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Improving influenza and tetanus, diphtheria, and acellular pertussis (Tdap) vaccination among pregnant women in Georgia

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Doctor of Philosophy

Epidemiology

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Improving influenza and tetanus, diphtheria, and acellular pertussis (Tdap) vaccination among pregnant women in Georgia

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An abstract of

A dissertation submitted to the Faculty of the

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Abstract

Improving influenza and tetanus, diphtheria, and acellular pertussis (Tdap) vaccination among pregnant women in Georgia

By Allison Chamberlain Abramson

Influenza and pertussis are two diseases which pose danger to pregnant women and newborns. Pregnant women are at increased risk for complications from influenza, and infants less than 2 months old have the greatest risk of mortality from pertussis. Vaccination during pregnancy (i.e. antenatal vaccination), is a safe and effective strategy to protect mothers and infants. Despite risks posed by these diseases and the protective benefits afforded by vaccination, antenatal vaccination rates against seasonal influenza and pertussis are suboptimal.

Considerable research has sought to understand why pregnant women remain unvaccinated. Reasons include safety concerns, perceptions of low disease susceptibility, inadequate knowledge of vaccination, and no provider recommendation. Barriers also exist for obstetric providers. Despite awareness of these barriers, little research has scientifically evaluated evidence-based interventions to improve vaccination rates.

In dissertation aim 1, we conducted the MOMVAX Study, a cluster-randomized trial among 325 pregnant women in 11 obstetric practices in Georgia from 2012-2013 to test the effectiveness of a comprehensive multi-component intervention package on increasing likelihood of antenatal influenza and/or Tdap receipt. While vaccination rates were higher in the intervention group compared to the control group, differences were not significant.

In aim 2, we examined the effectiveness of the MOMVAX intervention package on improving knowledge, attitudes and beliefs about antenatal vaccination. While we observed no overall effects of exposure to the package, we found that women enrolled in their third trimester were more likely to have requested family members to get vaccinated to protect the infant if they were in the intervention group versus the control group.

In aim 3, using 8 years of data from the Georgia Pregnancy Risk Assessment Monitoring System, we explored trends in reasons for non-receipt of antenatal influenza vaccination from 2004-2011. We found that while the prevalence of citing certain reasons decreased over time, safety concerns increased significantly following the 2009/2010 H1N1 influenza pandemic, and especially among Hispanic women.

Through the first experimental evaluation of a multi-component intervention package to improve antenatal vaccination and the analysis of trends in reasons for non-receipt, this dissertation contributes to the development of evidence-based interventions to improve antenatal vaccination.

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CHAPTER 1: OVERVIEW AND MOTIVATION

Overview

Influenza and pertussis, or "whooping cough," are two vaccine-preventable respiratory diseases that pose great harm to pregnant women and their newborns. As illustrated during seasonal and pandemic influenza outbreaks, pregnant women are at increased risk for complications from influenza due to their decreased lung capacity and altered immune system suppressed to accommodate the growing fetus.[1-5] Infants less than 6 months old are also one of the most likely cohorts to experience influenza-related complications requiring hospitalization.[6] Similarly, pertussis infections are most severe among newborns; children less than 2 months old are the age group with the highest mortality from the disease.[7-9] Despite concerted efforts by public health officials to protect pregnant women and their infants through antenatal vaccination, vaccination rates against these two diseases remain at or below 50%.

Vaccination among pregnant women, especially for influenza, is low for a myriad of reasons. First, women may not be familiar with the recommendation to receive the vaccine during pregnancy. If aware of the recommendation, they may not perceive themselves to be at risk for contracting influenza, or they may be unsure of the safety of the vaccine despite numerous studies supporting its safety during pregnancy.[10-18] While risks of adverse events do exist, no study to date has found increased risks for severe pregnancy-related adverse events on account of antenatal influenza vaccination. Since the recommendation to administer Tdap routinely during pregnancy has only been in place since 2011, information on patient-level barriers specific to antenatal Tdap vaccine receipt have not been published, although they are anticipated to be similar to those encountered for influenza vaccination.[19]

Lack of knowledge and misperceptions of risk and safety are not limited to the pregnant woman; they also affect the obstetric care provider. Numerous studies have demonstrated that obstetric care providers have concerns about antenatal vaccination, and while they can mirror the concerns pregnant women have, they can also be logistical, financial or legal in nature.[20-23] Supplying vaccines in an obstetric practice requires money, space and supplies, and some providers may not have the resources to sustain an in-house vaccine program. They may also fear legal repercussions if a woman blames her obstetrician for harm caused to herself or her fetus by antenatal vaccination.

Since recommendations to vaccinate pregnant women against influenza have been in existence in the U.S. since the 1960's, the majority of the research on antenatal vaccine uptake has been conducted on influenza vaccination. The recommendation for routine Tdap vaccination during pregnancy was established in 2011 and expanded further in 2012 to include administration of one dose of Tdap at every pregnancy regardless of vaccine history.[24] Since pertussis is so severe for infants less than 2 months old and vaccination against pertussis with the DTaP vaccine does not begin until 2 months of age, the primary purpose of antenatal vaccination with Tdap is to supply protection to the fetus through passive transfer of maternal antibodies. As such, the recommendation to vaccinate against pertussis during pregnancy represents the first time in history in which the primary entity targeted for protection is not the recipient of the vaccine.

In an effort to understand why pregnant women choose not to vaccinate themselves against diseases like influenza and pertussis, considerable research has been conducted to enumerate the reasons for refusal or hesitancy. Reasons often cited include lack of knowledge of vaccine recommendations, low perceptions of risk to the diseases, and concerns about the safety of vaccination during pregnancy. Research has also shown that concerns and misperceptions can

emanate from pregnant women and their obstetric providers suggesting that interventions aimed at improving antenatal vaccination coverage target both patients and providers.

While considerable research has been conducted on the reasons for non-receipt, little research has focused on developing and scientifically evaluating interventions to improve vaccine uptake during pregnancy. Many studies reporting results from retrospective, cross-sectional surveys of women have suggested that a provider's recommendation of antenatal vaccine receipt is the strongest factor associated with receipt. Few studies have prospectively assessed this assertion. The studies which have evaluated an intervention through a randomized trial design have usually focused on single-component interventions like informational brochures or text message reminders.[25-27]

Study Motivation

Despite knowing that barriers to vaccinating pregnant women exist at multiple levels, no study to date has evaluated an intervention that targets more than one type of end-user. Moreover, since recommendations to vaccinate pregnant women against pertussis have only existed since 2011, no studies have specifically evaluated interventions to improve uptake of antenatal Tdap vaccination.

To address these gaps, dissertation study 1 examines the effectiveness of a comprehensive, multi-component vaccine promotion package on improving antenatal vaccine uptake through the Emory MOMVAX Study. The MOMVAX study was a cluster-randomized trial was performed in 2012 – 2013 among 325 unvaccinated pregnant women in 11 obstetric practices in Georgia to evaluate the effectiveness of the intervention package on the likelihood pregnant women receive influenza and Tdap vaccinations prior to delivery. To our knowledge,

this is the first study to rigorously evaluate an evidence-based intervention package with components simultaneously targeting multiple users including the obstetric practice, the obstetric provider and the pregnant woman.

While achieving antenatal vaccination was the primary goal of the Emory MOMVAX study, changing women's knowledge, attitudes and beliefs towards influenza, pertussis and their associated vaccinations was also of interest. Since antenatal vaccination is increasingly being viewed as the first opportunity to vaccinate the future child, assessing a woman's understanding and perception of the process was a secondary aim of the study. Dissertation study 2 examines the impact of the MOMVAX study intervention package on improving women's knowledge, attitudes and beliefs about antenatal vaccination. It also evaluates any impact the package may have had on mothers' willingness to vaccinate their child.

While considerable research has evaluated reasons for non-receipt of antenatal influenza vaccination, most studies have done so at single points in time. While these studies are valuable at identifying such reasons, they offer no insights into how reasons for non-receipt may change over time or according to high-profile public health events like the 2009/2010 H1N1 pandemic. Using 8 years of data from the Georgia Pregnancy Risk Assessment Monitoring Survey (PRAMS), dissertation aim 3 examines whether and how reasons for non-receipt of influenza vaccination during pregnancy have changed over time between 2004 - 2011 and on account of the 2009/2010 pandemic.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

Epidemiology of Influenza and Pertussis

Influenza

Influenza is a contagious respiratory disease caused by the influenza virus. The epidemiology of influenza disease is typically categorized into two forms: seasonal influenza and pandemic influenza. Seasonal influenza occurs each year with predictable seasonality; the putative influenza season in the U.S. begins in October and continues until May, with cases typically peaking in the winter months between December – February. While seasonal influenza epidemics can vary in their severity from year to year, they typically result in approximately 23,600 deaths per year in the U.S.[28] Influenza strains responsible for seasonal disease arise from strains already in circulation, changing their surface antigens in relatively minor ways. Depending upon the nature of these antigenic changes, particular seasonal strains can be more or less virulent resulting in influenza seasons with differing severity.

Pandemic influenza strains arise when an entirely new influenza A virus appears in humans and can be transmitted readily between humans. Having acquired significant antigenic changes to enable them to transmit from animals to humans and then among humans, pandemic influenza strains can arise at any time and may or may not coincide with seasonal influenza. Pandemic strains are particularly dangerous to public health because of their novelty; since most humans have never been exposed to these new strains, they lack any immunologic memory to their antigens in order to mount an effective immune defense. Compared to seasonal influenza, pandemic influenza viruses can result in significantly more morbidity and mortality. It is estimated that the influenza pandemic of 1918 caused more than 50 million deaths worldwide with an estimated 675,000 deaths in the U.S.

Pertussis

Commonly known as whooping cough, pertussis is a respiratory disease caused by the bacterium *Bordetella pertussis*. Pertussis is generally transmitted through coughing or sneezing and has a secondary attack rate of 80% among susceptible household contacts.[7] The disease causes severe coughing fits that can cause infected people to gasp for air, often resulting in a characteristic "whoop" sound as people attempt to catch their breath. The disease is most dangerous to infants and young children due to their smaller airways and their inability to clear the thick mucus caused by the disease. Infants and young children are also at increased risk of contracting the disease due to their naïve immune systems and the need for multiple doses of DTaP to achieve full protection. The majority of the 4,298 infants reported with pertussis in 2010 required hospitalization[9], and of the 18 deaths reported to CDC through the National Notifiable Diseases Surveillance System in 2012, 13 (72%) were among infants less than 3 months of age.[8] Additionally, of the 111 deaths caused by pertussis between 2004 – 2008, 83% were among children who contracted the disease at less than 3 months of age. [7]

Prior to the introduction of pertussis vaccines in the 1940's, pertussis typically infected over 175,000 people per year.[7] Incidence dropped markedly after the introduction of effective vaccines, resulting in less than 5,000 reported cases by 1970.[7] During the 1980's, cases began to rise again, and by 2010, there were more than 27,000 cases reported across the U.S. In 2012, the provisional case count is above 41,000 which represents the highest case count since 1955.[29]

Risks to pregnant women in U.S.

Due to changes in immunology and physiology during pregnancy, a pregnant woman has a different risk profile for infectious diseases than when she is not pregnant. In order to tolerate the foreign fetus, research suggests that hormones associated with pregnancy contribute to a

suppression of cell-mediated immunity which is the type of immunity essential for combating intracellular pathogens like viruses.[30] Additionally, constraints on her lung capacity, especially in the later stages of pregnancy, can make respiratory infections more severe and harder to resolve. These changes can also make respiratory complications and secondary bacterial infections more severe.

Influenza

In the case of influenza infection, a pregnant woman has a greater risk of serious complications resulting in hospitalization and death than compared to when she is not pregnant.[2,5,31,32] Complications are exacerbated by co-morbidities like diabetes, obesity and smoking; late stage pregnancy is also an important risk factor.[33] Between April 15 – June 16, 2009 during the initial stages of the 2009 novel H1N1 influenza pandemic, six pregnant women died from infection with novel H1N1 influenza and secondary pneumonia infections.[34] In a 13-year population-based cohort study, Dodds, et. al. found the rate of third-trimester hospital admissions during the influenza season was 5 times higher than the rate during the influenza season in the year before pregnancy and more than twice as high as the rate during the non-influenza season.[2] Similarly, in a study examining influenza-attributed hospitalization rates among pregnant women in Canada between 1994 – 2000, Schnanzer, et. al. found that the hospital admission rate for healthy pregnant women corresponds to the rate for men and women aged 65 to 69 years.[4]

Pertussis

Since pertussis is also an infection of the respiratory tract, the concerns of acquiring whooping cough during pregnancy are similar to those of an influenza infection. A pregnant woman is likely to experience a bad cough with the illness, but the greatest burden caused by her illness is the threat she poses to her newborn baby.

Risks to the fetus

Recent research into inflammatory correlates for adverse birth outcomes suggest that infections during pregnancy may lead to adverse effects on the fetus. While vertical transmission of pathogens from an infected mother to her fetus has been documented in diseases like malaria and syphilis, it is believed to be rare, for seasonal influenza and pertussis.[35] The greater concern is how maternal infection during pregnancy may indirectly affect the placental environment and fetal growth. Studies examining fetal impacts of maternal influenza virus infection suggest that influenza infection during pregnancy can result in preterm birth or low birth weight; these adverse fetal outcomes have been documented following influenza pandemics, including the 2009 novel H1N1 influenza pandemic.[36-40] In a national cohort study conducted in the UK during the second wave of the 2009 novel H1N1 influenza pandemic, Pierce, et. al, found that perinatal mortality, and specifically stillbirth, were significantly higher among infants born to women infected with 2009/H1N1 during pregnancy.[40] The rate of stillbirth among infected women was 27 per 1,000 total births compared to 6 per 1,000 among total births ($P = 0.001$). The study also found a statistically significant association between premature birth and infection with 2009/H1N1, with infants of infected women being 4 times as likely to be born prematurely than infants born to comparison women (adjusted odds ratio 4.0, 95% confidence interval 2.7 – 5.9).[40]

Risks to the newborn

Since influenza and pertussis are both highly contagious respiratory diseases, each disease poses significant risks to immunologically naïve newborns. Among pediatric cases of influenza, infants under 6 months old have one of the highest rates of hospitalization from influenza.[41] Of infants under 1 year of age that contract pertussis, about half will be hospitalized, and infants under 2 months of age have the highest mortality rate from the disease.[42] Because vaccination against pertussis is not recommended to begin until 2 months of age and vaccination against influenza is not recommended until 6 months of age, maternal infection with either of these diseases can be very dangerous to newborns.

