Guidelines for Influenza Vaccination Uptake in Pregnant Women: A Cluster-Randomized Controlled Trial

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GUIDELINES FOR INFLUENZA VACCINATION UPTAKE IN PREGNANT WOMEN: A CLUSTER-RANDOMIZED CONTROLLED TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
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Master of Medical Science

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# TABLE OF CONTENTS

ABBREVIATIONS ................................................................................................................ IV

LIST OF TABLES AND FIGURES ........................................................................................ IV

ABSTRACT .......................................................................................................................... V

CHAPTER 1: INTRODUCTION ................................................................................................. 1

1.1 BACKGROUND ................................................................................................................ 1
1.2 STATEMENT OF THE PROBLEM .................................................................................. 3
1.3 OBJECTIVES AND GOALS .......................................................................................... 4
1.4 HYPOTHESIS .................................................................................................................. 4
1.5 DEFINITIONS .................................................................................................................. 5
1.6 REFERENCES .................................................................................................................. 5

CHAPTER 2: REVIEW OF THE LITERATURE .......................................................................... 7

2.1 INTRODUCTION .............................................................................................................. 7
2.2 BARRIERS TO INFLUENZA VACCINE UPTAKE .......................................................... 8
  2.2.1 Lack of Healthcare Provider Recommendation ...................................................... 8
  2.2.2 Lack of Information about Influenza Infection and Influenza Vaccine ....................... 9
  2.2.3 Concern for Safety of the Fetus ................................................................................. 10
2.3 FACILITATORS FOR INFLUENZA VACCINE UPTAKE ............................................. 11
  2.3.1 Healthcare Provider Recommendation .................................................................. 11
  2.3.2 History of Previous Influenza Vaccination ............................................................... 13
  2.3.3 Desire for Neonatal Protection ................................................................................ 14
  2.3.4 High Perceived Infection Susceptibility, Vaccine Safety, and Vaccine Benefit .......... 14
  2.3.5 Other Factors Associated with Influenza Vaccine Uptake in Pregnancy ................. 15
2.4 HEALTHCARE PROVIDER ATTITUDES AND PRACTICES ......................................... 18
2.5 LIMITATIONS OF CROSS-SECTIONAL SURVEYS ....................................................... 20
2.6 INTERVENTIONS FOR INFLUENZA VACCINE UPTAKE IN PREGNANT WOMEN ........ 20
  2.6.1 Pamphlet-Centered Interventions .......................................................................... 20
  2.6.2 Text-Centered Interventions .................................................................................. 21
  2.6.3 Internet-Centered Interventions ............................................................................. 24
  2.6.4 Patient-Centered Interventions ............................................................................. 26
  2.6.5 Provider-Centered Interventions ........................................................................... 27
2.7 CONCLUSION ................................................................................................................. 30
2.8 REFERENCES ................................................................................................................. 33

CHAPTER 3: STUDY METHODS ............................................................................................ 37

3.1 STUDY DESIGN .............................................................................................................. 37
3.2 STUDY POPULATION, SAMPLING, AND RECRUITMENT .......................................... 37
  3.2.1 Recruitment of Obstetric Clinics ............................................................................. 37
  3.2.2 Recruitment of Patient Subjects ............................................................................. 38
3.3 SUBJECT PROTECTION AND CONFIDENTIALITY ..................................................... 39
3.4 STUDY VARIABLES, MEASURES, AND OPERATIONALIZATION .............................. 40
  3.4.1 Assignment of Intervention .................................................................................... 40
  3.4.2 Independent Variable (Intervention) ....................................................................... 40
  3.4.3 Dependent Variable (Outcome) .............................................................................. 41
  3.4.4 Control Variable (Usual Care) ................................................................................ 42
  3.4.5 Covariates .............................................................................................................. 42
3.5 BLINDING OF INTERVENTION AND OUTCOME ....................................................... 42
3.6 DATA COLLECTION ...................................................................................................... 43
3.7 SAMPLE SIZE CALCULATION ..................................................................................... 44
Abbreviations

ACIP Advisory Committee on Immunization Practices
ACOG American College of Obstetricians and Gynecologists
AOR Adjusted Odds Ratio
APGAR Appearance, Pulse, Grimace, Activity, and Respiration
APR Adjusted Prevalence Ratio
CDC Centers for Disease Control and Prevention
CI Confidence Interval
COVID-19 Coronavirus Disease 2019
EMR Electronic Medical Record
FDA Food and Drug Administration
ICC Intracluster Correlation Coefficient
ICU Intensive Care Unit
OB-GYN Obstetrician-Gynecologist
OR Odds Ratio
RMB Renminbi (Unit of Chinese Currency)
SALHSA_50 Spanish Assessment of Health Literacy
TIV Trivalent Inactivated Vaccine
US United States of America
WHO World Health Organization

List of Tables and Figures

Table 1: Obstetric Clinic Inclusion and Exclusion Criteria…………………………38
Table 2: Patient Subject Inclusion and Exclusion Criteria…………………………39
Table 3: Patient-Level and Clinic-Level Covariates………………………………42
Figure 1: Study Timeline………………………………………………………46
Abstract

Influenza is a contagious respiratory illness caused by influenza viruses. Influenza infection during pregnancy poses unique risks to pregnant women and infants, including severe symptoms and adverse pregnancy outcomes. However, many pregnant women do not receive the influenza vaccination. Reasons for low vaccine uptake are multifactorial, with the lack of a healthcare provider’s recommendation being a critical barrier. In this cluster-randomized controlled trial, we will examine the effect of a structured vaccine recommendation program for obstetric providers on the mean proportion of pregnant women who receive the influenza vaccination. Specifically, this trial will use a custom provider education program based on resources used in pediatric settings. A recommendation program that effectively increases influenza vaccine uptake could decrease morbidity and mortality among pregnant woman and infants. Additionally, this vaccine recommendation program could be extended across patient populations and applied to other high-burden infectious diseases to increase vaccine uptake.
CHAPTER 1: INTRODUCTION

1.1 Background

Influenza is an acute respiratory illness caused by influenza A or B viruses that occurs in outbreaks and epidemics worldwide, mainly during the winter season. The illness presents with signs and symptoms of upper and lower respiratory tract infection, along with systemic symptoms such as fever, headache, myalgia, and weakness.\(^1\) Influenza is usually a self-limiting disease in the general population, but it is associated with increased morbidity and mortality in some high-risk populations including pregnant women.\(^1\) Influenza is responsible for a large disease burden worldwide; during the 2018-2019 influenza season in the United States (US) alone, the virus caused 4.4 million infections, 58,000 hospitalizations, and 3,500 deaths.\(^2\) Influenza illness poses unique risks to pregnant women and infants. Throughout pregnancy, physiologic changes such as decreased functional residual lung capacity, mucus hypersecretion, increased cardiac output, and increased plasma blood volume alter the mother’s respiratory and cardiovascular systems. These physiologic changes, along with changes to the mother’s immune system, contribute to a modified response to infection and increased risk of complications during pregnancy.\(^3\)

Pregnant women have a greater risk of morbidity and mortality if infected with influenza during influenza pandemics and interpandemic periods.\(^4\) Throughout the 2009 H1N1 pandemic, pregnant women accounted for 1% of the US population but 5% of H1N1-related deaths.\(^5\) In the influenza seasons spanning from 2010 through 2018, pregnant women accounted for up to 34% of influenza-associated hospitalizations among females aged 15-44 years.\(^6\)
In addition to maternal risks associated with influenza infection during pregnancy, infection also poses unique risks to the developing fetus, newborn infant, and infant less than six months old. Data from the 1918 H1N1 pandemic demonstrated an increased risk of pregnancy loss associated with influenza infection. Pregnant women who developed influenza had a significantly higher perinatal mortality rate (39 per 1,000 versus 7 per 1,000 total US births), as well as increased frequency of preterm delivery (63.3% versus 12.3% total US births), neonatal intensive care unit (ICU) admission (22% versus 6.1% total US births), and 5-minute Apgar scores less than six (29.2% versus 1.6% total US births) than non-pregnant women during the 2009 H1N1 influenza pandemic. Although influenza vaccinations are not approved for administration in infants less than six months, the vaccination of mothers during pregnancy may protect the infant in early life through the transfer of antibodies. The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) affirms that influenza vaccination of the mother during pregnancy is the only accepted way to prevent influenza infection in infants, who are particularly vulnerable.

Based on the risks that influenza infection poses, as well as the safety of the vaccine for pregnant women and their infants evidenced by current literature, the World Health Organization (WHO), the ACIP, and the American College of Obstetricians and Gynecologists (ACOG) recommend that all women who are or will be pregnant during influenza season receive a trivalent inactivated vaccine (TIV) as soon as it is available or at any time during pregnancy. Although 97.7% of US pregnant women in 2017 visited a doctor or medical professional, influenza vaccine coverage among pregnant women was only 35.6%; as a result, nearly two-thirds of pregnant women were not
protected from influenza.\textsuperscript{15} Among women who received prenatal care, 58.7\% reported being recommended and offered the vaccine, 15.6\% received a recommendation but no offer for the vaccine, and 25.7\% did not receive a recommendation or offer at all.\textsuperscript{15} Vaccination uptake among these groups of women, respectively, was 52.4\%, 26.1\%, and 5.7\%.\textsuperscript{15} These estimates of influenza vaccine coverage remain far below the Office of Disease Prevention and Health Promotion’s Healthy People 2020 goal of 80\% for pregnant women.\textsuperscript{16} Because of the large disease burden of influenza and the influenza-associated complications and risks among pregnant women and infants, addressing low uptake of the vaccination in pregnant women should be a priority.

The reasons for the disparity between the Centers for Disease Control and Prevention (CDC)’s recommendations and vaccine uptake in pregnant women is multifaceted; however, the lowest percentages of influenza vaccination uptake in pregnant women are from women who are not offered, referred, or recommended the vaccine by their prenatal care provider.\textsuperscript{6} This highlights the effect that healthcare providers have on vaccine uptake and the sizeable consequences that absences of offers, referrals, and recommendations have on maternal and fetal health.

\textbf{1.2 Statement of the Problem}

Influenza carries a large global disease burden and poses unique risks for pregnant women and infants.\textsuperscript{1,2} The WHO and the CDC recommend that all pregnant women receive the influenza vaccine during pregnancy; however, 64.4\% of pregnant women in the US do not receive the vaccine, putting them and their infants at risk for developing severe influenza infection and adverse pregnancy outcomes.\textsuperscript{11,12,15} Many pregnant women
are not recommended, offered, or referred for the influenza vaccine by their prenatal care providers, which contributes considerably to low uptake.\textsuperscript{15}

Since the WHO and the CDC began recommending the influenza vaccine to all pregnant women during influenza season, researchers have investigated various interventions and their effectiveness in improving influenza vaccination uptake; however, current literature lacks sufficient randomized controlled trials, particularly those focused on intervening to improve dialogue between patients and healthcare providers. In neonatal and pediatric settings, the CDC offers providers structured recommendations, including communication tools to use with new parents.\textsuperscript{17} These recommendations have been successful in improving pediatric vaccine uptake in the US, with rates of children 19-35 months receiving most vaccinations greater than 80-90%.\textsuperscript{17,18} Similar interventions have yet to be investigated thoroughly in the obstetric setting.

1.3 Objectives and Goals

The objective of this study is to examine the difference in the mean proportion of pregnant women who receive an influenza vaccine among those receiving prenatal care at obstetric clinics that provide a structured vaccine recommendation program versus usual care. The goal of this study is to increase influenza vaccine uptake among pregnant women, decrease influenza-associated adverse pregnancy outcomes, and decrease morbidity and mortality in both pregnant women and infants.

1.4 Hypothesis

Among pregnant women older than 18 years receiving prenatal care, there will be a statistically significant difference in the mean proportion of influenza vaccination uptake prior to date of delivery within the clusters of obstetric clinics receiving a
structured vaccine recommendation program compared to the clusters of obstetric clinics receiving usual care.

1.5 Definitions

**Prenatal**: Before birth; during or related to pregnancy.

**Cluster-Randomized Controlled Trial**: Randomized-controlled trial in which groups of individuals, or clusters, are randomized instead of individuals. In this study, an obstetric clinic will be a cluster that is randomized into the intervention or control study arm.

**Obstetric**: Related to childbirth and the associated processes.

**Structured Vaccine Recommendation Program**: See section 3.4.1 Independent Variable (Intervention) and Appendix F, Appendix G, Appendix H, and Appendix I for details.

**Usual Care**: Wide range of practices in which providers may individualize patient care. In this study, usual care will include any care that does not include the structured vaccine recommendation program. See section 3.4.3 Control Variable (Usual Care) for details.

