the manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Prof. Claire Roberts		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	Dr Luke Grzeskowiak		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	16/9/20

Name of Co-Author	A/Prof Lynne Giles		
Contribution to the Paper	Contributed to the design of the study, supervised development of work, provided methodological guidance and reviewed and edited the manuscript		
Signature		Date	16/9/20
Name of Co-Author	Dr Petra Verburg		
Contribution to the Paper	Reviewed and edited the manuscript		
Signature		Date	17/09/2020

Name of Co-Author	Prof Gustaaf Dekker		
Contribution to the Paper	Reviewed and edited the manuscript		
Signature		Date	17/09/2020
Name of Co-Author	Prof Helen Marshall		
Contribution to the Paper	Conceived and designed the study, supervised development of work, reviewed and edited the manuscript		
Signature		Date	15/09/2020

Vaccine 39 (2021) 324–331

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety of maternal pertussis vaccination on pregnancy and birth outcomes: A prospective cohort study

Hassen Mohammed [a,b], Claire T Roberts [b,c], Luke E Grzeskowiak [b,d], Lynne C Giles [b,e], Petra E Verburg [b], Gustaaf Dekker [f,b], Helen S Marshall [a,b,*]

[a] Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, Adelaide, South Australia, Australia
[b] Robinson Research Institute, Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia
[c] Flinders Health and Medical Research Institute, Flinders University, Bedford Park, South Australia, Australia
[d] SA Pharmacy, Flinders Medical Centre, SA Health, Bedford Park, Adelaide, Australia
[e] School of Public Health, The University of Adelaide, Adelaide, South Australia, Australia
[f] Women's and Children's Division, Lyell McEwin Hospital, Elizabeth Vale, South Australia, Australia

ARTICLE INFO

Article history:
Received 14 September 2020
Received in revised form 18 November 2020
Accepted 20 November 2020
Available online 19 December 2020

Keywords:
Maternal vaccination
Pertussis
Tdap
Safety
Pregnant women
Infants

ABSTRACT

Objective: To evaluate the safety of maternal pertussis vaccination on pregnancy and birth outcomes.
Methods: The study population comprised 1272 healthy nulliparous pregnant women who participated in Screening Tests to identify poor Outcomes in Pregnancy (STOP) study at two obstetric hospitals in South Australia between 2015 and 2018. Participants were followed prospectively, with vaccination (confirmed by medical records), extensive amounts of pregnancy and birth outcome data collected by research midwives. Adjusted relative risks (aRRs) and hazard ratios (aHRs) were estimated accounting for time-varying vaccine exposure and the temporal nature of each outcome.
Results: Of the 1272 women included in this study, 80.1% (n = 1019) received maternal pertussis vaccination. Vaccinated women had an average 0.22 weeks (95% CI 0.001, 0.44) longer gestation at delivery compared to unvaccinated women. Maternal pertussis vaccination was not associated with chorioamnionitis (aRR 0.71, 95% CI 0.27,1.82), gestational hypertension (aHR 1.24, 95% CI, 0.66, 2.30), preeclampsia (aHR 0.75, 95% CI 0.47, 1.18) nor preterm birth (aHR 0.99, 95% CI 0.47, 2.07). Neither risk of low birth weight (aHR 0.72, 95% CI 0.41, 1.27) nor small for gestational age infants (aHR 0.67,95% CI 0.29, 1.55) were increased following maternal pertussis vaccination. No associations between pertussis vaccination during pregnancy and adverse birth outcomes including admission to the neonatal care unit, low Apgar scores, and mechanical ventilation were observed. Results were not materially changed after adjustment for maternal influenza vaccination.
Conclusion: Our study provides reassuring evidence of the safety of maternal pertussis vaccination with no increased risk of adverse pregnancy and birth outcomes. These findings support recommendations for pertussis vaccination during pregnancy to prevent morbidity and mortality associated with early-infant pertussis disease.

1. Introduction

There has been a global resurgence in pertussis in recent years, with the highest rates of hospitalization and death in infants too young to be fully protected by routine childhood vaccination series [1–3]. Infection of young infants occurs primarily through household contacts, with new mothers identified as the most common sources of transmission [4]. Pertussis vaccination during pregnancy protects the mother from pertussis infection but more importantly offers passive immunity to her newborn via transplacental transport of maternal antibodies and is currently considered the most successful and effective intervention to prevent early infant disease [5]. Maternal pertussis vaccination at least seven days before delivery has been shown to protect against pertussis in up to 91% of infants in the first two months of life [6,7]. Following the implementation of government funded maternal pertussis vaccination

* Corresponding author at: Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, 72 King William Road, North Adelaide 5006, South Australia, Australia.
E-mail addresses: hassen.mohammed@adelaide.edu.au (H. Mohammed), claire.roberts@adelaide.edu.au (C.T Roberts), luke.grzeskowiak@adelaide.edu.au (L.E Grzeskowiak), lynne.giles@adelaide.edu.au (L.C Giles), petra.verburg@adelaide.edu.au (P.E Verburg), gustaaf.dekker@adelaide.edu.au (G. Dekker), helen.marshall@adelaide.edu.au (H.S Marshall).

https://doi.org/10.1016/j.vaccine.2020.11.052
0264-410X/

programs for pregnant women in different countries there has been an increasing general pertussis vaccine uptake in pregnancy [8]. However, uptake varies across and within countries in pregnant women and is suboptimal [8]. One of the reasons for low pertussis vaccination uptake is healthcare providers' and/or women's concerns about the safety of the vaccine during pregnancy [9,10].

Several systematic reviews [11–14] have demonstrated that maternal pertussis vaccination during pregnancy does not adversely affect obstetric or neonatal outcomes, although the quality of the evidence in underlying studies is low. Many previous studies have investigated the safety of pertussis vaccination during pregnancy retrospectively, due to the relatively cheaper cost, fewer ethical concerns, and difficulty in recruiting pregnant women to randomized controlled trials. Three retrospective cohort studies [15–17] reported a small but statistically significant increased relative risk of chorioamnionitis in women who had received pertussis vaccination during pregnancy. This unreplicated finding merits further investigation since chorioamnionitis is associated with severe short-term and long-term neonatal complications [18]. Most observational studies have been unable to account for the time-dependent nature of exposure to pertussis vaccination during pregnancy. To accurately determine any risk of maternal pertussis vaccination for pregnant women and their infants, prospectively designed studies incorporating statistical approaches suitable for analyzing time-dependent associations between maternal pertussis vaccine exposure on pregnancy and birth outcomes are warranted. The primary aim was to prospectively assess pregnancy and birth outcomes following pertussis vaccination during pregnancy considering time-dependent vaccine exposure and using the most comprehensive set of potential confounding variables considered to date.

2. Materials and methods

2.1. Study design and participants

The current study draws on data collected as part of a prospective cohort study (STOP), which aims to develop screening tests to identify adverse pregnancy outcomes. Healthy nulliparous pregnant women were recruited at two major maternity hospitals, the Lyell McEwin Hospital, the tertiary hospital serving a lower socio-economic community in Adelaide's Northern suburbs and the Women's and Children's Hospital, the primary tertiary maternity hospital for complex care in metropolitan Adelaide, South Australia. Between March 2015 and December 2017, nulliparous women with a singleton pregnancy attending their first antenatal clinic between 9^{+0} and 16^{+0} weeks' gestation were enrolled as part of the prospective cohort study described elsewhere [19–21]. Women were excluded if they were considered already at high risk of pregnancy complications at screening (i.e. experienced three or more previous miscarriages or with pre-existing hypertension or diabetes). Participants were followed prospectively, with vaccination, pregnancy, and birth outcome data collected by research midwives. As pertussis vaccination was recommended to be administered between 28 and 32 weeks' gestation, we restricted the analyses to data from women whose pregnancies reached at least 32 weeks' gestation to allow all women to have had the opportunity to receive the pertussis vaccine.

2.2. Exposure

The exposure of interest was pertussis-containing vaccine (tetanus-diphtheria-acellular pertussis: dTpa). A research midwife interviewed and collected maternal vaccination status of the women during their study visit interview at 32–36 weeks' gestation. Maternal vaccination date and gestation at administration were recorded. Following delivery, a research midwife verified final vaccination status by reviewing Pregnancy-Hand-Held-Records and interviewing women. Pregnancy-Hand-Held-Records are the primary medical record of pregnancy care in South Australia.

2.3. Outcomes

Pregnancy outcomes assessed were gestational hypertension (GH), preeclampsia (PE), chorioamnionitis and/or funisitis, pre-delivery hospitalisation due to acute respiratory infections or influenza-like illness, premature rupture of membranes (PPROM), placental abruption, spontaneous preterm birth (sPTB) and preterm birth (PTB). Birth outcomes included small for gestational age (SGA), low birthweight (<2500 g) (LBW), LBW at term (≥37 weeks' gestation), Apgar scores at 1 and 5 min, neonatal care unit admissions, respiratory distress and mechanical ventilation.

Pregnancy and birth complications were diagnosed using the Brighton Collaboration consensus list of terms [22] and the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project [23]. GH was defined as hypertension [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] after 20 weeks of gestation in previously normotensive women. PE was defined as GH with proteinuria (24 h urinary protein ≥ 300 mg or spot urine protein: creatinine ratio ≥ 30 mg/mmol creatinine or urine dipstick protein ≥ 2 +) or any multi-organ complication of PE, including SGA age infant. Suspected Chorioamnionitis was considered to be present only with a physician's diagnosis, which was dependent on maternal fever ≥ 38 °C, with at least two of the following: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odour of amniotic fluid, or maternal leucocytosis or increased CRP. Funisitis is a histopathologic diagnosis, and it is the extension of infection or inflammation to the umbilical cord. Preterm birth (PTB) was defined as any birth after 20^{+0} and before 37^{+0} weeks of gestation. SGA was defined as neonates with a birthweight < 10th percentile customized for maternal factors including maternal height, booking weight, ethnicity and gestational age at delivery. The estimated date of delivery was calculated from a certain last menstrual period (LMP) date and was only adjusted if either (1) a scan performed at < 16 weeks of gestation found a difference of ≥ 7 days between the scan gestation and that calculated by the LMP or (2) on 20-week scan a difference of ≥ 10 days was found between the scan gestation and that calculated from the LMP. If the LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery.

2.4. Covariates

During the first study visit at 9–16 weeks' gestation, information was obtained regarding baseline socio-demographic, lifestyle and clinical characteristics including age, ethnicity, level of education, household income, employment, exercise, smoking, supplement use, intake of alcohol and recreational drugs, medical and obstetric history, and complications during the current pregnancy. Participants also completed questionnaires assessing stress levels in the past month (Perceived Stress Scale (PSS-10)) [24], current anxiety symptoms (short form of the Spielberger State–Trait Anxiety Inventory (STAI)) [25] and depressive symptoms during pregnancy (Edinburgh Postnatal Depression Scale (EPDS)) [26].

2.5. Statistical analysis

Demographic, lifestyle and clinical characteristics of participants were summarized descriptively by pertussis vaccination

exposure during pregnancy. Continuous variables were summarized as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate, while counts and percentages were used to summarize categorical variables. To assess if there was an association between maternal pertussis vaccination status and each of the outcome variables, we initially conducted independent samples t-tests and Mann-Whitney U tests, as appropriate, for continuous variables and chi-square tests of association for binary and categorical variables.

The timing for vaccination exposures and time-at-risk windows were calculated for each time-sensitive pregnancy and birth outcome, accounting for the temporal nature of each outcome of interest. For instance, women were at risk for PTB from 20^{+0} until 36^{+6} weeks of gestation but had to attain at least 32 weeks' gestation for inclusion in the analysis data set. Cox proportional-hazards models with gestational age in weeks as the underlying time metric were used to derive hazard ratios (HRs) that compared the hazard rates between vaccinated and unvaccinated women for time-sensitive outcomes. Vaccination status was treated as a time-varying exposure in these models, in that each vaccinated woman's pregnancy was divided into unvaccinated and vaccinated exposure periods. Thus, a woman who did not receive the vaccine during pregnancy was classified into the unvaccinated group in any risk set, whereas a woman who received the vaccine at some point during her pregnancy was initially classified as unvaccinated and then classified as vaccinated from the time at vaccination onwards.

We used log-binomial models to estimate risk ratios (RR) and adjusted risk ratios (aRR) comparing the risk of late onset or early postpartum adverse pregnancy outcomes and time-independent birth outcomes between vaccinated and unvaccinated mothers. A multivariable linear regression model was applied to compare the difference in mean gestational age at delivery and mean birthweight by maternal pertussis vaccination status. For all multivariable models, age, level of education, ethnicity, gravidity, annual household income, alcohol intake, recreational drug use, smoking, pre-pregnancy body mass index (BMI), use of micronutrient supplements, asthma, assisted reproductive treatment and current psychological states were amongst the variables selected as potential confounders based on evidence in the literature [11–14] guided by directed acyclic graphs. Sensitivity analyses were conducted in all multivariable models to evaluate whether the effects of maternal pertussis vaccination on pregnancy and birth outcomes were maintained after adjustment for receipt of maternal influenza vaccination. The overall missing covariate data at baseline was < 5% and therefore all available data were used in the analyses of all pre-specified outcomes. For all analyses, p values < 0.05 were considered statistically significant. We did not correct for multiple comparisons to minimize the risk of Type II errors. Data were recorded in a REDCap [27,28] online database and all statistical analyses were conducted using Stata version 15. Written informed consent was obtained from all women. Personal identifying information in the study database was eliminated to ensure that confi-

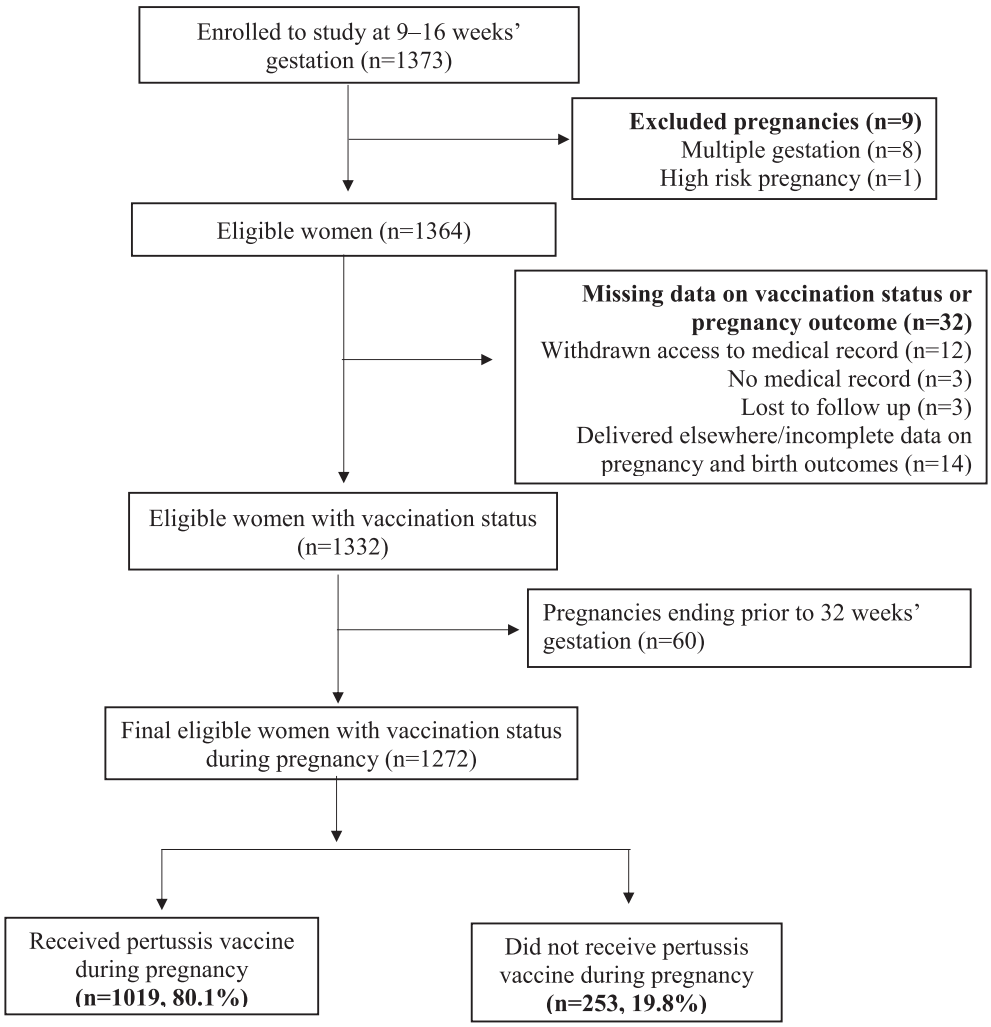


Fig.1. Participants flow diagram.

Table 1
Maternal characteristics of vaccinated and unvaccinated pregnant women who delivered at two obstetric hospitals in South Australia, 2015 to 2018 (N = 1272).

Variable	Vaccinated women N = 1019, n (%)	Unvaccinated women N = 253, n (%)
Maternal age (years)		
15–19	85 (8.3)	44 (17.3)
20–24	289 (28.3)	97 (38.3)
25–29	390 (38.2)	68 (26.8)
>30	255 (25.0)	44 (17.3)
Maternal age, mean (SD)	26.2 ± 4.9	24.5 ± 4.9
Race/ethnicity		
Caucasian	850 (83.4)	204 (80.6)
Aboriginal/TSI	15 (1.4)	8 (3.1)
Others	154 (15.1)	41 (16.2)
Household annual income in AUD		
<40,000	212 (20.8)	81 (32.0)
40,001–70,000	221 (21.6)	62 (24.5)
70,001–105,000	283 (27.7)	44 (17.3)
>105,001	293 (28.7)	61 (24.1)
Missing	10 (0.9)	5 (1.9)
Maternal education		
≤ Secondary school qualification	436 (42.7)	119 (47.0)
Diploma/certificate	365 (35.8)	90 (35.5)
Bachelor's or higher degree	216 (21.2)	42 (16.6)
Missing	2 (0.2)	2 (0.7)
Total years of formal education, mean (SD)	13.4 ± 2.4	13.0 ± 2.6
Moderate exercise during 1st trimester/pre-pregnancy		
≥ 4 per week	126 (12.3)	22 (8.7)
1–3 per week	493 (48.3)	118 (46.6)
Never	393 (38.5)	110 (43.4)
Missing	7 (0.6)	3 (1.1)
Gravidity > 1	296 (29.0)	57(22.5)
Asthma	146 (14.3)	31 (12.5)
Assisted reproductive technology (IVF)	60 (5.8)	10 (3.9)
Pre-pregnancy BMI (kg/m2)		
<18.5 (Under)	16 (1.5)	9 (3.5)
18.5–24 (Normal)	389 (38.1)	110 (43.4)
25–29.9 (Overweight)	274 (26.8)	81 (32.0)
≥ 30 (Obese)	340 (33.3)	53 (20.9)
Pre-pregnancy BMI (kg/m2), mean (SD)	28.2 ± 7.1	26.7 ± 6.7
Smoking status at 9–16 weeks' gestation		
Current smoker	87 (8.5)	34 (13.4)
Quit during pregnancy	112 (10.9)	25 (9.8)
Non-smoker	815 (79.9)	192 (75.8)
Missing	5 (0.4)	2 (0.7)
Illicit drug use during 1st trimester/pre-pregnancy	51 (5.0)	26 (10.2)
Multivitamin and mineral supplements use		
Pre-conception and 1st trimester	248 (24.3)	37 (14.6)
1st trimester	548 (53.7)	133 (52.5)
None	217 (21.3)	82 (32.4)
Missing	6 (0.5)	1 (0.4)
Psychological measures at 9–16 weeks' gestation		
Edinburgh Perinatal Depression Scale (EPDS) scores, mean (SD)	5.3 ± 4.8	5.7 ± 4.5
State and trait anxiety (STAI) scores, mean (SD)	33.2 ± 11.2	33.8 ± 11.0
Perceived stress scale (PSS) scores, mean (SD	12.9 ± 6.5	13.5 ± 6.4
Missing	30 (2.9)	12 (4.7)
Gestational week of vaccine administration, mean (SD)	30.3 ± 2.8	NA
Gestational week of vaccine administration, median (IQR)	30 (26–34)	NA
Received influenza vaccination during pregnancy	555 (54.4)	42 (16.6)

Data are mean (SD) or n (%)
SD = standard deviations IQR = interquartile range AUD = Australian dollars. BMI = body-mass-index.

dentiality of all patients' records was maintained. The STOP study protocol was approved by the Human Research Committee of the Women's and Children's Hospital Adelaide, Australia (HREC/14/WCHN/90) [19].

3. Results

Of 1364 pregnant women enrolled, 12 withdrew access to their medical records, six were lost to follow up, and 14 delivered elsewhere; all 32 women were excluded from our final analyses. After excluding 60 pregnancies that ended before 32 weeks' gestation, our final cohort consisted of 1272 women (Fig. 1). At enrolment, the mean (SD) maternal age of nulliparous women was 25.9 (4.9) years (range: 15–45 years). A total of 1040 (81.7%) women attended their first antenatal visit in first trimester at a mean gestational age of 11.4 (1.7) weeks.

The uptake of pertussis vaccination was 80.1%. Of the 1019 women who received maternal pertussis vaccination, 77.8% (n = 790) received the pertussis vaccine within the recommended timeframe of 28–32 weeks, 2.7% (n = 28) before 28 weeks (range 12–27 weeks) and 19.4% after 32 weeks' gestation. The mean gestational age at vaccination was 30.3 (2.8) weeks. Both pertussis and influenza vaccinations were administered in 555 of 1272 (43.6%) pregnancies. Those women who did not receive maternal pertussis vaccination were more likely to have no previous history of termination and/or miscarriage, be younger, in the healthy weight range, smoke cigarettes, use illicit drugs, physically inactive, in the lowest household income group, have lower educational attainment and were less likely to take micronutrient supplements preconception or during pregnancy compared with vaccinated pregnant women. Women who received pertussis vaccination were more likely to receive influenza vaccine (Table 1).

Of the 1272 women, 82 had a PTB (6.4%). The mean gestational age at delivery was 39.4 (1.5) weeks. After adjusting for covariates, women who had received pertussis vaccination during pregnancy had on average 0.22 weeks (95% CI 0.001, 0.44) longer gestation at delivery than unvaccinated women (Table 2). The time-dependent Cox proportional hazards regression model shows that receiving pertussis vaccination during pregnancy did not increase the risk of PTB (aHR 0.99, 95% CI 0.47, 2.07), sPTB (aHR 0.99, 95% CI 0.57, 1.70) or PPROM (aHR 1.01, 95% CI 0.52, 1.97) (Table 2). Our time dependent analyses also indicated that there was no increased risk for maternal hypertensive disorders (i.e. GH, PE),

Table 2
Crude and adjusted hazard ratios for time-based pregnancy and birth outcomes by maternal pertussis vaccination status at two obstetric hospitals in South Australia 2015–2018.

Pregnancy outcomes	Total [a]	Unvaccinated N (%)	Vaccinated N (%)	Crude HR [b] (95% CI)	p-value	Adjusted [c] aHR (95% CI)	p-value
Gestational hypertension [d]	86/1267 (6.7)	10/249 (4.0)	76/1018 (7.4)	1.45 (0.79, 2.66)	0.228	1.24 (0.66, 2.30)	0.497
Preeclampsia [d]	116/1268 (9.1)	26/250 (10.4)	90/1018 (8.8)	0.77 (0.49, 1.19)	0.246	0.75 (0.47, 1.18)	0.220
Pre-delivery hospitalization due to influenza like illness [e]	94/1272 (7.3)	24/253 (9.4)	70/1019 (6.8)	0.75 (0.47, 1.21)	0.245	0.84 (0.51, 1.36)	0.488
Preterm premature rupture of the membranes [f]	42/1272 (3.3)	12/263(4.7)	30/1019 (2.9)	0.83 (0.41, 1.69)	0.616	0.99 (0.47, 2.07)	0.987
Preterm birth [f]	82/1272 (6.4)	21/253 (8.3)	61/1019 (5.9)	0.95 (0.56, 1.60)	0.852	0.99 (0.57, 1.70)	0.984
Spontaneous preterm birth [f]	51/1272 (4.0)	14/253 (5.5)	37/1019 (3.6)	0.87 (0.46, 1.67)	0.693	1.01 (0.52, 1.97)	0.961
Birth outcomes							
LBW (<2500 g)	71/1268 (5.6)	21/250 (8.4)	50/1018 (4.9)	0.69 (0. 40, 1.19)	0.189	0.72 (0.41, 1.27)	0.261
LBW at term (<2500 g) [g]	31/1186 (2.6)	8/229 (3.4)	23/957 (2.4)	0.64 (0.28, 1.46)	0.299	0.67 (0.29, 1.55)	0.361
SGA	150/1266 (11.8)	36/249(14.4)	114/1017 (11.2)	0.77 (0.52, 1.15)	0.211	0.80 (0.53, 1.20)	0.295
				Difference in means (vaccinated - unvaccinated)		Difference in adjusted means (vaccinated -unvaccinated)	
Mean birth weight, grams (95% CI)	3368.0 ± 496.2	3313 ± 565.3	3381.2 ± 477.5	68.0 (-3.0, 139.1)	0.061	44.6 (-26.0, 115.3)	0.216
Mean gestational age at delivery, weeks (95% CI)	39.4 ± 1.5	39.2 ± 1.7	39.4 ± 1.4	0.23 (0.01, 0.44)	0.038	0.22 (0.001, 0.44)	0.048

CI, confidence interval; HR, hazard ratios; LBW, low birthweight; SGA, small for gestational age
a: Denominators differ due to missing data.
b: HR results compared outcome variable in vaccinated group to reference (unvaccinated).
c: Adjustments were made for maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, estimated season of delivery, Edinburgh Postnatal. Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, and asthma. Birth outcomes were additionally adjusted for infant's sex.
d: For hypertensive disorders analysis, women who were vaccinated at or after the gestational age at diagnosis were censored
e: Women admitted to hospital with respiratory tract infection/influenza-like illness were censored at their admission date
f: Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of preterm birth.
g: Low birthweight at term (<2500 g and $\geq$ 37 completed weeks' gestation at birth).