A literature review published in 2013 summarizing research conducted in developed countries on the potential sources of pertussis infection among hospitalized infants under 6 months of age found that mothers were responsible for infecting their newborn in approximately 39% of cases.[43] In contrast, fathers and grandparents were the source of the infection in 16% and 5% of the cases, respectively. One paper included in this review found mothers to be the source in 42% of cases.[44] One gap in knowledge of familial transmission of respiratory diseases to infants is rate of sibling transfer; this is an area where more research is needed.

Vaccination during Pregnancy

Vaccinating pregnant women against influenza and pertussis is one of the first preventive steps that can be taken to protect mother, fetus and infant. Influenza vaccination during pregnancy has been recommended for many years, and despite increases in antenatal influenza vaccination rates in recent years, the rates are not yet close to the Healthy People 2020 goal of

80% coverage among pregnant women.[45] Since pertussis vaccination only started being recommended during pregnancy in 2011, coverage rates for this vaccine have yet to reach optimal levels as well. Improving vaccination rates among pregnant women for both vaccines is needed.

Influenza vaccine

The recommendation to receive an influenza vaccine during pregnancy was first made in the 1960's, but until 1995, the recommendation focused primarily on women who had underlying medical conditions that would increase their risk of influenza-related complications.[46] Beginning in 1996, the recommendations were extended to promote influenza vaccination routinely among women in their second and third trimesters. In 2004, the Advisory Committee on Immunization Practices (ACIP) expanded their recommendation to all pregnant women, regardless of trimester.[47]

Influenza vaccination is considered safe during pregnancy. Since the vaccine has been given to pregnant women since the 1960's, considerable research has been conducted on the vaccine's safety during pregnancy. No study to date as reported an increased risk for serious adverse events among women who received a seasonal influenza vaccine during pregnancy versus those who have not. Only one recent study by Louik, et. al. found an increased risk for pre-term birth among women who received a 2009 pandemic H1N1 vaccine compared to those who did not receive any influenza vaccine during pregnancy.[13] The hazard ratio for women who received a pH1N1 at any time during pregnancy compared to non-exposed pregnant women was 2.82 (95% CI: 1.16, 6.86) after adjustment for maternal age, maternal race, maternal education, family income, marital status, parity, study center, body mass index (BMI), family history of birth defects, pregnancy intention, periconceptional folic acid use, alcohol use, smoking, asthma, diabetes, LMP quarter, infertility treatment, treatment for high blood pressure or toxemia, inter-

pregnancy interval, and season of exposure (2009–2010 or 2010–2011) using a propensity score.[13] When comparing the women who received the pH1N1 vaccine during the first trimester to those who were unexposed, the adjusted hazard ratio was 4.84 (95% CI: 1.45, 16.1). Upon examining differences in the actual gestational length of the pregnancies between the pH1N1-exposed and p-H1N1 unexposed mothers, the difference in the number of days preterm was less than 1 day for exposure to pH1N1 at any time during pregnancy and less than 2 days for first trimester exposure. Table 1 summarizes selected studies examining the safety and reactogenicity of influenza vaccine receipt during pregnancy. In 2014, Naleway, et. al. published a review of additional observational studies supporting the conclusion that antenatal influenza vaccination results in no increased risks of maternal obstetric outcomes.[15]

Table 2-1. Summary of selected studies examining the safety of influenza vaccination during pregnancy.

Study	Year(s) conducted	Study type	Sample size	Outcomes
Asian influenza outbreak study (Hulka, et. al.)[48]	1962 – 1963	RCT	398 (225 pregnant women received 2 injections of polyvalent vaccine)	No fetal anomalies or miscarriages associated with vaccination
Sumaya, et. al.[49]	1976-1977	Prospective cohort	112 (56 received inactivated influenza A/NJ/76 virus vaccine in second or third trimesters)	Pregnancy course and outcomes for vaccinated women were similar to those in the control group
Deinard, et. al.[50]	1976	Prospective cohort	706 (189 received Influenza A/New Jersey/8/76 virus vaccine just prior to or during pregnancy; 517 pregnant controls did not receive the vaccine)	No association between immunization and maternal, perinatal or infant complications.
Englund, et. al.[51]	1988-1989	RCT	30 pregnant women in third trimester (half randomized to receive trivalent influenza vaccine; half received tetanus toxoid (TT) vaccine)	No significant differences between the two groups on adverse maternal or infant outcomes.
Mother's Gift Project (Zaman,	2004 - 2005	RCT	340 pregnant women (170 received	No serious adverse events reported in mothers or

et. al.)[52]			trivalent inactivated influenza vaccine in 3rd trimester)	infants; no differences in pregnancy outcomes
Eick, et. al.[53]	2002 - 2005	Prospective cohort	1,169 mothers and infants (583 vaccinated during pregnancy)	No significant differences in gestational age or mean birth weight in babies born to vaccinated versus unvaccinated mothers; 41% reduction in risk of laboratory-confirmed influenza virus infection for infants of influenza-vaccinated mothers compared with infants of unvaccinated mothers
France, et. al.[54]	1995 - 2001	Retrospective cohort	41,129 infants (3,160 born to mothers who received antenatal influenza vaccine)	No differences in birth weight, gestational age, or length of hospital stay after delivery
Black, et. al.	1997 - 2002	Case-control	49,585 (3,719 vaccinated women, 45,866 controls)	No differences in rate of cesarean section or preterm birth
Jackson, et. al.[55]	2009	RCT	120 pregnant women in 2nd or 3rd trimester	Reactogeniticy profiles of two different doses of 2009 H1N1 vaccine in pregnant women was similar to those reported for 2009 H1N1 vaccines in nonpregnant adults
Chambers, et. al. [12]	2009-2012	Prospective cohort	1,032 (841 women exposed to pH1N1-containing vaccine during pregnancy vs. 191 women unexposed to any influenza vaccine during pregnancy)	No significant differences in major birth defects, spontaneous abortion, or small for gestational age between women who received a pH1N1 vaccine during pregnancy and those who were unexposed.
Louik, et. al.[13]	2009-2011	Case-control	4,191 subjects (3,104 mothers of malformed infants and 10,87 mothers of non-malformed infants)	Risk for preterm birth was increased in 2009 – 2010, especially after H1N1 vaccination in first trimester, but the decrease in gestational age was <2 days. No evidence for increased risk for major defects or congenital abnormalities among infants whose mothers received an H1N1 vaccine.

Despite a Healthy People 2020 goal of 80% influenza vaccination coverage among pregnant women, influenza vaccination rates among pregnant women have historically been lower than 20%. It was not until the 2009 – 2010 novel H1N1 pandemic that national coverage rates rose to approximately 50%. While seasonal influenza vaccination rates since 2009 - 2010

have remained high in some states, rates ranged from 26% to 68% among states participating in the Pregnancy Risk Assessment Monitoring System (PRAMS) in 2009 – 2010.[46] In Georgia, the estimate from 2009 – 2010 was 29.9%. National influenza vaccine coverage estimates among pregnant women have ranged between 47% - 50% for the three influenza seasons between 2010 – 2013.[56-58]

Influenza vaccination during pregnancy has been shown to have benefits for the mother, the fetus and the baby. For the mother, vaccination during pregnancy helps prevent her from getting sick with influenza and the resulting complications of the disease during pregnancy. For the fetus, maternal vaccination protects against pre-term birth and small for gestational age births. In a retrospective cohort analysis of Georgia PRAMS data collected between June 2004 – September 2006, Omer et. al. found that influenza vaccination during any trimester of pregnancy was protective against premature birth during the influenza season (adjusted OR = 0.60; 95% CI, 0.38-0.94) and small for gestational age birth when influenza activity was widespread (adjusted OR = 0.28; 95% CI, 0.11 – 0.74), as compared to birth outcomes among mothers who did not receive an influenza vaccine during pregnancy.[10] For the infant, maternal vaccination results in the transplacental transfer of antibodies that have proven to help protect the infant from infection. Studies which have examined the protective capacity of maternally-derived antibodies have found that maternal vaccination can delay onset of infection[59] and reduce laboratory-confirmed illness in infants.[52] Data from a randomized controlled trial also demonstrated that antenatal influenza vaccination results in higher breast milk-specific immunoglobulin A concentrations for up to 6 months post-partum.[60]

Pertussis vaccine (Tdap)

In an effort to more effectively protect newborns under 3 months of age from contracting pertussis, in 2006 the ACIP recommended that the Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine be administered to new mothers immediately post-partum and to any other family members or caregivers who had not previously received the vaccine.[61] The idea behind this strategy was to create a protective environment or "cocoon of immunity" around the infant. Due to sustained increases in pertussis cases in newborns despite this "cocooning" strategy, the ACIP changed their recommendation in 2011 to encourage pregnant women who had not received a Tdap vaccine in recent memory to receive the vaccine, preferably after 20 weeks gestation. This Tdap recommendation during pregnancy was unprecedented since it represented the first time the ACIP recommended vaccination for the primary benefit of someone other than the vaccine recipient; while maternal antenatal Tdap vaccination protects the mother from acquiring pertussis, its primary purpose is to protect the young infant before an active immune response can be induced. This antenatal recommendation was extended again in 2012 to include vaccination of all pregnant women regardless of trimester or vaccine history, but with a preference for vaccination between 27 – 36 weeks gestation.[24] The rationale behind this expanded recommendation is to ensure optimal antibody transfer to each fetus in order to confer protection to the infant during the first 3 months of life when complications from pertussis infection are greatest.

While there is considerable research on the safety of tetanus toxoid (TT) vaccine during pregnancy,[62,63] there is less information on the safety of Tdap during pregnancy, but the literature is growing.[64] In a retrospective cohort study published in 2014 among 123,494 women with singleton pregnancies between 2010 – 2012 in California, 21% received a Tdap vaccine during pregnancy and receipt was not associated with increased risk of preterm delivery (6.3% in

vaccinated mothers vs. 7.8% in unvaccinated mothers; adjusted risk ratio [aRR] = 1.03, 95% CI: 0.97 – 1.09) or small-for-gestational age birth (8.4% in vaccinated mothers vs. 8.3% in unvaccinated mothers; aRR = 1.00, 95% CI: 0.96 – 1.06).[65] Receiving a Tdap vaccination before 20 weeks gestation was not associated with pregnancy-related hypertension (aRR = 1.09, 95% CI: 0.99, 1.20). The study did however find a small, but statistically significant increased risk of chorioamnionitis in vaccinated mothers compared to unvaccinated mothers (6.1% vs. 5.5%; aRR = 1.19, 95% CI: 1.13-1.26). Chorioamnionitis, which is inflammation of a woman's amniotic fluids, membranes or placenta due to a bacterial infection, occurs in approximately 8% of pregnancies and can increase the risk of severe adverse events including stillbirth, rupture of membranes, premature labor and developmental delays in the child.[15] The authors provide a number of potential explanations for this elevated risk of chorioamnionitis including an inability to adjust for other chorioamnionitis risk factors including prolonged rupture of membranes, genital tract pathogens or receipt of an epidural. They also note that despite the elevated risk for chorioamnionitis, they did not observe an increased risk for pre-term birth which is a major adverse event related to chorioamnionitis.

In another observational study from the United Kingdom (UK), Donegan, et. al. found no increased risk of stillbirth in the 14 days immediately after vaccination (incidence rate ratio [IRR] = 0.69, 95% CI: 0.23, 1.62) or later in pregnancy (IRR = 0.85, 95% CI: 0.44, 1.61) among 20,074 women who received a pertussis vaccination during pregnancy compared to a matched historical unvaccinated control group.[66] Increased risks for other adverse events including maternal or neonatal death, pre-eclampsia, uterine rupture, and low birth weight were also not observed among vaccinated mothers compared to the historical controls. A key difference between this study and others conducted in the U.S. is that the pertussis-containing vaccine widely in the UK (and therefore among women in this study) contains a poliomyelitis component instead of a

tetanus component. Despite this difference, this study still contributes to the literature supporting the safety of pertussis-containing vaccines during pregnancy.

The first randomized controlled trial testing the safety and immunogenicity of antenatal Tdap vaccination was published in 2014.[67] Conducted among 48 healthy pregnant women and 32 healthy non-pregnant women from 2008 – 2012, this phase I randomized, double-masked, placebo-controlled trial found no serious adverse events associated with Tdap vaccination at 30 – 32 weeks gestation or post-partum. While localized reactions were reported in approximately 80% of women who received Tdap, they occurred with the same frequency regardless of timing of receipt (during pregnancy, post-partum or not pregnant). Compared to women immunized post-partum or non-pregnant women, women immunized during pregnancy were less likely to report systemic symptoms like headache, myalgia and malaise (post-partum receipt: 73.3%, non-pregnant receipt: 53.1%; antenatal receipt: 36.4%, $p = 0.055$). Serious adverse events were reported by 22 women, including 7 (21.2%) who received Tdap during pregnancy. None of the serious events were deemed attributable to the Tdap vaccine.

Vaccine Refusal and Barriers to Vaccinating Pregnant Women

Despite the benefits of antenatal vaccination, challenges exist in the effort to promote influenza and Tdap vaccination among pregnant women. Among others, reasons include lack of knowledge about the diseases or the vaccines (among both providers and patients), fear of harming their fetuses or themselves, reluctance on the part of pregnant women to put anything foreign into their bodies, distrust of the medical community, and not knowing their obstetric provider as a vaccine provider. Despite these barriers and others, pregnancy may be a "privileged time" to promote vaccination since pregnancy itself may motivate health-promoting behaviors.[21]

Patient Barriers

Lack of knowledge around the risks influenza infection poses to pregnant women and concern over the safety of the vaccine are predominant patient barriers to vaccination. A study conducted in Colorado between November 2009 and May 2010 on why women refused seasonal and novel H1N1 influenza vaccines during pregnancy found that 25% of those surveyed did not know the vaccine was important and 18% were concerned about the vaccine's effects on their fetuses' health.[68] Another study conducted in 2011 by Lu et. al. found that among 162 women who refused an influenza vaccine during pregnancy, 40% cited being worried about the safety of the vaccine, 24% were worried about vaccine side effects, and 22% did not think they were at risk of getting influenza.[69] In a study of Canadian women, 79% (46/58) of post-partum respondents believed that studies have shown influenza vaccine causes birth defects.[70]

Race is also a known barrier to vaccination, especially for influenza vaccine receipt. African-American women, pregnant or otherwise, are much less likely to receive influenza vaccine as compared to non-Hispanic whites.[71,72] In one study examining the uptake of seasonal and novel 2009 H1N1 vaccine, black women were significantly more likely to decline both seasonal and 2009 H1N1 influenza vaccines compared to non-black patients (6/25 [24%] vs 19/294 [6.5%], P value = .0017).[73] Among other reasons, African-Americans may be less likely to receive influenza vaccines than other racial groups may be related to negative perceptions of vaccines within their communities as well as unfavorable experiences with the health care in general.[72,74]

Cost and access issues are also barriers to antenatal vaccination, especially for uninsured or underinsured women. Determinations on which adult vaccinations are covered by Medicaid are made at the state level; in Georgia, influenza vaccinations for pregnant women are covered, but Tdap is not. At retail outlets like pharmacies or grocery stores, a seasonal influenza vaccine

costs $25 - $30 on average. In Georgia, Tdap shots can range between $34 - $125, depending upon the location. The high out-of-pocket cost of these vaccines, especially for Tdap, is a considerable barrier to many women. Moreover, if these vaccines are not offered at convenient locations, like OB/GYN practices, the hassle of traveling to get the vaccine(s) on top of the expense can be a major deterrent. In a study of 511 predominantly Hispanic and underinsured women from the Houston area surveyed post-partum between June 2010 – July 2012, Beel et. al. found that the overwhelming majority (97.2%) preferred clinic-based delivery of peripartum immunizations rather than retail outlets like pharmacies or supermarkets.[75] Additionally, financial constraints such as cost of vaccine, insurance co-payments or loss of earnings while attending clinic visits during the workday were cited as being barriers to vaccinating their family members by 31.4% of respondents.