1.6 References

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

A systematic literature search was conducted from December 2020 through May 2021 in PubMed, Ovid, and Cochrane databases. The search performed across the three databases was:

(pregna* OR birth OR prenat* OR gestat*) AND (program* OR educat* OR intervention* OR recommend* OR dialogue* OR regimen* OR exposure*) AND (influenza* or flu) AND (vaccin* OR immuniz* OR inject*), with MeSH terms (pregnancy) and (influenza vaccines*).

The search was limited to randomized controlled trials published during the years 2010 through 2020 and to cross-sectional surveys, prospective cohort studies, retrospective cohort studies, and literature reviews published during the years 2015 through 2020. All studies were retrieved into Endnote X9. We included studies that met the following criteria: 1) examined a population of pregnant women; 2) examined the influenza vaccination; and 3) evaluated vaccine uptake facilitators, vaccine uptake barriers, healthcare provider attitudes regarding patient vaccination, or involved interventions influencing vaccine uptake. We excluded studies that: 1) were written in a language other than English; 2) had a sample size less than 100 subjects; 3) exclusively focused on non-pregnant patients; 4) did not examine the influenza vaccine; and 5) exclusively discussed influenza vaccine safety. Each study was analyzed to identify its strengths and limitations to determine how our study can address current literature gaps.
2.2 Barriers to Influenza Vaccine Uptake

Studies conducted in the United States and abroad have assessed barriers that decrease the likelihood pregnant women will receive the influenza vaccination.\textsuperscript{1-14} Identifying these barriers is important when attempting to increase vaccine uptake; along with influencing uptake, these barriers may act as confounding variables in randomized controlled trials that examine a specific intervention’s effect on vaccine uptake.

2.2.1 Lack of Healthcare Provider Recommendation

Across the literature review, the most commonly reported barrier to influenza vaccine uptake was lack of healthcare provider recommendation.\textsuperscript{1-6} In a cross-sectional survey among pregnant women receiving prenatal care in Melbourne, Australia, the most commonly reported reason for non-vaccination was lack of provider recommendation (37\%).\textsuperscript{1} This survey included women “intending” to receive vaccination, which may have overestimated vaccine uptake.\textsuperscript{1} In another survey from Australia, 61\% of women randomly selected from a perinatal database were vaccinated during pregnancy (95\% confidence interval [CI], 55-66\%); of those unvaccinated, 53.6\% reported they would have been vaccinated if a healthcare provider recommended it (95\% CI, 45.9-61.3\%).\textsuperscript{2} 86\% of the self-reported vaccines in this study were verified by an immunization provider, decreasing potential overestimation from self-report bias.\textsuperscript{2} A cross-sectional survey conducted in Western Australia reported that the most common reason for being unimmunized in 2014 was lack of healthcare provider recommendation (48.5\%, 95\% CI 42.8-54.1\%).\textsuperscript{3} Random participant sampling increases this study’s generalizability. Researchers verified vaccine receipt with electronic medical record (EMR) data to limit self-report and recall bias.\textsuperscript{3}
A cross-sectional survey of pregnant women attending five obstetric clinics in Italy reported that low vaccination adherence was associated with a lack of vaccination promotion by healthcare providers (odds ratio [OR] 0.16, 95% CI 0.04-0.69, p=0.01).\(^5\) The high rate of refusal in this survey (96.1\%) may have been biased by the high percentage of women in their second trimester of pregnancy (78\%), who may have lower risk perception than women in their first trimester.\(^5\) In another cross-sectional survey conducted in Milan, Rome, and Jesi, Italy, the most prominent barrier, reported by 81\% of women, was a healthcare provider’s lack of vaccine recommendation.\(^7\) This study only assessed women in the third trimester of pregnancy, who may have had lower presumed risk, thus decreasing vaccine uptake. Multivariate regression analyses could not be conducted due to low vaccination coverage (6.5\%, 95% CI, 4.9-8.5\%).\(^7\)

In a 2019 cross-sectional survey from two Singapore hospitals, the most reported reason for not receiving the influenza vaccine was lack of recommendation (45\%).\(^4\) This study only surveyed patients attending public hospitals. Therefore, it may have underestimated the proportion of Singaporean women vaccinated.\(^4\) In a retrospective study conducted in Athens, Greece, 65.5\% of mothers reported that they would have been vaccinated if their doctor recommended it (95% CI, 58.8-72.25). However, no recommendation was made in 73.6\% of cases (95% CI, 67.4-79.8\%).\(^6\)

### 2.2.2 Lack of Information about Influenza Infection and Influenza Vaccine

Another barrier to influenza vaccine uptake is a lack of information about influenza and its increased danger in pregnancy, as well as the safety and efficacy.\(^4,8-11\) In a cross-sectional survey of mothers who gave birth at one hospital in France from 2014-2015, 46\% did not know influenza can cause adverse outcomes in infants.\(^8\) Logistic
regression analyses accounted for confounding variables, including medical comorbidities, parity, education, and vaccine history.\textsuperscript{8}

In a cross-sectional survey of mothers who gave birth at one university hospital in Valencia, Spain, of the 48\% of women who declined the influenza vaccination, 23\% felt that they had insufficient information to make an informed decision.\textsuperscript{9} A retrospective cohort study also from Valencia reported that 16\% of unvaccinated women “did not have adequate information”.\textsuperscript{11} This retrospective design allowed for data collection from an EMR, minimizing self-report bias.\textsuperscript{11}

A cross-sectional survey from Ireland randomly recruited pregnant women from prenatal clinics and found that only 57.6\% knew that the influenza vaccine is safe in pregnancy, although 75\% had heard about influenza vaccine in pregnancy.\textsuperscript{10} However, this study had a small patient sample size (n=113), which may limit its generalizability.\textsuperscript{10}

2.2.3 Concern for Safety of the Fetus

A 2018 literature review of 75 studies reported that vaccine safety perceptions were the most common barriers to accepting influenza vaccination.\textsuperscript{15} During the 2017-2018 influenza season in the United States, an internet panel survey of 1,771 pregnant women found that 16\% did not vaccinate their child because of concerns about safety risks to their infant.\textsuperscript{13} Although this survey had a large sample size, the nonprobability sample may not be generalizable across pregnant women in the United States.\textsuperscript{13} Another cross-sectional survey across clinics in Texas, New York, Illinois, and Pennsylvania found that the greatest barrier to influenza vaccination uptake was concern for the health and safety of the baby (44.5\%).\textsuperscript{14} However, 59\% of the sample was white and 71.5\% was highly educated, which may affect this study’s generalizability.\textsuperscript{14} In a prospective cohort
study from an obstetric clinic in Greece, the most common reason for refusing the vaccine was “fear of adverse events for their fetus” (27%).

The fourteen studies discussed above illustrate ubiquitous barriers to influenza vaccination from eight countries between 2012 and 2019, with respective reported uptake in pregnancy ranging widely from 3.9-77.9%. These barriers underscore both the need for prenatal care providers to recommend that pregnant women get vaccinated and the need to inform patients about the vaccine’s safety and the health risks posed to them and their unvaccinated infant.

2.3 Facilitators for Influenza Vaccine Uptake

Studies have also assessed facilitators that increase the likelihood pregnant women will receive the influenza vaccination. Since facilitators may also act as confounding variables, it is important to understand their independent effects on vaccination uptake.

2.3.1 Healthcare Provider Recommendation

Healthcare provider recommendation is the most commonly reported facilitator of influenza vaccine uptake in pregnant women. One systematic review and meta-analysis of 49 studies reported that pregnant women were ten to twelve times more likely to receive the vaccine if a healthcare provider recommended it. Another review of 32 studies from 15 countries similarly found that healthcare provider recommendation was the most common determinant of vaccination uptake. A cross-sectional survey conducted across the 2017-2018 influenza season in the United States found that of the 66.6% of women who received a provider recommendation, 63.8% of those were vaccinated. Of the 19% who did not receive a recommendation, only 30.1% were
Another cross-sectional survey across four American clinics found that accepting the influenza vaccine was associated with a healthcare provider’s recommendation (OR 2.60, p<0.01). Another cross-sectional survey reported that from September 2017-March 2018, provider recommendation was the most common reason for receiving the influenza vaccine among pregnant women in Ireland (39%). In Italy, vaccine recommendation from a healthcare provider during pregnancy was a significant predictor of vaccine uptake (OR 28, 95% CI 14-63, p<0.001). During Australia’s 2016 influenza season, healthcare provider recommendation was the strongest predictor of influenza vaccination uptake (OR 30, 95% CI 16-56, p<0.001). In a 2013 cross-sectional survey conducted at two hospitals in Managua, Nicaragua, vaccine recommendation from a healthcare provider was positively associated with receipt (adjusted odds ratio [AOR] 14.22, 95% CI 10.45-19.33, p<0.01). A cross-sectional survey conducted among women at prenatal clinics in Zhejiang, China from January-March 2014 found 93% of pregnant women agreed that “if a physician or nurse recommended the influenza vaccine, I would get vaccinated” (p<0.001), despite only 76% were willing to receive the vaccine otherwise. This study likely overestimated the population’s vaccination status because it merely reports willingness to accept the vaccine. In a cross-sectional survey of pregnant women and obstetric physicians in Rajavithi, Thailand, physician recommendation was the only facilitator associated with vaccination uptake. Women were 2.3-times more likely to get vaccinated when a physician recommended the vaccine (AOR 2.3, 95% CI 1.4-3.8, p<0.01). This study may have underestimated vaccination proportion, since it only accounted for uptake within 30 days of recruitment.
2.3.2 History of Previous Influenza Vaccination

Influenza vaccination in previous influenza seasons is also associated with vaccine uptake during pregnancy.\textsuperscript{1,7,14,18,21-23} A retrospective EMR review of pregnancies that overlapped with influenza seasons between 2002 and 2011 in integrated healthcare systems throughout California, Colorado, Oregon, Washington, and Wisconsin, found that vaccination in a previous influenza season was a significant predictor of vaccination during pregnancy (OR 4.66, 95% CI 4.57-4.75).\textsuperscript{21} However, it is unclear whether this study is generalizable to pregnant women in the United States because it did not record ethnicity data. Moreover, the study may underestimate vaccine proportions because it did not account for vaccines obtained outside of health systems utilizing this EMR.\textsuperscript{21} A cross-sectional survey across clinics in Texas, New York, Illinois, and Pennsylvania reported that previously accepting an influenza vaccine increased uptake probability during pregnancy (4.87, p<0.01).\textsuperscript{14}

Previous influenza vaccination was also associated with increased vaccination uptake among women who received prenatal care at a large university hospital in France between November 2014 and June 2015 (OR 4.1, 95% CI 3.1-5.5, p<0.001).\textsuperscript{23} Among pregnant women in Melbourne, Australia, previous receipt of the influenza vaccine was a predictor of vaccine uptake (OR 8, 95% CI 5-15, p<0.001).\textsuperscript{1} The same was true for hospitals in Italy (OR 28, 95% CI 14-63, p<0.001).\textsuperscript{7} A retrospective cohort study found that willingness to receive influenza vaccination during pregnancy was associated with ever having a previous influenza vaccination among pregnant women attending eight hospitals or affiliated prenatal care clinics in Beijing, China between March and April, 2016 (AOR 6.74, 95% CI 1.71-26.4, p=0.006).\textsuperscript{22} The high household income (63.4%
>5,000 renminbi [RMB], unit of Chinese currency) and education status (75.3% with a bachelor’s degree or higher) of the study’s sample population suggest the findings are not generalizable to all of China.22

2.3.3 Desire for Neonatal Protection

83% of 2,045 women who received prenatal care at a large university hospital in France between November 2014 and June 2015 stated that their primary motivator for vaccination was “protection of her baby”.23 Similarly, pregnant women in Western Australia reported that the most common reason for accepting the influenza vaccine was “to protect her baby” (92.8%, 95% CI 89.9-95.7%, p=0.002).3 Mothers across Italian hospitals in 2018 who knew that the influenza vaccine protects newborns during their first months of life were more likely to be vaccinated (OR 6.2, 95% CI 3.14-14, p<0.001).7

2.3.4 High Perceived Infection Susceptibility, Vaccine Safety, and Vaccine Benefit

Women are more likely to receive the influenza vaccine during pregnancy if they are aware of: 1) their increased susceptibility to infection; 2) increased risk of severe disease; and 3) the vaccination’s benefits.10,18,22 A cross-sectional survey of women attending prenatal clinics in Zhejiang, China from January-March 2014 reported the following factors were associated with vaccination uptake: high perceived susceptibility of influenza infection (AOR 1.75, 95% CI 1.36-2.08); high perceived levels of influenza severity (AOR 1.62, 95% CI 1.25-1.95); and high perceived levels of vaccination benefit (1.97, 95% CI 1.76-2.21).18 Moreover, an Irish cross-sectional survey found a relationship between knowing the influenza vaccine is safe and receiving it (p<0.001).10 Similarly, a retrospective cohort study from Beijing, China reported that high perceived
benefit of vaccination was associated with vaccination uptake (AOR 1.67, 95% CI 1.00-2.79, p=0.05).\textsuperscript{22}