Table 3
Pregnancy and birth outcomes following pertussis vaccination during pregnancy at two obstetric hospitals in South Australia 2015–2018.

Pregnancy outcomes	Total [a]	Unvaccinated N (%)	Vaccinated N (%)	Risk Ratios RR (95% CI)	p-value	Adjusted [b] aRR (95% CI)	p-value
Chorioamnionitis and/or funisitis	23/1272 (1.8)	7/253 (2.7)	16/1019 (1.5)	0.52 (0.21, 1.26)	0.149	0.71 (0.27, 1.82)	0.481
Placental abruption	32/1266 (3.3)	7/250 (2.8)	25/1016 (2.4)	0.90 (0.37, 2.20)	0.833	1.04 (0.41, 2.62)	0.923
Postpartum haemorrhage	115/1269 (9.0)	26/251 (10.3)	89/1018 (8.7)	0.85 (0.55, 1.31)	0.475	0.81 (0.52, 1.26)	0.357
Birth outcomes							
Apgar at 1 min < 7	149/1263 (11.8)	30/247 (12.1)	119/1016 (11.7)	0.91 (0.62, 1.34)	0.646	0.87 (0.59, 1.29)	0.496
Apgar at 5- min < 7	26/1265 (2.0)	6/248 (2.4)	20/1017 (1.9)	0.84 (0.31, 2.25)	0.738	0.75 (0.27, 2.06)	0.582
Admitted to Neonatal unit [c]	285/1272 (22.4)	65/253 (25.6)	220/1019 (21.5)	0.81 (0.64, 1.04)	0.115	0.84 (0.66, 1.07)	0.177
Respiratory distress syndrome	10/1272 (0.7)	3/253 (1.1)	7/1019 (0.6)	0.56 (0.14, 2.16)	0.406	0.61 (0.20, 1.82)	0.384
Mechanical ventilation	42/1272 (3.3)	9/253 (3.5)	33/1019 (3.2)	0.78 (0.38, 1.63)	0.526	0.71 (0.34, 1.50)	0.381

a: Denominators differ due to missing data.
b: Pregnancy outcomes were adjusted for maternal age, ethnicity, total years of full-time education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment and asthma. Birth outcomes were additionally adjusted for infant's sex.
c: Reasons for admission: preterm, respiratory distress infection, feeding problem, hypoglycaemia, drug withdrawal, SGA, birth asphyxia, congenital abnormality, phototherapy and cyanosis.

or hospitalisation with acute respiratory/influenza-like illness among vaccinated women compared with unvaccinated women (Table 2). In log-binomial models, maternal pertussis vaccination was not associated with chorioamnionitis, placental abruption, or postpartum hemorrhage (Table 3).

Of all 1272 births included in this study, 1269 (99.7%) were live births and three (0.2%) were stillbirths at term. The majority of infants (93.5%, n = 1190) were born at term. The mean birthweight of the infants was 3368 g. In the multivariable linear regression model, infants born to vaccinated mothers were on average 44.6 g heavier than infants born to unvaccinated mothers but the confidence intervals were wide (95% CI −26.0 g, 115.3 g) (Table 2). All birth outcomes had an adjusted relative risk of less than one, although all confidence intervals were wide (Table 2 & 3).

The time-dependent Cox proportional hazards regression models demonstrate that receiving pertussis vaccination during pregnancy was not associated with increased risk of delivering LBW infants (aHR 0.72, 95% CI 0.41, 1.27), LBW at term infants (aHR 0.67, 95% CI 0.29, 1.55) or SGA infants (aHR 0.80, 95% CI 0.53, 1.20) (Table 2). Our log-binomial models also suggest there was no increased risk of other adverse perinatal outcomes including Apgar scores < 7 at one and five minutes, admission to the neonatal care unit, mechanical ventilation, and respiratory distress syndrome following pertussis vaccination during pregnancy (Table 3). Adjustment for influenza vaccination did not appreciably change any of the findings (Table S1 & S2).

4. Discussion

This study provided a unique prospective assessment of accurate pregnancy and infant data with confirmed maternal vaccination status. The analytical framework treated pertussis vaccination as a time-varying exposure and computed time at risk windows for each of the time sensitive outcomes of interest and adjusted for a comprehensive set of confounding factors to reaffirm that maternal pertussis vaccination is safe for both the mothers and their newborn infants.

Our Cox proportional hazards models accounting for the time-dependent nature of exposure to vaccination during pregnancy, thereby avoiding the introduction of immortal time bias to our analyses, found no association between maternal pertussis vaccination and PTB, sPTB, nor PPROM, reaffirming the conclusion from previous systematic reviews [11–14].

In keeping with previous studies [11,12], our findings demonstrated no association between maternal pertussis vaccination and gestational hypertensive disorders. The new Australian guidelines recommend pregnant women to receive a pertussis vaccine from 20 weeks of gestation rather than 28 weeks' to maximize the opportunity for vaccination to protect all infants, including preterm infants [29]. Administration of maternal pertussis vaccination from 20 weeks' can align with other key routine antenatal visits such as morphology scanning and gestational diabetes testing, potentially improving the uptake of pertussis vaccination among pregnant women. However, there is a need for continued surveillance and monitoring to confirm that a broader window for pertussis vaccination during pregnancy is safe for the pregnant mother and the newborn.

Our study demonstrates that maternal pertussis vaccination was not associated with chorioamnionitis. In contrast, three large retrospective studies [15–17] conducted in the USA showed receipt of pertussis vaccination during pregnancy was associated with a small but significant increase in risk of developing chorioamnionitis. These studies [15–17] used commercial health data and ICD codes for identifying chorioamnionitis from electronic medical records with no clinical case definition. Coding for commercial reasons, such as insurance claims, is potentially subject to favoring more severe diagnoses and might be prone to poor external validity, selection bias, confounding and misclassification bias [30]. Furthermore, these studies did not find an association with an increased risk of PTB, which is an expected major clinical sequel of chorioamnionitis and most women with chorioamnionitis had at least one pre-existing risk factor for this complication. This suggests the observed relation between receipt of pertussis vaccination during pregnancy and chorioamnionitis was unlikely to be casual, and is probably more reflective of residual confounding affecting the results in these studies.

In our study, we found an association between maternal pertussis vaccination during pregnancy and longer gestation. There are no known biologically plausible direct effects of pertussis vaccination on pregnancy duration but women who remained pregnant longer have more opportunity to have received pertussis vaccine in the late third trimester of pregnancy. This may have created a spurious relationship between pregnancy duration and time-varying pertussis vaccine exposure during pregnancy because linear regression analysis is not suited to include both the event and time aspects in the model.

Our study provides further assurance that pertussis vaccination during pregnancy is not associated with any adverse birth outcomes including LBW or SGA births, consistent with previous findings [11–14]. Receipt of pertussis vaccination during pregnancy was not associated with increased risk of perinatal outcomes including admission to the neonatal care unit, respiratory distress, Apgar scores < 7 nor need for mechanical ventilation at

birth compared with infants born to unvaccinated women [11–14].

The major strength of this study is the prospective cohort design that recruited a large number of nulliparous women with singleton pregnancies at low risk for obstetric complications at two major maternity hospitals. Vaccinated women in our study were more likely to engage in healthy lifestyles i.e. pregnancy micronutrient supplementation, regular exercise, non-smoking than unvaccinated women. The analysis framework used herein adjusted for putative risk factors, including psychosocial factors, to mitigate the impact of any 'healthy vaccinee bias' on our findings. However, we cannot rule out the possibility of residual confounding. Our use of Cox proportional-hazards models accounting for time-varying vaccine exposure during pregnancy minimized the introduction of immortal time bias in our data. The potential for this bias arises because the opportunity for vaccination increases the longer a woman remains pregnant [31]. Furthermore, many studies use the earliest recommended maternal pertussis vaccination time (i.e. 28 weeks' gestation in this case) as a cut-off point to restrict their data but pregnancies must survive within the recommended timeframe (i.e. 28–32 weeks' gestation) to be eligible to receive the vaccines. Hence, immortal time bias may also be present in studies of maternal pertussis vaccination evaluating adverse pregnancy outcomes that develop in mid-to-late pregnancy, including PE and GH, where the bias may attenuate the true relative risk. Our analytic approach used 32 instead of 28 weeks' gestation as the cut-off point in order to allow all women to have had the chance to receive the recommended pertussis vaccination in that optimal 4-week window. This may have reduced the introduction of immortal time bias in our analyses. Additionally, including follow-up time during which pregnancies are no longer at risk of some adverse outcomes (e.g. gestation after 37 weeks considered for PTB outcomes) can lead to incorrect estimation of the effect of maternal vaccination on the outcome of interest but our time-to-event analytic approach minimized the risk of these biases occurring. Another major strength of our study is confirmed maternal vaccination status. As this study was a secondary analysis, we did not conduct an *a priori* power analysis to show sample size adequacy. A post-hoc power analysis was not conducted as there is a rich literature, in both medical and statistical journals, warning against post-hoc power calculations [32,33]. However, the cohort was originally powered on the basis of 25% of women affected by pregnancy complications (PE, SGA and sPTB) [19]. The recruitment of only healthy nulliparous women limits the generalizability of the study findings to women with high-risk pregnancies or multiparous women.

5. Conclusions

The present study offers a unique prospective and robust assessment of the safety of pertussis vaccination during pregnancy and provides reaffirming evidence of the safety of maternal pertussis vaccination for both mothers and their infants. Evidence presented in our study provide further reassurance to expecting women and healthcare providers about the safety of pertussis vaccination during pregnancy and supports recommendations for pertussis vaccination during pregnancy to prevent morbidity and mortality associated with early-infant pertussis disease. The study findings also aid evidence-based decision making for clinicians and policy makers in countries considering implementation of universal maternal pertussis immunization programs.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contribution to authorship

HM, CTR, LEG, LCG and HSM have all contributed to the planning and design of the study, and to the interpretations of the data. HM performed data analyses and prepared the first and final drafts of the manuscript. GD and PV have critically revised the manuscript. All named authors were involved in critically reviewing the content, and have approved the final version for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are available upon reasonable request to Prof. Claire Roberts (claire.roberts@adelaide.edu.au) and subject to regulatory approvals.

CRediT authorship contribution statement

Hassen Mohammed: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Claire T Roberts:** Conceptualization, Supervision, Writing - review & editing. **Luke E Grzeskowiak:** Conceptualization, Supervision, Writing - review & editing. **Lynne C Giles:** Methodology, Supervision, Writing - review & editing. **Petra E Verburg:** Writing - review & editing. **Gustaaf Dekker:** Writing - review & editing. **Helen S Marshall:** Conceptualization, Supervision, Writing - review & editing.

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.

Acknowledgments

The STOP Study was funded by a University of Adelaide Grant awarded to CTR. CTR was supported by a Lloyd Cox Professorial Research Fellowship from the University of Adelaide and is currently supported by an Australian National Health and Medical Research Council (NHMRC) Investigator Grant (GNT1174971) and a Matthew Flinders Fellowship from Flinders University. LEG is supported by a Mid-Career Fellowship from The Hospital Research Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.11.052.

References

[1] Munoz FM. Pertussis in infants, children, and adolescents: diagnosis, treatment, and prevention. Semin Pediatr Infect Dis. 2006;17(1):14–9.
[2] Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. Pediatrics 2008;121(3):484–92.
[3] Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995–2005–trends by region and age group. Communicable diseases intelligence quarterly report. 2007;31(2):205–15.
[4] Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013;31(4):618–25.
[5] Amirthalingam G. Strategies to control pertussis in infants. Arch Dis Child. 2013;98(7):552–5.
[6] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014;384(9953):1521–8.
[7] Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics 2017;139(5).
[8] Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS ONE 2019;14(3):e0214538.
[9] Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015;33(47):6420–9.

[10] MacDougall DM, Halperin SA. Improving rates of maternal immunization: Challenges and opportunities. Hum Vaccin Immunother. 2016;12(4):857–65.
[11] Furuta M, Sin J, Ng ESW, Wang K. Efficacy and safety of pertussis vaccination for pregnant women - a systematic review of randomised controlled trials and observational studies. BMC Pregnancy Childbirth. 2017;17(1):390-..
[12] McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129(3):560–73.
[13] Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis. 2020;20(1):136.
[14] D'Heilly C, Switzer C, Macina D. Safety of Maternal Immunization Against Pertussis: A Systematic Review. Infectious Diseases and Therapy. 2019;8(4):543–68.
[15] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA 2014;312(18):1897–904.
[16] Layton JB, Butler AM, Li D, Boggess KA, Weber DJ, McGrath LJ, et al. Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine. 2017;35(33):4072–8.
[17] DeSilva M, Vazquez-Benitez G, Nordin JD, Lipkind HS, Klein NP, Cheetham TC, et al. Maternal Tdap vaccination and risk of infant morbidity. Vaccine. 2017;35(29):3655–60.
[18] Johnson CT, Farzin A, Burd I. Current management and long-term outcomes following chorioamnionitis. Obstet Gynecol Clin North Am. 2014;41(4):649–69.
[19] Australian New Zealand Clinical Trials Registry.ACTRN12614000985684. Screening Tests to identify poor Outcomes in Pregnancy (STOP) Study 2014 [cited 01/09/2020. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366996.
[20] Mohammed H, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, et al. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study. Vaccine. 2020;38(17):3358–68.
[21] Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. EClinicalMedicine. 2020;26:100522.
[22] Munoz FM, Eckert LO, Katz MA, Lambach P, Ortiz JR, Bauwens J, et al. Key terms for the assessment of the safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions. Vaccine. 2015;33(47):6441–52.
[23] Jones CE, Munoz FM, Kochhar S, Vergnano S, Cutland CL, Steinhoff M, et al. Guidance for the collection of case report form variables to assess safety in clinical trials of vaccines in pregnancy. Vaccine. 2016;34(49):6007–14.
[24] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385–96.
[25] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(Pt 3):301–6.
[26] Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782–6.
[27] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
[28] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
[29] The Australian Government Department of Health and Ageing. Australian Technical Advisory Group on Immunisation Canberra2019.
[30] Hyman J. The limitations of using insurance data for research. J Am Dent Assoc. 2015;146(5):283–5.
[31] Hutcheon JA, Savitz DA. Invited Commentary: Influenza, Influenza Immunization, and Pregnancy-It's About Time. Am J Epidemiol. 2016;184(3):187–91.
[32] Senn SJ. Power is indeed irrelevant in interpreting completed studies. BMJ (Clinical research ed). 2002;325(7375):1304-.
[33] Hoenig JM, Heisey DM. The Abuse of Power. The American Statistician. 2001;55(1):19–24.

Chapter 8: Discussion, Future directions and Conclusion

The overall aims of this thesis were to provide i) evidence on the safety and protective effects of seasonal influenza and pertussis during pregnancy ii) to determine psychosocial factors influencing uptake of maternal vaccination and iii) to identify strategies that were effective in improving uptake of pertussis vaccines during pregnancy. In this final chapter, the main findings of the thesis are summarised, and originality and significance of the thesis findings are discussed. The strengths and limitations of the thesis are outlined and implications of the findings are described. Finally, potential areas for future research directions are suggested and a concluding remark is provided.

8.1 Summary of Key Findings of the Thesis

Interventions to improve uptake of maternal pertussis vaccination

The systematic review (Chapter 4) collected and summarised the available evidence on the effectiveness of interventions used to increase maternal pertussis vaccination among pregnant women. Implementation of automated electronic reminders for healthcare providers to vaccinate pregnant women at the point of antenatal care and a standing order, allow midwives to administer maternal vaccination without the need for a prescription from a medical doctor at the place of antenatal service. These were found to be effective strategies in increasing pertussis vaccine uptake among pregnant women. Educational interventions targeting pregnant women alone were not an effective strategy for increasing uptake of maternal pertussis vaccination. However, the review highlighted the need for well-designed educational interventions for pregnant women that are used alongside other interventions emphasising the role of maternal pertussis vaccination in mitigating the burden of pertussis infections in young infants. Furthermore, the review suggested cognisance of psychological and social factors in

relation to maternal vaccine uptake could aid in designing robust maternal immunisation programs.

Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women

This study (Chapter 5) extends our understanding of the role of psychosocial factors in influencing vaccine decision making during pregnancy. Using a prospective cohort study of nulliparous women at two obstetric hospitals in South Australia, we found overall, 48% and 79% of the women received seasonal influenza and pertussis vaccines respectively. Irrespective of psychosocial status, most women were willing to receive the recommended vaccinations during pregnancy. Conversely, the actual receipt of pertussis and influenza vaccines among pregnant women was influenced by psychosocial factors. Interestingly, a history of severe depression that required antidepressant medication was the strongest independent predictor of pertussis and influenza vaccine uptake during pregnancy. Moreover, screening positive for antenatal depression was associated with receipt of pertussis vaccine during pregnancy.

Based on The Edinburgh Postnatal Depression Scale (EPDS) score, pregnant women with elevated depressive scores at their first antenatal visit were referred to a GP for further assessment and interventions. Frequent encounters with a GP or mental health midwife services might have provided better opportunities for women with depressive symptoms to receive the recommended vaccinations during pregnancy. In contrast, women with high-perceived stress in the antenatal period were significantly less likely to receive maternal pertussis vaccination. This finding aligned with the research hypothesis that non-adherence to maternal healthy behaviours such as vaccine refusal during pregnancy is influenced by high level of stress during pregnancy. However, unlike the EPDS, the Perceived Stress Scale (PSS) as a tool to measure perception of stress during pregnancy does not have clinical cut-off values for appropriate referral pathways. Nevertheless, the findings of the thesis highlight that a strong patient-

healthcare provider interaction is an important determinant of uptake of the recommended vaccines during pregnancy. Addressing healthcare provider–patient barriers and examining the influence of antenatal psychological stressors on maternal vaccine decision making is crucial in improving vaccine uptake among pregnant women.

In the context of engaging in risky maternal health behaviours, uptake of pertussis and influenza vaccines during pregnancy were lower for smokers and illicit drug users; the differences were not statistically significant in the final adjusted model, but the disparity needs to be further studied, as they are a high-risk group for severe respiratory diseases. Furthermore, women who never exercise or who did not take multivitamins or supplements in the preconception or antenatal period were less likely to receive pertussis or influenza vaccination during pregnancy. Less engagement in periconceptional health-promoting behaviours or unplanned pregnancies were correlated with suboptimal uptake of the vaccines during pregnancy. Maternal vaccination information should be provided to women presenting in pre-pregnancy counselling to improve the uptake of the recommended vaccines during pregnancy.

Receipt of maternal pertussis vaccine was lower among Indigenous women and those born overseas, although the difference was not statistically significant. More research is needed to understand and reduce this disparity. Educational materials on maternal vaccinations should be easily readable and accessible to culturally and linguistically diverse women in different languages. There is a need to deliver culturally appropriate interventions to Indigenous women within Aboriginal health services. Other sociodemographic determinants such as younger maternal age and unemployment status were significantly associated with low pertussis and influenza vaccination uptake during pregnancy. Understanding the role of psychosocial factors in relation to vaccination receipt during pregnancy is crucial in designing effective interventions and implementing maternal pertussis and influenza vaccination programs.

Safety and benefits of seasonal influenza vaccination during pregnancy

The findings of our cohort study provided evidence of the safety and benefits of seasonal influenza vaccination during pregnancy in healthy nulliparous women. In robust nuanced analyses that accounted for time-varying maternal vaccine exposure and time at risk windows for each of the time sensitive pregnancy and birth outcomes, maternal influenza vaccination was demonstrated to be safe for both mothers and their newborn infants. The study findings reaffirm the evidence of no increased risk of spontaneous abortion, congenital anomalies, gestational diabetes, gestational hypertensive disorders, and preterm birth following seasonal influenza vaccination during pregnancy.

Newborns whose mothers received seasonal influenza vaccine in pregnancy were not more likely to experience any adverse perinatal outcomes. Most importantly, maternal seasonal influenza vaccination reduced the risk of hospitalisation for respiratory diseases during pregnancy by 39%. Furthermore, women who received seasonal influenza vaccines during pregnancy had a reduced risk of delivering low birthweight and small for gestational age infants during periods of widespread influenza activity.

Safety of pertussis vaccination during pregnancy

Additionally, in the prospective cohort of healthy pregnant women with confirmed vaccination status and accurate pregnancy and infant outcome data, we demonstrated maternal pertussis vaccination is safe for both the mother and newborn infant (Chapter 7). The study provided further reassurance that pertussis vaccination during pregnancy is not associated with increased risk of chorioamnionitis, gestational hypertensive disorders or preterm birth. Further, no increased risk was observed for adverse neonatal health outcomes including, small for gestational birth, low birth weight, admission to the neonatal care unit, respiratory distress, low Apgar scores and need for neonatal mechanical ventilation.

8.2 Originality and Significance of the Thesis

This thesis has many original contributions and significance. The systematic review was the first peer-reviewed protocol registered in the international prospective register of systematic reviews in February 2017 (PROSPERO, ID CRD42017058178) to summarise the evidence for effectiveness of interventions used to improve maternal pertussis vaccination coverage. The review solely focused on strategies to improve uptake of maternal pertussis vaccination to make recommendations in a global context considering the increasing implementation of antenatal pertussis vaccine programs around the world. Currently more than 40 countries including middle-income countries recommended pertussis vaccination for pregnant women (340).

Furthermore, the recommendations in the review considered the diversity of maternity care settings and antenatal vaccination service models available in different countries. For instance, the suggestion of incorporating a reminder in medical records to prompt healthcare providers to offer maternal vaccination could be either electronic alerts or paper medical records/case note reminders depending on the type and variability of maternity services nationally and internationally. Moreover, the recommendation of standing orders for midwives discussing and offering pertussis vaccination to pregnant women at the place of antenatal service could be applicable but not limited to countries where maternity settings have well-functioning midwifery programs. Midwife delivered immunisation programs for pregnant women could be feasible in low resource setting countries as there are on-going mechanisms to improve quality of midwifery care and to reduce maternal and neonatal mortality (341). The review is also unique in strengthening the generalisability and practicality of the findings by classifying interventions into three distinct groups: provider-focused interventions, pregnant women focused interventions and interventions to enhance access to maternal vaccination. Moreover, the absolute benefit increase (ABI) was computed to describe the standardised effect sizes of each intervention, thereby enhancing comparability between interventions of different studies.

This thesis was the first to explore a range of psychosocial factors including psychological, social, individual health-related behaviours, cognitive and emotional or mental wellbeing status in the perinatal period, in relation to willingness and uptake of pertussis and influenza vaccine among pregnant women. The thesis showed the decisions to receive the recommended pertussis and influenza vaccinations are complex, and influenced by many clinical and psychosocial factors. Importantly, this thesis is original in addressing whether experiencing psychological distress such as depression, anxiety, and/or perceived stress during pregnancy influence acceptance and uptake of maternal vaccinations. These psychosocial factors provide a number of targets for improving maternal immunisation programs and should be considered in the design of effective strategies or interventions in improving uptake of pertussis and influenza vaccines during pregnancy. Existing or new theoretical models should consider these psychosocial factors to better address inconsistencies in uptake of maternal vaccinations.

Additionally, the psychosocial factors explored in this thesis can help determine the focus and content of patient centered educational materials on maternal vaccination and can be utilized to explain how interventions work to facilitate decision-making processes around maternal vaccination uptake. This thesis is unique in not only examining a wide range of psychosocial factors in relation to uptake of vaccines during pregnancy but also including extensive antenatal psychological stressors as potential cofounders in evaluating the effects of maternal influenza and pertussis vaccination. Previous studies have demonstrated that the presence of psychosocial morbidity, particularly high levels of anxiety, depression and stress in pregnancy can adversely impact fetal development and lead to increased risk of intra-uterine growth restriction, preterm birth and delivering low birth weight infants (342, 343). Thus, the thesis employed the most comprehensive and accurate set of potential confounding factors to date, which are rarely included in maternal vaccination studies.