Obstetric provider barriers

Barriers to vaccinating pregnant women also exist among health care providers, namely obstetric providers. Many surveys and studies have identified concerns on the part of providers, and in a paper summarizing this research, Shavell et. al. suggest barriers among providers tend to cluster around safety concerns, vaccination not being "usual practice" for them, and financial concerns.[21] Additionally, concerns over legal risks associated with vaccinating pregnant women and the perception that pregnant women do not want to be vaccinated have also been cited.[22] Misconceptions over CDC recommendations can also serve as a barrier; one study found that 22% of obstetrician-gynecologists surveyed did not know pregnant women were at increased risk for influenza morbidity and about half were unaware that maternal vaccination could confer protection to the baby though antibody transfer.[76]

Obstetric barriers do not only involve physicians. In a survey conducted between 2006 – 2009 among 267 obstetric nurses, medical and nursing assistants, receptionists and clinical administrators, Broughton et. al found that nearly one-third of health care workers surveyed do not view vaccines as a safe way to decrease infections, and only 36% believed that vaccines are safe during pregnancy.[77] These results suggest that in addition to patient- and provider-level interventions geared towards improving maternal vaccination during pregnancy, practice-level components should be developed as well.

Improving Vaccination Rates among Pregnant Women

Improving vaccination rates among pregnant women is one of the primary foci of the U.S. National Vaccine Advisory Committee (NVAC). As the committee charged by the Assistant Secretary for Health to "recommend ways to achieve optimal prevention of human infectious diseases through vaccine development and provide direction to prevent adverse reactions to vaccines," this committee published explicit recommendations in early 2015 regarding ways to overcome known barriers to antenatal vaccination and increase antenatal vaccine coverage. To arrive at their recommendations, the committee did an extensive review of the literature available on barriers and facilitators to antenatal vaccination, much of which is described in more detail below and within the context of two theories related to behavioral change in the health care setting. Since vaccination is an example of a preventative care action, theories related to behavioral change in the health care setting are helpful to building successful interventions aimed at improving vaccine uptake.

Theoretical models affecting health behavior change – Health Beliefs Model and the Systems Model of Clinical Preventive Care

The Health Beliefs Model is a psychological model that attempts to both predict and explain individuals' health-related behaviors. Developed by Rosenstock in 1966 to understand why people refused to adopt certain preventative health behaviors, this model has been used in many studies attempting to understand the factors which influence a person's decision-making process regarding health behaviors.[78] This model promotes 6 main domains as predictive of health behavior change. These domains include:

1. Perceived susceptibility to the condition, illness or disease
2. Perceived severity of the condition, illness or disease
3. Perceived benefits (of an advised action to reduce risk to the condition, illness or disease)
4. Perceived barriers (to an advised action to reduce risk to the condition, illness or disease)
5. Cues to action (i.e., strategies to activate "readiness" for or against the condition, illness or disease)
6. Self-efficacy (i.e., confidence in the ability to take actionable steps to prevent or mitigate the condition, illness or disease)

The Health Beliefs Model has been applied to vaccination as a preventive health behavior. In 1984, Janz and Becker reviewed 4 studies---3 Swine Flu studies from the 1970's and 1 study of influenza vaccine receipt among high-risk population---that applied the HBM to influenza vaccination.[79] Each study found statistically significant associations with many HBM items. The only item that was either not significant or questionable in its utility was "perceived severity." Since vaccination itself can affect one's perception of disease severity, the

interpretation of "severity" may be different among those who received a vaccine versus those who did not. While "perceived severity" is an HBM item that should be taken into consideration in developing the educational components of an intervention to improve antenatal vaccination, understanding the limitations of how variables measuring perceptions of disease severity will be helpful upon evaluation the intervention itself.

Another theoretical model affecting health behavior change is the systems model of clinical preventive care. Published in 1992 by Walsh and McPhee the systems model of clinical preventive care considers both the patient and the physician as integral to affecting change in the patient.[80] The model includes components of behavioral, communication, health education and psychosocial theories, and can be applied to many situations, including vaccine promotion. Naleway, et. al. has applied the model specifically to influenza vaccination during pregnancy. [81] Because the model incorporates components regarding the physician-patient relationship, it is unique from the Health Belief Model, and may also be appropriate to use for the development of an intervention aimed at affecting change at multiple levels within clinical care.

Applying the themes and elements of these two theoretical constructs to improving antenatal vaccination in the clinical setting are addressed below.

Interventions to improve vaccination

Enabling Factors

For influenza vaccination, factors known to play important roles in influencing a woman's decision to receive an influenza vaccine during pregnancy are a doctor's recommendation and improved education on the importance of vaccination during pregnancy. A doctor's recommendation is believed to be one of the most important positive factors contributing to a woman's decision to receive an influenza vaccine. A study by Moniz, et. al. on attitudes

towards immunization found that 89% of pregnant women indicated they would be immunized if the vaccine was recommended by their obstetric physician.[82] In another study of post-partum women by Goldfarb, et. al, 60% of the women who received and influenza vaccine during pregnancy did so because their obstetrician recommended it [73], and Beel et. al. found that 93% of post-partum women surveyed were willing to be immunized during pregnancy if recommended by their healthcare provider.[75]

Regarding patient education, a recent randomized controlled trial evaluated the effectiveness of a patient-centered pamphlet aimed at increasing women's knowledge about influenza and the importance of antenatal vaccination.[27] One-hundred thirty five women were enrolled at 3 locations in Connecticut and randomized to one of 3 conditions: 1) receipt of the pamphlet, 2) receipt of the pamphlet along with a statement of benefit for the infant, or 3) receipt of neither (control group). Vaccine uptake was significantly higher in both the group that received the pamphlet (72.9%; $\chi^2 = 6.81$, df = 1 p = .009) and the pamphlet plus the infant benefit statement (86.1 %; $\chi^2 = 13.74$, df = 1, $p < .001$) than in the control group (46.9%).[27] Additionally, perceptions of vaccine safety and understanding of benefits to both the mother and infant improved for the intervention groups as compared to the control groups.

Education for physicians and staff is also a key enabling factor for successful promotion of a preventative health activity like vaccination. Periodically updating physicians on the latest vaccine recommendations is useful in keeping them abreast of the current guidance and importance of promoting certain vaccines at certain times. Provision of peer-to-peer training of physicians and staff within private pediatric practices has proven successful in increasing immunization rates among practice in Pennsylvania; practices receiving the peer-to-peer training through the Educating Practitioners in their Communities (EPIC) Program increased their immunization rates by 11% compared to increases of only 1% in non-participating practices.[83] While a subsequent randomized trial in Washington State did not find peer-to-peer education

particularly effective in improving vaccination rates among children within primary care practices, the control arm practices not receiving the peer-to-peer education received a substantial enhanced intervention above standard educational practice.[84] This contribution to the control arm intervention could have biased their results towards the null.

Reinforcing factors

Focusing on the benefits of vaccination to the baby, as opposed to the mother, has been supported by research from Steelfisher and others.[85] Pregnant women can be highly motivated to act when a preventative measure can be described as positively impacting the baby. While Walsh and McPhee claim that patient reinforcing factors are largely absent from the Systems Model of Clinical Preventive Care in the case of influenza vaccination, much has changed in the influenza vaccine research arena since publication of their model. One can argue that preventing preterm birth through influenza vaccination can be viewed and promoted as a significant reinforcing factor for the patient.

Organizational and situational factors

Other studies have examined the effectiveness of organizational solutions to improving vaccine uptake such as standing vaccine orders and other types of physician/patient reminder systems. Seen as both organizational factors or cues to action, these elements serve to continuously remind health care personnel to address vaccination with their patients. Standing vaccine orders authorize other health care personnel like nurses and pharmacists to give vaccines under a specific protocol without necessitating physician involvement. This strategy, which is endorsed by the ACIP, is designed to save time and allow health care providers to give vaccines

more readily to eligible patients. Studies which have examined the use of standing vaccine orders have largely concluded standing orders to be successful in improving vaccination rates.[86-88] In one retrospective study of women who received care in a university-based prenatal clinic, standing orders were the most important clinic-level intervention put in place to increase influenza vaccine uptake among pregnant women.[87]

Regarding physician/patient reminder systems such as EMR flag reminder systems or reminder messages to patients have had mixed results. Generally, provider-level reminder-recall systems aimed at increasing vaccination have proved effective. In a review of studies which have reported increases in rates of vaccination due to implementation of reminder-recall systems for providers, the Task Force for Community Preventative Services found a median improvement of 17% in vaccination rates.[21,88] Patient-centered reminder systems have been less effective, however. Text4Baby which is the largest patient-centered reminder program in the country has not yet been systematically evaluated for its effectiveness in improving antenatal maternal vaccination for influenza or other vaccines. While surveys of pregnant women suggest that the program is conceptually popular, its effectiveness in changing prenatal behaviors is less clear. One randomized trial demonstrated the program's effectiveness in improving a woman's perceived readiness for motherhood (OR = 2.73, CI = 1.04, 7.18, p = 0.042), however; it did not prove effective in changing or improving women's opinions on other targeted beliefs as compared to controls.[89] Another recent randomized trial evaluating the effectiveness of text message reminders to receive an influenza vaccine did not prove effective.[25] Among a low-income, primarily African-American, ambulatory obstetric population, the overall influenza vaccination rate among participants was 32% with no difference between participants who received general preventative health-related text messages and those who received health-related text messages plus messages about the importance of influenza vaccination during pregnancy (difference 1.7%, 95% confidence interval −11.1 to 14.5%). This null finding was observed

despite a majority of participants in both groups liking the text messages (90%) and believing them to be a good way for physicians to help improve patient health (94%).[25]

Studies explicitly examining methods to improve Tdap vaccine uptake among pregnant women have not been published. While some research has been done on what interventions influenza maternal acceptance of vaccines, especially influenza vaccine, more work needs to be done.

CHAPTER 3: MOMVAX STUDY DESIGN AND INTERVENTION

Study Design

Data presented in Chapters 4 – 6 of this dissertation are from the Emory MOMVAX study. This study was a pair-matched group randomized trial conducted among 11 obstetric practices in Georgia beginning in December 2012. The primary objective of the Emory MOMVAX study was to evaluate the effectiveness of a multi-component, evidence-based vaccine promotion package on improving the likelihood that a pregnant woman receives an influenza and/or Tdap vaccination before delivery. Secondary objectives included assessment of effectiveness of the vaccine promotion package on receipt of any Tdap vaccination (antenatal or post-partum) and evaluation of changes in knowledge, attitudes and beliefs about antenatal vaccination on account of exposure to the promotional package.

Group, or cluster, randomized trials are often used in community intervention studies or studies of health program promotion where the units of assignment are whole groups of people rather than individuals.[90] As with a traditional randomized trial, the group-randomized approach helps ensure that unmeasured confounders are equally distributed across study groups so that unbiased effect estimates and valid confidence intervals can be calculated. This method allowed us to evaluate the effectiveness of the intervention package on improving antenatal influenza and Tdap vaccination by randomizing obstetric practices to receive the package (intervention arm) or maintain their standard of care regarding vaccine promotion and administration (control arm). This method is superior to simply measuring vaccination rates before and after adoption of the intervention package; relying on pre- and post- intervention measurements of vaccination rates alone prohibits determination of whether any increase in the uptake of either vaccine would have occurred in the absence of the intervention package.

Obstetric practices volunteering to participate in this study were pair-matched on practice-level characteristics predictive of vaccine receipt by pregnant women prior to randomization. The purpose of this matching process was to attempt to balance factors known to influence the primary outcome across the experimental groups of the study. Since we could only include a small number of practices per condition (5 *a priori*), pair matching was recommended.[90] The following three factors known to influence vaccine receipt by pregnant women were used as our matching criteria:

1. Provision of influenza and Tdap vaccines in the participating obstetric practice prior to study initiation;

2. Estimated influenza vaccination rate among pregnant patients from the 2011 – 2012 influenza season, and

3. Estimated percent of a practice's patient population on Medicaid.

Intervention package

Provided to all intervention group practices at the initiation of the study and to the control group practices at the end of study follow-up, the MOMVAX intervention package consisted of the following items:

Practice-level components:

- Influenza and Tdap vaccination promotional posters
- Influenza and Tdap vaccination educational brochures
- Promotional lapel pins for providers and staff

- Lists and maps of nearby locations where patients can receive influenza and/or Tdap vaccines (if not available in the practice)
- Identification of a vaccine champion within the practice

Provider-level components:

- Georgia EPIC Women's Health peer-to-peer training on provision of vaccinations within the OB/GYN setting
    - EPIC training provided OB/GYN practices information on current guidance and recommendations for vaccinating women within OB/GYN practices.
- Doctor-to-patient talking points

Patient-level component:

- Interactive iPad-based educational application

CHAPTER 4: PRELIMINARY MANUSCRIPT

Factors Associated with Intention to Receive Influenza and Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine during Pregnancy: A Focus on Vaccine Hesitancy and Perceptions of Disease Severity and Vaccine Safety

[This chapter was published as an original article in the journal *PLOS Currents: Outbreaks* on February 25, 2015. While not formally part of the approved aims of this dissertation, the results presented here are pertinent to understanding the design of the Emory MOMVAX study, the recruitment of study subjects and the nature of the target population. It is reproduced here with permission from *PLOS Currents: Outbreaks*]

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Abstract

BACKGROUND: Improving influenza and tetanus, diphtheria and acellular pertussis (Tdap) vaccine coverage among pregnant women is needed.