2.3.5 Other Factors Associated with Influenza Vaccine Uptake in Pregnancy

Older maternal age has been associated with influenza vaccine uptake in pregnancy.\textsuperscript{21,24} Older age was a predictor of vaccination during pregnancy that overlapped with 2002-2011 influenza seasons in the US (OR 1.71, 95% CI 1.16, 1.17).\textsuperscript{21} A 2015 English retrospective cohort study reported age was a significant predictor of whether 4,817 mothers who gave birth at South London Hospital that year received the influenza vaccination; specifically, women above 26 years of age were more likely to receive the vaccine than women below 26 years of age (OR 1.84, 95% CI 1.27-2.67, p<0.001).\textsuperscript{24} This study’s retrospective design limits self-report bias with EMR review.\textsuperscript{24}

Nulliparity, or never having given birth, has also been associated with increased influenza vaccine uptake in pregnancy.\textsuperscript{23,24} Nulliparity was associated with increased vaccine uptake among women who received prenatal care at a large hospital in France (41.0\% vs. 31.3\%, OR 2.5, 95% CI 1.7-3.7, p=0.001).\textsuperscript{23} A 2018 English retrospective cohort study found a similar association (p<0.001).\textsuperscript{24} First-time pregnant women may attend more appointments, which may increase the likelihood they will receive a vaccine recommendation. Women with more prenatal visits during influenza season were also more likely to receive influenza vaccination.\textsuperscript{17,21,24} In Managua, Nicaragua in 2013, having four or more prenatal visits was associated with vaccine receipt (AOR 2.58, 95% CI 1.15-5.81, p<0.01).\textsuperscript{17} Similarly, an English 2018 retrospective cohort study reported that increased number of prenatal visits during fall and winter seasons was associated with increased vaccination uptake (p<0.001).\textsuperscript{24} Furthermore, an American retrospective
cohort study found that longer overlap between pregnancy and influenza season was associated with increased vaccination uptake (AOR 4.28, 95% CI 4.15-4.41).\textsuperscript{21}

Pregnant women with comorbidities may be more likely to receive the influenza vaccination during pregnancy.\textsuperscript{21,23} In the United States, a retrospective cohort study conducted during influenza seasons from 2002 to 2012 reported the following high-risk medical conditions are associated with increased vaccination uptake during pregnancy: chronic cardiac, pulmonary, liver, or renal disease, immunosuppression, diabetes mellitus, malignancy, or a neurologic or musculoskeletal condition (AOR 1.26, 95% CI 1.24-1.28).\textsuperscript{21} Medical comorbidities were associated with increased vaccination uptake among pregnant women in France from 2014 to 2015 (p=0.02).\textsuperscript{23}

Health literacy and education level have been shown to have both positive and negative effects on influenza vaccination uptake in pregnant women.\textsuperscript{9,22,27} The National Center for Health Statistics conducted a cross-sectional survey of 5 million pregnant women between the 2012-2016 influenza seasons in the United States and found the likelihood of vaccination uptake increased if the mother had a bachelor’s degree or higher as compared to mothers with a high school diploma or less (OR 2.09, 95% CI 1.35-3.22, p=0.002).\textsuperscript{27} This study’s strengths are its large sample size and comprehensive data encompassing five influenza seasons. However, its cross-sectional design merely shows associations, not causation.\textsuperscript{27} A 2016 retrospective cohort study from Beijing, China reported having more knowledge about influenza was associated with vaccination uptake (AOR 82.2, 95% CI 21.7-311.1, p<0.001).\textsuperscript{22} This suggests pregnant women with a lower education level are less likely to receive the influenza vaccination.\textsuperscript{22,27}

However, in a cross-sectional survey of mothers at a university hospital in Spain
between November 2015 and May 2016, mothers who did not receive the influenza vaccination during pregnancy had higher health literacy than those who received the vaccination (p=0.022). Notably, this statistically significant difference was only seen when health literacy was measured by the Spanish Assessment of Health Literacy (SAHLSA_50), and was not seen with two different screening tools (p=0.372, p=0.942).

One explanation for this discrepancy is the study’s small sample size; another explanation is these screening tools’ reliability may have been compromised because they have not been used extensively in Spanish-speaking populations. Further research should investigate whether increased health literacy is truly associated with vaccination refusal.

A provider’s ability to offer an in-clinic influenza vaccine shortly after recommendation is also associated with increased uptake. A cross-sectional survey conducted at three prenatal clinics in Paris reported that women who attended a clinic with vaccines available for in-clinic administration had higher vaccine uptake than those who attended a clinic requiring administration at a pharmacy (35.4% vs. 2.7%, p<0.01). Patients were reimbursed for in-clinic and pharmacy-administered vaccinations to control for cost as a confounding variable. This may make the results ungeneralizable because pharmacy-administered vaccines in France may require payments.

The above studies illustrate ubiquitous facilitators for influenza vaccination from ten countries. These facilitators should be considered when investigating methods to increase vaccination uptake and controlled for as potential confounding variables in randomized controlled trials.
2.4 Healthcare Provider Attitudes and Practices

Other cross-sectional studies surveyed healthcare providers to investigate their attitudes and practices about recommending the influenza vaccine to prenatal patients. An exploratory literature review of 75 studies found the most commonly cited barriers among American healthcare providers to recommending maternal influenza immunization were financial concerns including inadequate reimbursement, payment, or complexity of billing.

Some physicians believe insufficient evidence exists regarding the influenza vaccine’s efficacy in pregnancy, which decreases recommendation and administration rates. One cross-sectional survey of obstetrician-gynecologists (OB-GYNs) in the country of Georgia from June-July 2015 found only 43% of physicians recommended the vaccine to prenatal patients, despite that 88% perceived influenza to be a serious infectious disease. Of those who do not regularly recommend the vaccine, 75% perceived insufficient evidence supports administering the vaccination in pregnancy. This study surveyed OB-GYNs in both public and private clinics, so it considered the opinions of physicians working in multiple settings. However, 82% of the physicians in this sample were female, which may decrease its generalizability to male physicians.

Some physicians report lack of knowledge about or insufficient training in giving pregnant women the influenza vaccine. A retrospective cohort study reported only 19.4% of obstetricians in eight Beijing, China hospitals were willing to recommend the vaccine to pregnant patients. Moreover, 15.2% were aware China’s National Health Commission recommends the vaccine during pregnancy. A web-based cross-sectional survey of 3,441 midwives and nurses in England reported that 56% had not received
training on vaccinations in pregnancy and that healthcare providers who received immunization training were more confident in giving advice to pregnant women than those who did not (84%, 95% CI 81-85%). This survey was sent to all registered midwives and nurses in England and had a 10% response rate, which may limit the data’s generalizability to the larger population.

Some physicians report concern about vaccine safety and efficacy in pregnant patients. A cross-sectional survey of 150 attending or resident obstetric and family physicians at six hospitals in Israel reported 37% perceived the vaccine is dangerous or controversial in pregnancy, even though 92.5% were aware the health ministry recommends vaccination to pregnant women. This study surveyed physicians from major medical centers and small hospitals, which helped make the sample representative of the Israeli physician population. In Catalonia, Spain, a cross-sectional survey of 194 OB-GYNs and midwives reported 53.6% knew the influenza vaccine was indicated, yet only 43.4% prescribed it to prenatal patients. The main reason for this discrepancy was concerns of adverse side effects (25.9%). However, 91.8% of the sample were female, 70% were midwives, and 79% were younger than 55 years, thus the results are less generalizable to male providers, physicians, and older providers.

Although healthcare providers report financial concerns, perceptions of insufficient vaccine evidence, lack of knowledge or training, and concerns about vaccine safety and efficacy, they also report openness to receiving more education about the topic. Of OB-GYNs surveyed in Georgia, 93% would be receptive to receiving additional education on vaccination. Of OB-GYNs and midwives in Spain, 92.3% reported a willingness to receive vaccination training.
2.5 Limitations of Cross-Sectional Surveys

Many of the studies reviewed above are cross-sectional surveys, which merely capture data from single moments in time; thus, they can only establish association, not causation. Furthermore, self-report or recall bias are inherent risks in studies that rely on self-reported data. Self-report bias may lead to overestimated vaccination coverage, and recall bias may lead to either overestimated or underestimated vaccination coverage. For example, 77.9% of women in one study reported accepting the vaccine, but only 36.1% had confirmed vaccinations in their EMR. Although some women may have received the vaccination at a facility without an EMR, it is likely that self-report or recall bias plays a role in this discrepancy. Moreover, small sample sizes may limit the generalizability of findings reported in some cross-sectional surveys. Some studies were conducted at a single hospital or obstetric clinic, which may also limit their generalizability.

2.6 Interventions for Influenza Vaccine Uptake in Pregnant Women

Few studies have evaluated the effects of various interventions on the proportion of pregnant women vaccinated. Studies that discuss these interventions have evaluated pamphlet, text message, internet, patient, and provider-centered interventions.

2.6.1 Pamphlet-Centered Interventions

In a 2014 randomized controlled trial, Meharry et al. investigated using a patient-centered pamphlet and benefit statements to increase vaccine uptake in pregnancy. The study randomized women from three Connecticut obstetric clinics into three groups. One intervention group received an educational pamphlet about influenza, risks to the mother and fetus, and the vaccine’s safety profile. Another intervention group received both the...
pamphlet and a benefit statement, “If you have the flu shot during pregnancy, you will also help protect your baby against influenza from birth to six months”. Clinic nurses were asked to report the primary outcome measure, which was whether the patient received the vaccination within two months of enrollment. Chi-square tests found no significant differences in basic characteristics between groups. Women in both the pamphlet group and pamphlet plus benefit statement group had higher vaccine uptake than the control group that received usual care (79.2%, p=0.009 vs. 86.1%, p<0.001 vs. 46.9%, respectively). These findings suggest easy-to-access patient education and a simple statement about infant protection can increase vaccination uptake. The pamphlet used in this study was constructed from literature evidence and piloted before use. The sample was limited to Connecticut, which has higher average influenza vaccine uptake in pregnancy than the national average (66.9% vs. 36.5%, respectively). This limits the study’s generalizability. Additionally, the primary outcome measure of vaccination within two months of enrollment may not account for participants who received the vaccination later in their pregnancy course.

A prospective cohort study conducted at an outpatient clinic in Greece found providing pregnant women with an informational pamphlet about influenza vaccine safety and infection risks was associated with a ten-fold increase in vaccination proportion (20% vs. 2%, p<0.02). Prospective cohort study findings are limited because they can only declare an association between the intervention and vaccine uptake.

2.6.2 Text-Centered Interventions

From October to November 2012, Text4baby, a free, national text service built in collaboration with the CDC and ACOG, provided vaccine information and reminders to
pregnant women after enrollment. In a cross-sectional survey, Jordan et al. evaluated whether Text4baby’s vaccination reminders improved vaccine uptake among pregnant women. The study recruited women through an international survey sampling website. The primary outcome was self-reported influenza vaccination between October and January. Researchers found Text4baby reminder recipients were more likely than non-participants to report receiving the vaccination during pregnancy after adjusting for length of Text4baby enrollment, gestational age, language, and poverty group (AOR 2.0, 95% CI 1.4-2.9, p=0.01). The use of a survey sampling website provided the study with a large, geographically diverse sample, and external validity was supported by the similar vaccination rates among Text4baby participants compared to the CDC’s national rate for pregnant women reported at this time (51% vs. 47%, respectively).

In 2013-2014, Buschar et al. also used internet panel surveys to compare self-reported influenza vaccination rates during pregnancy among Text4baby participants and non-participants in the United States. The study’s primary outcome was self-reported influenza vaccination before delivery. Adjusted prevalence ratios (APRs) and multivariable logistic regressions were calculated to control for ethnicity, education status, poverty status, comorbidities, and provider recommendation and/or offer to vaccinate. Text4baby participants were more likely to report vaccination, regardless of receipt of provider recommendation and offer to vaccinate (provider recommendation or offer APR=1.29, 95% CI 1.21-1.37; no provider recommendation or offer APR=3.39, 95% CI 2.03-5.67). However, women who enrolled in Text4baby may have been more health-conscious and more likely to get vaccinated, which may have biased the results.
Also, comparison groups had unbalanced subject numbers, with only 377 women in the Text4baby group and 2,824 in the non-participant group.  