This thesis provided a unique prospective evaluation of the safety and protective effects of seasonal influenza and pertussis vaccination during pregnancy among healthy nulliparous women, with confirmed vaccination status and accurate pregnancy and infant outcome data using robust nuanced time-to-event analyses. This thesis is also original in presenting nuanced evidence that seasonal influenza vaccination is effective in reducing the risk of maternal hospitalisations with influenza-like illness by stratifying influenza activity according to the local laboratory confirmed influenza rate in South Australia during the study period as opposed to stratifying by typical influenza seasons in Australia (April/May through September). This analytical approach was extended to demonstrate the protective effects of maternal seasonal influenza vaccination on birth outcomes such as low birth weight and small for gestational age birth during peak influenza activity after controlling for the most comprehensive set of potential confounding factors and concurrent or sequential pertussis vaccine exposure during pregnancy as an effect modifier time varying covariate. Furthermore, this thesis investigated the protective effects of seasonal influenza vaccine on key birth outcomes by trimester of vaccine administration.

The work in this thesis was the first prospective cohort in the Southern Hemisphere to demonstrate that influenza vaccination is strongly associated with reduced risk of admission to hospital with influenza-like illness among pregnant women using a robust nuanced time to event analytical approach with confirmed maternal vaccination status. Although no clear trend of association by trimester of influenza vaccination administration on birth outcomes was observed, a protective effect of influenza vaccination on small for gestational age births was most pronounced in the third trimester. A subsequent analysis of the RCT in Nepal (344) demonstrated the protective effect of maternal influenza vaccination on birth weight, and small for gestational age birth was the strongest among pregnant women who were exposed to widespread influenza virus circulation during the third trimester. Although this thesis could not

identify an ideal time for maternal influenza vaccination in improving birth outcomes, it has highlighted the importance of accounting for level of influenza activity in relation to the stage of pregnancy.

The findings of this thesis are also distinctive in affirming safety of pertussis vaccination using a prospective cohort study with a large volume of accurate pregnancy and birth data, confirmed maternal vaccination exposure and analysed using a rigorous time dependent analysis. Moreover, the research is original in computing time at risk windows for each of the time sensitive outcomes of interest and adjusting for a comprehensive set of confounding factors to each outcome.

8.3 Strengths and Limitations of the Thesis

Strengths

This thesis has a number of strengths. Systematic reviews are a robust methodology for assessing interventions. The systematic review emphasised the role of patient-provider interactions in improving maternal vaccination uptake, and highlighted the knowledge gap in psychological and social factors influencing women's decisions to receive vaccines during pregnancy. These findings provided important conceptual understanding and aided the interpretation of psychosocial factors in predicting the uptake of maternal pertussis and influenza vaccines in the context of patient-provider interaction. Psychosocial determinants of maternal vaccination uptake were then used as potential confounding factors in evaluating the effect of maternal influenza and pertussis vaccines on pregnancy and birth outcomes. The analysis framework used in this thesis, herein adjusted for putative risk factors, including social and antenatal psychological risk factors, such as stress, anxiety and depression to reduce the impact of any 'healthy vaccinee bias' or confounding by indication bias on the findings.

The data presented in Chapters 5, 6 and 7 were sourced from the Screening Tests to predict poor Outcomes of Pregnancy (STOP) study. The STOP study aimed to validate algorithms to predict the risk of pregnancy complications as early as at the 12th week of gestation. Given the nature of predictive research, this comprehensive set of fine-grained prospectively routinely collected variables in the cohort was its distinctive strength. The prospective character of this multi-center observational cohort study and the collection of comprehensive baseline information made it the ideal cohort to conduct a high-quality prospective study on the safety and predictors of uptake the recommended vaccines during pregnancy. Other major strengths of the cohort approach included i) early pregnancy recruitment of a well-defined population of healthy nulliparous women with singleton pregnancies at low risk for obstetric complications, ii) first trimester screening tests to assess the health of the pregnant women and their fetus, iii) monitoring of the women throughout their pregnancy iv) strict diagnostic criteria for key pregnancy and birth complications and v) confirmed maternal vaccination. This enabled the thesis to provide a high level of evidence internationally on the safety and impact of influenza and pertussis vaccines for mothers and their newborn infants.

Additionally, the high quality of ultrasound measurement in determination of an accurate gestational age and expected date of delivery enabled this body of work to conduct robust nuanced time-to-event analyses in evaluating the effect of maternal influenza and pertussis vaccines, thereby avoiding critical time related biases. Furthermore, almost 8 out 10 women in the study cohort were recruited in the first trimester of pregnancy, which allowed assessment of the effect of first trimester influenza vaccination on early pregnancy outcomes such as spontaneous abortion and congenital anomaly. This was important considering the lack of robust evidence from prospective studies on safety of maternal influenza vaccine in early pregnancy and reluctance of pregnant women receiving the influenza vaccine in first trimester due to perceived safety concerns. Another strength of the cohort is the inclusion of any birth

(live or fetal death) reducing selection bias as most observational studies into maternal vaccine uptake and safety only include those women who delivered a live infant, which excludes women who had either a stillbirth, miscarriage, or late spontaneous abortion.

Another strength of the research presented in this thesis is the robust analytical framework applied in determining psychosocial predictors of maternal vaccination receipt in Chapter 5. The natural logarithm of the total time of a pregnancy in gestational weeks was included in the final adjusted model as an offset term to account for the shorter window of opportunity some women (i.e. women who had miscarriages or terminations) had to receive the vaccine. Moreover, the study cohort contains details of antenatal visits as well as information on pre-conception/early pregnancy lifestyle, psychological status and intention to receive maternal vaccines. This aided the study in Chapter 5 in identifying psychosocial predictors of maternal vaccination uptake as well as willingness to receive the recommended vaccines during pregnancy. Furthermore, the study was able to examine whether willingness to receive the recommended maternal vaccine is a good predictor of actual vaccination receipt during pregnancy.

Limitations

Although the limitations of each study are detailed in the respective chapters, some of the overall major limitations are summarised below. The use of secondary data sources for the three quantitative studies (Chapters 5, 6 and 7) meant the analysis was reliant on the variables collected through the cohort. Whilst the cohort included rich accurate data on pregnancy and birth outcomes, other factors that may be important for examining psychosocial predictors of maternal vaccination uptake might have been omitted. Information regarding the level of English proficiency, primary language, migration status (recent migrants, settled migrants) and requirement for interpreters during antenatal care are not available in the cohort, which may

have been important variables in assessing factors related to maternal vaccine uptake among culturally and linguistically diverse (CALD) women. There was also limited information collected in the study cohort regarding mothers' perceptions of pertussis and influenza as vaccine-preventable diseases in terms of perceived susceptibility, severity, benefits and knowledge of maternal vaccines. Furthermore, willingness to receive the recommended vaccines was not asked separately for pertussis and influenza vaccine. Previous research indicated that most women perceive influenza as a disease affecting the mother, whereas they perceive pertussis as a threat to the new born infant and thus relatively more risky (265). This has been suggested as one of the reasons for the relatively higher maternal pertussis vaccine rate compared to that for influenza.

Another potential limitation of studies in Chapters 6 and 7 is the prospective cohort study was not designed or powered to specifically evaluate the safety of maternal vaccination. The secondary data analysis of study cohort with a modest size (n=1364), yielded power to compare common adverse pregnancy and birth outcomes in vaccinated and unvaccinated pregnancies. This study was originally powered on the basis of 25% of women likely affected by pregnancy complications (preeclampsia, small for gestational age birth, spontaneous preterm birth and gestational diabetes mellitus). However, the studies in Chapters 6 and 7 are possibly underpowered to investigate the effect of maternal seasonal influenza and pertussis vaccination on rare outcomes such congenital anomalies. Post-hoc power calculation was not presented as there is a rich literature, in both medical and statistical journals, warning against post-hoc power calculations (338, 339).

In the study cohort, the gestational age at enrollment ranged from 6 to 16 weeks and the median gestational age at enrollment was 11 weeks. The fact that the pregnancies were not followed from the beginning (i.e., gestational age zero, first day of the last menstrual period), causes downward bias in estimation of early pregnancy outcomes including spontaneous abortion (left

truncated data). The studies in Chapters 6 and 7 used Cox proportional-hazards models to properly estimate the event rates by including a woman in the risk sets at the time points after she enrolled in the study. Another potential limitation that we could not take into account is that maternal vaccine administered in non-traditional settings (i.e. pharmacist or community health clinics or workplace-administered vaccination) might not be recorded in the South Australian Pregnancy Record (SAPR). Although it is possible that some women were misclassified as unvaccinated if they failed to report being vaccinated, the direct method of interviewing the mother about their maternal vaccination status (including gestational timing of vaccination) by a research midwife at several time points including after delivery suggests this would be unlikely to occur. Additionally, maternal immunisations were confirmed in the majority of cases.

Although seasonal influenza activity and vaccine effectiveness can differ from year to year, the study in Chapter 6 was unable to perform sub analyses of season-by-season estimates for all pregnancy and birth endpoints due to the modest sample size. However, the findings are generalizable, as the study and analyses were not restricted to one influenza season which could have introduced bias. Given the variation in antigenic match between the circulating viruses and the strains included in the annual seasonal vaccine (166), further studies with larger datasets are warranted to evaluate the effect of seasonal maternal influenza vaccine annually.

Another limitation of the thesis is inability to measure pre-delivery hospitalisations with laboratory confirmed influenza as an outcome and the unavailability of data on influenza illness or hospitalisations among newborns. Further studies with larger numbers of women and infants are needed to confirm effectiveness of influenza vaccination during pregnancy in reducing laboratory confirmed influenza infections or related hospitalisation in both the mother and her newborn infant. However, one of the challenges with conducting large population-based maternal vaccination studies in Australia is the lack of a coordinated national system for

routinely monitoring and recording antenatal vaccination coverage (52, 53, 345). Pregnancy status is not collected to the Australian Immunisation Register (AIR), making it challenging to ascertain maternal immunisation status using AIR alone (346). Western Australia, Queensland and the Northern Territory have introduced routine collection of maternal vaccination records via either state-based immunisation registers or through perinatal data collections. A large, population based, multi-jurisdictional cohort of mother-infant pairs is established to measure the uptake, safety and effectiveness of maternal influenza and pertussis vaccines in these three Australian states (346).

8.4 Research Implications

The findings of the studies in this thesis have a number of implications for public health practice and maternal vaccination programs. The results from the systematic review have reinforced the important role that healthcare providers play in driving vaccination uptake among pregnant women. In countries where routine maternal vaccination is implemented, policy makers and program managers for vaccination and antenatal care programs should consider strategies for alerting healthcare providers to target unvaccinated pregnant women and offering them the recommended vaccination during pregnancy. Incorporating an automated reminder within electronic medical records or medical case note reminders in an antenatal care setting may encourage healthcare provider–patient discussions on the safety, effectiveness and importance of the routinely recommended vaccines during pregnancy.

Furthermore, the use of provider reminders or an alert system would facilitate antenatal care providers to administer the vaccine at a moment when the pregnant women can act immediately with a minimum of additional time, effort or cost. Provider reminder or alert system to prompt healthcare providers could be implemented on the GP, obstetrics and antenatal shared care system considering the structural difference in pathways for pregnancy care in each country.

Systemic changes are required to incorporate alerts or reminders in medical records in combined settings for successful maternal vaccination programs.

The review findings also suggest that provision of maternal vaccination by midwives at the place of antenatal service is another effective strategy that can be considered by regional, national and international antenatal health policy makers for improving the success of maternal vaccination programs. The midwife vaccine delivery program is a relatively low-cost intervention and can also be feasible in low resource settings where well-functioning midwifery programs are incorporated. Training and equipping midwives with knowledge and skills to engage with pregnant women on the topic of the recommended maternal vaccinations and allowing them to administer the routinely recommended vaccinations to pregnant women using a standing medication order, without the requirement for a prescription from a medical doctor should be considered. Importantly, maternal vaccination programs should incorporate the recommended vaccines during pregnancy, as part of standard antenatal care.

The findings of this thesis can be utilized in developing a toolkit to assist healthcare providers with managing rollout and implementation of maternal vaccination program. The SKAI (Sharing Knowledge About Immunising) is a communication tool developed to improve communication during primary health care consultations about routine childhood vaccinations (347). The SKAI communication tool involves assessing parental attitudes and beliefs about vaccines and selecting information and communication strategies tailored to address parents' vaccine questions and concerns (347). A similar communication tools could be designed to address pregnant women’s concerns about vaccine safety during pregnancy. Additionally, there is a need for high-quality educational interventions targeting pregnant women and highlighting the safety and benefits of pertussis as well as influenza vaccination during pregnancy. High quality educational materials should be provided in a range of formats including posters, leaflets, videos and web-based maternal vaccination information. Educational materials should

be tailored to different vulnerable high-risk groups, particularly to Indigenous. Interventions designed to enhance maternal vaccination uptake among Indigenous women should be inclusive of Aboriginal healthcare workers as the primary healthcare providers in delivering information and offering the recommended maternal vaccines.

Findings described in this thesis demonstrated that most expectant mothers are willing to receive the recommended vaccination regardless of their antenatal psychosocial profile. However, psychosocial factors influenced the uptake of maternal vaccines highlighting the need to address healthcare provider–patient barriers and emphasising the role of provider cognisance of psychosocial factors in improving maternal vaccination rates. Mental health midwives or nurses are well positioned to recommend vaccines to pregnant women while undertaking psychosocial assessment. Additionally, the findings of this thesis could aid the implementation of maternal vaccination programs and development of tailored interventions for women with psychological stressors in the antenatal period. Providing education to pregnant women is not enough, a combination of approaches is required.

Evidence presented in the thesis provides further reassurance to expecting mothers and healthcare providers about the safety of pertussis vaccination during pregnancy and supports recommendations for pertussis vaccination during pregnancy to prevent morbidity and mortality associated with early-infant pertussis disease. The thesis findings also aid evidence-based decision making for national immunisation program managers and policy-makers in countries considering implementation of universal maternal pertussis programs.

Other important public health implications of the thesis findings are further evidence for the safety and benefits of maternal seasonal influenza vaccination that can be used to communicate to pregnant women, antenatal care providers, and community members. In addition to providing reassurance to pregnant women and healthcare providers about the safety of seasonal

influenza vaccination during pregnancy, the thesis findings reaffirmed the vaccine effectiveness in reducing pre-delivery hospitalisations with influenza like illness. As protecting vulnerable newborn infants against infection is the driving factor for mothers to receive a vaccine during pregnancy, evidence from this thesis on the potential protective effects of maternal influenza vaccination in reducing small for gestational age and low birth weight infants could be used in educational materials for pregnant women. In countries where maternal influenza vaccination is recommended, the potential benefits in improving birth outcomes presented in this thesis can be used to encourage healthcare providers to deliver evidence-based information to pregnant women. Furthermore, these findings may aid policy makers and governing bodies in instilling and improving public confidence in maternal influenza vaccination. Importantly, the potential benefits of receiving influenza vaccine during pregnancy in improving neonatal health outcomes can be important for countries weighing up the additional benefits of incorporating maternal influenza vaccination programs. This may be particularly important for low-and middle-income countries where the rates of low birthweight and small for gestational age births occur inordinately, resulting in long term consequences for offspring health and health systems have poor capacity to mitigate short and long-term effects.

8.5 Future Directions

Additional research should focus toward developing effective interventions that target healthcare providers as well as pregnant women to improve maternal pertussis and seasonal influenza uptake. With the potential for more vaccines to be incorporated to the antenatal vaccination programs, it is important to determine factors associated with vaccine decision making during pregnancy and design effective interventions to improve maternal vaccine uptake to ensure optimum protection for pregnant women and their infants.

Respiratory syncytial virus (RSV) (348) and Group B streptococcus (GBS) (349) vaccines are new vaccines in development or currently in clinical trials for pregnant women. A recent large-scale efficacy trial demonstrated that maternal RSV vaccine decreased the risk of hospitalisation with RSV during pregnancy by around 44% and reduced hospitalisation for infants with severe RSV disease by almost 50% (348). However, vaccine efficacy against RSV-associated medically significant lower respiratory tract infection in the first 3 months of life was 39% and did not meet prespecified criteria for vaccine efficacy, warranting further research (348).

The current global coronavirus disease 2019 (COVID-19) pandemic calls for a revisiting of frameworks for the inclusion of pregnant women in the development and deployment of COVID-19 vaccines (350). Pregnant women are not placed among the highest priority groups when COVID-19 vaccines are approved for use. However, mounting evidence suggest pregnant women are at increased risk of respiratory failure with the need for admission to intensive care and mechanical ventilation following confirmed COVID-19 infection compared with non-pregnant women of similar age (351, 352). Additionally, a growing body of evidence suggests women with confirmed COVID-19 in early pregnancy are at increased risk of preterm birth (353) and stillbirth (354). COVID-19 vaccines in pregnancy will be an important consideration for antenatal vaccination programs. The methods established as part of this thesis to provide reassuring evidence on safety and identifying predictors of maternal vaccine uptake could be adopted in future research of potential COVID-19 and other new maternal vaccines.

The new Australian guidelines recommend pregnant women to receive a pertussis vaccine in each pregnancy (including pregnancies that are closely spaced) from 20 weeks of gestation rather than 28 weeks to maximise the opportunity for vaccination to protect all infants, including preterm infants (44). Healthcare providers could use the routine morphology scan at 20 weeks or routine screening for gestational diabetes at 24–28 weeks gestation visit as a

prompt to offer pertussis vaccine or schedule a vaccination visit. A wider opportunity for maternal pertussis vaccination could also potentially increase concomitant administration of influenza vaccine. There is a need for continued surveillance and monitoring to confirm whether a broader window for pertussis vaccination during pregnancy and concomitant administration with influenza vaccination is safe for the mother and the newborn. Additionally, the safety of closely spaced doses in successive pregnancies should be explored. The time-to-event analytic approach used in this thesis could be utilised when conducting future studies on the safety of administrating pertussis vaccine from 20 weeks gestation with seasonal maternal influenza vaccination exposure as a time-dependent covariate.

Currently, seasonal influenza vaccine in Australia is available almost all year round for pregnant women due to the variability of peak influenza activity between years (355). The updated recommendation for pregnant women who received an influenza vaccine in the preceding year is to revaccinate if the influenza vaccine becomes available in the current year before the end of pregnancy (355). Moreover, the current recommendation for women who receive pre-conception influenza vaccine is to revaccinate during pregnancy to protect the unborn infant (355). Ongoing changes to recommendations require monitoring of vaccine safety and effectiveness particularly for receipt of two doses of inactivated influenza vaccine during the same pregnancy, and receipt of influenza vaccination during the preconception period and during pregnancy.

8.6 Concluding Remarks

The body of work provides reassuring evidence on the safety of maternal pertussis and seasonal influenza vaccination for both mothers and their newborn infants. Maternal seasonal influenza vaccination has health benefits to the mother such as a lower risk of hospitalisation with

influenza-like illness. Additionally, this thesis demonstrated potential protective effects of maternal influenza vaccination in improving neonatal health outcomes by modestly reducing the risk of delivering small for gestational age and low birth weight infants during periods of high influenza activity. Results from this thesis have identified a range of psychosocial factors influencing uptake of pertussis and influenza vaccination that can be used in designing and targeting effective interventions. Furthermore, the thesis findings provided evidence-based information for optimising effective communication between healthcare providers and expectant mothers about maternal vaccines. Healthcare provider prompts, incorporation of maternal vaccinations as part of standard antenatal care, and implementation of midwife delivered maternal vaccination programs are the most effective strategies to maximise uptake of pertussis vaccine among pregnant women to mitigate pertussis associated morbidity and mortality in neonates.

References

1. Munoz FM. Pertussis in infants, children, and adolescents: diagnosis, treatment, and prevention. Semin Pediatr Infect Dis. 2006;17(1):14-9.

2. World Health organization. Estimates of disease burden and cost- effectiveness 2015. Accessed: Feb 18, 2019. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/.

3. Greenberg DP, von Konig CH, Heininger U. Health burden of pertussis in infants and children. Pediatr Infect Dis J. 2005;24(5 Suppl):S39-43.

4. World Health Organization. Pertussis vaccines – WHO position paper. Wkly Epidemiol Rec; 2015.

5. Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J. 2003;22(7):628-34.

6. Smith C, Vyas H. Early infantile pertussis; increasingly prevalent and potentially fatal. Eur J Pediatr. 2000;159(12):898-900.

7. Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. Pediatrics. 2008;121(3):484-92.

8. Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995-2005--trends by region and age group. Communicable diseases intelligence quarterly report. 2007;31(2):205-15.

9. Crowcroft N, Andrews N, Rooney C, Brisson M, Miller E. Deaths from pertussis are underestimated in England. Archives of Disease in Childhood. 2002;86(5):336-8.

10. Straney L, Schibler A, Ganeshalingham A, Alexander J, Festa M, Slater A, et al. Burden and Outcomes of Severe Pertussis Infection in Critically Ill Infants. Pediatr Crit Care Med. 2016;17(8):735-42.

11. Pertussis vaccines: WHO position paper--recommendations. Vaccine. 2011;29(13):2355-6.

12. Wood N, Quinn HE, McIntyre P, Elliott E. Pertussis in infants: preventing deaths and hospitalisations in the very young. J Paediatr Child Health. 2008;44(4):161-5.

13. Chuk LM, Lambert SB, May ML, Beard FH, Sloots TP, Selvey CE, et al. Pertussis in infants: how to protect the vulnerable? Communicable diseases intelligence quarterly report. 2008;32(4):449-56.

14. Baptista PN, Magalhaes VS, Rodrigues LC. The role of adults in household outbreaks of pertussis. Int J Infect Dis. 2010;14(2):e111-4.

15. Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013;31(4):618-25.

16. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12(11):1638-43.

17. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol.207(3):S3-S8.

18. Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. Int J Womens Health. 2014;6:681-9.

19. Moniz MH, Beigi RH. Influenza infection during pregnancy: virology, pathogenesis and clinical challenges. Future Virol. 2013;8(1):11-23.

20. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies. Vaccine. 2017;35(4):521-8.

21. Creanga AA, Johnson TF, Graitcer SB, Hartman LK, Al-Samarrai T, Schwarz AG, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol. 2010;115(4):717-26.

22. The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. BMJ. 2010;340:c1279.

23. Wang R, Yan W, Du M, Tao L, Liu J. The effect of influenza virus infection on pregnancy outcomes: A systematic review and meta-analysis of cohort studies. International Journal of Infectious Diseases. 2021;105:567-78.

24. He J, Liu ZW, Lu YP, Li TY, Liang XJ, Arck PC, 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(2):232-43.

25. Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis. 1993;168(3):647-56.

26. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359(15):1555-64.

27. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014;384(9953):1521-8.

28. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics. 2017;139(5).

29. Steinhoff MC, Omer SB, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ. 2012;184(6):645-53.

30. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine. 2015;33(18):2108-17.

31. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother. 2019;15(3):687-99.

32. Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: A systematic review and Bayesian meta-analysis. PLoS One. 2019;14(8):e0220910-e.

33. Fell DB, Platt RW, Lanes A, Wilson K, Kaufman JS, Basso O, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG. 2015;122(1):17-26.

34. 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):1104-14.

35. Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: A systematic review and Bayesian meta-analysis. PLoS One. 2019;14(8):e0220910.

36. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2004;53(RR-6):1-40.

37. World Health Organization. Influenza vaccines. Wkly Epidemiol Rec. 2005;80(33):279-87.

38. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Pregnancy and Influenza Melbourne,Australia2015 [2/06/2016]. Available from: http://www.ranzcog.edu.au/womens-health/resources-for-women-a-practitioners/pregnancy-and-influenza.html.

39. Public Health England. Immunisation against Infectious Disease(The Green Book) 2013 [Available from: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book#the-green-book.

40. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010;59(RR-8):1-62.

41. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR - Morbidity & Mortality Weekly Report. 2013;62(7):131-5.

42. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(41):1424-6.

43. Service NH. Whooping cough vaccination in pregnancy UK.2012. Accessed: Aug 25, 2019. Available from: http://www.nhs.uk/conditions/pregnancy-and-baby/Pages/Whooping-cough-vaccination-pregnant.aspx

44. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian Immunisation Handbook. 10th ed (2015 update). Canberra: Australian Government Department of Health; 2015.

45. Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review. Vaccine. 2018;36(20):2751-9.

46. Healthy People 2020 objectives for influenza vaccination among pregnant women. Healthy People 2020 2019 [Available from: https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives.

47. Laenen J, Roelants M, Devlieger R, Vandermeulen C. Influenza and pertussis vaccination coverage in pregnant women. Vaccine. 2015;33(18):2125-31.

48. Koepke R, Kahn D, Petit AB, Schauer SL, Hopfensperger DJ, Conway JH, et al. Pertussis and Influenza Vaccination Among Insured Pregnant Women - Wisconsin, 2013-2014. MMWR Morb Mortal Wkly Rep. 2015;64(27):746-50.

49. 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(2):56-9.

50. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - a systematic review. Vaccine. 2014;32(36):4602-13.

51. Wong VWY, Lok KYW, Tarrant M. Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: A systematic review. Vaccine. 2016;34(1):20-32.

52. Kong KL, Giles ML, Wallace EM. Influenza and pertussis vaccination of women during pregnancy in Victoria, 2015–2017. Med J Aust. 2019;211(10):474-.e1.

53. McHugh L, Andrews RM, Lambert SB, Viney KA, Wood N, Perrett KP, et al. Birth outcomes for Australian mother-infant pairs who received an influenza vaccine during pregnancy, 2012-2014: The FluMum study. Vaccine. 2017;35(10):1403-9.