PURPOSE: To assess factors associated with intention to receive influenza and/or Tdap vaccinations during pregnancy with a focus on perceptions of influenza and pertussis disease severity and influenza vaccine safety.

METHODS: Participants were 325 pregnant women in Georgia recruited from December 2012 – April 2013 who had not yet received a 2012/2013 influenza vaccine or a Tdap vaccine while pregnant. Women completed a survey assessing influenza vaccination history, likelihood of receiving antenatal influenza and/or Tdap vaccines, and knowledge, attitudes and beliefs about influenza, pertussis, and their associated vaccines.

RESULTS: Seventy-three percent and 81% of women believed influenza and pertussis, respectively, would be serious during pregnancy while 87% and 92% believed influenza and pertussis, respectively, would be serious to their infants. Perception of pertussis severity for their infant was strongly associated with an intention to receive a Tdap vaccine before delivery ($p=0.004$). Despite perceptions of disease severity for themselves and their infants, only 34% and 44% intended to receive antenatal influenza and Tdap vaccines, respectively. Forty-six percent had low perceptions of safety regarding the influenza vaccine during pregnancy, and compared to women who perceived the influenza vaccine as safe, women who perceived the vaccine as unsafe were less likely to intend to receive antenatal influenza (48% vs. 20%; $p < 0.001$) or Tdap (53% vs. 33%; $p < 0.001$) vaccinations.

CONCLUSIONS: Results from this baseline survey suggest that while pregnant women who remain unvaccinated against influenza within the first three months of the putative influenza

season may be aware of the risks influenza and pertussis pose to themselves and their infants, many remain reluctant to receive influenza and Tdap vaccines antenatally. To improve vaccine uptake in the obstetric setting, our findings support development of evidence-based vaccine promotion interventions which emphasize vaccine safety during pregnancy and mention disease severity in infancy.

Introduction

Respiratory infections like influenza and pertussis during pregnancy can pose serious risks to mother and infant.[2,5,31,32,36,39,91,92] Pregnant women are at increased risk of complications from influenza, and infants are not recommended to receive an influenza vaccine until 6 months of age.[93] For pertussis, infants under 2 months of age, prior to the recommended age for vaccination, have the highest rates of hospitalization and death.[94,95] Antenatal vaccination against these diseases not only protects mothers, but studies have suggested protection can be conferred to infants through maternal-fetal transfer of antibodies through the placenta.[52,59] Influenza vaccination during pregnancy can also protect against adverse fetal outcomes like preterm birth and small for gestational age as well as respiratory illnesses during infancy.[10,96]

Antenatal influenza vaccination recommendations have been in place since the 1960's[46], and in the U.S., the Centers for Disease Control and Prevention (CDC) began recommending tetanus, diphtheria, and acellular pertussis (Tdap) vaccination during pregnancy, preferably in the third or late second trimester, in 2011.[42] Based on previous research among pregnant women and healthy adults, both vaccines are considered safe during pregnancy.[97-103] Despite CDC recommendations, coverage estimates for both vaccines remain suboptimal in the U.S. The influenza vaccine coverage rate estimated by CDC among pregnant women is the U.S. for the 2012 – 2013 season was 50.5%, and while coverage rates for antenatal Tdap vaccination are not yet available, estimates range between 2.6% - 10% (CDC, unpublished data, 2012).

Vaccinating pregnant women is a challenge. Studies exploring barriers to vaccinating women in the obstetric setting suggest that logistic barriers such as lack of storage space, knowledge gaps regarding vaccine safety or vaccine recommendations, and vaccine hesitancy all contribute to immunization decision-making.[70] The aim of this descriptive analysis is to identify factors associated with an intention to receive influenza and/or Tdap vaccines during pregnancy

among women who remained unvaccinated against influenza within the first three months (September – November) of the putative 2012/2013 influenza season in the U.S.

Methods

Pregnant women included in these analyses were enrolled as part of a larger group-randomized trial entitled the "Emory MOMVAX study" to evaluate the effectiveness of a comprehensive, evidence-based vaccine education and promotion package on increasing antenatal influenza and Tdap vaccination in the obstetric setting. Women were recruited between December 11, 2012 and April 22, 2013 from 11 obstetric practices in Georgia participating in the Emory MOMVAX study. Recruiting women who remained unvaccinated against influenza by December likely increased the number of vaccine-hesitant women in our sample since women more likely to seek or accept vaccinations would have already received an influenza vaccination.

Following provision of informed consent, women were given a 28-item baseline survey in English to complete in the waiting area. These survey results are the focus of this paper. The survey included questions on demographics, influenza vaccine history, and knowledge, attitudes, and beliefs about influenza, pertussis and their accompanying vaccines during pregnancy. Perceptions of influenza vaccine safety were assessed through the level of agreement with the statement "Getting a flu vaccine while pregnant seems risky." Perceptions of influenza and pertussis severity were assessed through the question "How serious do you think it would be if you got the following illnesses while pregnant?" Likewise, perceptions of influenza and pertussis severity during infancy were assessed through the question "After delivery, how serious do you think it would be if your newborn baby got the following illnesses within their first 6 months?" A

team of clinicians, behavioral researchers, and communication specialists reviewed the questionnaire items to ensure clarity and adequacy of comprehension prior to administration.

Women were recruited by trained study personnel from the waiting areas of each participating practice. Eligibility criteria for participation were: being between 18 years and 50 years old, English-reading, currently pregnant, had not yet received a 2012 – 2013 seasonal influenza vaccine, and had not yet received a Tdap vaccine during their current pregnancy. After screening, written informed consent was obtained from each eligible woman interested in enrolling prior to administration of the baseline survey. While the intent was to complete the baseline survey prior to exposure to any intervention materials under evaluation in the MOMVAX study, if a woman was unable to finish the baseline survey prior to being called back for her scheduled appointment, she could complete the survey following her appointment. If, however, the woman returned to complete the baseline survey and indicated she had received an influenza and/or Tdap vaccine during her visit, she was no longer eligible for enrollment. At the time of enrollment and completion of the baseline survey, no attempts were made by the study personnel to provide any information about influenza, pertussis or their respective vaccinations.

The Institutional Review Boards of Emory University and the Medical Center of Central Georgia reviewed and approved this study. SAS version 9.3 statistical software (SAS Institute, Cary, NC) was used in 2013 for data analysis, including frequency calculations and proportion comparisons with chi-square and Fisher's exact tests. Women for whom survey data were missing on any given variable were retained in the denominator for univariate frequency calculations; missing data occurring in <1% of women were excluded from bivariate analyses, unless otherwise noted. Bivariate associations with a p-value < 0.05 were considered statistically significant.

Results

One-thousand four-hundred and thirty-six women were screened between December 11, 2012 – April 22, 2013. [Figure 4-1] Three-hundred eighty-eight women were eligible, and 325 women were enrolled and completed the baseline survey. Among 1,037 pregnant women screened, 609 (59%) and 212 (20%) were ineligible because they had already received a 2012 – 2013 influenza vaccine or a Tdap vaccine, respectively. The mean age of participants was 27.2 years and the mean parity was 1.1 children. Approximately 47% of participants were Caucasian/White and 41% were African American/Black. [Table 4-1] The proportion of participants reporting at least some type of private health insurance was approximately equivalent to the proportion reporting no insurance or coverage only by Medicaid (43.4% vs. 42.5%).

More than half (57%) of the women reported not having received a seasonal influenza vaccine in the past five years, while another 19% reported having only received a seasonal influenza vaccine once in the past five years. [Table 4-1] Sixty percent of participants considered their OB/GYN their primary care physician, yet two-hundred sixteen (66%) reported never having received any type of vaccine in an OB/GYN doctor's office. Thirty women (9%) reported having received a seasonal and/or H1N1 influenza vaccine in an OB/GYN's office before. Over one quarter (26%) reported feeling hesitant (i.e. worried or concerned) about receiving vaccines recommended by their physician during pregnancy.

White women were significantly more likely to intend to receive a Tdap vaccine during their current pregnancy than women of other races, and intention to receive an influenza vaccine was significantly associated with the number of times treated by a healthcare provider in the past year. [Table 4-1] Intention to receive antenatal influenza and/or Tdap vaccines was also significantly associated with previous receipt of influenza vaccination in the past five years.

There were no significant differences in proportions of women enrolled in control arm practices versus intervention arm practices on perceptions of disease severity during pregnancy, perceptions of disease severity for their newborn, intended likelihood of antenatal influenza vaccine receipt, intended likelihood of antenatal Tdap vaccine receipt, vaccine hesitancy, or perceptions of safety of influenza vaccination during pregnancy (data available upon request).

Two-hundred sixty five women (82%) agreed with the statement "Influenza is a concern for pregnant women," and 238 (73%) believed influenza infection would be serious or very serious during pregnancy. Two-hundred sixty two (81%) believed contracting pertussis during pregnancy would be serious or very serious. Additionally, 87% and 92% believed influenza and pertussis, respectively, would be serious or very serious to their newborn within the first six months of life.

Despite perceptions of severity, only 112 (34%) and 143 (44%) reported they were likely to receive an influenza vaccine or Tdap vaccine, respectively, during their current pregnancy. [Figure 4-2] Perception of influenza disease severity for themselves or their newborns was not significantly associated with an intention to receive an influenza vaccine during pregnancy, but perception of pertussis severity for their infant was strongly associated with intention of antenatal Tdap vaccination ($p=0.004$). [Figure 4-2]

Regarding influenza vaccine safety, 149 women (46%) agreed with the statement "Getting an influenza vaccine while pregnant seems risky." Compared to women who perceived the vaccine as safe, women who had low perceptions of influenza vaccine safety were significantly less likely to intend to receive an influenza vaccine (48% vs. 20%; $p < 0.001$) or a Tdap vaccine (53% vs. 33%; $p < 0.001$) during their current pregnancy. [Figure 4-3] While a lower perception of influenza vaccine safety was associated with a higher probability of non-intention to be vaccinated, substantial proportions of women who perceived the influenza vaccine

as safe still did not intend to be vaccinated (52% and 47% for influenza and Tdap, respectively). [Figure 4-3]

Discussion

Antenatal vaccination against influenza and pertussis not only protects the mother from contracting these diseases, but it is also the first step towards protecting infants during their first 3 months of life.[35] Efforts have been made in the U.S. by the American Congress of Obstetrics and Gynecology (ACOG) and other public health entities to stress the importance of influenza and Tdap vaccination during pregnancy.[104-108] With nearly 60% of pregnant women screened for this study ineligible to enroll because they reported having already received a 2012 - 2013 influenza vaccine, efforts in promoting antenatal influenza vaccination have been successful. In contrast, this study suggests that among pregnant women who remain unvaccinated against influenza by December (when most women willing to get vaccinated probably would have already received the influenza vaccine), a hesitancy that surpasses general concerns about vaccine safety remains.

While results from this survey underscore findings from other studies which describe influenza vaccine hesitancy among pregnant women, the influenza-based findings are juxtaposed with new insights on perceptions of Tdap vaccination during pregnancy.[21,68-70,73] Most women enrolled in this study were aware of the dangers influenza and pertussis pose to themselves and their infants, yet over one-quarter indicated hesitancy about receiving any vaccines recommended during pregnancy. Nearly half of women perceived the influenza vaccine as unsafe during pregnancy, and more women were likely to receive a Tdap vaccine than an influenza vaccine for all levels of perceived disease severity for themselves. Since contracting influenza is more common and poses a greater threat to pregnant women than pertussis, it is concerning that more women perceived pertussis as more serious during pregnancy than influenza.[93]

Even though 60% of participants consider their OB/GYN to be their primary care physician, only one-third reported ever receiving a vaccine from their OB/GYN. These data mirror findings from other healthcare utilization studies and illuminate a gap in both service and expectation in the adult immunization system.[109,110] Continuing to make vaccination a routine part of women's health can help normalize vaccination within the obstetric setting.[111] As obstetric healthcare providers become more accustomed to and comfortable with providing vaccines, women (pregnant or otherwise) will have greater access to and possibly acceptance of vaccines.

It is important to note the chronological context of this survey in relation to recent changes in antenatal Tdap recommendations in the U.S. While the U.S. Advisory Committee on Immunization Practices (ACIP) first recommended provision of Tdap at every pregnancy in October 2012, there were gaps between when this recommendation was made and when it was published.[24,112,113] Since this survey was administered between December 2012 and April 2013, data were collected during the initial rollout of these new recommendations. By virtue of its timing, this survey provides a baseline assessment of pregnant women's perceptions towards pertussis and Tdap in the U.S., thereby enabling changes in perceptions to be measured from this point forward.

This study has some important limitations. Since data were collected by self-report and not verified with medical records or vaccine registry data, there is potential for recall bias. Any recall bias which may have been introduced is assumed to have been non-differential with respect to characteristics likely to be associated with intention to receive antenatal influenza and/or Tdap vaccines. Additionally, while we excluded women who indicated having received an influenza and/or Tdap vaccine before completing her baseline survey, some women enrolled from intervention arm practices could have been exposed to the vaccine promotion materials under

evaluation in the MOMVAX study prior to completing their baseline surveys. Since we did not find any significant differences between arms of the MOMVAX study on baseline measures of perceptions of disease severity, intended likelihood of vaccine receipt, vaccine hesitancy, or perceptions of safety of influenza vaccination during pregnancy, we do not believe limited exposure to promotional intervention materials related to the MOMVAX study prior to completion of the baseline survey had a differential impact on the women enrolled from intervention arm practices versus control arm practices. This study was also U.S.-based, so while results may be applicable to other countries, it may be important to replicate this type of survey among late-acceptors of antenatal influenza vaccines in other regions as well.

To further improve antenatal influenza vaccine coverage and to encourage antenatal Tdap vaccination, promotional efforts tailored specifically to late acceptors of influenza vaccination or vaccine-hesitant women is important. Other studies which have tested messaging techniques have started to emphasize this need to tailor messages based upon individuals' preconceptions and attitudes towards vaccination.[114] Since these results show that perceiving pertussis as serious for their infant is strongly associated with intention to receive an antenatal Tdap vaccine, explaining disease effects on infants may be an effective promotional strategy for women reluctant to receive vaccines. Continuing to promote, discuss, and offer influenza vaccine repeatedly and late into an influenza season is especially important for women who may be hesitant, but still interested in receiving an influenza vaccine. Likewise, continuing to discuss and promote Tdap vaccination throughout pregnancy can remind and encourage women to receive a Tdap vaccination before delivery. Since patient education on antenatal vaccination is likely to come from obstetricians, continuing to develop and evaluate nuanced tools for promoting influenza and Tdap vaccines during pregnancy is needed.