At an obstetric clinic in Toronto from November 2013 through March 2014, Yudin et al. sent pregnant women two, weekly text messages for four weeks that reinforced the influenza vaccine recommendation and emphasized its safety during pregnancy and breastfeeding. The objective was to increase the proportion of pregnant women who would receive the vaccination.  

After enrollment and consent in the clinic waiting area, women were randomized into intervention (text) or control (no text) groups. The primary outcome was vaccination uptake, assessed by post-partum telephone call. Researchers used Fisher’s exact tests to compare vaccination rates and logistic regression to adjust for characteristics independently associated with vaccine uptake, including marital status (married) (p<0.001), higher household income (p=0.03), and history of influenza vaccination (p<0.001). With 80% power and alpha set at 5%, weekly text messages did not increase the likelihood of receiving the influenza vaccine among pregnant women (31% vs. 27%, p=0.51).  

32% of women in the intervention group reported feeling that there were too many messages, thus irritation may have contributed to vaccine refusal. The study sample came from an urban care center where 88% of the sample had post-secondary education or higher, so these results may not be generalizable to women in different settings.  

A randomized-controlled trial by Moniz et al. also used text messaging to improve influenza vaccination rates in pregnancy. Pregnant women at an obstetric clinic in Pittsburgh, Pennsylvania were randomized into two groups. Both groups received usual prenatal care and completed pre- and post-intervention surveys. The comparison
group received twelve, weekly text messages with information about general preventive health, whereas the intervention group received these text messages with information about both preventative health and influenza vaccine safety and benefit in pregnancy. The primary outcome was influenza vaccine uptake, measured by prenatal record review. Using 80% power and intention-to-treat protocol, there was no significant difference between vaccination uptake in either group, meaning this text message education had a limited effect on uptake (33% vs. 31%, 95% CI -11.1-14.5%, p=0.88). In post-intervention surveys, 52% of women reported they would have received the vaccine if recommended by their prenatal care provider, thus a provider’s recommendation may be a more effective method for increasing uptake. The study used EMRs to obtain outcome data, which limited self-report bias. Many participants had less than a high school education (90%) and predominantly public or no insurance (88%), which may limit the data’s generalizability.

2.6.3 Internet-Centered Interventions

One randomized controlled trial assessed the use of a website containing vaccine information and interactive social media modules, such as an interactive blog, discussion forum, and chatroom on influenza vaccination uptake in pregnant women. At one obstetric clinic in Colorado, women in the third trimester of pregnancy with internet access were recruited and randomized into three groups. The first group received access to a website with information on maternal vaccination, national recommendations, and common vaccine questions. The second group received access to both the website and the interactive social media modules. The control group received usual care. The primary outcome was vaccination before delivery, extracted from EMRs. Women in both
intervention arms had a higher proportion of vaccine uptake than the usual care arm, while no difference existed between intervention arms (57% intervention vs. 35% control, p=0.01).\textsuperscript{38} Although it appeared that women who utilized these internet interventions were more likely to receive the vaccine, website access analysis revealed only 35% of women in the intervention arm visited the website. This suggests other unstudied reasons accounted for this increased vaccine uptake.\textsuperscript{38} Additionally, only third-trimester patients were included, which may have contributed to the sample’s vaccine hesitancy, as women in the third trimester may have lower presumed risk.\textsuperscript{7,38}

Another randomized controlled trial assessed the effectiveness of a pre-visit educational video on vaccination rates in pregnant women at three obstetric clinics in Cleveland, Ohio.\textsuperscript{39} Women randomized into the intervention group watched a 3.5-minute video titled, “Protect Yourself, Protect Your Baby” before seeing their prenatal care provider, who was blinded from the patient’s random allocation. The primary outcome was influenza receipt on the day of intervention, obtained by EMR review. The video did not impact vaccination rates (28% intervention, 25% control, p=0.7). However, the intervention did influence belief that vaccination can protect the mother and baby as a secondary outcome (p=0.003, p=0.001, respectively).\textsuperscript{39} This short video was unable to substantially influence vaccination uptake. This primary outcome, vaccination receipt on the day of intervention, may have missed patients who were influenced by the video, but received the influenza vaccination later in their pregnancy course. These results are also limited by the study’s small sample size (n=105).\textsuperscript{39}
2.6.4 Patient-Centered Interventions

One randomized controlled trial at prenatal clinics in Hong Kong evaluated the effect of 10 minutes of pre-appointment patient education about vaccine safety, efficacy, and recommendations on influenza vaccine uptake before delivery.\textsuperscript{40} Vaccination rates were higher in the brief education group than in the usual care group (21.1\% vs. 10\%, \(p=0.006\)), which suggests a brief education session is a successful method for increasing uptake.\textsuperscript{40} Strengths of this study include the use of random allocation and concealment to minimize bias in treatment assignment, the ease and consistency of providing a 10-minute intervention by a single nurse, and minimal attrition bias due to on-site intervention. This study was limited by potential self-report bias and effect overestimation resulting from the use of self-report data, and research nurses and participants not being blinded due to the nature of the intervention.\textsuperscript{40}

Another randomized controlled trial among 276 pregnant women of color in Atlanta, Georgia compared the effect on vaccine uptake of “gain-frame messages” that emphasize positive outcomes of vaccination versus “loss-frame messages” that emphasize negative outcomes of not vaccinating.\textsuperscript{41} Researchers found that neither gain nor loss messages were associated with increased likelihood of immunization during pregnancy (\(p=0.166, p=0.154\), respectively).\textsuperscript{41} However, healthcare provider recommendation was correlated with increased vaccine uptake as a secondary outcome (\(p=0.013\)). Only 46\% of the participants completed the post-partum questionnaire, thus the study had considerable loss-to-follow up.\textsuperscript{41}
2.6.5 Provider-Centered Interventions

In 2016, an integrative literature review of 22 articles affirmed that although provider recommendation was the most important predictor of vaccine acceptance among pregnant women, there has been minimal provider-centered research.\textsuperscript{42} Only two cluster-randomized controlled trials have examined the effectiveness of provider-centered interventions on increasing influenza vaccination uptake in pregnant women.\textsuperscript{43} In 2015, Chamberlain et al. assessed the effectiveness of a multimodal vaccination promotion package on improving prenatal uptake.\textsuperscript{43} Eleven obstetric practices in Georgia were pair-matched on the following factors associated with vaccination uptake: in-clinic vaccine administration capability, percentage of patients with Medicaid, and estimated proportion of prenatal patients vaccinated in the previous influenza season. Patients were then randomized into two arms using stratified randomization. Practices in the intervention arm received practice-level (a vaccine champion, posters, brochures), provider-level (talking-points for promoting vaccination), and patient-level intervention components (informational videos, maps to local pharmacies that provide vaccines), while practices in the control arm provided usual care. Researchers used the intention-to-treat principle to calculate risk differences and ratios and covariate-adjusted models were used for statistical analyses.\textsuperscript{43} No significant difference in vaccine rates existed between intervention and control groups after the intervention (RD 3.6%, 95% CI -4.0-11.2%, p=0.30).\textsuperscript{43}

Another cluster-randomized controlled trial in Colorado in 2019 also used a multimodal intervention to encourage influenza vaccination in pregnant women.\textsuperscript{44} Eight obstetric clinics were randomized using covariate constrains to balance study arms by
clinic size and percentage of patients with Medicaid, both of which may have influenced the primary outcome, vaccine receipt before delivery. Clinics in the intervention arm had staff and provider trainings about best practice guidelines for vaccines, influenza vaccine purchasing assistance, standing order implementation, and patient education materials. Control clinics received usual care. Like Chamberlain et al., O’Leary et al. did not find a statistically significant difference in influenza vaccine uptake between the intervention and control arms (27% baseline both arms, 29% intervention vs. 41% control, p=0.15).

The pair-matched cluster design of these studies helped control for factors known to influence vaccination uptake, and verification with EMR data mitigated self-report bias. The multimodal design of these interventions, however, makes it difficult to tease out which components were unsuccessful. Interventions with too many components may have been difficult for providers to implement, which likely contributed to the lack of effect seen in these provider-centered studies.

Three retrospective studies used provider-centered interventions to increase the rate of influenza vaccination among pregnant women. One study during the 2008-2009 influenza season at an obstetric clinic in Wisconsin examined the effect of an EMR “best-practice alert,” which alerted healthcare providers when a prenatal patient had not yet received the vaccination. The primary outcome of vaccination during pregnancy was collected through EMR review and the proportion of pregnant women vaccinated was compared to the clinic’s pre-intervention proportion during the 2007-2008 influenza season. The 2008-2009 vaccination rate was higher, which suggests a best-practice alert for providers may be helpful for increasing vaccination uptake (61% vs. 42%, p<0.01).
A 2012 retrospective cohort study compared vaccination rates among pregnant women seen at an obstetric clinic in October-November 2003 with those seen in October-November 2005 after provider-focused reminders to recommend influenza vaccination were placed on each patient’s chart. This study reported an increase in influenza vaccination rates after implementing a provider-focused chart reminder, with no significant differences in covariates including maternal age, ethnicity, language, insurance status, education status, or chronic illness diagnoses (15% vs. 52%, p<0.001).

Another retrospective cohort study conducted at a tertiary hospital in Australia examined the effectiveness of a multi-component educational program for prenatal care providers on influenza vaccine uptake in pregnant women. The program, conducted in 2011, included provider education and reminders, information brochures for patients, and increased vaccine access. The proportion of women vaccinated in 2011 was compared to that in 2010, before the program was implemented. Researchers found that influenza vaccination coverage increased after the intervention (30% vs. 40%, p = 0.03). These three studies were conducted at single clinics, limiting their generalizability. Additionally, these retrospective cohort studies cannot claim that the interventions caused this vaccination proportion increase because they merely report on associations.

One prospective study conducted at Bridgeport Hospital assessed the impact of a provider-centered intervention on influenza vaccination uptake in pregnant women. This intervention was implemented over the 2008-2009 influenza season and consisted of a multi-component educational program with provider-focused components, including e-mail reminders to providers about recommendation guidelines, information posters advertising influenza vaccines, and vaccine offers during prenatal ultrasounds. Compared
with patients who received usual prenatal care during the 2007-2008 influenza season, influenza vaccination rates increased from 19% to 31% after the intervention (p<0.0001). Like the interventions implemented in prior cluster-randomized controlled trials, it is difficult to analyze which subsets of the multi-component intervention were the most effective in increasing vaccine uptake.

Another prospective cohort study conducted at a maternity hospital in Australia compared the proportion of pregnant women vaccinated against influenza before and after the implementation of a midwife vaccination program. Researchers reported a higher vaccination rate after the implementation of the midwife program compared to those who delivered before the program was implemented (AOR 5.95, 95% CI 2.13-16.61, p<0.001). Maternal age, country of birth, and parity were independently associated with vaccination rates and were adjusted for using multivariable logistic regression. It is difficult to assess whether the results of this study are reproducible because it reported minimal details about the vaccination program.

2.7 Conclusion

Low influenza vaccination uptake in pregnant women is a worldwide problem. The fundamental importance of a healthcare provider’s recommendation of indicated maternal influenza vaccination cannot be overstated. Across cross-sectional studies, the most commonly reported barrier to vaccination uptake was the lack of a healthcare provider’s recommendation, and the most commonly reported facilitator for uptake was a healthcare provider’s recommendation. Consequently, providers are in a unique position to increase influenza vaccination rates in pregnant women. Yet, many providers feel like they have insufficient training and knowledge about the vaccine in...
pregnancy to make recommendations.\textsuperscript{22,29-32} Since provider recommendations are the most effective facilitator for vaccination uptake, a study with an objective of increasing influenza vaccination uptake in pregnant women should aim to increase provider recommendation rates. Providers should receive training, education about current guidelines, and literature about influenza vaccination in pregnant women so that they feel comfortable making these recommendations.

A cluster-randomized controlled trial would best allow for the implementation of a provider-centered intervention at the clinic level, where all providers in a clinic receive an educational intervention. The cluster-randomized design also allows clinics to be pair-matched based on factors associated with vaccination uptake, which from the studies reviewed above, include clinic size, vaccine availability for in-house administration, percentage of patients with Medicaid insurance, and EMR use. It is also important to control for variables that may independently influence the primary outcome, influenza vaccination prior to date of delivery. From the studies reviewed above, patient-level variables to consider include maternal age, gestational age, parity, race, ethnicity, number of prenatal visits during influenza season, medical comorbidities, history of previous influenza vaccination, education level, and employment status.