54. Deverall EJ, Gilmore B, Illing S, Peiris-John R. Pertussis vaccination uptake in pregnancy: lessons to be learned from an integrated healthcare approach. N Z Med J. 2018;131(1473):42-7.

55. Housey M, Zhang F, Miller C, Lyon-Callo S, McFadden J, Garcia E, et al. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid--Michigan, 2011-2013. MMWR Morb Mortal Wkly Rep. 2014;63(38):839-42.

56. Kahn KE, Black CL, Ding H, Williams WW, Lu PJ, 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.

57. McAuslane H, Utsi L, Wensley A, Coole L. Inequalities in maternal pertussis vaccination uptake: a cross-sectional survey of maternity units. Journal of public health (Oxford, England). 2018;40(1):121-8.

58. Chamberlain AT, Seib K, Ault KA, Rosenberg ES, Frew PM, Cortes M, et al. Impact of a multi-component antenatal vaccine promotion package on improving knowledge, attitudes and beliefs about influenza and Tdap vaccination during pregnancy. Hum Vaccin Immunother. 2016;12(8):2017-24.

59. Mazzoni SE, Brewer SE, Pyrzanowski JL, Durfee MJ, Dickinson LM, Barnard JG, et al. Effect of a multi-modal intervention on immunization rates in obstetrics and gynecology clinics. Am J Obstet Gynecol. 2016;214(5):617 e1-7.

60. Chamberlain AT, Seib K, Ault KA, Rosenberg ES, Frew PM, Cortes M, et al. Improving influenza and Tdap vaccination during pregnancy: A cluster-randomized trial of a multi-component antenatal vaccine promotion package in late influenza season. Vaccine. 2015;33(30):3571-9.

61. Kriss JL, Frew PM, Cortes M, Malik FA, Chamberlain AT, Seib K, et al. Evaluation of two vaccine education interventions to improve pertussis vaccination among pregnant African American women: A randomized controlled trial. Vaccine. 2017;35(11):1551-8.

62. Morgan JL, Baggari SR, Chung W, Ritch J, McIntire DD, Sheffield JS. Association of a Best-Practice Alert and Prenatal Administration With Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination Rates. Obstet Gynecol. 2015;126(2):333-7.

63. Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS One. 2018;13(6):e0197867.

64. Weinstein ND, Kwitel A, McCaul KD, Magnan RE, Gerrard M, Gibbons FX. Risk perceptions: assessment and relationship to influenza vaccination. Health Psychol. 2007;26(2):146-51.

65. Wilcox CR, Calvert A, Metz J, Kilich E, MacLeod R, Beadon K, et al. Determinants of Influenza and Pertussis Vaccination Uptake in Pregnancy: A Multi-Centre Questionnaire Study of Pregnant Women and Healthcare Professionals. Pediatr Infect Dis J. 2018.

66. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015;33(47):6420-9.

67. Yuen CYS, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women – A systematic review. Vaccine. 2014;32(36):4602-13.

68. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015;33(47):6420-9.

69. Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. Vaccine. 2013;31(27):2874-8.

70. MacDougall DM, Halperin BA, Langley JM, McNeil SA, MacKinnon-Cameron D, Li L, et al. Knowledge, attitudes, beliefs, and behaviors of pregnant women approached to participate in a Tdap maternal immunization randomized, controlled trial. Hum Vaccin Immunother. 2016;12(4):879-85.

71. Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev. 2007;65(12 Pt 2):S194-202.

72. Furuta M, Sin J, Ng ESW, Wang K. Efficacy and safety of pertussis vaccination for pregnant women - a systematic review of randomised controlled trials and observational studies. BMC Pregnancy Childbirth. 2017;17(1):390-.

73. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129(3):560-73.

74. Vygen-Bonnet S, Hellenbrand W, Garbe E, von Kries R, Bogdan C, Heininger U, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis. 2020;20(1):136.

75. D'Heilly C, Switzer C, Macina D. Safety of Maternal Immunization Against Pertussis: A Systematic Review. Infectious Diseases and Therapy. 2019;8(4):543-68.

76. Weiss AA, Hewlett EL. Virulence factors of Bordetella pertussis. Annu Rev Microbiol. 1986;40:661-86.

77. Cotter PA, and J. F. Miller. 2001. Bordetella, p. 619-674. In E. A. Groisman (ed.), Principles of bacterial pathogenesis. Academic Press, Ltd., London, United Kingdom,.

78. Hewlett EL. Pertussis: current concepts of pathogenesis and prevention. Pediatr Infect Dis J. 1997;16(4 Suppl):S78-84.

79. Rappuoli R, Podda A, Pizza M, Covacci A, Bartoloni A, de Magistris MT, et al. Progress towards the development of new vaccines against whooping cough. Vaccine. 1992;10(14):1027-32.

80. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005;18(2):326-82.

81. Winter K, Zipprich J, Harriman K, Murray EL, Gornbein J, Hammer SJ, et al. Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study. Clin Infect Dis. 2015;61(7):1099-106.

82. Hewlett EL, Edwards KM. Clinical practice. Pertussis--not just for kids. N Engl J Med. 2005;352(12):1215-22.

83. Cornia PB, Hersh AL, Lipsky BA, Newman TB, Gonzales R. Does this coughing adolescent or adult patient have pertussis? JAMA. 2010;304(8):890-6.

84. Heininger U. Pertussis: what the pediatric infectious disease specialist should know. Pediatr Infect Dis J. 2012;31(1):78-9.

85. WHO. Pertussis surveillance. A global meeting, Geneva, 16-18 October 2000.Available from: https://apps.who.int/iris/handle/10665/66828.

86. Australian Government Department of Health. Australian national notifiable diseases case definitions: Pertussis case definition 2014 [accessed 23 June 2021]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_pertus.htm.

87. Ebell MH, Marchello C, Callahan M. Clinical Diagnosis of Bordetella Pertussis Infection: A Systematic Review. J Am Board Fam Med. 2017;30(3):308-19.

88. Markey K, Douglas-Bardsley A, Asokanathan C, Fry NK, Barkoff AM, Bacci S, et al. Improvement in serological diagnosis of pertussis by external quality assessment. J Med Microbiol. 2019;68(5):741-7.

89. Gabutti G, Rota MC. Pertussis: a review of disease epidemiology worldwide and in Italy. Int J Environ Res Public Health. 2012;9(12):4626-38.

90. Wood N, McIntyre P. Pertussis: review of epidemiology, diagnosis, management and prevention. Paediatr Respir Rev. 2008;9(3):201-11; quiz 11-2.

91. Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection. Pediatrics. 2005;115(5):1422-7.

92. Celentano LP, Massari M, Paramatti D, Salmaso S, Tozzi AE. Resurgence of pertussis in Europe. Pediatr Infect Dis J. 2005;24(9):761-5.

93. Tan T, Dalby T, Forsyth K, Halperin SA, Heininger U, Hozbor D, et al. Pertussis Across the Globe: Recent Epidemiologic Trends From 2000 to 2013. Pediatr Infect Dis J. 2015;34(9):e222-32.

94. Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: a modelling study. Lancet Infect Dis. 2017;17(9):974-80.

95. Centers for Disease Control and Prevention (CDC).Pertussis outbreak trends; 2017; Accessed: May 5, 2020. Available from: http://www.cdc.gov/pertussis/outbreaks/trends.html.

96. Public Health England.Enhanced pertussis surveillance 2013.Accessed: May 5, 2020 Available from:

http://webarchive.nationalarchives.gov.uk/20140714084352/http:/www.hpa.org.uk/hpr/archives/2013/news0513.htm.

97. Masseria C, Martin CK, Krishnarajah G, Becker LK, Buikema A, Tan TQ. Incidence and Burden of Pertussis Among Infants Less Than 1 Year of Age. Pediatr Infect Dis J. 2017;36(3):e54-e61.

98. Public Health England.Laboratory confirmed cases of pertussis reported to the enhanced pertussis surveillance programme in England:annual report for 2016; 2016. Accessed: May 5, 2020. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/602950/hpr1217_prtsss_ann.pdf.

99. World Health Organization.Pertussis 2015 Global estimates. 2017[accessed 01 August 2020]. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/.

100. Li-Kim-Moy J, Yin JK, Patel C, Beard FH, Chiu C, Macartney KK, et al. Australian vaccine preventable disease epidemiological review series: Influenza 2006 to 2015. Communicable diseases intelligence quarterly report. 2016;40(4):E482-E95.

101. Elliott E, McIntyre P, Ridley G, Morris A, Massie J, McEniery J, et al. National study of infants hospitalized with pertussis in the acellular vaccine era. Pediatr Infect Dis J. 2004;23(3):246-52.

102. McIntyre P, Wood N. Pertussis in early infancy: disease burden and preventive strategies. Curr Opin Infect Dis. 2009;22(3):215-23.

103. Hull BP, Dey A, Menzies RI, Brotherton JM, McIntyre PB. Immunisation coverage, 2012. Communicable diseases intelligence quarterly report. 2014;38(3):E208-31.

104. Milton A, Stirzaker S, Trungove M, Knuckey D, Martin N, Hastie C, et al. Australia's notifiable disease status, 2010: annual report of the National Notifiable Diseases Surveillance System. Communicable diseases intelligence quarterly report. 2012;36(1):1-69.

105. National Notifiable Diseases Surveillance System (NNDSS) Annual Report Writing Group. Australia's notifiable disease status, 2011: annual report of the National Notifiable Diseases Surveillance System. Communicable diseases intelligence quarterly report. 2013; 37(4):E313-93.

106. Australia's notifiable disease status, 2011: annual report of the National Notifiable Diseases Surveillance System. Communicable diseases intelligence quarterly report. 2013;37(4):E313-93.

107. Crowcroft NS, Andrews N, Rooney C, Brisson M, Miller E. Deaths from pertussis are underestimated in England. Arch Dis Child. 2002;86(5):336-8.

108. Haberling DL, Holman RC, Paddock CD, Murphy TV. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. Pediatr Infect Dis J. 2009;28(3):194-8.

109. Bozio C, Skoff T, Pondo T, Liang J. Epidemiology and Trends of Pertussis among Infants: United States, 2000–2015. Open Forum Infectious Diseases. 2017;4(Suppl 1):S5-S.

110. The Centers for Disease Control and Prevention (CDC). Pertussis 2019 [Available from: https://www.cdc.gov/pertussis/surv-reporting.html.

111. Centers for Disease Control and Prevention. Pertussis. In: Atkinson W WS, Hamborsky J, editors. Epidemiology and Prevention of Vaccine-Preventable Diseases. 12th ed.Washington, DC: Public Health Foundation; 2012,.

112. Kaczmarek MC, Ware RS, McEniery JA, Coulthard MG, Lambert SB. Epidemiology of pertussis-related paediatric intensive care unit (ICU) admissions in Australia, 1997-2013: an observational study. BMJ open. 2016;6(4):e010386-e.

113. Pillsbury A, Quinn HE, McIntyre PB. Australian vaccine preventable disease epidemiological review series: pertussis, 2006-2012. Communicable diseases intelligence quarterly report. 2014;38(3):E179-94.

114. McHugh L, Viney KA, Andrews RM, Lambert SB. Pertussis epidemiology prior to the introduction of a maternal vaccination program, Queensland Australia. Epidemiol Infect. 2018;146(2):207-17.

115. Naidu L, Chiu C, Habig A, Lowbridge C, Jayasinghe S, Wang H, et al. Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia 2006-2010. Communicable diseases intelligence quarterly report. 2013;37 Suppl:S1-95.

116. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in Pertussis Among Infants in the United States, 1980-1999. JAMA. 2003;290(22):2968-75.

117. World Health Organization. Pertussis vaccines: WHO position paper. Weekly Epidemiological Record. 2010;85(40):385-400.

118. Skoff TH, Cohn AC, Clark TA, Messonnier NE, Martin SW. Early Impact of the US Tdap vaccination program on pertussis trends. Arch Pediatr Adolesc Med. 2012;166(4):344-9.

119. Anderson RM, May RM. Immunisation and herd immunity. Lancet. 1990;335(8690):641-5.

120. World Health Organization.Summary of WHO position papers - recommended routine immunizations for children.Updated Feb 27 2015.

121. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2017. MMWR Morbidity and mortality weekly report. 2018;67(40):1123-8.

122. Communicable Diseases Intelligence. Immunisation Coverage Annual Report (2019) 2021 [23 June 2021]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/5C71FABF639650F6CA2586520081286B/$File/immunisation_coverage_annual_report_2019.pdf.

123. World Health Organization. Global and regional immunization profile. July 2015.http://www.who.int/immunization/monitoring_surveillance/data/gs_gloprofile.pdf?ua=1 (Accessed 2 July 2020).

124. World Health Organization.Global Immunization Data. July 2013.www.who.int/hpvcentre/Global_Immunization_Data.pdf (Accessed 2 July 2020).

125. Chit A, Zivaripiran H, Shin T, Lee JKH, Tomovici A, Macina D, et al. Acellular pertussis vaccines effectiveness over time: A systematic review, meta-analysis and modeling study. PLoS One. 2018;13(6):e0197970.

126. Cattaneo LA, Reed GW, Haase DH, Wills MJ, Edwards KM. The seroepidemiology of Bordetella pertussis infections: a study of persons ages 1-65 years. J Infect Dis. 1996;173(5):1256-9.

127. Gerbie MV, Tan TQ. Pertussis disease in new mothers: effect on young infants and strategies for prevention. Obstet Gynecol. 2009;113(2 Pt 1):399-401.

128. Wendelboe AM, Hudgens MG, Poole C, Van Rie A. Estimating the role of casual contact from the community in transmission of Bordetella pertussis to young infants. Emerg Themes Epidemiol. 2007;4:15-.

129. Tan T, Dalby T, Forsyth K, Halperin SA, Heininger U, Hozbor D, et al. Pertussis Across the Globe: Recent Epidemiologic Trends From 2000 to 2013. The Pediatric Infectious Disease Journal. 2015;34(9):e222-e32.

130. Cherry JD. Epidemic pertussis in 2012--the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367(9):785-7.

131. Quinn HE, Mahajan D, Hueston L, Campbell P, Menzies RI, Gilbert GL, et al. The seroepidemiology of pertussis in NSW: fluctuating immunity profiles related to changes in vaccination schedules. N S W Public Health Bull. 2011;22(11-12):224-9.

132. Forsyth K, Plotkin S, Tan T, Wirsing von König CH. Strategies to decrease pertussis transmission to infants. Pediatrics. 2015;135(6):e1475-82.

133. Forsyth KD, Wirsing von Konig CH, Tan T, Caro J, Plotkin S. Prevention of pertussis: recommendations derived from the second Global Pertussis Initiative roundtable meeting. Vaccine. 2007;25(14):2634-42.

134. Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis. 2011;52(2):157-62.

135. Urwyler P, Heininger U. Protecting newborns from pertussis - the challenge of complete cocooning. BMC Infect Dis. 2014;14:397-.

136. Murphy TV, Slade BA, Broder KR, Kretsinger K, Tiwari T, Joyce PM, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008;57(RR-4):1-51.

137. Halperin BA, Morris A, Mackinnon-Cameron D, Mutch J, Langley JM, McNeil SA, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis. 2011;53(9):885-92.

138. Kirkland KB, Talbot EA, Decker MD, Edwards KM. Kinetics of pertussis immune responses to tetanus-diphtheria-acellular pertussis vaccine in health care personnel: implications for outbreak control. Clin Infect Dis. 2009;49(4):584-7.

139. Le T, Cherry JD, Chang SJ, Knoll MD, Lee ML, Barenkamp S, et al. Immune responses and antibody decay after immunization of adolescents and adults with an acellular pertussis vaccine: the APERT Study. J Infect Dis. 2004;190(3):535-44.

140. Lloyd KL. Protecting pregnant women, newborns, and families from pertussis. Journal of midwifery & women's health. 2013;58(3):288-96.

141. Wright, PF, Webster RG.Orthomyxoviruses. In: Fields, B.N. and Knipe, D.M. Eds., Fields Virology, 4th Edition, Lippincott Williams & Wilkins, Philadelphia.2001; 1533-1579.

142. Hause BM, Collin EA, Liu R, Huang B, Sheng Z, Lu W, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. mBio. 2014;5(2):e00031-14.

143. World Health Organization. Influenza vaccine viruses and reagents. 2016. www.who.int/influenza/vaccines/virus/en/

144. Su S, Fu X, Li G, Kerlin F, Veit M. Novel Influenza D virus: Epidemiology, pathology, evolution and biological characteristics. Virulence. 2017;8(8):1580-91.

145. Matsuzaki Y, Katsushima N, Nagai Y, Shoji M, Itagaki T, Sakamoto M, et al. Clinical features of influenza C virus infection in children. J Infect Dis. 2006;193(9):1229-35.

146. Rogers GN PJ, Daniels RS, Skehel JJ, Wilson IA, et al. (1983) Single amino acid substitutions in influenza haemagglutinin change receptor binding specificity. Nature 304: 76–78,.

147. Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk H-D. Neuraminidase is important for the initiation of influenza virus infection in human airway epithelium. J Virol. 2004;78(22):12665-7.

148. Nelson MI, Holmes EC. The evolution of epidemic influenza. Nature Reviews Genetics. 2007;8(3):196-205.

149. Cox NJ, Subbarao K. Influenza. The Lancet. 1999;354(9186):1277-82.

150. Chen R, Holmes EC. The evolutionary dynamics of human influenza B virus. J Mol Evol. 2008;66(6):655-63.

151. Thomas P, Riffelmann M, Schweiger B, Dominik S, von König CH. Fatal influenza A virus infection in a child vaccinated against influenza. Pediatr Infect Dis J. 2003;22(2):201-2.

152. Lyytikäinen O, Hoffmann E, Timm H, Schweiger B, Witte W, Vieth U, et al. Influenza A outbreak among adolescents in a ski hostel. Eur J Clin Microbiol Infect Dis. 1998;17(2):128-30.

153. Laing R, Slater W, Coles C, Chambers S, Frampton C, Jackson R, et al. Community-acquired pneumonia in Christchurch and Waikato 1999-2000: microbiology and epidemiology. N Z Med J. 2001;114(1143):488-92.

154. Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. Chest. 2001;119(6):1717-23.

155. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. Clin Infect Dis. 2003;37(8):1094-101.

156. Lowen AC, Mubareka S, Steel J, Palese P. Influenza Virus Transmission Is Dependent on Relative Humidity and Temperature. PLoS Pathog. 2007;3(10):e151.

157. Mitamura K, Sugaya N. [Diagnosis and Treatment of influenza--clinical investigation on viral shedding in children with influenza]. Uirusu. 2006;56(1):109-16.

158. Kageyama S. Pandemic influenza: a never-ending story. Yonago Acta Med. 2011;54(3):41-8.

159. Hilleman MR. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. Vaccine. 2002;20(25-26):3068-87.

160. Hampson AW, Mackenzie JS. The influenza viruses. Med J Aust. 2006;185(S10):S39-S43.

161. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360(25):2605-15.

162. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009;325(5937):197-201.

163. Australian Government Department of Health and Ageing. Australian influenza surveillance report. No. 44, 2010, reporting period: 30 October – 5 November 2010 2010 [Available from: www.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-no44-10.htm.

164. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet. 2018;391(10127):1285-300.

165. World Health Organisation (WHO). Influenza (Seasonal) 2018 [7 July 2020]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

166. Fiore AE, Bridges CB, Cox NJ. Seasonal influenza vaccines. Curr Top Microbiol Immunol. 2009;333:43-82.

167. Recommended composition of influenza virus vaccines for use in the 2010 influenza season (southern hemisphere winter). Wkly Epidemiol Rec. 2009;84(41):421-31.

168. Vasileiou E, Sheikh A, Butler C, El Ferkh K, von Wissmann B, McMenamin J, et al. Effectiveness of Influenza Vaccines in Asthma: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2017;65(8):1388-95.

169. Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. International journal of women's health. 2014;6:681-9.

170. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14(1):95-100.

171. Creanga AA, Kamimoto L, Newsome K, D'Mello T, Jamieson DJ, Zotti ME, et al. Seasonal and 2009 pandemic influenza A (H1N1) virus infection during pregnancy: a

population-based study of hospitalized cases. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S38-45.

172. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12(11):1638-43.

173. Raj RS, Bonney EA, Phillippe M. Influenza, immune system, and pregnancy. Reproductive sciences (Thousand Oaks, Calif). 2014;21(12):1434-51.

174. Littauer EQ, Esser ES, Antao OQ, Vassilieva EV, Compans RW, Skountzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. PLoS Pathog. 2017;13(11):e1006757-e.

175. Harris JW. Influenza occuring in pregnant women: A statistical study of thirteen hundred and fifty cases. J Am Med Assoc. 1919;72(14):978-80.

176. Freeman DW. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol. 1959;78(6):1172.

177. Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med. 2011;8(7):e1001053.

178. Kelly H, Mercer G, Cheng A. Quantifying the risk of pandemic influenza in pregnancy and indigenous people in Australia in 2009. Euro Surveill. 2009;14(50).

179. Ohfuji S, Deguchi M, Tachibana D, Koyama M, Takagi T, Yoshioka T, et al. Estimating influenza disease burden among pregnant women: Application of self-control method. Vaccine. 2017;35(36):4811-6.

180. Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. Can Med Assoc J. 2007;176(4):463.

181. Ahluwalia IB, Jamieson DJ, Rasmussen SA, D'Angelo D, Goodman D, Kim H. Correlates of seasonal influenza vaccine coverage among pregnant women in Georgia and Rhode Island. Obstet Gynecol. 2010;116(4):949-55.

182. Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG : an international journal of obstetrics and gynaecology. 2017;124(1):48-59.

183. Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination. N Engl J Med. 2013;368(4):333-40.

184. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol. 2012;207(3):S3-S8.

185. Hansen C, Desai S, Bredfeldt C, Cheetham C, Gallagher M, Li DK, et al. A large, population-based study of 2009 pandemic Influenza A virus subtype H1N1 infection diagnosis during pregnancy and outcomes for mothers and neonates. J Infect Dis. 2012;206(8):1260-8.

186. Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, Kuypers J, et al. Impact of Timing of Influenza Vaccination in Pregnancy on Transplacental Antibody Transfer, Influenza Incidence, and Birth Outcomes: A Randomized Trial in Rural Nepal. Clin Infect Dis. 2018;67(3):334-40.

187. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Jr., Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med. 2000;342(4):225-31.

188. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P, Staat MA, Iwane MK, et al. The underrecognized burden of influenza in young children. N Engl J Med. 2006;355(1):31-40.

189. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. The Lancet.378(9807):1917-30.

190. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian Technical Advisory Group on Immunisation (ATAGI) 59th face-to-face meeting Canberra, Australia2016 [1/6/2016]. Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/821BCD8E0E63EAE5CA257F9C000A1237/$File/ATAGI-59-Bulletin.pdf.

191. 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). Eurosurveillance. 2016;21(30):30301.

192. MacDonald NE, McDonald JC. The benefits of influenza vaccine in pregnancy for the fetus and the infant younger than six months of age. Paediatr Child Health. 2014;19(9):e121-2.

193. Faucette AN, Unger BL, Gonik B, Chen K. Maternal vaccination: moving the science forward. Hum Reprod Update. 2015;21(1):119-35.

194. Saji F, Samejima Y, Kamiura S, Koyama M. Dynamics of immunoglobulins at the feto-maternal interface. Rev Reprod. 1999;4(2):81-9.

195. Brambell FW. The transmission of immunity from mother to young and the catabolism of immunoglobulins. Lancet. 1966;2(7473):1087-93.

196. Morphis LG, Gitlin D. Maturation of the maternofoetal transport system for human gamma-globulin in the mouse. Nature. 1970;228(5271):573.

197. Englund JA. The influence of maternal immunization on infant immune responses. J Comp Pathol. 2007;137 Suppl 1:S16-9.

198. Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in pregnancy. Curr Opin Infect Dis. 2017;30(3):268-73.

199. Tapia MD, Sow SO, Tamboura B, Tégueté I, Pasetti MF, Kodio M, 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(9):1026-35.

200. Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis. 2017;17(9):981-9.

201. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014;371(10):918-31.

202. Omer SB. Maternal Immunization. N Engl J Med. 2017;376(13):1256-67.

203. Marshall H, McMillan M, Andrews RM, Macartney K, Edwards K. Vaccines in pregnancy: The dual benefit for pregnant women and infants. Hum Vaccin Immunother. 2016;12(4):848-56.

204. Bergin N, Murtagh J, Philip RK. Maternal Vaccination as an Essential Component of Life-Course Immunization and Its Contribution to Preventive Neonatology. Int J Environ Res Public Health. 2018;15(5):847.

205. Gkentzi D, Katsakiori P, Marangos M, Hsia Y, Amirthalingam G, Heath PT, et al. Maternal vaccination against pertussis: a systematic review of the recent literature. Arch Dis Child Fetal Neonatal Ed. 2017;102(5):F456-F63.

206. Soofie N, Nunes MC, Kgagudi P, van Niekerk N, Makgobo T, Agosti Y, et al. The Burden of Pertussis Hospitalization in HIV-Exposed and HIV-Unexposed South African Infants. Clin Infect Dis. 2016;63(suppl 4):S165-S73.

207. Winter K, Glaser C, Watt J, Harriman K. Pertussis epidemic--California, 2014. MMWR Morb Mortal Wkly Rep. 2014;63(48):1129-32.