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Figure 4-1. Schematic of study population included and excluded from baseline survey analyses

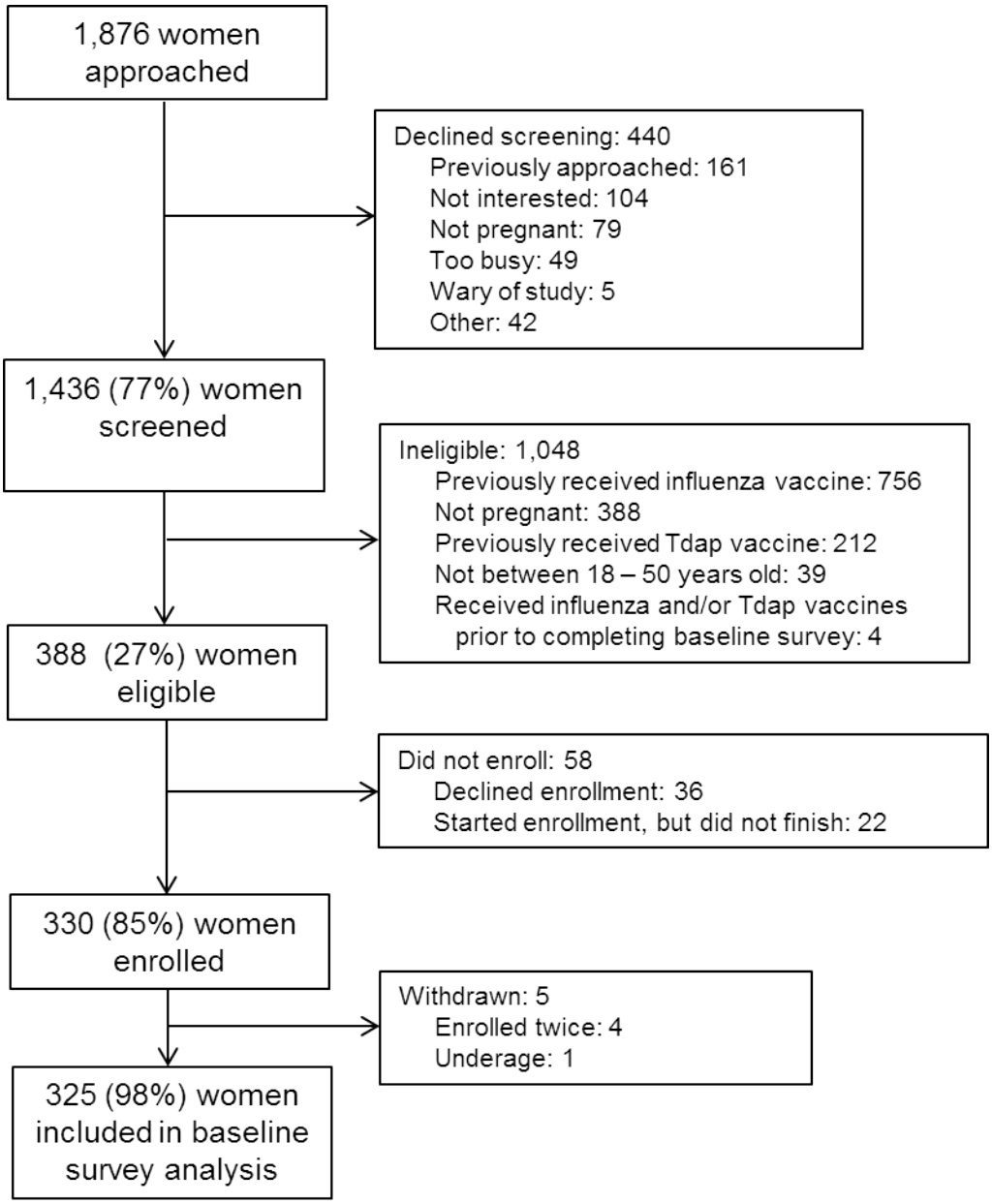


Table 4-1. Maternal characteristics and associations with intention to receive antenatal influenza and Tdap vaccines

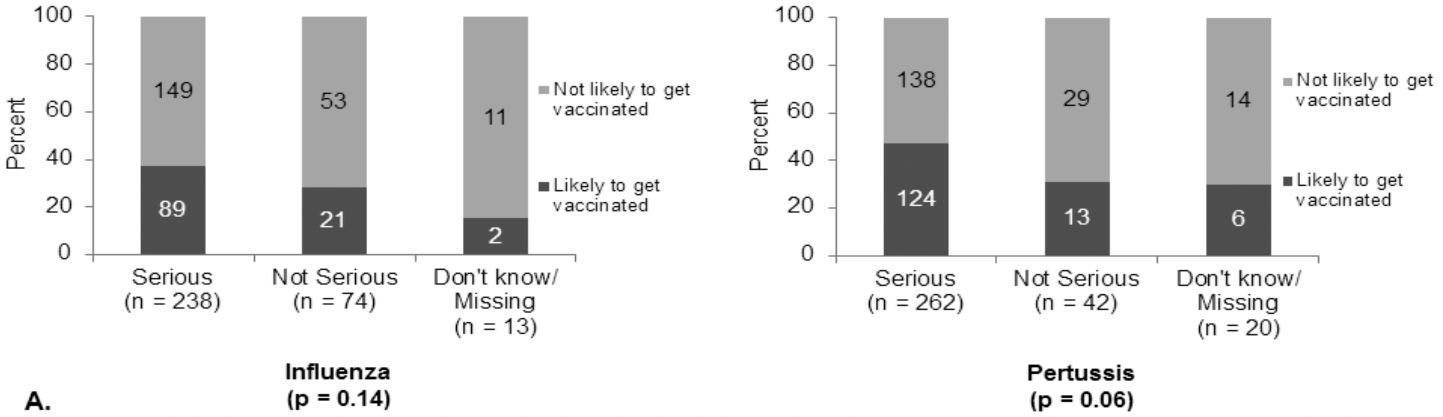
	Total (N = 325)	Likely to receive antenatal influenza vaccine (n = 112)	Unlikely to receive antenatal influenza vaccine (n = 213)	*p*-value [a]	Likely to receive antenatal Tdap vaccine (n = 143)	Unlikely to receive antenatal Tdap vaccine (n = 181)	*p*-value [a]
Age at enrollment				0.94			0.32
18 - 25	141 (43)	50 (45)	91 (43)		69 (48)	72 (40)	
26 - 35	155 (48)	53 (47)	102 (48)		62 (43)	92 (51)	
36 or older	28 (9)	9 (8)	19 (9)		12 (8)	16 (9)	
Race				0.17			**0.04**
Caucasian/White	154 (47)	55 (49)	99 (47)		80 (56)	73 (40)	
African American/Black	133 (41)	47 (42)	86 (40)		51 (36)	82 (45)	
Asian	7 (2)	4 (4)	3 (1)		2 (1)	5 (3)	
Other or missing	31 (10)	6 (5)	25(12)		10 (7)	21 (12)	
Ethnicity				0.96			0.40
Hispanic	20 (6)	7 (6)	13 (6)		7 (5)	13 (7)	
Non-Hispanic or missing	305(94)	105 (94)	200 (94)		136 (95)	168 (93)	
Parity (number of current children)				0.65			0.27
0	126 (39)	40 (36)	86 (40)		48 (34)	77 (43)	
1	105 (32)	41 (37)	64 (30)		53 (37)	52 (29)	
2	59 (18)	21 (19)	38 (18)		28 (20)	31 (17)	
3+	33 (10)	10 (9)	23 (11)		13 (9)	20 (11)	
Education				0.38			0.17
< High school graduate/GED	25 (8)	8 (7)	17 (8)		12 (8)	13 (7)	
High school graduate/GED	127 (39)	51 (46)	76 (36)		64 (45)	62 (34)	
Technical/vocational/Assoc.	73 (23)	21 (19)	52 (24)		26 (18)	47 (26)	
≥ Bachelor's degree	98 (30)	32 (29)	66 (31)		40 (28)	58 (32)	
Health insurance[b]				0.67			0.83
Any private insurance	141 (43)	47 (42)	94 (44)		61 (43)	80 (44)	
Medicaid or no insurance	138 (43)	51 (46)	87 (41)		63 (44)	74 (41)	
Missing	46 (14)	14 (13)	32 (15)		19 (13)	27 (15)	
Number of times treated by healthcare provider in the past year				**0.04**			0.11
0 times	140 (43)	37 (33)	103 (48)		52 (36)	88 (49)	
1 – 4 times	160 (49)	67 (60)	93 (44)		80 (56)	80 (44)	
5+ times	20 (6)	7 (6)	13 (6)		10 (7)	10 (6)	
Don't know	4 (2)	1 (1)	3 (2)		1 (1)	3 (2)	
Receipt of seasonal influenza vaccine in past 5 years				**<.001**			**<.001**
0 times	184 (57)	37 (33)	147 (69)		67 (47)	116 (64)	
1 time	60 (19)	25 (22)	35 (16)		23 (16)	37 (20)	
2 - 4 times	52 (16)	30 (27)	22 (10)		35 (25)	17 (9)	
5 times	11 (3)	9 (8)	2 (1)		7 (5)	4 (2)	
Don't know	18 (6)	11 (10)	7 (3)		11(8)	7 (4)	

[a] *p*-values for comparing differences in maternal characteristics between those likely to receive each vaccine and those not likely to receive each vaccine were based on χ^2 tests for categorical variables or Fisher's exact tests when expected cell counts < 5.

[b] Initial question received by the first 50 participants regarding health insurance asked "Do you have health insurance?" Upon noting confusion on behalf of participants, the survey was amended to include 2 questions: "Do you currently have private health insurance?" and "Are you currently covered by Medicaid?"

Abbreviations: GED, General Education Development; Tdap, Tetanus, diphtheria, acellular pertussis.

Figure 4-2. A). Perceived severity of influenza and pertussis during pregnancy and intention to get vaccinated during pregnancy B). Perceived severity of influenza and pertussis during first 6 months of infancy and intention to get



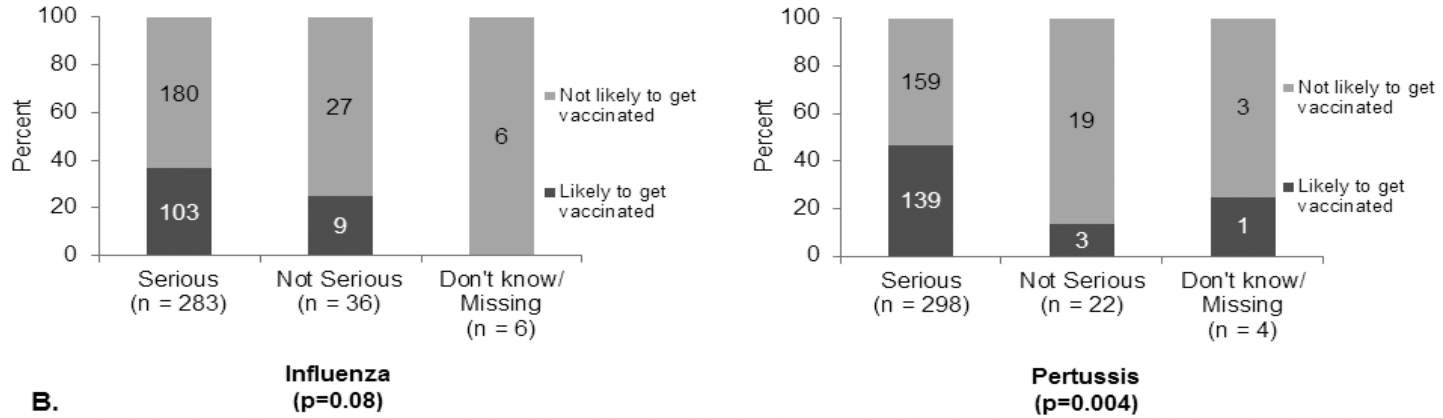
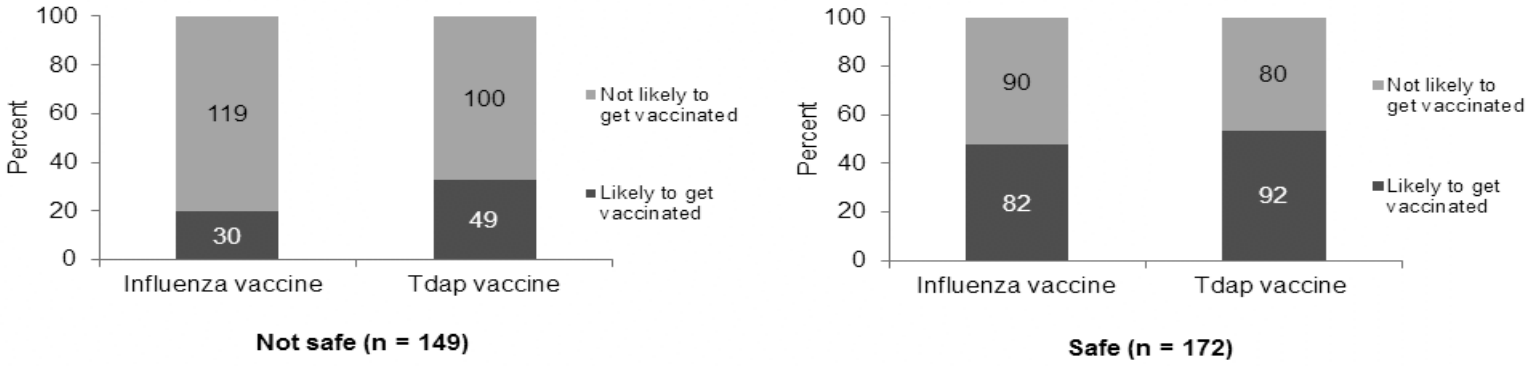


Figure 4-3. Perception of safety of influenza vaccine during pregnancy and intention to receive influenza or Tdap vaccinations during pregnancy.



CHAPTER 5: MANUSCRIPT 1

Improving Influenza and Tdap Vaccination during Pregnancy: A Cluster-randomized Trial of a Multi-component Antenatal Vaccine Promotion Package in Late Influenza Season

[This chapter appears as initially submitted for publication in the journal *Vaccine*.]