Current literature lacks randomized controlled trials that aim to increase influenza vaccination uptake in pregnant women through provider-centered interventions. A 2016 systematic review of eleven studies affirmed that high-quality, randomized controlled trials are needed to develop successful maternal influenza vaccination programs.\textsuperscript{50} To date, only two cluster-randomized controlled trials with more than 100 participants have taken this approach, and neither study reported statistically significant findings.\textsuperscript{43,44,51} The
multimodal design of these studies makes it difficult to discern which intervention components were unsuccessful. Therefore, a cluster-randomized controlled trial should construct a simple intervention that is easy for providers to implement.\textsuperscript{43,44}

Interventions used to increase vaccination rates in neonatal and pediatric settings show promise for increasing influenza vaccination rates in pregnant women. For example, training providers to use presumptive communication with new parents has been successful in improving vaccination uptake.\textsuperscript{52-56} The CDC provides pediatric providers with structured dialogues to reference when speaking to new parents about vaccinating children. These dialogues include presumptive recommendations, which assume parents will vaccinate their children, stating initially, “your child needs DTaP, Hib, and Hepatitis B shots today.”\textsuperscript{51,55} If parents express concern, providers give strong recommendations and personal anecdotes, such as: “I strongly recommend your child get these vaccines today” or “this office has given thousands of doses of vaccines and we have never seen a serious reaction.”\textsuperscript{55} If parents still decline vaccination after this dialogue, further promotion strategies include re-addressing the topic at the next visit and sharing fact sheets provided by the CDC.\textsuperscript{51} These simple, structured interventions have successfully maintained high pediatric vaccination rates. Greater than 80\% to 90\% of children ages 19-35 months in the United States receive most vaccinations.\textsuperscript{52,55,56} Similar interventions have yet to be tested thoroughly in the obstetric setting. Interventions like this could have a powerful impact on vaccination uptake, given healthcare providers’ potential to increase influenza vaccination rates in pregnant women.
2.8 References


CHAPTER 3: STUDY METHODS

3.1 Study Design

This study will be a cluster-randomized controlled trial involving the randomization of obstetric clinics in the Greater New Haven area into intervention or control arms. The unit of randomization and analysis will be the obstetric clinic, which will minimize contamination. All obstetric healthcare providers at clinics randomized into the intervention arm will be trained uniformly on the structured vaccine recommendation program, which will be utilized consistently among all prenatal patients at these clinics. Because patients may be seen by multiple different healthcare providers at an obstetric clinic throughout their pregnancy, all healthcare providers at clinics randomized into the intervention arm will use the structured vaccine recommendation program with all prenatal patients.

3.2 Study Population, Sampling, and Recruitment

3.2.1 Recruitment of Obstetric Clinics

All obstetric clinics within a 30-mile radius of Yale New Haven Hospital will be identified, approached, and evaluated based on the inclusion and exclusion criteria (Table 1). For a clinic to be eligible for inclusion, all obstetric healthcare providers working in the clinic must provide informed, written consent to participate in the study (Appendix A). Participation will first include randomization into either study arm; if randomized into the intervention arm, participation will then include attending a 1-hour training about the intervention and committing to consistently using the structured vaccine recommendation program with prenatal patients throughout the 7-month
intervention period. After providing consent, obstetric providers will be asked to complete a questionnaire with basic information about their clinic (Appendix B).

**Table 1:** Obstetric Clinic Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>• Clinic location within 30-mile radius of Yale New Haven Hospital</td>
<td>• Clinic location not within 30-mile radius of Yale New Haven Hospital</td>
</tr>
<tr>
<td>• Current population ≥ 50 prenatal patients</td>
<td>• Current population &lt; 50 prenatal patients</td>
</tr>
<tr>
<td>• All obstetric providers in the clinic (including physicians, nurse midwives, physician associates, nurse practitioners, and nurses) have provided informed, written consent and have agreed to consistently utilize the structured vaccine recommendation program with their prenatal patients throughout the 7-month intervention period</td>
<td>• All obstetric providers in the clinic have not provided consent to participate and/or have not agreed to consistently utilize the structured vaccine recommendation program with their prenatal patients throughout the 7-month study period</td>
</tr>
<tr>
<td>• If a clinic does not use an EMR, a clinic staff member has agreed to collect and report post-partum data for consented patient subjects</td>
<td>• If a clinic does not use an EMR, a clinic staff member has not agreed to collect and report post-partum data for consented patient subjects</td>
</tr>
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</table>

3.2.2 Recruitment of Patient Subjects

Within eligible clinics in both intervention and control arms, all women who present for prenatal care, either at the start of the study period or at their initial prenatal visit, will be handed a brief eligibility and interest questionnaire (Appendix C).

Interested women who meet inclusion and exclusion criteria will be telephoned by a researcher (Table 2). The researcher will provide the patient with more information and explain the consent form, which will be sent either electronically to the patient’s email or in-person at their next prenatal visit, if preferred (Appendix D). Clinics will also be given the option of having a recruiting researcher remain in their clinic waiting area; if this option is preferred, all women who present for prenatal care during the study period will be approached in the clinic waiting area by a researcher. Patients will be recruited using the same screening checklist to determine eligibility (Appendix C, Table 2). Regardless
of the selected recruitment method, informed, written consent will be obtained from all patient subjects (Appendix D). Following consent, patient subjects will be asked to complete a brief demographic questionnaire (Appendix E).

**Table 2:** Patient Subject Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥ 18 years</td>
<td>• Age &lt; 18 years</td>
</tr>
<tr>
<td>• Pregnant (confirmed by prenatal ultrasound)</td>
<td>• Not currently pregnant</td>
</tr>
<tr>
<td>• Ability to read or understand English</td>
<td>• Inability to read or understand English</td>
</tr>
<tr>
<td>• No known contraindication to influenza vaccine</td>
<td>• Known contraindication to influenza vaccine (life-threatening allergy to a vaccine component including egg protein, history of an anaphylactic reaction to a vaccine) (^1)</td>
</tr>
<tr>
<td>• Has not received the 2022-2023 influenza vaccine</td>
<td>• Has already received the 2022-2023 influenza vaccine</td>
</tr>
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</table>

### 3.3 Subject Protection and Confidentiality

We will submit an application to the Yale Institutional Review Board (IRB), which must be approved prior to study initiation. We will include two Consent for Participation in a Research Project 200 FR. 1 forms, which include an invitation to participate, description of the research study, potential risks and benefits, economic considerations, confidentiality and privacy agreements, and information about voluntary participation and withdrawal (Appendix A, Appendix D). Because pregnant women are a vulnerable research population, it is important that they are aware of the minor risks and common side effects associated with influenza vaccination. All participants, including healthcare providers and patient subjects, must provide written, informed consent.

All research team members must complete Human Subjects Protection Training and Health Insurance Portability and Accountability (HIPAA) privacy training and provide evidence of certification to the Yale IRB. All health information of patient
subjects will remain protected under HIPAA compliance. Patient information will be de-
identified and coded, and all data will be kept on an encrypted web-based data
management system that is only accessible by approved researchers. Once analyses are
complete, we will destroy all participant data.

3.4 Study Variables, Measures, and Operationalization

3.4.1 Assignment of Intervention

Cluster randomization will be used to allocate obstetric clinics into intervention or
control arms. Each outpatient clinic will be considered a cluster. Participating clinics will
be pair-matched on clinic-level covariates associated with vaccine uptake, which include
clinic size, percentage of clinic patients with Medicaid insurance, percentage of clinic
patients with self-pay or no insurance, vaccine availability for in-clinic administration,
and the clinic’s use of an EMR. Within each pair-matched group, one obstetric clinic will
then be randomly assigned to receive the intervention (structured vaccine
recommendation program), and one will serve as a control (usual care). Random
assignment of condition (intervention vs. control) will be determined by coin-toss by a
researcher otherwise unaffiliated with the study.

3.4.2 Independent Variable (Intervention)

The structured vaccine recommendation program will begin with a 1-hour training
with obstetric healthcare providers during their clinic’s lunch hour. To limit variability in
intervention training, the same researcher will discuss the Talking with Pregnant Women
about Vaccines resource guide with each clinic assigned to the intervention arm
(Appendix F). The resource guide will present a structured, three-step method for
healthcare providers to use when discussing vaccines with their patients, which includes
assuming women will vaccinate, giving a strong recommendation, and listening and responding to patients’ questions. It also provides guidance on what to do if women refuse the vaccine, as well as additional vaccine-related resources for both providers and patients. This resource guide was created using the CDC’s Talking with Parents about Vaccines for Infants fact sheet, tailored to address obstetric providers.\textsuperscript{2} After explaining how to use the resource guide, the researcher will answer any questions that obstetric providers have. Providers will be given PDF and paper copies of the resource guide for future reference.

In addition to the 1-hour training, healthcare providers will also receive PDF and paper copies of two reader-friendly fact sheets created by the CDC, to be distributed to patients who request more information about the vaccine and its safety during pregnancy. These fact sheets are titled Pregnant? You Need a Flu Shot! and Pregnancy and Vaccination (Appendix G, Appendix H).

Finally, each healthcare provider at clinics assigned to the intervention arm will receive biweekly email reminders that aim to encourage adherence to the structured vaccine recommendation program (Appendix I). Healthcare providers can reply to the biweekly email with specific questions or concerns, as well as request paper or PDF copies of the resource guide and fact sheets.

3.4.3 Dependent Variable (Outcome)

The primary study outcome will be the receipt of the influenza vaccination prior to date of delivery. There will be no secondary outcomes.
3.4.4 Control Variable (Usual Care)

The obstetric clinics who are not randomly allocated to receive the intervention will be assigned to the control group, or “usual care”. Usual care encompasses a wide range of practices in which providers may individualize patient care. In this study, usual care will include any care that does not include the structured vaccine recommendation program beginning with a 1-hour healthcare provider training. Clinics assigned to the usual care arm will not be provided with resource guides, fact sheets, or biweekly emails.

3.4.5 Covariates

**Table 3**: Patient-Level and Clinic-Level Covariates

<table>
<thead>
<tr>
<th>Patient-Level Covariates</th>
<th>Clinic-Level Covariates</th>
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<tbody>
<tr>
<td>• Maternal age</td>
<td>• Clinic size (total deliveries in 2021)</td>
</tr>
<tr>
<td>• Ethnicity/race</td>
<td>• Percentage of clinic patients with Medicaid insurance in 2021</td>
</tr>
<tr>
<td>• Gestational age at time of recruitment</td>
<td>• Percentage of clinic patients with self-pay or no insurance in 2021</td>
</tr>
<tr>
<td>• Parity</td>
<td>• Influenza vaccine availability for in-clinic administration</td>
</tr>
<tr>
<td>• Education level</td>
<td>• Clinic EMR use</td>
</tr>
<tr>
<td>• Employment status</td>
<td></td>
</tr>
<tr>
<td>• Health insurance status</td>
<td></td>
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<tr>
<td>• Influenza vaccination history</td>
<td></td>
</tr>
<tr>
<td>• Number of prenatal visits during influenza season (October 2022 through April 2023)</td>
<td></td>
</tr>
<tr>
<td>• Gestational age on date of vaccination</td>
<td></td>
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<tr>
<td>• Medical comorbidities</td>
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3.5 Blinding of Intervention and Outcome

Patient subjects presenting for prenatal care at participating clinics will need to provide informed written consent to participate in the study but will not be specifically told whether they are receiving the intervention or control. Due to the nature of the intervention, healthcare providers will not be blinded to their random allocation, as they will be required to undergo training and carry out the structured vaccine recommendation program with their patients. The researchers involved in training healthcare providers and
responding to biweekly healthcare provider emails will not be blinded to the clinic’s random allocation. However, research staff involved in consenting patient subjects, collecting baseline demographic information, collecting outcome data, and performing statistical analyses will be blinded to clinic random allocations.

### 3.6 Data Collection

Clinic-level data including clinic size, percentage of patients with Medicaid insurance, percentage of patients with self-pay or no insurance, vaccine availability for in-clinic administration, and EMR use will be collected during clinic recruitment and used to pair-match clinics before conducting stratified randomization (Appendix B).

Patient-level data collection will begin during the intervention period. Data involving patient information will be de-identified, coded, and stored in an encrypted web-based data management system that is only accessible by approved researchers (Appendix J). Data collected during the intervention period will include information from the baseline demographic questionnaire, which will be completed in the clinic waiting area immediately after written consent (Appendix E).