208. Elahi S, Buchanan RM, Babiuk LA, Gerdts V. Maternal immunity provides protection against pertussis in newborn piglets. Infect Immun. 2006;74(5):2619-27.

209. Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015;60(3):333-7.

210. Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, et al. Impact of the US Maternal Tetanus, Diphtheria, and Acellular Pertussis Vaccination Program on Preventing Pertussis in Infants <2 Months of Age: A Case-Control Evaluation. Clin Infect Dis. 2017;65(12):1977-83.

211. Winter K, Cherry JD, Harriman K. Effectiveness of Prenatal Tetanus, Diphtheria, and Acellular Pertussis Vaccination on Pertussis Severity in Infants. Clin Infect Dis. 2017;64(1):9-14.

212. Saul N, Wang K, Bag S, Baldwin H, Alexander K, Chandra M, et al. Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study. Vaccine. 2018;36(14):1887-92.

213. Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clin Infect Dis. 2015;61(11):1637-44.

214. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311(17):1760-9.

215. Maertens K, Hoang TT, Nguyen TD, Caboré RN, Duong TH, Huygen K, et al. The Effect of Maternal Pertussis Immunization on Infant Vaccine Responses to a Booster Pertussis-Containing Vaccine in Vietnam. Clin Infect Dis. 2016;63(suppl 4):S197-S204.

216. Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clin Infect Dis. 2013;56(4):539-44.

217. Committee on Obstetric Practice Immunization and Emerging Infections Expert Work Group Opinion No. 718: Update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination. Obstet Gynecol. 2017;130(3):e153-e7.

218. Long PH. Recommendations for influenza immunization and control: 1964–1965. Med Times. 1964;92:1203–5.

219. World Health Organization. Vaccines against influenza WHO position paper – November 2012. 2012.

220. Hwang SD, Shin JS, Ku KB, Kim HS, Cho SW, Seo SH. Protection of pregnant mice, fetuses and neonates from lethality of H5N1 influenza viruses by maternal vaccination. Vaccine. 2010;28(17):2957-64.

221. Mbawuike IN, Six HR, Cate TR, Couch RB. Vaccination with inactivated influenza A virus during pregnancy protects neonatal mice against lethal challenge by influenza A viruses representing three subtypes. J Virol. 1990;64(3):1370-4.

222. Thompson MG, Li DK, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010-2011 and 2011-2012 influenza seasons. Clin Infect Dis. 2014;58(4):449-57.

223. Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med. 2013;368(4):333-40.

224. Shakib JH, Korgenski K, Presson AP, Sheng X, Varner MW, Pavia AT, et al. Influenza in Infants Born to Women Vaccinated During Pregnancy. Pediatrics. 2016;137(6).

225. Poehling KA, Szilagyi PG, Staat MA, Snively BM, Payne DC, Bridges CB, et al. Impact of maternal immunization on influenza hospitalizations in infants. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S141-8.

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

227. 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):1355-61.

228. 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):e11-9.

229. Omer SB, Goodman D, Steinhoff MC, Rochat R, Klugman KP, Stoll BJ, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Med. 2011;8(5):e1000441.

230. Sheffield JS, Greer LG, Rogers VL, Roberts SW, Lytle H, McIntire DD, et al. Effect of influenza vaccination in the first trimester of pregnancy. Obstet Gynecol. 2012;120(3):532-7.

231. Sukumaran L, McCarthy NL, Kharbanda EO, McNeil MM, Naleway AL, Klein NP, et al. Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes

Among Pregnant Women With Prior Tetanus-Containing Immunizations. JAMA. 2015;314(15):1581-7.

232. Olsen SJ, Mirza SA, Vonglokham P, Khanthamaly V, Chitry B, Pholsena V, et al. The effect of influenza vaccination on birth outcomes in a Cohort of Pregnant Women in Lao PDR, 2014-2015. Clin Infect Dis. 2016;63(4):487-94.

233. 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.

234. Nunes MC, Cutland CL, Jones S, Downs S, Weinberg A, Ortiz JR, 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(7):1066-71.

235. Omer SB, Clark DR, Aqil AR, Tapia MD, Nunes MC, Kozuki N, 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(5):436-40.

236. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep. 2013;62(7):131-5.

237. Department of Health UK.Pregnant women to be offered whooping cough vaccination.[updated 28.09.2012].Available from:http://www.dh.gov.uk/health/2012/09/whooping-cough

238. Beard FH. Pertussis immunisation in pregnancy: a summary of funded Australian state and territory programs. Communicable diseases intelligence quarterly report. 2015;39(3):E329-36.

239. The Australian Immunisation Handbook 10th Edition. 10th ed. Canberra: The Australian Government Department of Health 2015.

240. Taksdal S, Mak D, Joyce S, Tomlin S, Carcione D, Armstrong P, et al. Predictors of uptake of influenza vaccination A survey of pregnant women in Western Australia. Australian Family Physician. 2013;42:582-6.

241. 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):1-7.

242. Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake of influenza vaccine by pregnant women: a cross-sectional survey. Med J Aust. 2013;198(7):373-5.

243. Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey Canberra: AIHW; 2011 [cited 2016 2/8/2016]. Available from: http://www.aihw.gov.au/publication-detail/?id=10737418409.

244. McCarthy EA, Pollock WE, Nolan T, Hay S, McDonald S. Improving influenza vaccination coverage in pregnancy in Melbourne 2010–2011. Aust N Z J Obstet Gynaecol. 2012;52.

245. Lu AB, Halim AA, Dendle C, Kotsanas D, Giles ML, Wallace EM, et al. Influenza vaccination uptake amongst pregnant women and maternal care providers is suboptimal. Vaccine. 2012;30(27):4055-9.

246. Maher L, Hope K, Torvaldsen S, Lawrence G, Dawson A, Wiley K, et al. Influenza vaccination during pregnancy: coverage rates and influencing factors in two urban districts in Sydney. Vaccine. 2013;31(47):5557-64.

247. Kennedy ED, Ahluwalia IB, Ding H, Lu PJ, Singleton JA, Bridges CB. Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. Am J Obstet Gynecol. 2012;207(3 Suppl):S9-16.

248. 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 Morbidity and mortality weekly report. 2018;67(38):1055-9.

249. Goldfarb IT, Little S, Brown J, Riley LE. Use of the combined tetanus-diphtheria and pertussis vaccine during pregnancy. Am J Obstet Gynecol. 2014;211(3):299 e1-5.

250. McQuaid F, Jones C, Stevens Z, Meddaugh G, O'Sullivan C, Donaldson B, et al. Antenatal vaccination against Group B streptococcus: attitudes of pregnant women and healthcare professionals in the UK towards participation in clinical trials and routine implementation. Acta Obstet Gynecol Scand. 2018;97(3):330-40.

251. Dempsey AF, Brewer SE, Sevick C, Pyrzanowski J, Mazzoni S, O'Leary ST. Tdap vaccine attitudes and utilization among pregnant women from a high-risk population. Hum Vaccin Immunother. 2016;12(4):872-8.

252. O'Grady K-AF, Dunbar M, Medlin LG, Hall KK, Toombs M, Meiklejohn J, et al. Uptake of influenza vaccination in pregnancy amongst Australian Aboriginal and Torres Strait Islander women: a mixed-methods pilot study. BMC Res Notes. 2015;8:169-.

253. Mak DB, Regan AK, Vo DT, Effler PV. Antenatal influenza and pertussis vaccination in Western Australia: a cross-sectional survey of vaccine uptake and influencing factors. BMC Pregnancy Childbirth. 2018;18(1):416-.

254. McHugh L, Binks MJ, Gao Y, Andrews RM, Ware RS, Snelling T, et al. Influenza vaccination in pregnancy among a group of remote dwelling Aboriginal and Torres Strait Islander mothers in the Northern Territory: The 1+1 Healthy Start to Life study. Commun Dis Intell (2018). 2019;43.

255. Myers KL. Predictors of maternal vaccination in the United States: An integrative review of the literature. Vaccine. 2016;34(34):3942-9.

256. 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.

257. Poliquin V, Greyson D, Castillo E. A Systematic Review of Barriers to Vaccination During Pregnancy in the Canadian Context. J Obstet Gynaecol Can. 2019;41(9):1344-55.

258. Nitsch-Osuch A, Wozniak Kosek A, Brydak LB. [Vaccination against influenza in pregnant women - safety and effectiveness]. Ginekol Pol. 2013;84(1):56-61.

259. Wong CY, Thomas NJ, Clarke M, Boros C, Tuckerman J, Marshall HS. Maternal uptake of pertussis cocooning strategy and other pregnancy related recommended immunizations. Hum Vaccin Immunother. 2015;11(5):1165-72.

260. Bödeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. Vaccine. 2014;32(33):4131-9.

261. Collins J, Alona I, Tooher R, Marshall H. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. Hum Vaccin Immunother. 2014;10(10):2922-9.

262. Bodeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. Vaccine. 2014;32(33):4131-9.

263. Collins J, Alona I, Tooher R, Marshall H. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. Hum Vaccin Immunother. 2014;10(10):2922-9.

264. Gorman JR, Brewer NT, Wang JB, Chambers CD. Theory-based predictors of influenza vaccination among pregnant women. Vaccine. 2012;31(1):213-8.

265. Wiley KE, Cooper SC, Wood N, Leask J. Understanding Pregnant Women's Attitudes and Behavior Toward Influenza and Pertussis Vaccination. Qual Health Res. 2015;25(3):360-70.

266. Omidvar S, Faramarzi M, Hajian-Tilak K, Nasiri Amiri F. Associations of psychosocial factors with pregnancy healthy life styles. PLoS One. 2018;13(1):e0191723-e.

267. de Jager E, Broadbent J, Fuller-Tyszkiewicz M, Nagle C, McPhie S, Skouteris H. A longitudinal study of the effect of psychosocial factors on exclusive breastfeeding duration. Midwifery. 2015;31(1):103-11.

268. Pearce A, Marshall H, Bedford H, Lynch J. Barriers to childhood immunisation: Findings from the Longitudinal Study of Australian Children. Vaccine. 2015;33(29):3377-83.

269. Fortner KB, Swamy GK, Broder KR, Jimenez-Truque N, Zhu Y, Moro PL, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. Vaccine. 2018;36(42):6354-60.

270. Hoang HT, Leuridan E, Maertens K, Nguyen TD, Hens N, Vu NH, et al. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. Vaccine. 2016;34(1):151-9.

271. Petousis-Harris H, Walls T, Watson D, Paynter J, Graham P, Turner N. Safety of Tdap vaccine in pregnant women: an observational study. BMJ open. 2016;6(4):e010911.

272. Regan AK, Tracey LE, Blyth CC, Richmond PC, Effler PV. A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. Vaccine. 2016;34(20):2299-304.

273. Villarreal Pérez JZ, Ramírez Aranda JM, de la OCM, Zamudio Osuna MJ, Perales Dávila J, Ballesteros Elizondo MR, et al. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. Hum Vaccin Immunother. 2017;13(1):128-35.

274. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway AL, et al. Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. Vaccine. 2016;34(7):968-73.

275. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012;207(1):59 e1-7.

276. Wanlapakorn N, Maertens K, Chaithongwongwatthana S, Srimuan D, Suratannon N, Vongpunsawad S, et al. Assessing the reactogenicity of Tdap vaccine administered during pregnancy and antibodies to Bordetella pertussis antigens in maternal and cord sera of Thai women. Vaccine. 2018;36(11):1453-9.

277. Moro PL, Cragan J, Tepper N, Zheteyeva Y, Museru O, Lewis P, et al. Enhanced surveillance of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011-2015. Vaccine. 2016;34(20):2349-53.

278. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ. 2014;349:g4219.

279. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA. 2014;312(18):1897-904.

280. Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. J Pediatr. 2013;163(5):1422-6 e1-4.

281. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA. 2014;312(18):1897-904.

282. Layton JB, Butler AM, Li D, Boggess KA, Weber DJ, McGrath LJ, et al. Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine. 2017;35(33):4072-8.

283. DeSilva M, Vazquez-Benitez G, Nordin JD, Lipkind HS, Klein NP, Cheetham TC, et al. Maternal Tdap vaccination and risk of infant morbidity. Vaccine. 2017;35(29):3655-60.

284. Morgan JL, Baggari SR, McIntire DD, Sheffield JS. Pregnancy outcomes after antepartum tetanus, diphtheria, and acellular pertussis vaccination. Obstet Gynecol. 2015;125(6):1433-8.

285. Berenson AB, Hirth JM, Rahman M, Laz TH, Rupp RE, Sarpong KO. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. Hum Vaccin Immunother. 2016;12(8):1965-71.

286. Datwani H, Moro PL, Harrington T, Broder KR. Chorioamnionitis following vaccination in the Vaccine Adverse Event Reporting System. Vaccine. 2015;33(27):3110-3.

287. Johnson CT, Farzin A, Burd I. Current management and long-term outcomes following chorioamnionitis. Obstet Gynecol Clin North Am. 2014;41(4):649-69.

288. Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol. 2005;192(4):1098-106.

289. Bednarczyk RA, Adjaye-Gbewonyo D, Omer SB. Safety of influenza immunization during pregnancy for the fetus and the neonate. Am J Obstet Gynecol. 2012;207(3 Suppl):S38-46.

290. Carcione D, Blyth CC, Richmond PC, Mak DB, Effler PV. Safety surveillance of influenza vaccine in pregnant women. Aust N Z J Obstet Gynaecol. 2013;53(1):98-9.

291. Regan AK, Blyth CC, Mak DB, Richmond PC, Effler PV. Using SMS to monitor adverse events following trivalent influenza vaccination in pregnant women. Aust N Z J Obstet Gynaecol. 2014;54(6):522-8.

292. Regan AK, Tracey LE, Blyth CC, Richmond PC, Effler PV. A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. Vaccine. 2016;34(20):2299-304.

293. Irving SA, Kieke BA, Donahue JG, Mascola MA, Baggs J, DeStefano F, et al. Trivalent inactivated influenza vaccine and spontaneous abortion. Obstet Gynecol. 2013;121(1):159-65.

294. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol. 2004;21(6):333-9.

295. Naleway AL, Irving SA, Henninger ML, Li DK, Shifflett P, Ball S, 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(26):3122-7.

296. Nordin JD, Kharbanda EO, Vazquez Benitez G, Lipkind H, Vellozzi C, Destefano F. Maternal influenza vaccine and risks for preterm or small for gestational age birth. J Pediatr. 2014;164(5):1051-7 e2.

297. Ahrens KA, Louik C, Kerr S, Mitchell AA, Werler MM. Seasonal influenza vaccination during pregnancy and the risks of preterm delivery and small for gestational age birth. Paediatr Perinat Epidemiol. 2014;28(6):498-509.

298. Dodds L, MacDonald N, Scott J, Spencer A, Allen VM, McNeil S. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. J Obstet Gynaecol Can. 2012;34(8):714-20.

299. Regan AK, Moore HC, de Klerk N, Omer SB, Shellam G, Mak DB, et al. Seasonal Trivalent Influenza Vaccination During Pregnancy and the Incidence of Stillbirth: Population-Based Retrospective Cohort Study. Clin Infect Dis. 2016;62(10):1221-7.

300. Nordin JD, Kharbanda EO, Benitez GV, Nichol K, Lipkind H, Naleway A, et al. Maternal safety of trivalent inactivated influenza vaccine in pregnant women. Obstet Gynecol. 2013;121(3):519-25.

301. Donahue JG, Kieke BA, King JP, DeStefano F, Mascola MA, Irving SA, et al. Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12. Vaccine. 2017;35(40):5314-22.

302. Risch HA, Weiss NS, Clarke EA, Miller AB. Risk factors for spontaneous abortion and its recurrence. Am J Epidemiol. 1988;128(2):420-30.

303. Donahue JG, Kieke BA, King JP, Mascola MA, Shimabukuro TT, DeStefano F, et al. Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink in 2012–13, 2013–14, and 2014–15. Vaccine. 2019;37(44):6673-81.

304. Candela S, Pergolizzi S, Ragni P, Cavuto S, Nobilio L, Di Mario S, et al. An early (3-6 weeks) active surveillance study to assess the safety of pandemic influenza vaccine Focetria in a province of Emilia-Romagna region, Italy - part one. Vaccine. 2013;31(10):1431-7.

305. Mackenzie IS, MacDonald TM, Shakir S, Dryburgh M, Mantay BJ, McDonnell P, et al. Influenza H1N1 (swine flu) vaccination: a safety surveillance feasibility study using self-reporting of serious adverse events and pregnancy outcomes. Br J Clin Pharmacol. 2012;73(5):801-11.

306. Tavares F, Nazareth I, Monegal JS, Kolte I, Verstraeten T, Bauchau V. Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study. Vaccine. 2011;29(37):6358-65.

307. Omon E, Damase-Michel C, Hurault-Delarue C, Lacroix I, Montastruc JL, Oustric S, et al. Non-adjuvanted 2009 influenza A (H1N1)v vaccine in pregnant women: the results of a French prospective descriptive study. Vaccine. 2011;29(52):9649-54.

308. Moro PL, Broder K, Zheteyeva Y, Revzina N, Tepper N, Kissin D, et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System. Am J Obstet Gynecol. 2011;205(5):473 e1-9.

309. Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine. 2012;30(30):4445-52.

310. Huang WT, Tang FW, Yang SE, Chih YC, Chuang JH. Safety of inactivated monovalent pandemic (H1N1) 2009 vaccination during pregnancy: a population-based study in Taiwan. Vaccine. 2014;32(48):6463-8.

311. Fabiani M, Bella A, Rota MC, Clagnan E, Gallo T, D'Amato M, et al. A/H1N1 pandemic influenza vaccination: A retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy. Vaccine. 2015;33(19):2240-7.

312. Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. Am J Obstet Gynecol. 2012;207(3):177 e1-8.

313. Kochhar S, Bonhoeffer J, Jones CE, Muñoz FM, Honrado A, Bauwens J, et al. Immunization in pregnancy clinical research in low- and middle-income countries - Study design, regulatory and safety considerations. Vaccine. 2017;35(48 Pt A):6575-81.

314. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017;129(3):560-73.

315. Savitz DA, Fell DB, Ortiz JR, Bhat N. Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. Vaccine. 2015;33(47):6430-5.

316. Cantu J, Biggio J, Jauk V, Wetta L, Andrews W, Tita A. Selective uptake of influenza vaccine and pregnancy outcomes. J Matern Fetal Neonatal Med. 2013;26(12):1207-11.

317. Ng S, Gordon A. Influenza Burden and Transmission in the Tropics. Curr Epidemiol Rep. 2015;2(2):89-100.

318. Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. Birth Defects Res A Clin Mol Teratol. 2014;100(9):658-62.

319. Hutcheon JA, Savitz DA. Invited Commentary: Influenza, Influenza Immunization, and Pregnancy-It's About Time. Am J Epidemiol. 2016;184(3):187-91.

320. Xu R, Luo Y, Chambers C. Assessing the effect of vaccine on spontaneous abortion using time-dependent covariates Cox models. Pharmacoepidemiol Drug Saf. 2012;21(8):844-50.

321. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.

322. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31 (Pt 3):301-6.

323. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-6.

324. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

325. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

326. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med. 2009;3(3):e123-30.

327. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. Jama. 1998;280(19):1690-1.

328. Greenland S. Interpretation and choice of effect measures in epidemiologic analyses. Am J Epidemiol. 1987;125(5):761-8.

329. Australian New Zealand Clinical Trials Registry.ACTRN12614000985684. Screening Tests to identify poor Outcomes in Pregnancy (STOP) Study 2014 [cited 01/09/2020. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366996.

330. Amirthalingam G. Strategies to control pertussis in infants. Arch Dis Child. 2013;98(7):552-5.

331. Mohammed H, McMillan M, Roberts CT, Marshall HS. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PLoS One. 2019;14(3):e0214538.

332. MacDougall DM, Halperin SA. Improving rates of maternal immunization: Challenges and opportunities. Hum Vaccin Immunother. 2016;12(4):857-65.

333. Mohammed H, Roberts CT, Grzeskowiak LE, Giles L, Leemaqz S, Dalton J, et al. Psychosocial determinants of pertussis and influenza vaccine uptake in pregnant women: A prospective study. Vaccine. 2020;38(17):3358-68.

334. Mohammed H, Roberts CT, Grzeskowiak LE, Giles LC, Dekker GA, Marshall HS. Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study. EClinicalMedicine. 2020;26:100522.

335. Munoz FM, Eckert LO, Katz MA, Lambach P, Ortiz JR, Bauwens J, et al. Key terms for the assessment of the safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions. Vaccine. 2015;33(47):6441-52.

336. Jones CE, Munoz FM, Kochhar S, Vergnano S, Cutland CL, Steinhoff M, et al. Guidance for the collection of case report form variables to assess safety in clinical trials of vaccines in pregnancy. Vaccine. 2016;34(49):6007-14.

337. Hyman J. The limitations of using insurance data for research. J Am Dent Assoc. 2015;146(5):283-5.

338. Senn SJ. Power is indeed irrelevant in interpreting completed studies. BMJ (Clinical research ed). 2002;325(7375):1304-.

339. Hoenig JM, Heisey DM. The Abuse of Power. The American Statistician. 2001;55(1):19-24.

340. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. Expert review of vaccines. 2020:1-18.

341. Filby A, McConville F, Portela A. What Prevents Quality Midwifery Care? A Systematic Mapping of Barriers in Low and Middle Income Countries from the Provider Perspective. PLoS One. 2016;11(5):e0153391.

342. Accortt EE, Cheadle ACD, Dunkel Schetter C. Prenatal depression and adverse birth outcomes: an updated systematic review. Maternal and child health journal. 2015;19(6):1306-37.

343. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women Birth. 2015;28(3):179-93.

344. Kozuki N, Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, et al. Impact of maternal vaccination timing and influenza virus circulation on birth outcomes in rural Nepal. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2018;140(1):65-72.

345. 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):423-9.

346. Sarna M, Andrews R, Moore H, Binks MJ, McHugh L, Pereira GF, 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(6):e030277-e.

347. Berry NJ, Danchin M, Trevena L, Witteman HO, Kinnersley P, Snelling T, et al. Sharing knowledge about immunisation (SKAI): An exploration of parents' communication

needs to inform development of a clinical communication support intervention. Vaccine. 2018;36(44):6480-90.

348. Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA, Simões EAF, et al. Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants. N Engl J Med. 2020;383(5):426-39.

349. Donders GG, Halperin SA, Devlieger R, Baker S, Forte P, Wittke F, et al. Maternal Immunization With an Investigational Trivalent Group B Streptococcal Vaccine: A Randomized Controlled Trial. Obstet Gynecol. 2016;127(2):213-21.

350. Farrell R, Michie M, Pope R. Pregnant Women in Trials of Covid-19: A Critical Time to Consider Ethical Frameworks of Inclusion in Clinical Trials. Ethics Hum Res. 2020;42(4):17-23.

351. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(25):769-75.

352. Collin J, Byström E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand. 2020;99(7):819-22.

353. Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020;25:100446.

354. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. JAMA. 2020;324(7):705-6.

355. Australian Technical Advisory Group on Immunisation (ATAGI). ATAGI statement on the administration of seasonal influenza vaccines in 2020; 2020. Accessed: Sep 18, 2019. Available from https://www.health.gov.au/resources/publications/atagi-advice-on-seasonal-influenza-vaccines-in-2020

Appendices

Appendix A – Supplementary materials for Chapter 4

- Systematic review protocol
- S1 Table. PRISMA checklist
- S2 Table. Database search strategies
- S3 Table. Quality assessment of the reviewed randomized controlled trials
- S4 Table. Quality assessment of the reviewed observational studies
- S5 Table. Characteristics of the excluded studies

A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy

Hassen Mohammed, Helen Marshall, Claire Roberts

Citation
Hassen Mohammed, Helen Marshall, Claire Roberts. A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. PROSPERO 2017 CRD42017058178 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017058178

Review question
What are the most effective interventions used to improve pertussis vaccination uptake in pregnant women?

Searches
Relevant literature will be sought from: PubMed, Embase, MEDLINE, CINAHL, The Cochrane Library, unpublished studies, the European Society for Paediatric Infectious Diseases (ESPID), and the World Society for Pediatric Infectious Diseases (WSPID).

Types of study to be included
Inclusion: Human studies only; observational prospective studies; randomized controlled trials; international comparisons; studies which include maternal pertussis as part of the immunization.

Condition or domain being studied
Pertussis or whooping cough: vaccinating women in their third trimester of pregnancy in order to protect young infants against pertussis.

Participants/population
Inclusion: Pregnant women (women of childbearing age).
Exclusion: Interventions on the non-pregnant population.

Intervention(s), exposure(s)
1. Interventions to overcome provider and system barriers (i.e., health care provider-focused interventions);
2. Interventions to increase demand for maternal pertussis vaccination (i.e., pregnant woman-focused interventions);
3. Interventions to enhance maternal pertussis vaccine access.

Comparator(s)/control
Placebo: a group of pregnant women who have not been exposed to the intervention.

Main outcome(s)
The uptake of pertussis vaccines in pregnancy, confirmed by either medical records or self-reported data.

Additional outcome(s)
None.