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Conflict of interest statement

Allison Chamberlain, Katherine Seib, Eli Rosenberg, Paula Frew, Marielysse Cortés, Ellen Whitney, Ruth Berkelman, Walter Orenstein and Saad Omer have no conflicts of interest to report. Kevin Ault has acted as a consultant on maternal immunization with the Centers for Disease Control and Prevention (CDC), the National Institute of Allergy and Infectious Diseases (NIAID), and the American College of Obstetricians and Gynecologists (ACOG). Dr. Ault serves on a data safety and monitoring committee with Novartis and is the site principal investigator for a clinical trial sponsored by Novavax.

Abstract

BACKGROUND: Evidence-based interventions to improve influenza vaccine coverage among pregnant women are needed, particularly among those who remain unvaccinated late into the influenza season. Improving rates of antenatal tetanus, diphtheria and acellular pertussis (Tdap) vaccination is also needed.

PURPOSE: To test the effectiveness of a practice-, provider-, and patient-focused influenza and Tdap vaccine promotion package on improving antenatal influenza and Tdap vaccination in the obstetric setting.

METHODS: A cluster-randomized trial among 11 obstetric practices in Georgia was conducted in 2012 – 2013. Intervention practices adopted the intervention package that included identification of a vaccine champion, provider-to-patient talking points, educational brochures, posters, lapel buttons, and iPads loaded with a patient-centered tutorial. Participants were recruited from December 2012 – April 2013 and included 325 unvaccinated pregnant women in Georgia. Random effects regression models were used to evaluate primary and secondary outcomes.

RESULTS: Data on antenatal influenza and Tdap vaccine receipt were obtained for 300 (92.3%) and 291 (89.5%) women, respectively. Although antenatal influenza and Tdap vaccination rates were higher in the intervention group than the control group, improvements were not significant (For influenza: risk difference (RD) = 3.6%, 95% confidence interval (CI): -4.0%, 11.2%; for Tdap: RD = 1.3%, 95% CI: -10.7%, 13.2%). While the majority of intervention package components were positively associated with antenatal vaccine receipt, a provider's recommendation was the most influential factor in actual receipt, regardless of study group or vaccine.

CONCLUSIONS: The intervention package did not significantly improve antenatal influenza or Tdap vaccine coverage. More research is needed to determine what motivates women remaining unvaccinated against influenza late into the influenza season to get vaccinated. Future research should specifically examine the role of baseline intent in antenatal vaccine acceptance and should quantify the extent to which clinical interventions can bolster a provider's recommendation for vaccination. This study is registered with clinicaltrials.gov, study ID NCT01761799.

Keywords: maternal immunization, antenatal immunization, influenza, Tdap, randomized clinical trial

Introduction

Influenza and pertussis are two infectious respiratory diseases that pose danger to pregnant women and newborns. Influenza can cause more severe illness in pregnant women than in their non-pregnant counterparts as evidenced by higher rates of hospitalization and mortality among pregnant women during the 2009 – 2010 H1N1 pandemic.[5,30,31,33,34,115] Pregnant women are strongly encouraged to receive an influenza vaccine anytime during pregnancy.[116] Research has shown that antenatal vaccination not only reduces maternal influenza risk, but is associated with reduced risks of preterm birth and small-for-gestational age birth, especially among babies born during influenza season.[10] Furthermore, maternal antibodies produced following vaccination pass through the umbilical cord and placenta, and infants of vaccinated mothers have been shown to be protected against clinical influenza during the first six months of life compared to infants of unvaccinated mothers.[52,117] Similarly, antenatal vaccination against pertussis helps protect young infants from the disease which is most severe in the first few months of life prior to the infants' eligibility for vaccination.[118,119] Since 2012, the Centers for Disease Control and Prevention (CDC) has recommended antenatal Tdap vaccination during every pregnancy.[24]

With annual influenza epidemics and outbreaks of pertussis occurring over the last decade, the American College of Obstetricians and Gynecologists (ACOG) has emphasized the importance of antenatal influenza and Tdap vaccine receipt.[112,113] Despite these endorsements, national antenatal influenza vaccination coverage estimates hover around 50% and state-based estimates of Tdap vaccine receipt during pregnancy have typically not exceeded 20%.[58,120,121]

Substantial research has explored facilitators and barriers to vaccinating pregnant women, especially against influenza.[68-70,122] Barriers can arise from a variety of sources, including a woman's personal hesitancy or lack of knowledge about vaccination during pregnancy. These

challenges are partly attributable to lack of education and/or support of vaccination on the part of obstetric care providers.[21,22,76] Less research has focused on scientifically evaluating interventions to barriers associated with maternal vaccination. Many studies have focused on single message delivery interventions via educational brochures, provider recommendations or text-message reminders.[25,26,87,123] Few studies have examined the impact of multi-component interventions on improving antenatal vaccination rates within the obstetric setting.[27] The purpose of this study is to evaluate the effectiveness of a comprehensive practice, provider, and patient-focused vaccine promotion package on improving the likelihood that a pregnant woman receives an influenza and/or Tdap vaccine before delivery.

Methods

Study Design and initiation

To evaluate the effectiveness of the intervention package (i.e. the package; described below), we employed a cluster-randomized trial design involving randomization of obstetric practices to two intervention groups. Unvaccinated pregnant women were recruited from each practice and followed to 3 months post-partum to assess outcomes. Due to late receipt of study funding, patient recruitment was initiated later in the 2012/2013 influenza season than anticipated.

Practice recruitment

We recruited ten obstetric practices from Georgia from August 2012 through November 2012 to participate in the Emory MOMVAX study. Practice eligibility criteria included willingness to be randomized to either study group and having an estimated influenza vaccination

rate of <60% among pregnant patients during the previous 2011/2012 season. If a practice did not offer influenza vaccine in the 2011/2012 season, their antenatal vaccination rate was estimated to be 29% based upon the 2009 state-wide Georgia antenatal vaccination rate.[124] One interested practice was deemed ineligible due to having an estimated vaccination rate exceeding 60%.

Prior to randomization, practices were pair-matched on factors known to be associated with antenatal influenza vaccine receipt: provision of influenza vaccination in-house, percent patient population on Medicaid, and estimated influenza vaccine coverage among pregnant patients during the 2011/2012 influenza season. Assignment of condition (intervention vs. control) within each matched practice pair was determined by coin-toss by a biostatistician otherwise unaffiliated with the study. An 11th practice was added after randomization to supplement enrollment from one intervention practice. This study was approved by the institutional review boards of Emory University and the Medical Center of Central Georgia.

Patient recruitment

Following randomization and provision of the package to the 6 intervention practices, women were approached and screened for eligibility by trained study personnel in the practices' waiting areas after signing in for their appointments. Eligibility criteria included: ages 18 – 50 years, able to read and write English, currently pregnant, and not having received a 2012/2013 seasonal influenza vaccine or a Tdap vaccine during their current pregnancy.

Signed informed consent was obtained from all eligible women interested in participating. Following consent, each woman completed a paper-based baseline questionnaire measuring demographics and knowledge, attitudes and beliefs about infectious diseases and vaccination during pregnancy.

Upon enrollment, women received a $10 gift card to their choice of either Target or Walmart. They were also informed that they would receive a second $25 gift card to either Target or Walmart upon completion of a follow-up survey 2 -3 months post-partum.

Intervention Package

Practices randomized to the intervention group received all components of the package. [Figure 5-1] Package components are available for download at www.momvax.org.

The iPad-based interactive tutorial was a patient-centered educational iBook-based app explaining the benefits of antenatal influenza and pertussis vaccination. Each intervention practice received 2 iPads pre-loaded with the tutorial. Practices were instructed to distribute the iPads to obstetric patients in examination rooms while waiting to be seen by a physician; this period within a prenatal visit was determined during preliminary research to be the time when women were least distracted, had time to focus on the 10-minute tutorial, and staff could feasibly account for the iPads.

The 1-hour in-house training session was provided by the Georgia Educating Physicians within their Communities (EPIC) program on the importance of providing vaccinations, including influenza and Tdap, within the obstetric setting.[111]

All package materials except for the iPad were based upon approaches found to be previously beneficial in promoting vaccination, and where possible, to obstetric patients specifically.[27,123,125] The educational content developed for the patient-focused components of the package (posters, brochures, lapel buttons and iPad tutorial) was written at the 8th-grade level and pre-tested among currently or recently pregnant women for feedback on content, design and usability. The content was also informed by our previous work that suggested positive, gain-

frame messaging is preferable than loss-frame messaging in promoting influenza vaccination to pregnant women.[126]

Control group practices did not receive any package materials for the duration of the study. They were requested to maintain their standard of care regarding influenza and/or Tdap vaccine promotion and administration.

Outcome measures

The primary outcomes were receipt of influenza vaccination and Tdap vaccination prior to date of delivery. Vaccine receipt was assessed in 3 ways: obstetric chart review if the vaccine(s) were stocked by the patient's obstetric practice, patient recall during a follow-up survey conducted 2 – 3 months post-partum and queries to the Georgia Registry for Immunization Transactions and Services (GRITS).[127] A priori rules for determining final antenatal vaccination status are provided in Appendix A.

Secondary outcomes included any Tdap vaccination (antenatal or post-partum receipt) and recollection of specific package materials. Recollection of post-partum Tdap vaccination and the package materials were measured via self-report during the post-partum follow-up survey. Feedback on the clinical usability of the package components was collected through post-study interviews with the vaccine champions at each intervention practice.

Study power and Statistical analysis

We calculated our a priori sample size based upon detecting a 20% absolute increase in the proportion of women receiving an antenatal influenza vaccine among intervention practices compared to control practices with 80% power at the 5% level of significance. A 20% absolute increase was based upon previous studies obtaining 11% - 39% increases in vaccination following adoption of single- or dual-component interventions to improve clinical vaccine

coverage.[27,83,87,125] Assuming 29% of pregnant women in Georgia receive an antenatal influenza vaccination and using an intra-cluster correlation coefficient of 0.01, we required a sample size of 150 pregnant women per trial group. Assuming 10% loss to follow-up at the participant level, our target sample size was 330.

Data are presented as risk differences (RD) and risk ratios (RR) with 95% confidence (Cis) intervals unless otherwise noted. SAS software version 9.3 (Cary, NC) was used to analyze the data. Differences in the likelihood of vaccine receipt between women in the intervention and control groups were tested in SAS GLIMMIX using generalized linear mixed models with a log-binomial link to calculate relative risks; similar models were fit in SAS NLMIXED to obtain risk differences and their 95% CIs. A random effect for practice was included in models evaluating primary and secondary outcomes to account for correlation among women recruited from the same practice. Only variables associated with the outcome that appeared imbalanced across study groups after randomization were included in covariate-adjusted models. We used the intention-to-treat (ITT) principle to compare outcomes between the groups, with participants analyzed according to the group to which their obstetric practice was randomly assigned. Intracluster correlation coefficients (ICC) were calculated using adjustments described by Yelland, et al. for log-binomial models.[128]

Results

Three-hundred and twenty-five women were enrolled in the Emory MOMVAX study from 11 obstetric practices in Georgia from December 2012 – April 2013. Characteristics of the pair-matched participating practices are presented in Table 5-1 and participant characteristics stratified by study group are provided in Table 5-2. Most participant characteristics appeared

balanced across study groups, although compared to the control group, mean scores measuring baseline intention to receive either vaccine were slightly higher in the intervention group (Influenza: 3.2 vs. 2.6; Tdap: 3.9 vs. 3.5) and fewer women were enrolled from practices stocking the vaccines (Influenza: 50% vs. 60%; Tdap: 40% vs. 60%).

Data on antenatal influenza and Tdap vaccine receipt were obtained for 300 (92.3%) and 291 (89.5%) women, respectively. [Figure 5-2] Two-hundred seventy-seven (85.2%) women responded to the post-partum follow-up survey and were included in analyses of secondary outcomes.

Twenty-seven (9.0%) women received an antenatal influenza vaccine and 32 (11.0%) women received an antenatal Tdap vaccine. Nine (3.0%) received both vaccines prior to delivery. The majority of women who received either vaccine were white, not Hispanic, had health insurance, were enrolled from practices that offered the vaccines, and had received a seasonal influenza vaccine at least one time in the past five years. [Data available upon request.] While intention to receive an antenatal Tdap vaccine as measured at baseline was of borderline significance with regard to actual vaccine receipt (Mean intention-to receive scores: intervention group: 4.7, standard error [s.e.]: 3.8 vs. control group: 3.5, s.e. 3.5; $p = 0.07$), intention to receive an antenatal influenza vaccine was significantly associated with receipt (Mean intention-to-receive scores: intervention group: 5.6, s.e. 3.5 vs. control group: 2.5, s.e. 3.0; $p < .0001$). Women who received an antenatal Tdap vaccination were also significantly more likely to have been enrolled from a practice stocking Tdap than women who did not receive a Tdap vaccine during pregnancy (78% vs. 51%; $p < 0.01$).

More intervention group women received antenatal influenza and Tdap vaccines than did control group women, but the absolute RDs before and after adjustment for the clustered study design were small and non- significant (study-adjusted antenatal influenza RD: 3.6%, 95% CI: -

4.0, 11.2; study-adjusted antenatal Tdap RD: 1.3%, 95% CI: -10.7, 13.2). [Table 5-4] Although also non-significant, women from the intervention group were nearly 50% more likely to receive any Tdap vaccine than women in the control group (RR = 1.47, 95% CI: 0.70, 3.12), with a 13.1% design-adjusted absolute difference favoring the intervention group.

In analyses adjusting for baseline intent to receive the vaccines as measured at enrollment, the effect of the package on antenatal influenza vaccination diminished (RR dropped from 1.47 to 1.12), whereas the measures of effect for Tdap vaccination remained relatively unaffected (RR for antenatal receipt: 1.15 vs. 1.13; RR for any Tdap receipt remained at 1.47). [Table 5-3] When examining baseline intent to get vaccinated as a possible effect modifier, the interaction term between intent to receive an antenatal influenza vaccine and intervention group approached significance ($p = 0.06$), with the package having had the greatest positive absolute effect among women with moderate intentions to receive the vaccine. [Figure 5-3A] Similarly, for antenatal Tdap receipt, the intervention appeared most effective among women with a moderate degree of baseline intent to receive Tdap before delivery. [Figure 5-3B]

Recollection of provider recommendations of antenatal vaccination was strongly associated with antenatal receipt of both influenza and Tdap vaccines regardless of study group. Among intervention group women, no other package component was as strongly associated with vaccine receipt as the provider's recommendation. [Table 5-4] The majority of physical package components were positively associated with vaccine receipt, with recollection of the iPad associated with a greater likelihood of antenatal influenza vaccination (RR = 3.17, 95% CI: 1.06, 9.53), and recollection of the lapel buttons resulting in a greater likelihood of any Tdap vaccine receipt (RR = 1.60, 95% CI: 1.08, 2.37).