Patient-level data collection will also continue after the 7-month intervention period. Post-partum data, which will include influenza vaccination receipt prior to date of delivery, gestational age on date of vaccination, number of prenatal visits during the intervention period, and medical comorbidities will be collected primarily through EMR review. For patients who attended obstetric clinics that did not use an EMR, post-partum data will be collected from a clinic staff member, to whom the role of storing this data for patient subjects will have been assigned and accepted during the clinic recruitment.
process. All post-partum data will be collected by a researcher who is blinded to the random allocation of the patient and clinic.

3.7 **Sample Size Calculation**

Sample size will be calculated based upon detecting a 35% absolute increase in the mean proportion of pregnant women receiving an influenza vaccine among intervention clinics compared to control clinics. A standardized effect size of 35% is based upon previous studies following multi-component interventions to improve vaccine coverage in pregnant women.\(^3,^4\) The randomization of clinics rather than participant subjects to avoid contamination between study groups leads to a decrease in statistical efficacy. Individuals may have chosen the cluster to which they belong, for example, by choosing to live in a particular area, or choosing a healthcare provider with similar demographic characteristics to them; therefore, an intracluster correlation coefficient (ICC) will be used because patient subjects within a cluster cannot be assumed to be independent from each other. Using a 35% standardized effect size, 2-tailed significance level of 0.05(\(\alpha\)), and ICC of 0.01 from a cluster-randomized controlled trial evaluating similar outcomes, we will require 10 obstetric clinics (5 intervention, 5 control) with 50 pregnant women per clinic to obtain statistical power of 0.801 (Appendix K).\(^5\) We expect negligible loss to follow-up at the participant level because most of the data collection will come from EMR review or clinic records.

3.8 **Statistical Analysis**

Statistical analysis for the primary outcome will be conducted at the cluster and individual levels. At the cluster level, mean proportions will be calculated as a summary measure for each cluster. A student’s t-test will be used to compare cluster mean
proportions; if a regression analysis is needed to adjust for differences in cluster characteristics, such a test, most likely a mixed-effects linear regression model, will need to include adjustment for the ICC.6

At the individual level, we will use chi-square tests to compare influenza vaccination before delivery, reported as a dichotomous outcome, and receipt of the structured vaccine recommendation program. We will also examine the relationships between the primary outcome and patient-level covariates in Table 3. Dichotomous outcomes and categorical variables will be compared using chi-square tests. Continuous variables will be reported as a mean and standard deviation and compared using student’s t-tests. Multiple logistic regression will be used for patient-level covariates found to have an independent influence on the primary outcome.

Each estimate will be accompanied by a 95% confidence interval (CI). A 5% level of significance (p≤0.05) will be considered statistically significant. An intention-to-treat approach will be used to compare outcomes between the study arms, with participants analyzed according to the study arm which their obstetric clinic was randomly assigned. Statistical analyses will be conducted by researchers blinded to participant allocations.

3.9 Timeline and Resources

Obstetric clinic recruitment will occur from June through August 2022. Pair-matching and stratified randomization of obstetric clinics, as well as researcher training, will occur from in August 2022. Healthcare provider training at clinics assigned to the intervention arm will occur in September 2022. Recruitment of patient subjects and intervention, as well as baseline demographic data collection will occur during the 2022-2023 influenza season from October 2022 through April 2023. Post-partum data
collection will continue for 10 months, from May 2023 through February 2024, to ensure that all pregnant women have delivered. Data analysis will occur following post-partum data collection. See Figure 1 for the proposed study timeline.

**Figure 1: Study Timeline**

<table>
<thead>
<tr>
<th>Year</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
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<tbody>
<tr>
<td>Month</td>
<td>June</td>
<td>July</td>
<td>August</td>
</tr>
<tr>
<td>Obstetric Clinic Recruitment</td>
<td></td>
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<tr>
<td>Researcher Training</td>
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<tr>
<td>Healthcare Provider Training</td>
<td></td>
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<tr>
<td>Study Period (Intervention)</td>
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<tr>
<td>Demographic Data Collection</td>
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<td></td>
</tr>
<tr>
<td>Post-Partum Data Collection</td>
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</tbody>
</table>

This study will require multiple researchers. Two to three researchers will assist in obstetric clinic recruitment, one of whom will be trained to conduct healthcare provider training sessions. This study will also require researchers to recruit patient subjects in clinic waiting areas throughout the intervention period; the number of participating clinics will determine the number of recruitment researchers needed. One researcher will send and respond to biweekly adherence emails. Throughout the intervention, post-partum data collection, and statistical analysis periods, one to two blinded researchers will assist with data collection, data entry, and statistical analyses. In obstetric clinics that do not use an EMR, one clinic staff member must agree to collect post-partum data on consented participant subjects.

This study will require multiple computers for communication, data collection, and statistical analyses. Patient subject recruitment and intervention will occur in
previously established obstetric clinic waiting areas and exam rooms. Printing materials will be needed to supply healthcare providers with resource guides and fact sheets.

3.10 References

CHAPTER 4: CONCLUSION

4.1 Advantages and Disadvantages

This study has multiple advantages. The cluster-randomized design limits contamination, which can dilute observed differences between study arms and affect reliability and validity of the results. The design maintains the internal validity of an individually randomized trial while enhancing its external validity through various methodological features. It includes representative patient subjects from a variety of urban and suburban settings, diverse outpatient clinics, healthcare providers with different credentials and patient care approaches, and a comparison condition that represents usual care rather than no treatment. Pair-matching clinics prior to randomization decreases the effects of potential confounding variables, while also including clinics with different baseline characteristics to increase the generalizability of study results. The intention-to-treat approach used in statistical analyses helps protect randomization from bias due to imbalanced baseline characteristics. The intervention itself is cost-effective and requires minimal resources. Healthcare providers only need to attend a 1-hour training and will be provided with all resources required to implement the intervention, which should make study participation inviting.

This study also has multiple limitations. The intervention will be applied to clinics in a single state and affiliated with one health system, therefore the results may not be generalizable to other locations or health systems. Based on the intervention nature, neither healthcare providers nor researchers involved in healthcare provider training will be blinded to the random allocations of clinics. This cluster-randomized controlled trial has an inherent risk of selection bias, as particular patient groups with similar qualities
may be more or less likely to participate. To decrease this risk, all patients at participating clinics will be screened for eligibility and welcomed to participate. The structured vaccine recommendation program requires healthcare provider adherence, which is difficult to monitor. Low adherence could make it difficult to detect differences between conditions. Biweekly adherence emails will be sent to promote the adherence of providers to the vaccine recommendation program. Some healthcare providers in the usual care group may promote influenza vaccination more than others, which may also contribute to difficulty detecting differences between conditions. Compared with individually randomized trials, cluster-randomized trials are more complex to design, require more participants to obtain equivalent statistical power, and require complex analysis.\(^2\) The use of an intracluster correlation coefficient (ICC) has a major effect on sample size calculation and data analysis, most notably requiring more patient subjects than an individually randomized trial to retain statistical power.\(^2\)

### 4.2 Clinical and Public Health Significance

Influenza infection is associated with increased risk of morbidity and mortality in pregnant women and infants.\(^3\) During influenza pandemics and interpandemic periods, influenza infection during pregnancy was associated with greater risk of death, hospitalization, and pregnancy loss.\(^4-6\) Influenza infection also presents risks to the developing fetus, newborn infant, and infant less than six month old, with an increased risk of preterm delivery, neonatal intensive care unit (ICU) admission, and low newborn Apgar scores.\(^7\) This structured vaccine recommendation program, if successful in increasing vaccine uptake, could decrease influenza-associated adverse pregnancy outcomes and decrease morbidity and mortality in both pregnant women and infants.
Efforts to inform pregnant women about the influenza vaccine and encourage vaccination are vital for achieving the Healthy People target of 80% vaccination coverage.⁸

A structured vaccine recommendation program that effectively increases influenza vaccine uptake in pregnant women could be applied to patient populations beyond pregnant women and to other high-burden infectious diseases. Since the United States Food and Drug Administration (FDA) authorized the first COVID-19 vaccines, public health experts and healthcare providers have been working to decrease vaccine hesitancy. Patients consider their healthcare providers to be their most trusted source of information when it comes to vaccines, so healthcare providers play a critical role in helping people choose COVID-19 vaccination.⁹ The three-step resource guide modified for obstetric providers in this study emphasizes assuming patients will vaccinate, giving a strong recommendation, and listening and responding to patients’ questions; this method could be easily adopted by providers in any medical field to decrease vaccine hesitancy, increase uptake, and decrease transmission and illness for any infectious disease, including COVID-19.

4.3 References


APPENDICES

Appendix A: Consent Form (Healthcare Providers)

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: *Guidelines For Influenza Vaccination Uptake In Pregnant Women: A Cluster-Randomized Controlled Trial*

Principle Investigators: Katherine H. Campbell, MD, MPH

**Invitation to Participate and Description of Project**

You are invited to participate in a research study designed to examine the effect of a structured vaccine recommendation program for obstetric providers on the mean proportion of pregnant women who receive the influenza vaccination. You have been asked to participate because you are a healthcare provider at an obstetric clinic near Yale New Haven Hospital.

To decide whether you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

**Description of Procedures**

Because patients may be seen by multiple different obstetric providers at your clinic throughout their pregnancy, all physicians, midwives, physician assistants, nurse practitioners, and/or nurses in your clinic must agree to participate and provide informed, written consent to be included in our study. If your obstetric clinic agrees to participate, our research team will provide each healthcare provider with a brief questionnaire about your clinic. These questions will help us pair-match your clinic with another like yours.

Once your clinic has been pair-matched, it will be randomized into either the intervention or control study arm. If randomized into the intervention arm, participation will begin with a 1-hour educational training about our structured influenza vaccine recommendation program and our easy-to-use resource guide. This 1-hour training will be conducted by a member of our research team at your clinic during your lunch hour, for your convenience. You will have the opportunity to ask our researcher questions about the intervention during this time.

After this training, you will be expected to utilize the structured vaccine recommendation program with your prenatal patients consistently throughout the 7-month study period,
which takes place during the 2022-2023 influenza season from October 2022 through April 2023. You will be provided both paper and PDF copies of our resource guide, as well as paper and PDF copies of fact sheets created by the CDC for distribution to your patients. Finally, you will receive a biweekly email from our research team with opportunities to ask specific questions or request more materials.

Following the initial questionnaire about your clinic, no data about you will be collected. If your clinic agrees to participate, your clinic will have the option of distributing an eligibility/interest questionnaire to patients at their initial prenatal visit, or if you would prefer, a member of our research team will greet patients in your waiting area using a screening checklist to determine their eligibility. Written, informed consent will be obtained from eligible women. Following consent, subjects will be asked to complete a brief demographic questionnaire. After each patient’s delivery, blinded research staff will collect limited, specific information about her health and medical care from the electronic medical record (EMR). If your clinic does not use an EMR for patient health records, we will need a clinic staff member to collect this information and present it to us at the end of the post-partum data collection period (May 2023 through February 2024). Post-partum data for each patient subject will include influenza vaccine receipt prior to date of delivery, gestational age on date of vaccination, number of prenatal visits during the intervention period (October 2022 through April 2023), and medical comorbidities.

**Risks and Inconveniences**
We identify no physical risks to you associated with the study. Few inconveniences include attending a 1-hour training session with a researcher about the intervention. This session will occur at your obstetric clinic for your convenience. Agreement to participate also includes agreement to utilize the structured vaccine recommendation program consistently with each of your prenatal patients throughout the 7-month intervention period from October 2022 through April 2023. A member of our research team will send you a biweekly email to encourage adherence. If you so choose, a member of our research team will remain in your clinic’s waiting area to greet patients and determine their eligibility throughout the study period, which may be a minor inconvenience for your clinic.

**Benefits**
Potential benefits of this study include the opportunity to increase influenza vaccination uptake among pregnant women, decrease influenza-associated adverse pregnancy outcomes, and decrease morbidity and mortality in both pregnant women and infants.

**Economic Considerations**
There are no costs associated with participation in this study. However, if your clinic provides in-clinic administration of the influenza vaccine, your clinic, patients, and/or patients’ insurance providers will be responsible for the coverage of vaccine costs.

**Confidentiality and Privacy**
We understand that information about you and your clinic is personal, and we are committed to protecting the privacy of that information. Any identifiable information that
is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person. Information will be kept confidential by coding data with numbers, storing research materials in locked cabinets, and password-protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal you or your clinic’s identity unless your specific permission for this activity is obtained.

The information about your clinic that will be collected in this study includes: Total number of deliveries in 2021, vaccine availability for in-clinic administration, percentage of clinic patients with Medicaid insurance in 2021, percentage of clinic patients with self-pay or no insurance in 2021, and EMR use.