Data extraction (selection and coding)
Titles of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full texts of these potentially eligible studies will then be retrieved and independently assessed for eligibility by two review team members.The following information from each study will be collected: type of study including study design, multi-site or single site, study period, intervention type, population including sample size, country, follow-up duration and results.

Risk of bias (quality) assessment
The Cochran Collaboration's method will be used for the risk of bias assessment for randomized controlled

trials. Risk of bias will be assessed in six domains: sequence generation, allocation concealment, blinding, and handling of incomplete outcome data, selective outcome reporting, and “other” potential threats to validity. The GRADE criteria will be used in addition to the Cochrane Collaboration tool because these criteria take into account the consistency, directness, and precision of the results.

Strategy for data synthesis
Data will be pooled in statistical meta-analysis using Stata software. Standardized study effects will be reported as the ratio of the odds to be vaccinated in the intervention group compared with the standard care group and risk differences (RD) and 95% confidence intervals (CI) will also be calculated. A list of all confounders, adjusted for in the data analysis, and the differences in the vaccination rate after adjustment, will also be described.

Analysis of subgroups or subsets
None planned.

Contact details for further information
Hassen Mohammed
hassen.mohammed@student.adelaide.edu.au

Organisational affiliation of the review
Vaccinology and Immunology Research Trials Unit (VIRTU)
http://wch.sa.gov.au/services/az/divisions/paedm/virtu/index.html

Review team members and their organisational affiliations
Mr Hassen Mohammed. University of Adelaide, School of Medicine, Pediatrics and Reproductive Health
Professor Helen Marshall. Vaccinology and Immunology Research Trials Unit (VIRTU), School of Medicine, Pediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia
Professor Claire Roberts. Robinson Research Institute, School of Medicine, University of Adelaide, Adelaide, South Australia

Type and method of review
Systematic review

Anticipated or actual start date
06 February 2017

Anticipated completion date
04 September 2017

Funding sources/sponsors
This research is supported by an Australian Government Research Training Program (RTP) Scholarship

Conflicts of interest
None known

Language
English

Country
Australia

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Female; Health Behavior; Humans; Immunization, Secondary; Infant Health; Maternal Health; Patient

Acceptance of Health Care; Pregnancy; Pregnancy Complications; Pregnancy Outcome; Vaccination; Whooping Cough

Date of registration in PROSPERO
27 February 2017

Date of first submission

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
27 February 2017

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE: A systematic review of interventions used to improve uptake of pertussis vaccination in pregnancy			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4(see Table 1)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	see S2 Table
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	see S2 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 (see also Fig 1)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6,7 (see also S3&S4 Table)

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5,6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6 (see also S3&S4 Tables)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6,7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8,9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10 (table 3)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13 (see also Table 3)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,9 (see also Fig 2, S3&S4 Tables)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15,16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

S2 Table. Database search strategies

PubMed

1. Pertussis vaccine	2. Pregnant women
Pertussis vaccine [majr] OR Pertussis vaccin*[ALL] OR Whooping cough vaccin*[ALL] OR Diphtheria-Tetanus-acellular Pertussis Vaccin* [ALL] OR DTaP Vaccin* [ALL] OR Diphtheria-Tetanus-Pertussis Vaccin*[ALL]	Pregnant women [majr] OR Pregnan*[ALL] OR Maternal* [ALL]

(Pregnant women [MH] OR Pregnan*[ALL] OR Maternal* [ALL]) AND (Pertussis vaccine [MH] OR Pertussis vaccin*[ALL] OR Whooping cough vaccin*[ALL] OR Diphtheria-Tetanus-acellular Pertussis Vaccin* [ALL] OR DTaP Vaccin* [ALL] OR Diphtheria-Tetanus-Pertussis Vaccin*[ALL) NOT (ANIMALS[MH] NOT Humans[MH])

1 AND 2

Hits= 578

Filter= Pub dates 10 years

Hits= 350

PMC

(Pregnant women [majr] OR Pregnant[ALL] OR Pregnancy[ALL] OR Maternal [ALL]) AND (Pertussis vaccine [majr] OR Pertussis vaccin*[ALL] OR Whooping cough vaccin*[ALL] OR Diphtheria-Tetanus-acellular Pertussis Vaccin* [ALL] OR DTaP Vaccin* [ALL] OR Diphtheria-Tetanus-Pertussis Vaccin*[ALL) NOT (ANIMALS[MH] NOT Humans[MH])

Hits =1631

Filter= Pub dates 10 years

Hits= 865

Medline- Ovid

1. exp *Pregnant women/

2. Pregnan$.MP.

3. Maternal$ .MP.

4. 1 or 2 or 3 AND

5. exp *Pertussis vaccine/

6. Pertussis vaccin$.MP.

7. Whooping cough vaccin$.MP.

8. Diphtheria-Tetanus-acellular Pertussis Vaccin$ .MP.

9. DTaP Vaccin$ .MP.

10. Diphtheria-Tetanus-Pertussis Vaccin$.MP.

11 5 or 6 or 7 or 8 or 9 or 10

12. 4 and 11

13 limit 12 to yr= "2006 -Current"

14. Humans/

15. exp animals/

16.15 NOT 14

17. 13 NOT 16

Hits= 1946

CINAHL

#	**Query**
S13	S9 AND S12
S12	(MM "Pertussis Vaccine") OR TX "Pertussis vaccin*" OR TX "Whooping cough vaccin*" OR TX "DTap vaccin*"
S11	(MM "Pertussis Vaccine")
S10	(MH "Pertussis Vaccine+")
S9	(MM "Expectant Mothers") OR TX Pregnan* OR TX Maternal*
S8	(MM "Expectant Mothers")
S7	S2 AND S5
S6	S2 AND S5
S5	(MM "Pertussis Vaccine") OR TX "Pertussis vaccin*" OR TX "Whooping cough vaccin*" OR TX "DTap vaccin*"
S4	(MM "Pertussis Vaccine")
S3	(MH "Pertussis Vaccine+")
S2	(MM "Expectant Mothers") OR TX Pregnan* OR TX Maternal*
S1	(MM "Expectant Mothers")

Hits= 381

Combined hits after removing duplicated articles on Endnotes= 1935

Other Sources

I. European Society for Paediatric Infectious Diseases (ESPID)

Abstracts from 2011- 2016

Hits = 0

II. World Society for Paediatric Infectious Diseases (WSPID)

WSPID 2015 and WSPID 2013 and WSPID 2011

Hits= 0

III. International Congress on Infectious Diseases (ICID)= 0

Total hits = 1935

Study	Risk of Bias						GRADE - Level of evidence			
	Random sequence generation reporting	Allocation concealment	Blinding of participants & outcome assessment	Incomplete outcome data	Selective Reporting	Other bias	Inconsistency	Indirectness	Imprecision	Quality of evidence
Kriss [24]	Quote: "A master database which provided randomization assignments was generated by non-study personnel" Judgement Low risk of bias	Investigators enrolling participants could possibly foresee assignment using a list. Judgement High risk of bias	Participant: No Assessor: Unclear Judgement High risk of bias	15% of the control group and 10% in intervention groups were not included in the analysis Judgement High risk of bias	The study did not validate vaccination from vaccination records as described in their protocol on clinicaltrials.gov Judgement High risk of bias	Quote: "limited to African American women in a south-eastern metropolitan area" Comments: findings may not be generalizable to non-African American populations	No serious Inconsistency	No serious Inconsistency	Insufficient number of participants in both arms (80%power)	Low
Payakachat [33]	Randomly assigned by a coin toss into two groups. Judgement Low risk of bias.	Investigators enrolling participants and participants could not possibly foresee assignment. Judgement Low risk of bias.	Participants: No Assessor: unclear Judgement High risk of bias.	Quote"16 (3%) did not complete the survey due to technical problems with the electronic device" Comments: The proportion of missing outcomes compared with observed event risk was not enough to induce relevant bias in intervention effect estimates. Judgement Low risk of bias	Quote "intention to receive the vaccine; and to determine associations between health perceptions with Tdap vaccine receipt" Comments The study likely included all pre-specified primary outcomes.	Quote "the majority of patients were of low socioeconomic level and had limited health literacy, the findings have limited generalizability to other pregnant women in different US regions" Comments The study may be affected by selection bias.	No serious inconsistency	No serious indirectness	Sufficient number of participants in both arms A sample of 250 was required but 291 participants were consented and randomized	Moderate
Chamberlain [23]	Randomisation was achieved using a coin toss by blinded statistician on paired practices. Judgement Low risk of bias.	Participants and investigators enrolling participants could possibly foresee assignment. Judgement High risk of bias	Participants: No Assessor: Unclear Judgement High risk of bias	Quote "Of the 48 women who did not complete the follow-up questionnaire, equal proportions were from the intervention (n = 24) and control (n = 24) groups" Comments: The proportion of missing outcomes compared with observed event risk was not enough to induce relevant bias in intervention effect estimates.	The study reports primary and secondary outcomes described by pre-specified criteria on clinicaltrials.gov Judgement Low risk of bias	Self-report was the primary method used to judge if a Tdap vaccine was administered The study participants may be subjected social desirability bias Judgement High risk of bias	No serious Inconsistency	No serious Indirectness	"since the study was designed to detect differences in antenatal vaccine receipt, we likely lacked the sample size necessary to detect significant changes in measures of knowledge, attitudes and beliefs" Comments Underpowered to detect a difference on outcome	Moderate

S3 Table. Quality assessment of the reviewed randomized controlled trials

S4 Table. Quality assessment of the reviewed observational studies

Quality assessment	Morgan [25]			Healy [32]			Mohammed [34]		
	Yes	No	Unclear	Yes	No	Unclear	Yes	No	Unclear
1. Is it clear in the study what is the cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Y			Y			Y		
2. Were the participants included in any comparisons similar?			U			U			U
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?			U		N		Y		
4. Was there a control group?	Y			Y			Y		
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?		N			N			N	
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?			U			U	Y		
7. Were the outcomes of participants included in any comparisons measured in the same way?	Y			Y			Y		
8. Were outcomes measured in a reliable way?	Y			Y				N	
9. Was appropriate statistical analysis used?	Y				N		Y		

S5 Table. Characteristics of the excluded studies

Study (year)	Reasons for exclusion
Donaldson (2015)	No standard care group was available for comparison
Barber (2017)	No intervention component (Adequate prenatal care is not an intervention)
Manzoni (2016)	Ineligible participants: study was not directed to pregnant women only
Celikel (2013)	Pertussis vaccination uptake was not included
Goldfarb (2014)	No standard care or comparator group
Mazzoni (2016)	Ineligible participants: study was not directed to pregnant women only
Bonville (2015)	No intervention component
Maertens (2016)	No intervention component
Kharbanda (2011)	study was directed to postpartum
Bödeker (2014)	No intervention component

Appendix B – Supplementary materials for Chapter 6

- STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) Checklist
- Supplementary Table 1. Comparison of women included and excluded from the study (for whom data are available) in terms of key variables of interest
- Supplementary Table 2. Time-based pregnancy and birth outcomes by maternal influenza vaccination status after controlling for the receipt of a pertussis vaccine in pregnancy at two obstetric hospitals in South Australia 2015-2018
- Supplementary Table 3. Crude and adjusted hazard ratios for pre-delivery hospitalisation due to influenza like illness and key adverse birth outcomes stratified by trimester of influenza vaccination and influenza activity after controlling for the receipt of maternal pertussis vaccination.
- Supplementary Table 4. Pregnancy and birth outcomes following influenza vaccination in pregnancy after controlling for the receipt of a pertussis vaccine in pregnancy at two obstetric hospitals in South Australia 2015-2018

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	2, 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study Size	10	Explain how the study size was arrived at	5 (The original
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	6,7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7, figure 1
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, table 1
		(b) Indicate number of participants with missing data for each variable of interest	table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8, table 2,3,4
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7,8
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, appendix p 1
Discussion			
Key Results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Title: Safety and protective effects of maternal influenza vaccination on pregnancy and birth outcomes: A prospective cohort study

Authors: Hassen Mohammed, BHSc-Hons,[1,2,3] Claire T Roberts, PhD [2,3,4], Luke E Grzeskowiak, PhD,[2,3,5] Lynne Giles, PhD,[2,3,6] Gustaaf A Dekker, MD,[2,3,7] Helen S Marshall, MD,[1,2,3,6]

Supplementary Material:

Supplementary Table 1: Comparison of women included and excluded from the study (for whom data are available) in terms of key variables of interest

Key Variables	Excluded n/N (%)	Included n/N (%)
Pre-delivery hospitalisation due to influenza like illness	5/93 (5.3)	95/1253 (7.5)
Spontaneous abortion	5/93 (5.3)	34/1253 (2.7)
Gestational hypertension	5/76 (6.5)	81/1205 (6.7)
Pre-eclampsia	10/77 (12.9)	111 /1205 (9.2)
Preterm birth	7/79 (8.8)	89/1207 (7.3)
LBW	5/77 (6.4)	80/1205 (6.6)
LBW at term	2/70 (2.8)	29 /1116 (2.6)
SGA	11/76 (14.4)	142/1203 (11.8)

LBW=low birthweight. SGA=small for gestational age.

Supplementary Table 2: Time-based pregnancy and birth outcomes by maternal influenza vaccination status after controlling for the receipt of a pertussis vaccine in pregnancy at two obstetric hospitals in South Australia 2015-2018

Variables	Total	Unvaccinated N (%)	Vaccinated N (%)	Crude HR * (95% CI)	p-value	Adjusted † aHR (95% CI)	p-value
Pre-delivery hospitalisation due to influenza like illness ‡	95/1253 (7·5)	60/650 (9·2)	35/603 (5·8)	0·58 (0·37, 0·91)	0·018	0·60 (0·37, 0·97)	0·040
Accounting the 2-weeks period required for full protection				0·58 (0·37, 0·91)	0·021	0·60 (0·37, 0·98)	0·044
Gestational hypertension §	81/1205 (6·7)	41/606 (6·7)	40/599 (6·6)	0·80 (0·49, 1·31)	0·391	0·72 (0·43, 1·21)	0·299
Pre-eclampsia §	111/1205 (9·2)	58/606 (9·5)	53/599 (8·8)	0·85 (0·58, 1·26)	0·445	0·89 (0·57, 1·38)	0·622
Severe pre-eclampsia §	28/1204 (2·3)	14/606 (2·3)	14 /598 (2·3)	0·86 (0·37, 1·96)	0·725	0·68 (0·25, 1·81)	0·450
Gestational diabetes ‖	190/1207 (15·7)	85/608 (13·9)	105/599 (17·5)	1·33 (0·95, 1·84)	0·088	1·10 (0·75, 1·60)	0·611
Preterm premature rupture of the membranes ¶	47/1207 (3·8)	27/608 (4·4)	20/599 (3·3)	0·82 (0·43, 1·56)	0·561	0·90 (0·44, 1·82)	0·722
Preterm birth ¶	89/1207 (7·3)	49/608 (8·0)	40/599 (6·6)	0·94 (0·60, 1·47)	0·802	1·01 (0·61, 1·66)	0·951
Spontaneous preterm birth ¶	59/1207 (4·8)	36/608(5·9)	23/599 (3·8)	0·71 (0·40, 1·26)	0·253	0·71 (0·38, 1·32)	0·287
LBW (<2500 g) **	80/1205 (6·6)	49/606 (8·0)	31/599 (5·1)	0·70 (0·42, 1·14)	0·158	0·81 (0·47, 1·39)	0·450
LBW at term(<2500 g) **, ††	29/1116 (2·6)	20/557 (3·5)	9 /559 (1·6)	0·43 (0·18, 0·99)	0·048	0·38 (0·15, 0·94)	0·037
SGA **	144/1207 (11·9)	83 /608(13·6)	61/599 (10·1)	0·77 (0·54, 1·09)	0·152	0·91 (0·62, 1·34)	0·710
				Difference in means (vaccinated-unvaccinated)		**Difference in adjusted means (vaccinated - unvaccinated)**	
Mean birth weight h, g (95% CI)	3360·3± 505	3343·7 ± 526	3376·9 ± 484	33·1 (-24·3, 90·7)	0·258	18·3 (- 42·2, 79·0)	0·552
Mean gestational age at delivery, weeks (95% CI))	39·4 ± 1·5	39·3 ± 1·5	39·4 ± 1·5	0·07 (-0·09, 0·25)	0·381	0·05 (-0·13, 0·24)	0·570

CI=confidence interval. HR=hazard ratios. LBW=low birthweight. SGA=small for gestational age.

* HR results compared outcome variable in vaccinated group to reference (unvaccinated).

† Adjustments were made for pertussis vaccine in pregnancy, maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal· Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery.

‡ Women admitted to hospital with influenza/ acute respiratory tract infection were censored at their admission date.

§ For hypertensive disorders analysis, women who were vaccinated at or after the gestational age at diagnosis (≥ 20 weeks' gestation) and pregnancies ending prior to 20 weeks of gestation were censored.

‖ Women who were vaccinated at or after the gestational age at diagnosis of gestational diabetes mellitus (median gestational age at screening was 27·8 (IQR, 26·5-29) weeks) were censored.

¶ Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of preterm birth.

** Additionally adjusted for infant's sex.

†† Low birthweight at term (<2500 g and ≥ 37 completed weeks' gestation at birth).

Supplementary Table 3: Crude and adjusted hazard ratios for pre-delivery hospitalisation due to influenza like illness and key adverse birth outcomes stratified by trimester of influenza vaccination and influenza activity after controlling for the receipt of maternal pertussis vaccination.

Variables	Unvaccinated N (%)	Vaccinated N (%)	Crude HR * (95% CI)	p-value	Adjusted †, ‡ aHR (95% CI)	p-value
Pre-delivery hospitalisation due to influenza like illness	60/650 (9·2)	35/603 (5·8)	0·58 (0·37, 0·91)	0·018	0·60 (0·37, 0·97)	0·040
1st trimester			0·43 (0·18, 0·99)	0·049	0·45 (0·19, 1·08)	0·075
2nd trimester			0·09 (0·01, 0·68)	0·019	0·09 (0·01, 0·71)	0·022
3rd trimester			0·70 (0·43, 1·13)	0·149	0·71 (0·41, 1·22)	0·224
Low influenza activity			0·58 (0·33, 0·99)	0·049	0·59 (0·33, 1·04)	0·070
High influenza activity			0·47 (0·26, 0·85)	0·013	0·51 (0·27, 0·95)	0·035
Preterm birth §	49/608 (8·0)	40/599 (6·6)	0·94 (0·60, 1·47)	0·802	1·01 (0·61 1·66)	0·951
1st trimester			0·46 (0·18, 1·16)	0·111	0·51 (0·19, 1·32)	0·167
2nd trimester			0·91 (0·43, 1·93)	0·811	0·93 (0·42, 2·03)	0·859
3rd trimester			0·79 (0·47, 1·33)	0·384	0·77 (0·44, 1·37)	0·390
Low influenza activity			0·61 (0·33, 1·12)	0·112	0·62 (0·34, 1·17)	0·143
High influenza activity			0·85 (0·50, 1·45)	0·571	0·93 (0·53, 1·63)	0·807
Spontaneous preterm birth §	36/608(5·9)	23/599 (3·8)	0·71 (0·40, 1·26)	0·253	0·71 (0·38, 1·32)	0·287
1st trimester			0·37 (0·11, 1·22)	0·104	0·39 (0·11, 1·32)	0·134
2nd trimester			0·61 (0·21, 1·73)	0·361	0·57 (0·20, 1·69)	0·318
3rd trimester			0·61 (0·31, 1·18)	0·147	0·59 (0·29, 1·21)	0·156
Low influenza activity			0·53 (0·25, 1·11)	0·096	0·52 (0·24, 1·13)	0·101
High influenza activity			0·58 (0·28, 1·17)	0·131	0·56 (0·26, 1·21)	0·143
LBW (<2500 g) ‖	49/606 (8·0)	31/599 (5·1)	0·70 (0·42, 1·14)	0·158	0·81 (0·47, 1·39)	0·450
1st trimester			0·56 (0·24, 1·35)	0·206	0·58 (0·24, 1·41)	0·233
2nd trimester			0·47 (0·16, 1·30)	0·161	0·44 (0·15, 1·28)	0·137
3rd trimester			0·57 (0·32, 1·03)	0·065	0·66 (0·35, 1·22)	0·191
Low influenza activity			0·66 (0·37, 1·19)	0·171	0·67 (0·36, 1·24)	0·255
High influenza activity			0·43 (0·22, 0·86)	0·018	0·51 (0·24, 1·05)	0·068
LBW at term (<2500 g) ‖, ¶, **	20/557 (3·5)	9 /559 (1·6)	0·43 (0·18,1·09)	0·048	0·38 (0·15, 0·94)	0·037
Low influenza activity			0·61 (0·24, 1·54)	0·303	0·47 (0·17, 1·26)	0·139
High influenza activity			0·20 (0·05, 0·89)	0·035	0·19 (0·04, 0·88)	0·034
SGA e	83 /608 (13·6)	61/599 (10·1)	0·77 (0·55, 1·09)	0·152	0·91 (0·62, 1·34)	0·710
1st trimester			1·15 (0·71, 1·86)	0·549	1·27 (0·77, 2·11)	0·335
2nd trimester			0·79 (0·42, 1·49)	0·476	0·84 (0·43, 1·61)	0·603
3rd trimester			0·57 (0·36, 0·89)	0·014	0·66 (0·40, 1·08)	0·105
Low influenza activity			0·88 (0·59, 1·32)	0·596	0·98 (0·64, 1·50)	0·941
High influenza activity			0·60 (0·37, 0·95)	0·030	0·71 (0·43, 1·16)	0·175

CI=confidence interval. HR=hazard ratios. LBW=low birthweight. SGA=small for gestational age.

* HR results compared outcome variable in vaccinated group to reference (unvaccinated).

† Adjustments were made for maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal· Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery.

‡ Additionally adjusted for receipt of pertussis vaccine during pregnancy.

§ Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of having a preterm birth.

‖ Additionally adjusted for infant's sex.

¶ Low birthweight at term (<2500 g and ≥ 37 completed weeks' gestation at birth).

** Analysis by trimester of influenza vaccination was not performed because a small number of mothers who delivered LBW at term babies received the vaccine prior to their third trimester (n=1 during 1st trimester, n =1 during 2nd trimester).

Supplementary Table 4: Pregnancy and birth outcomes following influenza vaccination in pregnancy after controlling for the receipt of a pertussis vaccine in pregnancy at two obstetric hospitals in South Australia 2015-2018

Pregnancy outcomes	Total	Unvaccinated N (%)	Vaccinated N (%)	Risk Ratios RR (95% CI)	p-value	Adjusted *, † aRR (95% CI)	p-value
Chorioamnionitis and/or funisitis	25/1207 (2·0)	15/608 (2·4)	10/599 (1·6)	0·65 (0·28, 1·49)	0·316	0·93 (0·36, 2·43)	0·893
Postpartum haemorrhage	113/1205 (9·3)	62/606 (10·2)	51/599 (8·5)	0·79 (0·55, 1·14)	0·215	0·73 (0·49, 1·09)	0·129
Caesarean delivery (Vs Vaginal) ‡	349/1205 (28·9)	176/606 (29·0)	173/599 (28·8)	1·01 (0·93, 1·08)	0·758	0·91 (0·79, 1·05)	0·239
Birth outcomes							
Low Apgar at 1 min (<7)	151/1201 (12·5)	72/603 (11·9)	79/598 (13·2)	1·13 (0·83, 1·53)	0·433	1·26 (0·90, 1·77)	0·160
Low Apgar at 5-min (<7)	31/1203 (2·5)	16/604 (2·6)	15/599 (2·5)	0·93 (0·44, 1·97)	0·874	1·05 (0·46, 2·39)	0·902
Admitted to Neonatal unit §	282/1207 (23·3)	140/608 (23·0)	142/599 (23·7)	0·98 (0·80, 1·22)	0·780	1·12 (0·89, 1·40)	0·309
Respiratory distress syndrome	14/1207 (1·1)	10/608 (1·6)	4/599 (0·6)	0·40 (0·12, 1·26)	0·120	0·78 (0·20, 2·95)	0·722
Mechanical ventilation	51/1207 (4·2)	30/608 (4·9)	21/599 (3·5)	0·72 (0·41, 1·26)	0·258	0·97 (0·52, 1·81)	0·933

* Pregnancy outcomes were adjusted for maternal age, ethnicity, total years of full time education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous) , use of multivitamin supplements, Edinburgh Postnatal· Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, asthma and estimated season of delivery. Birth outcomes were additionally adjusted for infant's sex.

† Additionally adjusted for receipt of pertussis vaccine during pregnancy.

‡ Poisson regression model was used because the log binomial model failed to converge for the adjusted model.

§ Reasons for admission: Preterm, Respiratory distress Infection, Feeding problem, Hypoglycaemia, Drug withdrawal, SGA, Birth asphyxia, Congenital abnormality, Phototherapy and Cyanosis.

Appendix C – Supplementary materials for Chapter 7

- Table S1. Crude and adjusted hazard ratios sensitivity analysis for time-based pregnancy and birth outcomes by maternal pertussis vaccination status adjusted for maternal influenza vaccination at two obstetric hospitals in South Australia 2015-2018.
- Table S2. Pregnancy and birth outcomes following pertussis vaccination during pregnancy adjusted for maternal influenza vaccination at two obstetric hospitals in South Australia 2015-2018

Table S1. Crude and adjusted hazard ratios sensitivity analysis for time-based pregnancy and birth outcomes by maternal pertussis vaccination status adjusted for maternal influenza vaccination at two obstetric hospitals in South Australia 2015-2018.