Clinical usability of intervention package components

Regarding the clinical usability of the package, posters were hung in exam rooms and in ≥1 target area in all 6 intervention practices. Two practices indicated receiving inquiries from patients on account of the posters, and one practice mentioned that the posters reminded physicians to discuss vaccination.

All intervention practices distributed the provider-to-patient talking points, primarily during a single staff meeting; however, vaccine champions would periodically remind physicians and staff to promote vaccination to pregnant patients. One practice posted the talking points on a bulletin board in a common break area.

All 5 practice-based vaccine champions believed their staff learned from the one-hour peer-to-peer vaccine promotion training session provided by Georgia EPIC. One practice not yet offering Tdap indicated the training could have been improved by including more detailed information on the financial considerations associated with starting an obstetric Tdap vaccination program.

Most intervention practices found the brochures useful with 3 intervention practices adding the brochures to new obstetric kits. All 6 practices distributed lapel buttons and encouraged wear. For the 3 practices that received maps of nearby locations to receive influenza and/or Tdap because they did not provide the vaccines in-house, 2 practices physically distributed the lists to patients. The other practice preferred to verbally recommend locations to receive the Tdap vaccine.

Regarding the iPad-based educational app, three practices indicated that managing the iPads (e.g. distributing and collecting them from patients, ensuring staff were utilizing them, and confirming their security) was challenging. Two practices found the iPads helpful for patient

education, with one practice indicating the iPad was helpful in enabling vaccine hesitant patients to articulate questions to providers. Only one practice indicated the tutorial was hard to use.

Discussion

To our knowledge, this is the first study to evaluate the effectiveness of a multi-component vaccine promotion package on improving the likelihood a pregnant woman receives an influenza and/or Tdap vaccine prior to delivery. The absolute differences in antenatal vaccine uptake were modest and non-significant, yet they favored the intervention group and were comparable in magnitude to other recent studies evaluating the effectiveness of single-component interventions to improve antenatal vaccination.[26] Absolute differences in any Tdap vaccine receipt were larger, suggesting that addressing Tdap vaccination during pregnancy may achieve higher, albeit less than ideal, post-partum coverage.

While the results of this study did not find a significant effect of the package on antenatal vaccine receipt, it is important to put this study in context. Late-season participant recruitment may have dampened the effect of the package since pregnant women remaining unvaccinated against influenza by December may have been less likely to get immunized than early acceptors. Of the pregnant women approached for this study, 59% were ineligible because they indicated having already received a 2012/2013 influenza vaccine and 20% indicated having already received a Tdap vaccination.[129] Since remaining unvaccinated late into the influenza season is likely correlated with greater vaccine hesitancy, these are precisely the types of women among whom evidence-based interventions like this package need to be evaluated. While seasonality should not have affected Tdap vaccine uptake, underlying vaccine hesitancy could have. Additionally, since we began enrollment for this study only 2 months after the CDC expanded the

antenatal Tdap recommendations in October 2012 to include vaccination at every pregnancy, we anticipated relatively low antenatal Tdap vaccine uptake among control group practices.[24] Compared to the antenatal Tdap vaccination rates observed, this timing could also partially explain the higher rates for any Tdap vaccination if obstetric providers – and patients – still relied on hospitals to vaccinate women who did not receive Tdap during pregnancy.

While the aim of this study was to examine the effectiveness of the package as a whole, the most noteworthy finding was that a provider's recommendation remains the most influential factor in antenatal vaccine acceptance. Despite this, antenatal vaccination among those recalling a recommendation was low: 16.9% and 25.4% among those recalling a recommendation for influenza vaccination and Tdap vaccination, respectively. These low percentages may reflect the reticence of this particular population of women towards vaccination, suggesting the need for more research on effective messaging to women who are not early acceptors of influenza vaccination. Moreover, 22% more intervention group women recalled the poster component of the package than a provider's recommendation of antenatal Tdap, a finding which signals that researchers designing future intervention studies should intend to measure interactions between the intervention and a provider's recommendation. While this study lacked statistical power to independently examine each package component's interaction with a provider's recommendation, quantifying the extent to which future interventions can work synergistically with a provider's recommendation will be imperative.

Results examining the role of baseline intent to get vaccinated are also worth considering. In models adjusting for baseline intent to vaccinate before delivery, the likelihood of antenatal influenza vaccination was attenuated, suggesting a strong intention to receive the vaccine may outweigh effects of the intervention. In contrast, adjusting for baseline intent had little effect on the likelihood of antenatal Tdap receipt. When examined as a possible effect modifier, there was

variation in the effectiveness of the package across degrees of baseline intent. For influenza vaccination, a strong intention to vaccinate again appears to overcome any impact of the package. This finding is congruent with other studies suggesting that those with more favorable attitudes towards vaccination are likely to get vaccinated regardless of exposure to external interventions, thus reducing the opportunity for a positive intervention effect.[114] The greatest potential for positive impact from exposure to the package appeared among women with moderate attitudes towards antenatal vaccination, a finding aligning with previous research suggesting that hesitant "fence-sitters" should be the target audience for interventions promoting vaccination.[130]

Despite being the most innovative component of the package, the iPad-based app was recalled by very few participants, so results demonstrating a significant association between recollection of the iPad and antenatal influenza vaccine receipt should be interpreted cautiously. Providers reported that the devices were cumbersome to manage and that they were concerned with security of the devices. In future studies involving electronic tablets for patient education, collecting more detailed information on device management, device security, and device usage will be important.

This study has important limitations. It was a small cluster randomized trial, powered to find a larger absolute difference between study groups than what was observed. Including more practices in subsequent studies employing a cluster-randomized design would increase the power to observe smaller, but still clinically relevant effect sizes. Due to budgetary and practical constraints, not every intervention evidenced to improve vaccine coverage was included in the package. Notably absent were practice-level interventions like automated provider reminders within electronic medical records (EMR) and standing vaccine orders. Not every practice enrolled in this study used EMRs and since standing orders are only feasible when practices stock vaccines, these two evidence-based components could not have reasonably been adopted by every

practice in this study. In larger trials with more resources or conducted only among practices providing vaccines in-house, inclusion of these types of evidenced-based practice-level components would be worthwhile to include.[131]

Key strengths of this study include the multi-facetted nature of the package, the pair-matched cluster-randomized trial design, and the statistical analyses accounting for the clustered design. Because barriers to maternal vaccination involve both women and their providers, the package was designed to address concerns and improve education for both parties. Since each practice likely implemented the package materials slightly differently, our analysis methods appropriately accounted for practice-based differences and made a substantial difference in interpretation of the results from our Tdap models. We also achieved high rates of follow-up, especially for our primary outcomes. Verifying vaccine receipt through obstetric chart reviews and GRITS helped mitigate information bias (e.g. recall bias, social desirability bias, vaccine reporting errors) across both study groups. Any remaining information bias is presumed to be non-differential with respect to the intervention, thus biasing results towards the null.

With at least 50 studies examining the knowledge, attitudes and beliefs of pregnant women towards influenza vaccination,[132] this trial provides necessary research towards development of evidence-based interventions to improve vaccine coverage. By developing non-burdensome interventions tailored to baseline intent and evaluated using study designs able to measure the synergy between the intervention and a provider's verbal recommendation, we will get closer to obtaining evidence-based interventions effective in pushing antenatal influenza and Tdap coverage well beyond 50%.

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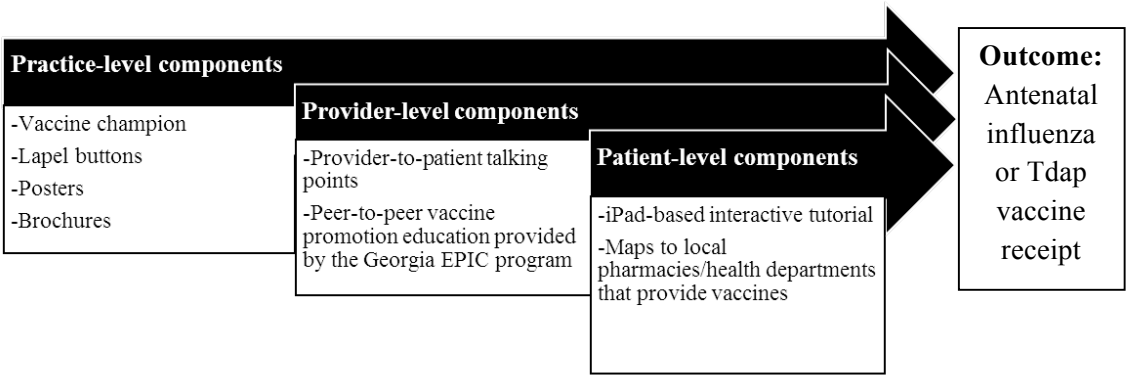
Figure. 5-1. MOMVAX study package components and descriptions



Practice-level component descriptions	
Vaccine champion	A staff member identified by the practice to be the primary resource for vaccine-related information for all practice staff. This individual could hold any position (i.e. practice manager, nurse, physician), but needed a positive attitude about vaccination and be willing to promote the MOMVAX study throughout its duration.
Lapel buttons	Produced in two styles, these buttons promoted antenatal vaccination. All staff were encouraged to pin these on the lapels of their jackets or scrubs.
Posters	Produced in two sizes, the poster promoted antenatal influenza and Tdap vaccination. Practices were encouraged to hang them in prominent places around their office including waiting rooms, exam rooms, restrooms and hallways.
Brochures	Brochures provided education on the importance of antenatal vaccination, composition of influenza and Tdap vaccines, safety of the vaccines, timing of vaccination and protection of an infant through vaccinating close contacts. Brochures also provided links to additional online resources about both maternal and childhood immunizations.

Provider-level component descriptions	
Provider-to-patient talking points	Based on content published by ACOG and CDC, talking points for promoting antenatal influenza and Tdap vaccination were provided on colored paper to vaccine champions. Enough copies for all staff were provided. Three primary talking points were produced for each vaccine, followed by additional safety-related talking points. The talking points emphasized protecting the fetus and newborn.
Peer-to-peer vaccine promotion education	Provided over one lunch session, the peer-to-peer vaccine promotion education was provided by the Georgia Educating Physicians in their Communities (EPIC) program. Led by a nurse or physician, this 1-hour session covered the importance of antenatal vaccination, tips for starting an in-house vaccination program, and financial aspects of managing vaccines in the obstetric setting.
Patient-level components	
IPad-based interactive tutorial	Produced using the iBook-platform, this tutorial included text and audio/video content covering the importance of vaccination during pregnancy, dangers of influenza and pertussis to infants, safety of antenatal vaccination, timing of antenatal vaccination and an introducing to childhood vaccination. Videos included obstetric physicians talking about antenatal vaccination as well as two testimonials from mothers whose infants contracted influenza and pertussis.
Maps to local pharmacies/health departments that provide vaccines	Provided only to practices that did not offer one or both vaccines, these handouts included a list and map of health departments and retail outlets within 5 – 10 miles of a practice. Handout also included facility addresses, phone numbers, distance from the practice, maximum price of influenza and/or Tdap vaccines, and whether the facility would file insurance claims.

Table 5-1. Characteristics of MOMVAX study practices according to matched pair

	Matched pair 1		Matched Pair 2		Matched Pair 3		Matched Pair 4		Matched Pair 5	
	Intervention	Control	Intervention†	Control	Intervention	Control	Intervention	Control	Intervention	Control
Stocked influenza vaccine	Yes	No	Yes (Yes, but did not reorder at initiation of recruitment	Yes	Yes, but did not reorder at initiation of recruitment	Yes	Yes	Yes	No	No
Stocked Tdap vaccine	No, but started on account of study	No	Yes (Yes)	Yes	No	Yes	No	Yes	No	No
Baseline antenatal influenza vaccination rate	29%	29%	50% (50%)	50 – 60%	30%	24%	40%	43%	29%	29%
% patient population on Medicaid	80%	80%	15% (45%)	5%	17%	7%	20%	67%	60%	60%

†Characteristics of the intervention group practice added after randomization are provided in parentheses.

Table 5-2. Participant characteristics by MOMVAX study group

Characteristic	Study group; no. (%) of patients		
	Intervention (n = 161)	**Control (n = 164)**	**Total (N = 325)**
Maternal age at enrollment[a]	26.9 (5.2)	27.5 (6.0)	27.2 (5.6)
Race			
Caucasian/White	78 (48)	76 (46)	154 (47)
African American/Black	64 (40)	69 (42)	133 (41)
Asian	2 (1)	5 (3)	7 (2)
Other or missing	17 (11)	14 (9)	31 (10)
Ethnicity			
Hispanic	12 (7)	8 (5)	20 (6)
Non-Hispanic or missing	149 (93)	156 (95)	305 (94)
Parity (number of current children)[a]	1.0 (1.1)	1.1 (1.2)	1.1 (1.1)
Education			
< High school graduate/GED	9 (6)	16 (10)	25 (8)
High school graduate or GED test	69 (43)	58 (36)	127 (39)
Technical/vocational/Associates	32 (20)	41 (25)	73 (23)
Bachelor's degree or higher	51 (32)	47 (29)	98 (30)
Health insurance[b]			
Health insurance	19 (12)	25 (15)	44 (14)
Any private insurance	68 (42)	73 (45)	141 (43)
Medicaid or no insurance	73 (45)	65 (40)	138 (43)
Missing	1 (1)	1 (0)	2 (0)
Number of times treated by healthcare provider in the past year			
0 times	67 (42)	73 (45)	140 (43)
1 – 4 times	84 (52)	76 (46)	160 (49)
5+ times	7 (4)	13 (8)	20 (6)
Don't know	2 (1)	2 (1)	4 (2)
Previous receipt of seasonal influenza vaccine in past 5 years			
0 times	91 (57)	93 (57)	184 (57)
1 time	27 (17)	33 (20)	60 (19)
2 - 4 times	28 (17)	24 (15)	52 (16)
5 times	6 (4)	5 (3)	11 (3)
Don't know	9 (6)	9 (5)	18 (6)
Enrolled from a practice stocking influenza vaccine	81 (50)	98 (60)	179 (55)
Enrolled from a practice stocking Tdap	64 (40)	98 (60)	162 (50)
Likelihood of receiving an influenza vaccine prior to delivery[a,c]	3.2 (3.4)	2.6 (2.9)	2.9 (3.2)
Likelihood of receiving a Tdap vaccine prior to delivery[a,c]	3.9 (3.8)	3.5 (3.3)	3.7 (3.5)

[a]Mean (standard deviation)

[b]Initial question received by the first 50 participants regarding health insurance asked "Do you have health insurance?" Upon noting confusion on behalf of participants, the survey was amended to include 2 questions: "Do you currently have private health insurance?" and "Are you currently covered by Medicaid?"