The information about your patients that will be collected in this study includes: Age, ethnicity/race, gestational age, parity, education level, employment status, health insurance status, history of previous influenza vaccines, receipt of the influenza vaccine prior to date of delivery, number of prenatal visits during the intervention period, gestational age on date of vaccination, and medical comorbidities. Patient subjects will be required to provide informed, written consent before we obtain this information.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes. All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information.

**Voluntary Participation and Withdrawal**

You do not give up any of your legal rights by signing this form. Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study as a study participant if you do not allow use of your clinic’s information as part of this study.

If you do participate, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. The researchers may also withdraw you from participating in the research if necessary. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with Yale New Haven Hospital. When you withdraw from the study, no new information will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.
Questions
We have used some technical terms in this form. Please feel free to ask about anything you don’t understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization
I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: ____________________________________________________________
Signature: _________________________________________________________________
Date: _________________________________________________________________

Signature of Principal Investigator                                      Date
or

Signature of Person Obtaining Consent                                   Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix B: Clinic Questionnaire (Healthcare Providers)

Clinic Name and Mailing Address:

Your Name:

Your Email Address: Your Phone #:

Credentials (circle one): Physician Nurse Midwife Physician Associate Nurse Practitioner Registered Nurse Other: _____________

1. How many total deliveries (vaginal and operational) did your clinic complete in 2021?
   ______ total deliveries

2. What was your clinic’s total number of patients in 2021?
   ______ total patients

3. What was your clinic’s total number of patients with Medicaid insurance in 2021?
   ______ total patients with Medicaid in 2021

4. What was your clinic’s total number of patients with self-pay or no insurance in 2021?
   ______ total patients with self-pay or no insurance in 2021

5. What is your clinic’s influenza vaccine availability for in-clinic administration?
   a. Vaccine always available for in-clinic administration
   b. Vaccine sometimes available for in-clinic administration
   c. Vaccine never available for in-clinic administration/referral to outside hospital or pharmacy only

6. Does your clinic use an electronic medical record (EMR) for patient health information and vaccination records?
   a. Yes
   b. No
Appendix C: Study Eligibility Screening Questionnaire (Patient Subjects)

For use by a research team member when screening patients for study eligibility. If a patient responds with underlined question choices, then she most likely meets the inclusion criteria.

1. Are you ≥ 18 years old?
   • Yes • No

2. Are you currently pregnant?
   • Yes • No

3. Are you able to read or understand English?
   • Yes • No

4. Have you received this season’s (2022-2023) influenza vaccine?
   • Yes • No

5. Do you have a known contraindication to the influenza vaccine?
   • Yes • No

6. Have you ever had an anaphylactic reaction to a vaccine?
   • Yes • No

7. Do you have a life-threatening allergy to a vaccine component or egg protein?
   • Yes • No

8. I am interested in participating in a research study and/or I am willing to be contacted by a research team member for more information.
   • Yes • No

9. If yes above (question 8), what is your first name, telephone number, and email address?

   First Name: ________________________________________________________________

   Telephone Number: _________________________________________________________

   Email Address: _____________________________________________________________
YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Guidelines For Influenza Vaccination Uptake In Pregnant Women: A Cluster-Randomized Controlled Trial

Principle Investigators: Katherine Campbell, MD, MPH

Invitation to Participate and Description of Project
You are invited to participate in a research study designed to examine the effect of a structured vaccine recommendation program for obstetric providers on the mean proportion of pregnant women who receive the influenza vaccination. You have been asked to participate because you are receiving prenatal care at one of our participating obstetric clinics. You have identified that you are ≥ 18 years old, currently pregnant, able to read or understand English, have no known contraindication to the influenza vaccine, and have not already received the 2022-2023 influenza vaccine.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures
If you agree to participate in this study, our research coordinator will provide you with a brief questionnaire with basic demographic information. Questions will include your age, parity, gestational age, ethnicity/race, influenza vaccination history, education level, insurance status, and employment status.

You will then proceed to your prenatal care visit as usual. You may engage in a dialogue with your healthcare provider regarding the influenza vaccination during your pregnancy. You may be offered the vaccine for in-clinic administration, or you may be referred to a local hospital or pharmacy where you can obtain the vaccine at your earliest convenience. You may also be provided with fact sheets about the vaccine and its safety in pregnancy.

More information about the Centers for Disease Control (CDC) and Prevention and the American College of Obstetricians and Gynecologists (ACOG)’s influenza vaccine recommendations can be found at:

https://www.acog.org/womens-health/faqs/the-flu-vaccine-and-pregnancy
https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/flu-vaccine-pregnancy.html
After your delivery, blinded research staff will request limited, specific information about your medical care from your clinic’s electronic medical record (EMR). This information will be limited to your influenza vaccination status, your gestational age on the date of vaccination, the number of prenatal visits you had during influenza season, and your medical comorbidities. If your clinic does not use an EMR, a clinic staff member will collect this information from your medical chart and supply it to us.

**Risks and Inconveniences**
We do not anticipate significant risks associated with this study. Although pregnant women are a vulnerable research population, safety of the influenza vaccine in pregnancy has been shown repeatedly in medical literature, and our intervention simply promotes current World Health Organization (WHO), Centers for Disease Control (CDC), and American College of Obstetricians and Gynecologists (ACOG) guidelines. There are, however, minor risks associated with the influenza vaccine that participants should be aware of. Common side effects experienced by pregnant women are the same as those experienced by other people. These risks include:

- Soreness, redness, and/or swelling at the vaccine site
- Fainting
- Headache
- Fever
- Muscle aches
- Nausea
- Fatigue

If side effects occur, they usually begin soon after the vaccine is given and last for 1-2 days. Rarely, flu shots can cause serious problems like allergic reactions. Anyone with a severe, life-threatening allergy to the vaccine ingredients should not get the shot. Participation in this study may also involve risks that are not currently known.

**Benefits**
Potential benefits of this study include protection against the influenza virus, lower risk of influenza-associated adverse pregnancy outcomes, and lower risk of influenza-associated morbidity and mortality, or illness and death, for you and your infant.

**Economic Considerations**
There are no costs associated with participation in this study. However, you and/or your insurance provider will be responsible for covering the cost of the influenza vaccine. These costs may vary based on vaccination site and insurance provider. For more information about the cost of your influenza vaccine, please speak with your healthcare and insurance providers.

**Confidentiality and Privacy**
We understand that information about your health is personal, and we are committed to protecting the privacy of that information. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Information will be kept confidential by coding data with numbers, storing research materials in locked cabinets, and password-
protecting data stored on a computer. When the results of the research are published or
discussed in conferences, no information will be included that would reveal your identity
unless your specific permission for this activity is obtained.

The information about your health that will be collected in this study includes: Your age,
etnicity/race, influenza vaccination history, parity, gestational age, education level,
current employment status, health insurance status, influenza vaccination receipt prior to
date of delivery, gestational age on the date of vaccination, number of prenatal care visits
during the influenza season, and medical comorbidities.

By signing this form, you authorize the use and/or disclosure of the information described
above for this research study. The purpose for the uses and disclosures you are
authorizing is to ensure that the information relating to this research is available to all
parties who may need it for research purposes. All health care providers subject to
HIPAA (Health Insurance Portability and Accountability Act) are required to protect the
privacy of your information. The research staff at the Yale School of Medicine are
required to comply with HIPAA and to ensure the confidentiality of your information.

Voluntary Participation and Withdrawal
You do not give up any of your legal rights by signing this form. Participating in this
study is voluntary. You are free to choose not to take part in this study. Refusing to
participate will involve no penalty or loss of benefits to which you are otherwise entitled
(such as your health care outside the study, the payment for your health care, and your
health care benefits). However, you will not be able to enroll in this research study as a
study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time
during its course. To withdraw from the study, you can call a member of the research
team at any time and tell them that you no longer want to take part. The researchers may
also withdraw you from participating in the research if necessary. Withdrawing from the
study will involve no penalty or loss of benefits to which you are otherwise entitled. It
will not harm your relationship with your doctors or Yale New Haven Hospital. When
you withdraw from the study, no new health information identifying you will be gathered
after that date. Information that has already been gathered may still be used and given to
others until the end of the research study, as necessary to ensure the integrity of the study
and/or study oversight.

Questions
We have used some technical terms in this form. Please feel free to ask about anything
you don’t understand and to consider this research and the consent form carefully – as
long as you feel is necessary – before you make a decision.

Authorization
I have read (or someone has read to me) this form and have decided to participate in the
project described above. Its general purposes, the particulars of my involvement, and
possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: _________________________________________________________
Signature: _______________________________________________________________
Date: _________________________________________________________________

_____________________________________________________________________
Signature of Principal Investigator                                      Date

or

_____________________________________________________________________
Signature of Person Obtaining Consent                                   Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix E: Demographic Questionnaire (Patient Subjects)

Participant Study ID (filled in by research staff): ________________________________

1. What is your age? ________

2. What is your ethnicity/race? (check all that apply)
   • White/Caucasian • Black/African American • Hispanic/Latino
   • Other: __________________

3. What is the gestational age of your current pregnancy? ________ weeks

4. How many pregnancies have you carried for >20 weeks, including deliveries? ________

5. What is your education level?
   • Some high school • High school graduate or equivalent • Some college
   • Associate degree • Bachelor’s degree • Graduate or professional degree
   • Prefer not to answer

6. What is your current employment status?
   • Employed • Unemployed

7. Do you currently have health insurance?
   • Yes • No

8. Have you ever received the influenza vaccine before?
   • Yes • No

9. If yes, when did you last receive the influenza vaccine?
   • Last influenza season • <5 years ago • ≥5 years ago
Influenza carries a large global disease burden and poses unique risks for pregnant women and infants.\(^1\) During pregnancy, physiologic changes like decreased functional residual lung capacity, mucus hypersecretion, increased cardiac output, and increased plasma blood volume alter the mother's respiratory and cardiovascular systems. These physiologic changes, along with changes to the mother's immune system, contribute to a modified response to infection and increased risk of complications during pregnancy.\(^1\)

The World Health Organization (WHO) and The Centers for Disease Control and Prevention (CDC) recommend that all pregnant women receive the influenza vaccine during pregnancy; however, 64.4% of pregnant women in the United States do not receive the vaccine, putting them and their infants at risk for developing severe illness and adverse pregnancy outcomes.\(^4\) Many women are not recommended, offered, or referred for the vaccine by their obstetric providers, which contributes to low vaccine uptake.\(^5\)

Researchers have investigated various interventions and their effectiveness at improving influenza vaccination uptake; however, current literature lacks sufficient randomized controlled trials. In neonatal and pediatric settings, the CDC offers providers structured recommendations, including communication tools to use with new parents.\(^3\) These recommendations have been successful in improving pediatric vaccine uptake in the United States, with rates of children 19-35 months receiving moth vaccinations greater than 80-90%.\(^5\) Similar interventions have yet to be investigated thoroughly in the obstetric setting.

Healthcare providers play a critical role in maintaining a clinic-wide commitment to communicating effectively about vaccines. Patients consider their healthcare providers to be their most trusted source of information when it comes to vaccines. You play a critical role in helping women choose vaccination.\(^9\)

You may feel that committing to challenging vaccine conversations are time-consuming and stressful amidst a day of providing important prenatal care. Because of this, we designed this easy-to-use resource guide with conversational techniques and resources for discussing vaccines with pregnant women.

### 1. Assume women will Vaccinate

State which vaccines the patient should receive.

When discussing vaccines with pregnant women, it is best to remember that many women are planning to accept vaccines and to introduce the topic with that in mind. State the patient will receive the vaccine, as though you presume that she is ready to accept the recommendation during that visit. For example:

- Instead of saying "What do you want to do about vaccines?" say, "You need the influenza vaccine today."
- Instead of saying "Have you thought about the vaccines you need during pregnancy?" say, "You need the influenza vaccine during pregnancy."

### 2. Give your strong recommendation

If women express concerns, share your strong recommendation.

State your strong recommendation. If appropriate and useful, you can add a statement that uses a mix of science and anecdote. Share the importance of the influenza vaccine to protect both the mother and her baby from life-threatening illness and adverse pregnancy outcomes. For example:

- "I strongly recommend you get this vaccine today…"
- "…This vaccine is very important to protect you and your baby from serious illness."
- "…I believe in vaccines so strongly that I was vaccinated against influenza during my own pregnancy."
- "…This office has given thousands of doses of vaccines and we have never seen a serious reaction."

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**Appendix F: Talking with Pregnant Women About Vaccines Resource Guide**

**Talking with Pregnant Women about Vaccines**

1. **Assume women will Vaccinate**

State which vaccines the patient should receive.