Pregnancy outcomes	Total [a]	Unvaccinated N (%)	Vaccinated N (%)	Adjusted [b, c] aHR (95% CI)	p-value	Adjusted [c, d] aHR (95% CI)	p-value
Gestational hypertension [e]	86/1267 (6.7)	10/249 (4.0)	76/1018 (7.4)	1.24 (0.66, 2.30)	0.497	1.33 (0.70, 2.53)	0.368
Preeclampsia[e]	116/1268 (9.1)	26/250 (10.4)	90/1018 (8.8)	0.75 (0.47, 1.18)	0.220	0.74 (0.46, 1.20)	0.226
Pre-delivery hospitalization due to influenza like illness [f]	94/1272 (7.3)	24/253 (9.4)	70/1019 (6.8)	0.84 (0.51, 1.36)	0.488	0.98 (0.59, 1.64)	0.958
Preterm premature rupture of the membranes [g]	42/1272 (3.3)	12/263(4.7)	30/1019 (2.9)	0.99 (0.47, 2.07)	0.987	1.06 (0.48, 2.31)	0.878
Preterm birth [g]	82/1272 (6.4)	21/253 (8.3)	61/1019 (5.9)	0.99 (0.57, 1.70)	0.984	1.01 (0.57, 1.79)	0.967
Spontaneous preterm birth [g]	51/1272 (4.0)	14/253 (5.5)	37/1019 (3.6)	1.01 (0.52, 1.97)	0.961	1.11 (0.55, 2.24)	0.763
Birth outcomes							
LBW (<2500 g)	71/1268 (5.6)	21/250 (8.4)	50/1018 (4.9)	0.72 (0.41, 1.27)	0.261	0.80 (0.44, 1.45)	0.472
LBW at term (<2500 g) [h]	31/1186 (2.6)	8/229 (3.4)	23/957 (2.4)	0.67 (0.29, 1.55)	0.361	0.92 (0.38, 2.21)	0.867
SGA	150/1266 (11.8)	36/249 (14.4)	114/1017 (11.2)	0.80 (0.53, 1.20)	0.295	0.83 (0.55, 1.28)	0.418
				Difference in adjusted means (vaccinated - unvaccinated)		**Difference in adjusted means (vaccinated - unvaccinated)**	
Mean birth weight, grams (95% CI)	3368.0 ± 496.2	3313 ± 565.3	3381.2 ± 477.5	44.6 (-26.0, 115.3)	0.216	43.4 (-32.6, 119.5)	0.263
Mean gestational age at delivery, weeks (95% CI)	39.4 ± 1.5	39.2 ± 1.7	39.4 ± 1.4	0.22 (0.00, 0.44)	0.048	0.20 (-0.03, 0.44)	0.094

CI, confidence interval; HR, hazard ratios; LBW, low birthweight; SGA, small for gestational age

a: Denominators differ due to missing data.

b: Adjusted aHR results compared outcome variable in vaccinated group to reference (unvaccinated).

c: Adjustments were made for maternal age, race/ethnicity, education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, and asthma. Birth outcomes were additionally adjusted for infant's sex.

d: Additional adjustments were made for influenza vaccination during pregnancy

e: For hypertensive disorders analysis, women who were vaccinated at or after the gestational age at diagnosis were censored.

f: Women admitted to hospital with respiratory tract infection/influenza like illness were censored at their admission date

g: Women vaccinated at 37 weeks' or later were censored because they were no longer at risk of preterm birth.

h: Low birthweight at term (<2500 g and ≥ 37 completed weeks' gestation at birth).

Table S2. Pregnancy and birth outcomes following pertussis vaccination during pregnancy adjusted for maternal influenza vaccination at two obstetric hospitals in South Australia 2015-2018

Pregnancy outcomes	Total [a]	Unvaccinated N (%)	Vaccinated N (%)	Adjusted [b] aRR (95% CI)	p-value	Adjusted [b, c] aRR (95% CI)	p-value
Chorioamnionitis and/or funisitis	23/1272 (1.8)	7/253 (2.7)	16/1019 (1.5)	0.71 (0.27, 1.82)	0.481	0.60 (0.21, 1.70)	0.399
Placental abruption	32/1266 (3.3)	7/250 (2.8)	25/1016 (2.4)	1.04 (0.41, 2.62)	0.923	0.98 (0.35, 2.75)	0.978
Postpartum haemorrhage	115/1269 (9.0)	26/251 (10.3)	89/1018 (8.7)	0.81 (0.52, 1.26)	0.357	0.89 (0.56, 1.42)	0.923
Birth outcomes							
Apgar at 1 min <7	149/1263 (11.8)	30/247 (12.1)	119/1016 (11.7)	0.87 (0.59, 1.29)	0.496	0.76 (0.50, 1.16)	0.213
Apgar at 5- min <7	26/1265 (2.0)	6/248 (2.4)	20/1017 (1.9)	0.75 (0.27, 2.06)	0.582	0.71 (0.24, 2.01)	0.521
Admitted to Neonatal unit [d]	285/1272 (22.4)	65/253 (25.6)	220/1019 (21.5)	0.84 (0.66, 1.07)	0.177	0.82 (0.63, 1.06)	0.136
Respiratory distress syndrome	10/1272 (0.7)	3/253 (1.1)	7/1019 (0.6)	0.61 (0.20, 1.82)	0.384	0.64 (0.18, 2.24)	0.495
Mechanical ventilation	42/1272 (3.3)	9/253 (3.5)	33/1019 (3.2)	0.71 (0.34, 1.50)	0.381	0.73 (0.33, 1.60)	0.438

a: Denominators differ due to missing data.

b: Pregnancy outcome were adjusted for maternal age, ethnicity, total years of full-time education, household income, gravidity, intake of alcohol and recreational drugs, smoking, pre-pregnancy body mass index (continuous), use of multivitamin supplements, Edinburgh Postnatal. Depression Scale (EPDS), The State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS-10), physical activity, infertility treatment, and asthma. Birth outcomes were additionally adjusted for infant's sex.

c: Additionally adjusted for receipt of influenza vaccine during pregnancy.

d: Reasons for admission: preterm, respiratory distress infection, feeding problem, hypoglycaemia, drug withdrawal, SGA, birth asphyxia, congenital abnormality, phototherapy and cyanosis.

Appendix D – Ancillary publication not included in this thesis

- During the period of candidature, the candidate led the publication of the following article which was included in the systematic review and relate to the body of work described in this thesis.
- Findings of this study has been used by the Commonwealth Government to develop key messages for pregnant women and their partners about the importance of maternal immunisation.
- Cited 38 times

Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS One. 2018;13(6): e0197867.

PLOS ONE

RESEARCH ARTICLE

Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia

Hassen Mohammed[1,2,3]*, Michelle Clarke[1,2,3], Ann Koehler[4], Maureen Watson[4], Helen Marshall[1,2,3,5]

1 The Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia, **2** Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia, **3** Vaccinology and Immunology Research Trials Unit (VIRTU), Women's and Children's Hospital, North Adelaide, South Australia, Australia, **4** The Communicable Disease Control Branch (CDCB), South Australia, Australia, **5** School of Public Health, University of Adelaide, Adelaide, South Australia, Australia

* hassen.mohammed@adelaide.edu.au

OPEN ACCESS

Citation: Mohammed H, Clarke M, Koehler A, Watson M, Marshall H (2018) Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS ONE 13(6): e0197867. https://doi.org/10.1371/journal.pone.0197867

Editor: Guy AM Berbers, RIVM, NETHERLANDS

Received: January 23, 2018

Accepted: May 9, 2018

Published: June 14, 2018

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This research has been funded by the Communicable Disease Control Branch (CDCB)-SA Health, Government of South Australia.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Maternal immunization is an effective strategy to protect pregnant women and their infants from vaccine-preventable diseases. Despite the recommendation of maternal influenza and more recently pertussis immunization in Australia, uptake of these vaccines has been sub-optimal. A midwife delivered immunization program for pregnant women at the Women's and Children's Hospital in South Australia commenced in April 2015. Monitoring the uptake of the current funded vaccine programs for pregnant women is limited. The study aimed to estimate maternal vaccine uptake and assess factors associated with influenza and pertussis vaccine uptake among pregnant women.

Methods

This prospective study was undertaken between November 2014 and July 2016 at the Women's and Children's Hospital. Following consent, demographic details and vaccination history for South Australian pregnant women who attended the antenatal clinic were collected. A standardised self-reported survey was completed during pregnancy with a follow up telephone interview at 8–10 weeks post-delivery.

Results

205 women consented and completed the self-reported survey. Of the 180 pregnant women who completed the study, 76% and 81% received maternal influenza and pertussis vaccines respectively. The adjusted odds of women receiving maternal vaccines during pregnancy were significantly higher for women delivering after the implementation of the midwife delivered program compared with women who delivered babies prior to the program for both pertussis vaccination (AOR 21.17, 95% CI 6.14–72.95; p<0.001) and influenza vaccination (AOR 5.95, 95% CI 2.13–16.61, p<0.001). Women receiving a recommendation from a

health care provider and first time mothers were significantly more likely to receive influenza vaccination during pregnancy.

Conclusions

High uptake of influenza and pertussis vaccines during pregnancy can be attained with health care provider recommendation and inclusion of maternal immunization as part of standard antenatal care. A midwife delivered maternal immunization program is a promising approach to improve maternal vaccine uptake by pregnant women.

Introduction

Pregnant women are at increased risk of morbidity and death from influenza infection during seasonal and pandemic influenza outbreaks [1–3]. This was particularly evident during the 2009 'H1N1' influenza pandemic outbreak in Australia, in which the admission rate of pregnant women to an intensive care unit following infection with influenza was significantly higher compared to non-pregnant adults [4, 5]. Infants born to women affected by influenza during pregnancy are at increased risk of adverse birth outcomes such as preterm birth and low birthweight [6]. Similarily, *Bordetella pertussis* infections can also pose high risk to infants prior to their receipt of a complete primary course of pertussis immunization [7,8].

Immunization of pregnant women with influenza and pertussis has now been shown to be effective in not only protecting the mother but also the fetus /newborn via transfer of transplacental antibodies [9, 10] and through breastfeeding [11]. Maternal pertussis vaccination at least 7 days before delivery can prevent up to 91% of pertussis disease in infants under 3 months of age [12]. Similarly, influenza vaccination during pregnancy can prevent up to 91% of influenza related hospital admissions in infants under 6 months of age [13] and has been shown to reduce influenza infections in pregnant women [14]. The safety of maternal influenza and pertussis immunization is well established, with no reports of serious adverse complications to the unborn infant and pregnant women [15, 16]. Concomitant influenza and pertussis vaccination will occur in pregnancies that overlap with the influenza season, with the potential for different responses compared to separate adminsation of the vaccines in pregnant women [17]. However, a study evaluating the safety of co-administering pertussis-containing vaccine (Tdap) and influenza vaccines in pregnant women has not found an increased risk of adverse events [18].

The Australian Immunisation Handbook was updated in March 2015 to recommend pertussis-containing vaccine (Tdap) for all pregnant women during the third trimester of each pregnancy [19]. State government funded pertussis vaccination programs for pregnant women were introduced progressively between August 2014 and June 2015 in all Australian states and territories [20]. All Australian states provide pertussis vaccine for pregnant women via general practitioners and hospital antenatal clinics, local councils, community health care centres, and obstetricians. In South Australia, the funded vaccine was introduced from April 2015 and accompanied with a large state-wide promotional campaign targeting health professionals and pregnant women [20]. Influenza immunization for pregnant women has been supplied free of charge and recommended at any time during pregnancy in Australia through the National Immunization Program since 2010 [19]. Additionally, a midwife delivered maternal immunization program for influenza and pertussis vaccine was introduced in the antenatal clinic at the Women's and Children's Hospital in South Australia (WCH) from April 2015. This

program enables registered midwives to administer maternal influenza and pertussis vaccination using a standing medication order, without the need for a prescription from a medical doctor [19].

Despite the recommendation of maternal influenza and more recently pertussis vaccinations in Australia, uptake of the recommended vaccines has historically been poor. Maternal influenza vaccine uptake in Australia has been estimated to range from about 7% to 40% [21–26]. However, these estimates are usually derived from relatively small sample studies. There are no published data on national maternal pertussis vaccine coverage in Australia. It is important to monitor and evaluate the impact of government funded pertussis vaccination programs for pregnant women and determine strategies to maximize uptake of vaccination for this population group. The primary objective of this study was to identify factors associated with the uptake of pertussis and influenza vaccines during pregnancy and to determine the uptake of influenza and pertussis vaccines among pregnant women in South Australia.

Materials and methods

Study population and design

This observational prospective study was undertaken between Nov-2014 and Jun-2016 at the WCH (a major tertiary maternity hospital in South Australia with an annual birth cohort of approximately 5000). Participation involved answering 26 questions about vaccination for protection against influenza and pertussis. A total of 300 pregnant women were approached and invited to participate in this research study. Participation in the survey was voluntary. A research nurse/medical officer discussed the study with the participants prior to obtaining written informed consent

Eligibility criteria

Pregnant women were eligible to participate if they were aged 18 years or over at the time of enrolment and had sufficient understanding of the English language. Pregnant women were eligible to partake in this study regardless of their gestational stage or expected delivery date.

Data collection instrument

A standardised self-report questionnaire was designed to collect socio-demographic details and information on awareness and uptake of the recommended maternal influenza and pertussis immunizations among pregnant women. A follow up telephone interview were conducted 8–10 weeks post-delivery. Participants were classified as 'lost to follow- up' and omitted from the analysis, if incorrect contact details were provided, if they refused further participation, or did not answer six phone call attempts at different times and on different days. The follow up telephone interview included questions to confirm whether they received influenza and/or pertussis vaccination during their pregnancy, a date and location, and if not during pregnancy, whether they had received influenza or pertussis vaccine post birth of their baby (See supplement). Delivery date of the woman was used to compare maternal influenza and pertussis immunization coverage prior to and following the implementation of the midwife delivered maternal immunization program. The midwife vaccine delivery program equipped midwives with knowledge and skills to engage with pregnant women on the topic of maternal immunizations and administer pertussis and influenza immunizations to pregnant women [27].

Statistical analysis

The sample size was calculated assuming 55% of pertussis vaccine uptake during pregnancy based on a self-reported survey (FluMum cohort study) [28] in 2015 collected over a three month period at the Women's and Children's Hospital in South Australia. For this study, an expected sample size of 200 participants enabled the uptake of pertussis vaccination amongst pregnant women to be estimated and to determine predictors of maternal influenza and pertussis vaccination uptake with a ±5% precision at a 95% confidence level.

Survey data were analysed using STATA Version 14. Descriptive analysis such as proportions for categorical variables and mean (median) for continuous variables were calculated. Chi squared tests (χ^2) were used to determine any crude association between categorical variables. Results were considered to indicate statistical significance, if a two-tailed p-value was less than 0.05. Univariate and multivariable logistic regression models were used to estimate unadjusted (ORs) and adjusted odds ratios (AORs) to identify variables related to the uptake of maternal influenza and pertussis vaccines.

Human research ethics approval

The study protocol was approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/14/WCHN/3).

Results

Participant's characteristics

Of 300 pregnant women approached at the WCH, 205 women consented and completed the antenatal survey questionnaire. Of the 205 participants, 24 were lost to follow up for the postnatal interview and one participant was excluded from the study because of fetal death during the pregnancy. Overall, 180 (88%) of the enrolled participants completed both the antenatal survey and the postnatal follow-up telephone call questionnaire (Fig 1). Data analysis was performed based on the 180 participants who completed both portions of the study.

The median age of participants was 31.1 years (range 21–43 years old), similar to the median age (30.6 years) of South Australian pregnant women reported by Australian Bureau of Statistics (ABS) in 2014 [29]. The majority of the pregnant women who participated in this study were born in Australia (74%) (Table 1). These sample characteristics are similar to South Australian for pregnant women according to the 2013 Pregnancy outcome SA report [30]. No indigenous women particpated in this study. A total of 82 (46%) of the women were first time mothers, while 54% of the participants were multiparous (Table 1).

Uptake of the recommended maternal vaccines

Pertussis. Almost all the participants (167/180, 93%) had heard of 'pertussis', regardless of their immunization status. Of the 180 participants, 66% (n = 119) were aware of the recommendation of pertussis vaccination during the 3rd trimester and 46% (n = 83) were aware that they could receive a pertussis vaccination shortly after delivery if the vaccine was not given during pregnancy. Overall, 82% (148/180) of the participants received pertussis vaccination; 81% (n = 145/180) during pregnancy and 2% (n = 3/180) post-delivery of their baby. Overall, 63% (92/145) of the women reported receiving the vaccine during pregnancy from a midwife during their antenatal visit at WCH, 32% (47/145) from a general practitioner (GP), 3% (4/145) from an occupational immunization provider and 1% from a community health center. Women who had heard of the availability of maternal pertussis vaccination prior to study participation had almost 8 times higher odds of receiving the vaccine during pregnancy (OR 7.8,

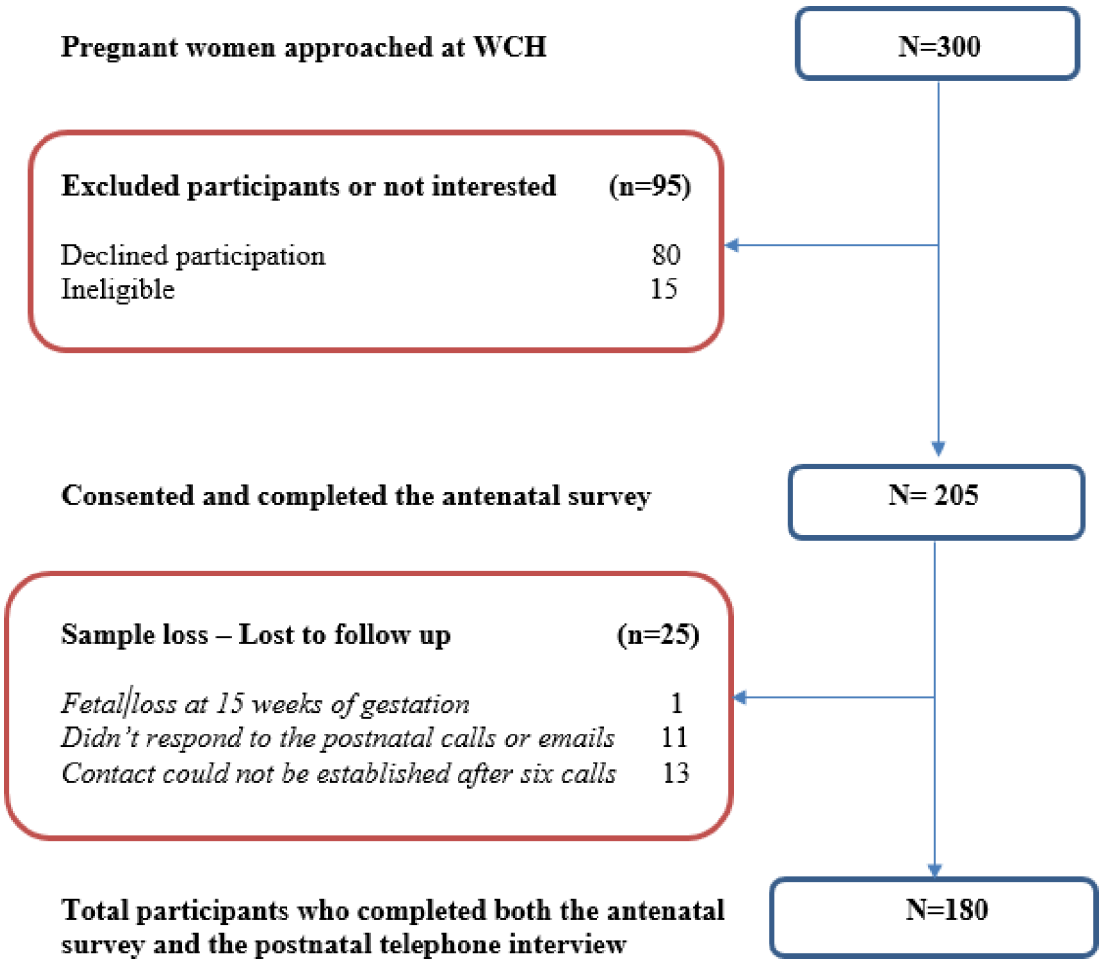


Fig 1. Recruitment flowchart.

https://doi.org/10.1371/journal.pone.0197867.g001

CI 3.3–18.3; p<0.001) (Table 2). Almost all infants 97% (175/180) were vaccinated with the routine diphtheria, tetanus and acellular pertussis (DTaP) vaccines (scheduled at 6–8 weeks of age).

Table 1. Baseline characteristics of the study population.

		Study population (n = 180)	
Characteristics	**Level**	**Total number**	**Percentage**
Maternal Age	18–31	96	53
	32–41	84	47
Born in Australia	Yes	116	74
	No	42	26
Parity	Primiparous	82	46
	Multiparous	98	54
Pregnancy trimester (at the time of enrolment)	1st	17	9
	2nd	62	34
	3rd	101	56

NB: Country of birth missing data, n = 22.

https://doi.org/10.1371/journal.pone.0197867.t001

Table 2. Factors potentially associated with pertussis vaccine uptake during pregnancy.

			Univariate binomial regression			Multivariable logistic regression		
Variable	**Level**	**Received maternal pertussis vaccine n (%)**	**Odds ratio (OR)**	**95% CI**	**p-value[b]**	**Adjusted odds ratio (AOR)[a]**	**95% CI**	**p-value**
Maternal age category	21–31	85/96 (89%)	1.00			1.00		
	32–43	60/82 (73%)	0.35	0.18–0.78	0.010	0.39	0.130–1.11	0.078
Country of birth	Australia	102/116(88%)	1.00					
	Other	32/42(76%)	0.30	0.28–2.14	0.124			
Parity	Primiparous	70/82 (85%)	1.00					
	Multiparous	75/98 (77%)	0.53	0.24–1.18	0.116			
Awareness of maternal pertussis recommendation	No	37/64 (63%)	1.00			1.00		
	Yes	108/117(82%)	7.78	3.31–18.2	<0.001	4.43	1.61–12.23	0.009
A midwife delivered maternal immunization program	Prior	5/25 (20%)	1.00			1.00		
	Post introduction	140/155(90%)	31.73	10.25–98.27	<0.001	21.17	6.14–72.95	<0.001

[a]Adjusted odds ratio comparing odds of receiving pertussis vaccine during pregnancy if offered, controlling for other variables.

[b]Only univariate associations with p value <0.1 were included in the multivariable logistic regression.

https://doi.org/10.1371/journal.pone.0197867.t002

Influenza. Overall, 80% (144/180) of the women who participated in this study received influenza vaccination; 76% (n = 136) of the participants received influenza vaccination during pregnancy and 5% (n = 8) received the vaccine post-delivery. Overall, 38% of the women reported receiving the vaccine during pregnancy from a general practitioner (GP), 37% from a midwife at WCH, 8% from occupational immunization provider, 1% from a community health center and 16% of the women failed to report where they have received the vaccine. Of the 180 study participants, 82% of them were aware that influenza vaccine is recommended during pregnancy, 67% were aware that they could receive influenza vaccine at any stage of their pregnancy and 65% of the women had discussed maternal influenza vaccination with their health care providers (HCPs). Pregnant women who had received a recommendation from their HCP had 3 times greater odds of receiving maternal influenza vaccination than women who had not received a recommendation (Table 3). Of the 130 women who received influenza vaccination during pregnancy (6 participants did not report their dates of vaccination), the majority (62%, 81/130) received the influenza vaccine in April (n = 47) or May (n = 34). A further 45 women (35%) received the vaccine during the influenza season which is typically between May to October in South Australia, with very few women (3%) being vaccinated between January and March. It should also be noted that influenza vaccine has generally not been available between January and March prior to release of the new seasonal vaccine. Among the most common reasons women cited for not receiving the vaccine during pregnancy were lack of recommendations from their HCPs (28%, n = 14) (Table 4).

Maternal vaccine uptakes pre-post introduction of a midwife delivered immunization program at WCH in SA

Pertussis. The proportion of women who received pertussis vaccine during pregnancy following the introduction of the midwife delivered vaccination program for pregnant women was significantly higher (140/155, 90%) compared with women who delivered prior to the introduction of the program (5/25, 20%; p <0.001) (Fig 2). The univariate odds of women

Table 3. Factors potentially associated with influenza vaccine uptake during pregnancy.