When discussing vaccines with pregnant women, it is best to remember that many women are planning to accept vaccines and to introduce the topic with that in mind. State the patient will receive the vaccine, as though you presume that she is ready to accept the recommendation during that visit. For example:

- Instead of saying "What do you want to do about vaccines?" say, "You need the influenza vaccine today."
- Instead of saying "Have you thought about the vaccines you need during pregnancy?" say, "You need the influenza vaccine during pregnancy."

2. **Give your strong recommendation**

If women express concerns, share your strong recommendation.

State your strong recommendation. If appropriate and useful, you can add a statement that uses a mix of science and anecdote. Share the importance of the influenza vaccine to protect both the mother and her baby from life-threatening illness and adverse pregnancy outcomes. For example:

- "I strongly recommend you get this vaccine today…"
- "…This vaccine is very important to protect you and your baby from serious illness."
- "…I believe in vaccines so strongly that I was vaccinated against influenza during my own pregnancy."
- "…This office has given thousands of doses of vaccines and we have never seen a serious reaction."
3. Listen and respond to patients’ questions

Seek to understand patients’ concerns & provide information. Although research supports the safety of the influenza vaccine during pregnancy, you will encounter patients with questions. If a patient voices concerns or questions your strong recommendation, this doesn’t mean they won’t accept the vaccine. Sometimes patients simply want your answers to their questions. Your willingness to listen to their concerns will play an important role in building trust in you and your recommendation.

When listening to patients, seek to understand the concerns behind their questions before responding. If you encounter questions you don’t know the answers to, or information from sources you are unfamiliar with, acknowledge the patient’s concerns and share what you do know. Offer to review the information they have found and, if possible, consider scheduling another appointment to discuss it further.

What if women refuse the vaccine?

If pregnant women decline the influenza vaccine after your strong recommendation and dialogue, you can use the following strategies:

- Continue the conversation about the vaccine at her next visit and restate your strong recommendation.
- Inform women about clinical presentations of influenza, including early symptoms of cough, fever, sore throat, runny or stuffy nose, headache, body aches, and fatigue.

Wrapping up the conversation

Remember that success comes in many forms. It may mean that all pregnant women accept the influenza vaccine when you recommend it, or that they schedule the vaccine for another day. For very vaccine-hesitant patients, success may simply mean agreeing to future conversations.

Work with your patients to agree on at least one action, such as:

- Scheduling another appointment, or
- Encouraging the patient to read additional information you provide them.

If a patient denies the vaccine once, this does not mean they always will. Continue to remind patients about the importance of the influenza vaccination during pregnancy.

This resource guide was created with help from the CDC’s information sheet: Talking with parents about vaccines for infants.

Find resources for specific patient questions:

For information on influenza vaccine safety and pregnancy:

For a list of local hospitals and pharmacies for influenza vaccination:
https://www.cdc.gov/fh/freeresources/fly-finder-widget.html

References

Pregnant? You Need a Flu Shot!

**Information for Pregnant Women**

*Flu can be a serious illness, especially when you are pregnant.*

Getting sick with flu can cause serious problems when you are pregnant. Even if you are generally healthy, changes in the immune system, heart, and lungs during pregnancy make you more likely to get severely ill from flu. Pregnant women who get flu are at high risk of developing serious illness, including being hospitalized.

*Flu shots are the best available protection for you – and your baby.*

Getting a flu vaccine is the first and most important step in protecting against flu. Pregnant women should get a flu shot and not the live attenuated influenza vaccine (LAIV), also known as nasal spray flu vaccine. When you get your flu shot, your body starts to make antibodies that help protect you against flu. It takes about two weeks after vaccination for antibodies that protect against flu to develop in the body. In addition to protecting you, a flu shot given during pregnancy has been shown to help protect your baby from flu infection for several months after birth, when they are too young to get vaccinated. If you breastfeed your infant, antibodies also can be passed through breast milk. You should get a flu vaccine by the end of October. However as long as flu viruses are circulating, vaccination should continue throughout the flu season, even in January or later.

If you have additional questions, talk to your doctor or health care provider about flu vaccination during pregnancy.

*Flu shots have a long safety record.*

Flu shots are recommended at any time, during any trimester, while you are pregnant. Millions of flu vaccines have been given for decades, including to pregnant women, with a good safety record. There is a lot of evidence that flu vaccines can be given safely during pregnancy, though these data are limited for the first trimester.

If you deliver your baby before getting your flu shot, you still need to get vaccinated.

Flu is spread from person to person. You, or others who care for your baby, may get sick with flu, and spread it to your baby. It is important that everyone who cares for your baby get a flu vaccine, including other household members, relatives, and babysitters.

Common side effects of a flu vaccine are mild and may include soreness, tenderness, redness and/or swelling where the shot was given. Sometimes you might have a headache, muscle aches, fever, and nausea or feel tired.

Because you are pregnant, CDC and your ob-gyn or midwife recommend you get a flu shot to protect yourself and your baby from flu.

You should get vaccinated by the end of October. This timing can help ensure that you are protected before flu activity begins to increase. Talk to your ob-gyn or midwife about getting a flu shot.
If you have flu symptoms, call your doctor immediately.

If you get flu symptoms (e.g., fever, cough, body aches headache, etc.) – even if you have already had a flu shot – call your doctor, nurse, or clinic right away. Doctors can prescribe influenza antiviral medicine to treat flu. Antiviral drugs can shorten your illness, make it milder and lessen the chance of developing serious complications. Because pregnant women are at high risk of serious flu complications, CDC recommends that they be treated quickly with flu antiviral drugs if they get flu symptoms. Oseltamivir (generic or brand name Tamiflu®) is the preferred treatment for pregnant women because it has the most studies available to suggest that it is safe and beneficial. Flu antiviral medications work best when started early.

Fever is often a symptom of flu. Having a fever early in pregnancy increases the chances of having a baby with birth defects or other problems. Acetaminophen (brand name Tylenol®) can reduce a fever, but you should still call your doctor or nurse and tell them about your illness.

If you have any of the following signs, call 911 and seek emergency medical care right away:
- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness or confusion
- Severe or persistent vomiting
- High fever that is not responding to Tylenol® (or store brand acetaminophen equivalent)
- Decreased or no movement of your baby

For more information about the flu or the vaccine, call: 1-800-CDC-INFO or visit: www.cdc.gov/flu/

Appendix H: CDC Fact Sheet for Patient Subjects (2)

Pregnancy and Vaccination

Keep Protecting Your Baby after Pregnancy

Your ob-gyn or midwife may recommend you receive some vaccines right after giving birth. Postpartum vaccination will help protect you from getting sick and you will pass some antibodies to your baby through your breastmilk. Vaccination after pregnancy is especially important if you did not receive certain vaccines before or during your pregnancy.

Your baby will also start to get his or her own vaccines to protect against serious childhood diseases. You can learn more about CDC’s recommended immunization schedule for children and the diseases vaccines can prevent at www.cdc.gov/vaccines/parents/.

Even before becoming pregnant, make sure you are up to date on all your vaccines. This will help protect you and your child from serious diseases. For example, rubella is a contagious disease that can be very dangerous if you get it while you are pregnant. In fact, it can cause a miscarriage or serious birth defects. The best protection against rubella is MMR (measles-mumps-rubella) vaccine, but if you aren’t up to date, you’ll need it before you get pregnant.

Talk to your ob-gyn or midwife about maternal vaccines and visit:
www.cdc.gov/vaccines/pregnancy/

Keep in mind that many diseases rarely seen in the United States are still common in other parts of the world. Talk to your ob-gyn or midwife about vaccines if you are planning international travel during your pregnancy. More information is available at www.cdc.gov/travel/.
Pregnancy and Vaccination

Information for pregnant women

Vaccines help protect you and your baby against serious diseases.

You probably know that when you are pregnant, you share everything with your baby. That means when you get vaccines, you aren't just protecting yourself—you are giving your baby some early protection too. You should get a flu shot and whooping cough vaccine (also called Tdap) during each pregnancy to help protect yourself and your baby.

Whooping Cough Vaccine

Whooping cough (or pertussis) can be serious for anyone, but for your newborn, it can be life-threatening. Up to 20 babies die each year in the United States due to whooping cough. About half of babies younger than 1 year old who get whooping cough need treatment in the hospital. The younger the baby is when he or she gets whooping cough, the more likely he or she will need to be treated in a hospital. It may be hard for you to know if your baby has whooping cough because many babies with this disease don't cough at all. Instead, it can cause them to stop breathing and turn blue.

When you get the whooping cough vaccine during your pregnancy, your body will create protective antibodies and pass some of them to your baby before birth. These antibodies will provide your baby some short-term, early protection against whooping cough.

Learn more at [www.cdc.gov/pertussis/pregnant/](http://www.cdc.gov/pertussis/pregnant/).

Flu Vaccine

Changes in your immune, heart, and lung functions during pregnancy make you more likely to get seriously ill from the flu. Catching the flu also increases your chances for serious problems for your developing baby, including premature labor and delivery. Get the flu shot if you are pregnant during flu season—it's the best way to protect yourself and your baby for several months after birth from flu-related complications.

Flu seasons vary in their timing from season to season, but CDC recommends getting vaccinated by the end of October, if possible. This timing helps protect you before flu activity begins to increase.

Find more on how to prevent the flu by visiting [www.cdc.gov/flu/](http://www.cdc.gov/flu/).

Appendix I: Email Reminder to Healthcare Providers

Dear (Name of Healthcare Provider),

We hope that you are having a wonderful week and we know that you are hard at work encouraging your prenatal patients to receive the influenza vaccine. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend that all pregnant women receive the influenza vaccine during pregnancy; however, **64.4% of pregnant women in the United States do not receive the vaccine**, putting them and their infants at risk for developing severe illness and adverse pregnancy outcomes.\(^1\)\(^-\)\(^3\)

Many women are not recommended, offered, or referred for the vaccine by their obstetric providers, which contributes to low vaccine uptake.\(^3\)

Our 3-step resource guide can help you encourage your pregnant patients to get vaccinated.

\[\text{Our team is here to help make flu vaccine conversations easy. Please tell us how we can help.}\]

- I need more paper resource guides
- I need a PDF copy of the resource guide
- I need more paper CDC fact sheets
- I need PDF copies of CDC fact sheets
- I have specific questions for a member of the research team
- Other: ________________________________

Best, The Research Team

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**Appendix J: Data Collection Form**

<table>
<thead>
<tr>
<th>Participant Study ID:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Demographic Data</strong></td>
</tr>
<tr>
<td>Age (Years)</td>
</tr>
<tr>
<td>Ethnicity/Race (White/Caucasian, Black/African American, Hispanic/Latino, Other)</td>
</tr>
<tr>
<td>Gestational Age (Number in Weeks)</td>
</tr>
<tr>
<td>Parity (Number)</td>
</tr>
<tr>
<td>Education Level (Some high school, High school graduate or equivalent, Some college, Associate degree, Bachelor’s degree, Graduate or professional degree, Prefer not to answer)</td>
</tr>
<tr>
<td>Employment Status (Employed, Unemployed)</td>
</tr>
<tr>
<td>Health Insurance Status (Insured, Uninsured)</td>
</tr>
<tr>
<td>History of Previous Influenza Vaccine (Yes, No)</td>
</tr>
<tr>
<td>Date of Previous Influenza Vaccine (Last influenza season, &lt;5 years ago, &gt;5 years ago)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Post-Partum Data</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection Means (EMR, Clinic Medical Records)</td>
</tr>
<tr>
<td>Influenza Vaccine Receipt before Date of Delivery (Yes, No)</td>
</tr>
<tr>
<td>Gestational Age on Date of Vaccination (Number in Weeks)</td>
</tr>
<tr>
<td>Number of Prenatal Visits Between October 1, 2022 and April 30, 2023 (Number)</td>
</tr>
<tr>
<td>Medical Comorbidities (Listed by Name)</td>
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</table>
Appendix K: Sample Size Calculation

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Clinics</td>
</tr>
<tr>
<td>d</td>
<td>0.35</td>
</tr>
<tr>
<td>ICC</td>
<td>0.010</td>
</tr>
</tbody>
</table>

There is an 80.1% likelihood that the study will yield a statistically significant result. This projection is based on the following assumptions:
The standardized effect size (d) is 0.35.
The intracluster correlation coefficient (ICC) = 0.010.
Each group (intervention and control) will include 5 clinics with 50 pregnant women per clinic.
Criterion for statistical significance is alpha (2-tailed) set at 0.05.
Standard Error = 0.1092, Power = 0.801


76. Wong VW, Fong DY, Tarrant M. Brief education to increase uptake of influenza vaccine among pregnant women: a study protocol for a randomized controlled trial. *BMC Pregnancy & Childbirth.* 2014;14:19.