			Univariate binomial regression			Multivariable binomial regression		
Variable	**Level**	**Received maternal influenza vaccine n (%)**	**Unadjusted odds ratio (OR)**	**95% CI**	**p-value[b]**	**Adjusted odds ratio (AOR)[a]**	**95% CI**	**p-value**
Maternal age category	21–31	81/96 (84%)	1.00			1.00		
	32–43	55/83 (66%)	0.36	0.17–0.74	0.005	0.40	0.17–0.92	0.031
Country of birth	Australia	91/116 (78%)	1.00					
	Other	32/42 (76%)	0.50	0.16–1.57	0.763			
Parity	Primiparous	69/82 (84%)	1.00					
	Multiparous	67/97 (71%)	0.42	0.20–0.87	0.021	0.43	0.19–0.99	0.048
Provider recommendation received	No	40/64 (63%)	1.00			1.00		
	Yes	96/115 (83%)	3.03	1.49–6.14	0.001	2.81	1.19–6.68	0.002
A midwife delivered maternal immunization program	Prior	8/25 (32%)	1.00			1.00		
	Post introduction	128/155(83%)	8.00	3.06–20.91	<0.001	5.95	2.13–16.61	<0.001

[a] Adjusted odds ratio comparing odds of receiving influenza vaccine during pregnancy if offered, controlling for other variables.

[b] Only univariate associations with p value <0.1 were included in the multivariable logistic regression

https://doi.org/10.1371/journal.pone.0197867.t003

receiving maternal pertussis vaccine following the implementation of the government funded pertussis program and midwife delivered maternal immunization program in the antenatal clinic of the WCH was almost 32 times higher than women who delivered babies prior to the program (OR 31.73, CI 10.24–98.27; p<0.001) (Table 2).

Influenza. Women who had received pertussis vaccine during pregnancy were also more likely to have both been recommended the influenza vaccine during their pregnancy (90% vs 66%; p<0.001) and been immunized against influenza during pregnancy (92% vs 49%, p<0.001) compared to pregnant women who had not received pertussis vaccine. The univariate odds of women receiving influenza vaccine following the implementation of the midwife program was 8 times higher than women who have given birth prior to the program (OR 8.0, CI 3.06–20.9; p<0.001) (Table 3).

Table 4. Reasons cited for not receiving maternal influenza vaccination.

Reasons cited for NOT receiving the influenza vaccination during pregnancy	Number (n)	Percentage %
It was not suggested/recommended to me	14	28%
Prior experience of an adverse reaction after being vaccinated	8	16%
I did not know that pregnant women should be vaccinated	8	16%
I was unsure of the benefits or effectiveness of the vaccine	5	10%
Never had time to receive the vaccine	3	6%
Received the vaccine earlier this year	3	6%
I was not pregnant during the flu season	3	6%
Prefer natural immunity	2	4%
Flu vaccine exacerbates my Asthma	2	4%
Prefer to receive the vaccine after the baby is born	2	4%

NB. Women were allowed to report >1 reason.

https://doi.org/10.1371/journal.pone.0197867.t004

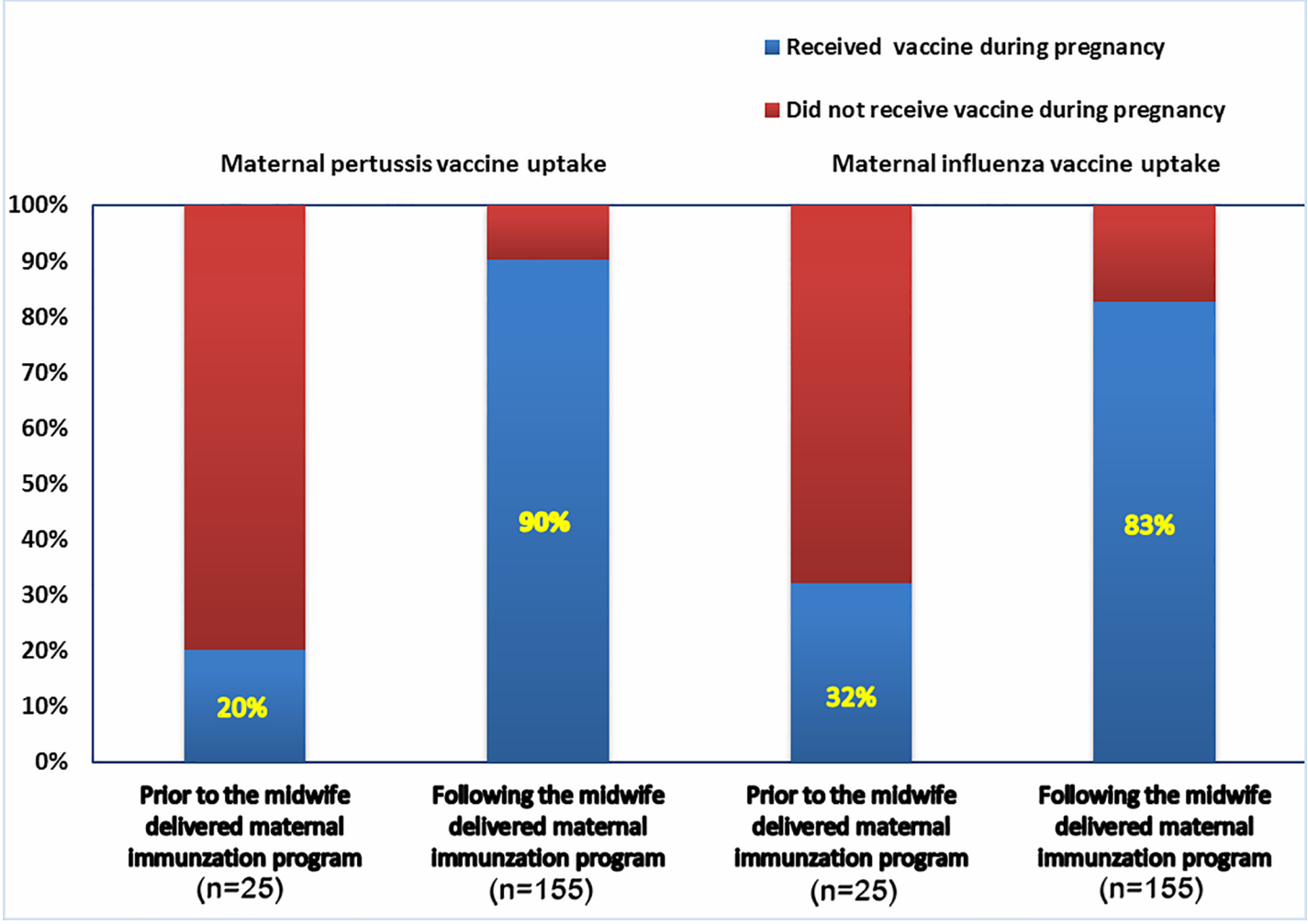


Fig 2. Maternal receipt of pertussis and influenza vaccine pre-and post-implementation of a midwife delivered maternal immunization program at the WCH in South Australia.

https://doi.org/10.1371/journal.pone.0197867.g002

Association between socio-demographic factors and maternal vaccination rates

Maternal age. The median age of participating women was 31 years. Maternal age older than 31 years was associated with lower uptake of maternal influenza and pertussis immunizations. The odds of older women (32–43 years) receiving maternal influenza vaccine was less than half that of younger women (OR 0.36; CI 0.17–0.74; p = 0.005). In multivariable logistic regression analysis, maternal age remained a strong predictor for the uptake of influenza vaccine during pregnancy (AOR 0.40; CI 0.17–0.92 p = 0.031) (Table 3). Similarly, the odds of older women receiving maternal pertussis vaccine was less than half that of younger women (OR 0.35; CI 0.18–0.78; p = 0.010). However, after adjusting for all independent variables, the association between maternal age and pertussis vaccine uptake during pregnancy was no longer statistically significant (AOR 0.39 CI 0.130–1.11; p = 0.078) (Table 2).

Country of birth. The proportion of women vaccinated against influenza and pertussis during pregnancy was not statistically significantly different between women who were born

in Australia and women born overseas (78% vs 76%; p = 0.763) (88% vs 76%; p = 0.124) (Tables 2 and 3).

Parity. In the univariate analysis, the odds of multiparous women having received maternal influenza vaccine was less than half that of first time mothers (OR 0.42 CI 0.20–0.87; p = 0.022). In multivariate analysis, the odds of mothers with previous children receiving maternal influenza vaccine remained less than half that of women with no previous children (AOR 0.43; 95% CI 0.19–0.99 p = 0.048) (Table 3). However, for pertussis vaccine uptake, whilst the odds of multiparous women receiving the vaccine was lower compared to first time mothers in a univariate analysis, this was not statistically significant (OR 0.53 CI 0.24–1.18; p = 0.116) (Table 2).

Discussion

Our results showed high uptake of pertussis (81%) and influenza (76%) vaccines during pregnancy. The higher uptake of pertussis vaccine during pregnancy compared to influenza vaccine in our study could be because most women perceive influenza as a disease affecting the mother, whereas they see pertussis as a threat to the infant and thus relatively more risky [31]. Uptake of maternal pertussis vaccine by women who delivered at the WCH prior to the government funded immunization programs was 20%, which significantly improved to 90% following the introduction of a midwife delivered and government funded pertussis program. Similarly, the uptake of influenza vaccine during pregnancy has improved from 32% to 83% following the implementation of a midwife delivered immunization program. National coverage for maternal pertussis vaccination programs in other countries is limited to local surveys of vaccine coverage, for example an estimated coverage of over 60% was reported in the UK in 2016 [32], and 51% of women delivering during March 2014 in Wisconsin [33] while uptake of 51–67% was reported in Argentina in 2014 [34].

The rise in vaccination rates could also be attributed to introduction of free pertussis vaccine for all pregnant women in South Australia in March 2015 [15]. The higher uptake of pertussis compared to influenza vaccine suggests pertussis vaccine uptake is driving influenza vaccine uptake in pregnant women as the vaccines are co administered. Our results demonstrate that the provision of maternal pertussis and influenza vaccination by midwives at the place of antenatal service was an independent strong predictor of vaccination uptake during pregnancy. It is a relatively low cost intervention, which has produced a significant increase on vaccine uptake. Pregnant women view midwives as a trusted source of health information [35]. A previous study suggested that administering maternal immunizations into standard antenatal care through midwives could improve immunization uptake among pregnant women [36].

Our study demonstrated that receiving a recommendation from a HCP was a strong predictor for receipt of maternal influenza vaccine. Women who had not received influenza vaccine during their pregnancy were less likely to have been offered influenza vaccines. About one-quarter of the women who had not received the vaccines reported they had not received a recommendation to have influenza vaccine during pregnancy. This suggest there is room for improvement for HCPs in discussing maternal vaccinations with pregnant women. Several other studies suggested that a recommendation from a HCP is the most significant factor in improving vaccination uptake during pregnancy [27, 37, 38].

Previously identified factors associated with poor uptake of vaccines in pregnancy include lack of perceived benefit by pregnant women [22], concern about the safety of maternal vaccination [39], lack of awareness of vaccine recommendation during pregnancy [40, 41] and expectant mother's attitudes toward immunization during pregnancy [42, 43]. In this study,

maternal age and parity were associated with uptake of influenza vaccines during pregnancy. Multiparous women were less likely to be vaccinated against the influenza during pregnancy compared to first time mothers. A similar finding has been reported from a previous study in South Australia [44]. Multiparous women are more likely to attend fewer antenatal visits than first time mothers [45]. They also tend to have lower emotional attachment to their unborn baby [46] and have been found to think less about the health of their fetus than first time mothers [47]. This may describe why women who had been pregnant before were less likely to be immunized against influenza vaccine during pregnancy. However, our findings have shown that there is no influence of parity on pertussis vaccine uptake during pregnancy

Our study also demonstrated that older women were less likely to be vaccinated against influenza during pregnancy. A previous study also suggested that older women are less likely to seek antenatal health care [48]. This could explain why older women were less likely to be vaccinated against influenza during pregnancy. Our study findings indicate the need for tailored and targeted interventions for older multiparous women in maternal influenza vaccination campaigns. However, a study conducted in the Netherlands has found that influenza vaccine uptake during pregnancy was higher among older and multiparous pregnant women which is in contrast to our study findings [49]. Our study also indicates that there is no influence of age on pertussis vaccination coverage, which is in contradiction with previous studies [44, 50]. Hence, further research is needed to explore if older multiparous women are more or less likely to receive maternal influenza or pertussis vaccine compared with young first time mothers.

The primary strength of our study sample is the inclusion of pregnant women prior to and following the implementation of a midwife delivered pertussis immunization programs for pregnant women. This enabled us to compare the antenatal vaccination uptake rates prior to and following the introduction of midwife delivered maternal immunization program. This study has also examined the intention of pregnant women to receive the recommended vaccines during or post pregnancy and uptake of these vaccines was verified by follow up telephone interview with the mothers after delivery.

This study was subject to some limitations. The participants in this study were recruited through a public hospital antenatal clinic. Thus, the study findings may not be a representative of the overall population of pregnant women in South Australia. Our relatively small sample size could also be a limitation to this study. Results from the vaccination coverage before the government funded immunization programs are based on a very small sample size and this could be a potential limitation of the study. The study sample also excluded non-English-speaking women and no indigenous women participated in the study therefore our findings may not be representative of culturally and linguistically diverse (CALD) and Aboriginal and Torres Strait Islander women. Vaccine uptake among women who reported they had received influenza and pertussis vaccination during their pregnancy was not verified through audit of medical records. Our study has also a potential selection bias, as women who are more accepting of vaccination may have been more likely to agree to participate in the survey. Another limitation of the study is that the questionnaire did not capture primary language, ethnicity, household income, educational level, working situation and marital status, which may also be important variables in assessing factors related to vaccine uptake during pregnancy.

Conclusions

High uptake of influenza and pertussis vaccines during pregnancy can be attained with health care provider recommendation and inclusion of maternal immunization as part of standard antenatal care. A midwife delivered maternal immunization program is a promising approach

to improve maternal vaccine uptakes by pregnant women. Additional studies are needed to monitor and evaluate the impact of government funded pertussis programs for pregnant women to ensure optimum protection for pregnant women and their infants.

Supporting information

S1 File. Maternal vaccination survey.
(DOCX)

S2 File. Dataset.
(XLSX)

Acknowledgments

The authors would like to acknowledge and thank all the women who participated in the questionnaire and the staff of the Vaccinology and Immunology Research Trials Unit (VIRTU) at the Women's and Children's Hospital; Louise Goodchild, Sue Evans, Suja Mathew, Mary Walker and Kathryn Riley for their assistance with recruitment and survey data collection

Author Contributions

Conceptualization: Michelle Clarke, Maureen Watson, Helen Marshall.

Data curation: Hassen Mohammed.

Formal analysis: Hassen Mohammed, Michelle Clarke.

Funding acquisition: Ann Koehler, Helen Marshall.

Methodology: Hassen Mohammed, Michelle Clarke, Ann Koehler, Maureen Watson, Helen Marshall.

Project administration: Helen Marshall.

Resources: Helen Marshall.

Supervision: Michelle Clarke.

Validation: Ann Koehler, Maureen Watson, Helen Marshall.

Writing – original draft: Hassen Mohammed.

Writing – review & editing: Hassen Mohammed, Michelle Clarke, Ann Koehler, Maureen Watson, Helen Marshall.

References

1. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006; 12:1638–43. https://doi.org/10.3201/eid1211.060152 PMID: 17283611
2. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012; 207:S3–S8. https://doi.org/10.1016/j.ajog.2012.06.068 PMID: 22920056
3. Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. Int J Womens Health. 2014; 6:681–9. https://doi.org/10.2147/IJWH.S47235 PMID: 25114593
4. ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. BMJ. 2010; 340:c1279. https://doi.org/10.1136/bmj.c1279 PMID: 20299694
5. Somerville LK, Basile K, Dwyer DE, Kok J. The impact of influenza virus infection in pregnancy. Future Microbiol. 2018; 13;263–74. https://doi.org/10.2217/fmb-2017-0096 PMID: 29320882

6. McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol. 2011; 204:S54–7. https://doi.org/10.1016/j.ajog.2011.04.031 PMID: 21640231
7. Munoz FM. Pertussis in infants, children, and adolescents: diagnosis, treatment, and prevention. Semin Pediatr Infect Dis. 2006; 17:14–9. https://doi.org/10.1053/j.spid.2005.11.005 PMID: 16522501
8. Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995–2005 trends by region and age group. Communicable diseases intelligence quarterly report.2007; 31:205–15. PMID: 17724997
9. Blanchard-Rohner G, Siegrist CA. Vaccination during pregnancy to protect infants against influenza: why and why not? Vaccine. 2011; 29:7542–50. https://doi.org/10.1016/j.vaccine.2011.08.013 PMID: 21820480
10. Reuman PD, Ayoub EM, Small PA. Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J. 1987; 6:398–403. PMID: 3588113
11. Maertens K, De Schutter S, Braeckman T, Baerts L, Van Damme P, De Meester I, et al. Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. Vaccine. 2014; 32:1786–92. https://doi.org/10.1016/j.vaccine.2014.01.083 PMID: 24530929
12. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. The Lancet. 384:1521–8.
13. 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; 51:1355–61. https://doi.org/10.1086/657309 PMID: 21058908
14. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza Vaccination of Pregnant Women and Protection of Their Infants. N Engl J Med. 2014; 371:918–31. https://doi.org/10.1056/NEJMoa1401480 PMID: 25184864
15. McMillan M, Clarke M, Parrella A, Fell DB, Amirthalingam G, Marshall HS. Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review. Obstet Gynecol. 2017; 129:560–73. https://doi.org/10.1097/AOG.0000000000001888 PMID: 28178054
16. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine. 2015; 33:2108–17. https://doi.org/10.1016/j.vaccine.2015.02.068 PMID: 25758932
17. Szekeres-Bartho J. Immunological relationship between the mother and the fetus. Int Rev Immunol. 2002; 21:471–95. PMID: 12650238
18. Sukumaran L, McCarthy NL, Kharbanda EO, Weintraub ES, Vazquez-Benitez G, McNeil MM, et al. Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy. Obstet Gynecol. 2015; 126;5:1069–74 https://doi.org/10.1097/AOG.0000000000001066 PMID: 26444109
19. The Australian Government Department of Health and Ageing. The Australian Immunisation Handbook 10th Edition. Canberra 2015.
20. Beard FH. Pertussis immunisation in pregnancy: a summary of funded Australian state and territory programs. Communicable diseases intelligence quarterly report. 2015; 39:E329–36. PMID: 26620346
21. 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. [journal article]. 2015; 15(1):1–7.
22. Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake of influenza vaccine by pregnant women: a cross-sectional survey. Med J Aust. 2013; 198:373–5. PMID: 23581957
23. Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey. Canberra: AIHW; 2011. Available from: http://www.aihw.gov.au/publication-detail/?id=10737418409.
24. McCarthy EA, Pollock WE, Nolan T, Hay S, McDonald S. Improving influenza vaccination coverage in pregnancy in Melbourne 2010–2011. Aust N Z J Obstet Gynaecol. 2012; 52
25. Lu AB, Halim AA, Dendle C, Kotsanas D, Giles ML, Wallace EM, et al. Influenza vaccination uptake amongst pregnant women and maternal care providers is suboptimal. Vaccine. 2012; 30:4055–9. https://doi.org/10.1016/j.vaccine.2012.04.012 PMID: 22521842
26. Taksdal S, Mak D, Joyce S, Tomlin S, Carcione D, Armstrong P, et al. Predictors of uptake of influenza vaccination A survey of pregnant women in Western Australia. Aust Fam Physician. 2013; 42:582–6. PMID: 23971070
27. SA Health. Understanding Vaccines for Midwives-vaccination requirements during pregnancy and early childhood Adelaide: Goverment of South Australia. Available from: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/professional+development/

immunisation+provider+training+and+education/understanding+vaccines+for+midwives-vaccination+requirements+during+pregnancy+and+early+childhood Accessed 15 November, 2016.

28. O'Grady K-AF, McHugh L, Nolan T, Richmond P, Wood N, Marshall HS, et al. FluMum: a prospective cohort study of mother–infant pairs assessing the effectiveness of maternal influenza vaccination in prevention of influenza in early infancy. BMJ open. 2014; 4(6).
29. Australian Bureau of Statistics. 3301.0—Births, Australia Canberra, Australia2013. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3301.02013?OpenDocument.
30. Scheil W SJ CB, Sage L, Kennare R,. Pregnancy Outcome in South Australia South Australia Pregnancy Outcome Unit. 2013.
31. Wiley KE, Cooper SC, Wood N, Leask J. Understanding Pregnant Women's Attitudes and Behavior Toward Influenza and Pertussis Vaccination. Qual Health Res. 2015; 25(3):360–70. https://doi.org/10.1177/1049732314551061 PMID: 25246330
32. Amirthalingam G, Letley L, Campbell H, Green D, Yarwood J, Ramsay M. Lessons learnt from the implementation of maternal immunization programs in England. Hum Vaccin Immunother. 2016; 12:2934–9 https://doi.org/10.1080/21645515.2016.1210730 PMID: 27454010
33. Koepke R, Kahn D, Petit AB, Schauer SL, Hopfensperger DJ, Conway JH, et al. Pertussis and Influenza Vaccination Among Insured Pregnant Women—Wisconsin, 2013–2014. MMWR Morb Mortal Wkly Rep. 2015; 64:746–50. PMID: 26182193
34. Vizzotti C, Neyro S, Katz N, Juarez MV, Perez Carrega ME, Aquino A, et al. Maternal immunization in Argentina: A storyline from the prospective of a middle income country. Vaccine. 2015 Nov 25; 33 (47):6413–9. https://doi.org/10.1016/j.vaccine.2015.07.109 PMID: 26277071
35. Soltani H, Dickinson FM. Exploring women's views on information provided during pregnancy. British Journal of Midwifery. 2005; 13(10):633–6. Cited in: Scopus.
36. Robbins SC, Leask J, Hayles EH, Sinn JK. Midwife attitudes: an important determinant of maternal postpartum pertussis booster vaccination. Vaccine. 2011 Aug 5; 29(34):5591–4. https://doi.org/10.1016/j.vaccine.2011.05.049 PMID: 21624420
37. Webb H, Street J, Marshall H. Incorporating immunizations into routine obstetric care to facilitate Health Care Practitioners in implementing maternal immunization recommendations. Hum Vaccin Immunother. 2014; 10:1114–21. https://doi.org/10.4161/hv.27893 PMID: 24509790
38. Hayles EH, Cooper SC, Sinn J, Wood N, Leask J, Skinner SR. Pertussis vaccination coverage among Australian women prior to childbirth in the cocooning era: a two-hospital, cross-sectional survey, 2010 to 2013. Aust N Z J Obstet Gynaecol. 2016; 56:185–91. https://doi.org/10.1111/ajo.12429 PMID: 26751804
39. Bodeker B, Walter D, Reiter S, Wichmann O. Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. Vaccine. 2014 Jul 16; 32(33):4131–9. https://doi.org/10.1016/j.vaccine.2014.06.007 PMID: 24928791
40. Collins J, Alona I, Tooher R, Marshall H. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. Hum Vaccin Immunother. 2014; 10:2922–9. https://doi.org/10.4161/21645515.2014.971606 PMID: 25483464
41. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015; 33:6420–9. https://doi.org/10.1016/j.vaccine.2015.08.046 PMID: 26320417
42. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women—a systematic review. Vaccine. 2014; 32:4602–13. https://doi.org/10.1016/j.vaccine.2014.06.067 PMID: 24996123
43. MacDougall DM, Halperin BA, Langley JM, McNeil SA, MacKinnon-Cameron D, Li L, et al. Knowledge, attitudes, beliefs, and behaviors of pregnant women approached to participate in a Tdap maternal immunization randomized, controlled trial. Hum Vaccin Immunother. 2016; 12:879–85. https://doi.org/10.1080/21645515.2015.1130193 PMID: 27176822
44. Wong CY, Thomas NJ, Clarke M, Boros C, Tuckerman J, Marshall HS. Maternal uptake of pertussis cocooning strategy and other pregnancy related recommended immunizations. Hum Vaccin Immunother. 2015; 11:1165–72. https://doi.org/10.1080/21645515.2015.1019188 PMID: 25874807
45. Zafar AA, Ehiri JE, Anyanwu EC. Use of antenatal services in Kampung District, Cambodia. ScientificWorldJournal. 2003; 3:1081–92. https://doi.org/10.1100/tsw.2003.95 PMID: 14612613
46. Condon JT, Esuvaranathan V. The influence of parity on the experience of pregnancy: a comparison of first- and second-time expectant couples. Br J Med Psychol. 1990; 63 (Pt 4):369–77.
47. van Bakel HJ, Maas AJ, Vreeswijk CM, Vingerhoets AJ. Pictorial representation of attachment: measuring the parent-fetus relationship in expectant mothers and fathers. BMC Pregnancy Childbirth. 2013; 13:138. https://doi.org/10.1186/1471-2393-13-138 PMID: 23806122

48. Hildingsson I, Waldenstrom U, Radestad I. Women's expectations on antenatal care as assessed in early pregnancy: number of visits, continuity of caregiver and general content. Acta Obstet Gynecol Scand. 2002; 81:118–25. PMID: 11942901

49. van Lier A, Steens A, Ferreira JA, van der Maas NAT, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine. 2012; 30:2892–9. https://doi.org/10.1016/j.vaccine.2012.02.030 PMID: 22374374

50. Butler AM, Layton JB, Li D, Hudgens MG, Boggess KA, McGrath LJ, et al. Predictors of Low Uptake of Prenatal Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Immunization in Privately Insured Women in the United States. Obstet Gynecol. 2017; 129:629–37. https://doi.org/10.1097/AOG.0000000000001927 PMID: 28277354