[c]Measured on a scale from 0 to 10 with 0 being "Definitely not" likely to receive the vaccine to 10 being "Definitely will receive the vaccine. Abbreviations: GED, General Education Development; Tdap, Tetanus, diphtheria, acellular pert.

Figure 5-2. Obstetric practice and participant enrollment for MOMVAX study

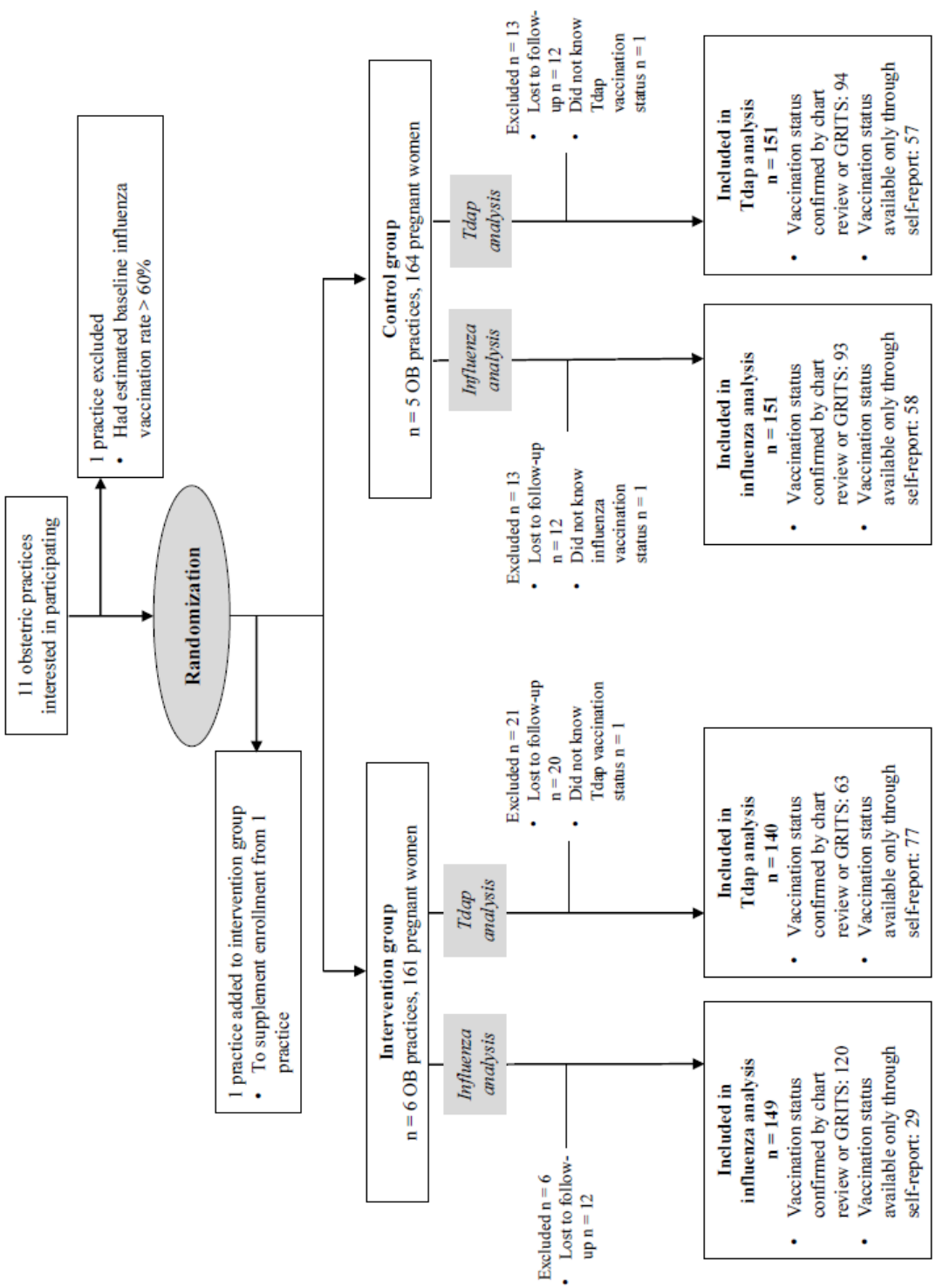


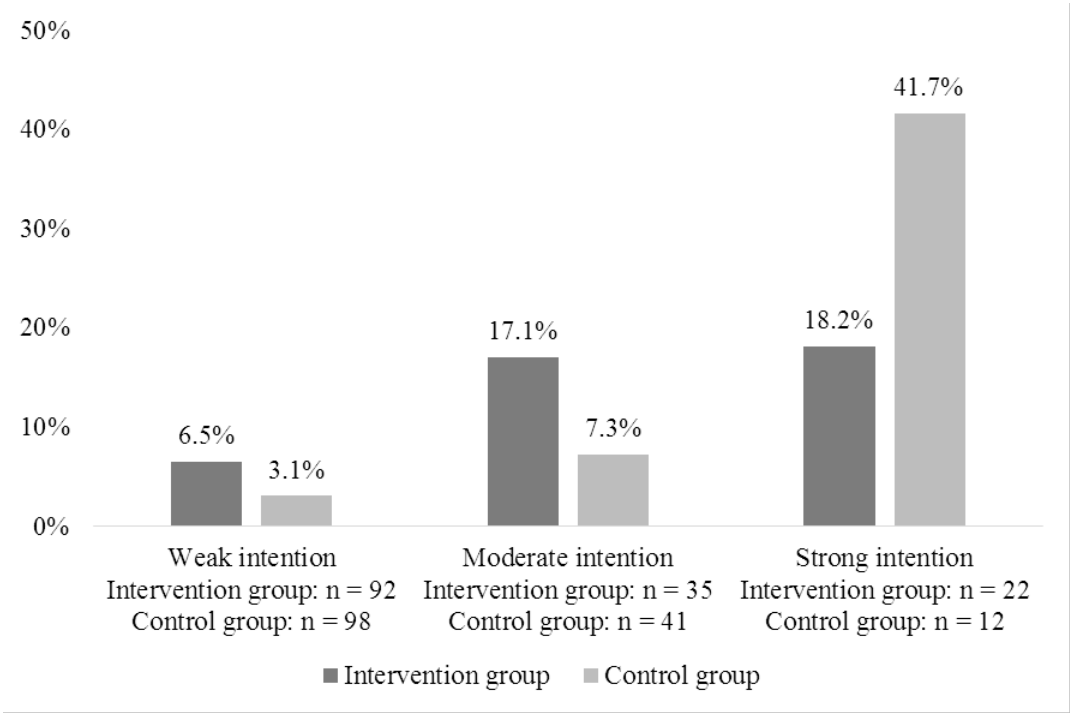
Table 5-3. Effect of the MOMVAX study intervention package on antenatal influenza vaccination, antenatal Tdap vaccination, and any Tdap vaccination among women enrolled in the MOMVAX Study

	Antenatal influenza vaccination (n = 300)				Antenatal Tdap vaccination (n = 291)				Any Tdap vaccination (n = 291)			
Proportions vaccinated in each study group	Intervention: 16/149 (10.7%) Control: 11/151 (7.3%)				Intervention: 19/140 (13.6%) Control: 13/151 (8.6%)				Intervention: 61/140 (43.6%) Control: 44/151 (29.1%)			
Intervention effect	RD (95% CI)	RR (95% CI)	p-value	ICC	RD (95% CI)	RR (95% CI)	p-value	ICC	RD (95% CI)	RR (95% CI)	p-value	ICC
Unadjusted for study design†	3.5% (-3.0, 9.9)	1.47 (0.71, 3.07)	0.30	N/A	5.0% (-2.3, 12.2)	1.58 (0.81, 3.07)	0.18	N/A	**14.4% (3.5, 25.4)**	**1.50 (1.09, 2.04)**	**0.01**	N/A
Adjusted for clustered study design	3.6% (-4.0, 11.2)	1.47 (0.57, 3.81)	0.38	0.01	1.3% (-10.7, 13.2)	1.15‡ (0.22, 6.00)	0.85	0.15	13.1% (-8.9, 35.0)	1.47‡ (0.70, 3.12)	0.27	0.11
Adjusted for study design and intention to receive the vaccine before delivery	0.4% (-2.2, 3.2)	1.12 (0.49, 2.56)	0.77	0.001	1.0% (-8.4, 10.3)	1.13‡ (0.23, 5.71)	0.86	0.13	Model would not converge	1.47‡ (0.72, 2.99)	0.25	0.10
Adjusted for study design, intention to receive the vaccine before delivery and stocking vaccine in-house	0.5% (-1.8, 2.8)	1.16 (0.49, 2.78)	0.69	0.001	1.2% (-3.8, 6.1)	1.25‡ (0.26, 6.00)	0.74	0.10	Model would not converge	1.41‡ (0.65, 3.04)	0.32	0.11

†Generated using SAS PROC GENMOD and not accounting for clustered study design.
‡Random effect for practice is significant at $p < 0.05$ level.
Abbreviations: risk difference (RD), risk ratio (RR), confidence interval (CI), intracluster correlation coefficient (ICC), tetanus, diphtheria and acellular pertussis (Tdap)

Figure 5-3. Proportion of women receiving an antenatal A) influenza and B) Tdap vaccine by intervention group and baseline level of intent to receive the vaccines prior to delivery

A)



B)

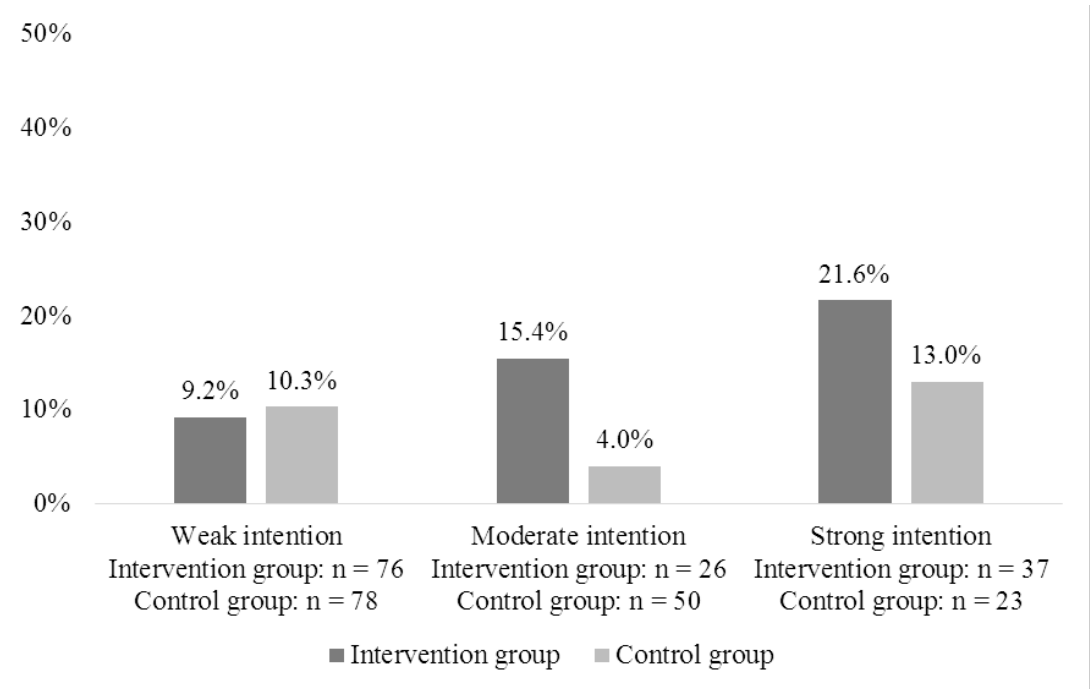


Table 5-4. Impact of individual intervention package components on vaccine receipt among intervention group women

Variable measured		Unadjusted proportions		Adjusted for study design		Unadjusted proportions		Adjusted for study design		Unadjusted proportions		Adjusted for study design	
		% receiving antenatal influenza vaccine	p-value‡	RR (95% CI)	p-value	% receiving antenatal Tdap vaccine	p-value‡	RR (95% CI)	p-value	% receiving any perinatal Tdap vaccine	p-value‡	RR (95% CI)	p-value
Recollection of OB/GYN or midwife recommending antenatal influenza vaccination	**Yes (n=89)**	16.9%	<0.01	--⁺	--⁺	N/A				N/A			
	No (n=48)	0.0%											
Recollection of OB/GYN or midwife recommending antenatal Tdap vaccination	**Yes (n=63)**	N/A				25.4%	<0.01	6.49† (1.55, 27.31)	0.01	65.1%	<0.01	2.45 (1.54, 3.91)	<0.01
	No (n=73)					2.7%				26.0%			
Recollection of poster about influenza and Tdap vaccination	**Yes (n=93)**	14.0%	0.14	3.28 (0.77, 17.07)	0.11	10.8%	0.27	0.89† (0.42, 1.88)	0.75	47.3%	0.35	1.26 (0.82, 1.92)	0.29
	No (n=43)	4.7%				19.1%				38.1%			
Recollection of educational brochure about influenza and Tdap vaccination	**Yes (n=60)**	16.7%	0.10	2.57 (0.92, 7.18)	0.07	18.6%	0.13	1.87† (0.86, 4.02)	0.11	47.5%	0.60	1.12† (0.79, 1.60)	0.52
	No (n=77)	6.5%				9.1%				41.6%			
Recollection of lapel buttons promoting vaccination worn by doctors and nurses	**Yes (n=23)**	21.7%	0.13	2.49 (0.93, 6.67)	0.07	13.0%	1.00	0.86† (0.31, 2.42)	0.78	65.2%	0.04	1.60 (1.08, 2.37)	0.02
	No (n=114)	8.8%				13.3%				39.8%			
Recollection of iPad-based educational app	**Yes (n=10)**	30.0%	0.08	3.17 (1.06, 9.53)	0.04	30.0%	0.13	--⁺⁺	--⁺⁺	60.0%	0.34	1.26† (0.76, 2.09)	0.37
	No (n=127)	9.5%				11.9%				42.9%			

⁺Estimates could not be obtained due to infinite relative risk.
‡Obtained from Fisher's exact tests comparing proportions.
†Random effect for practice is significant at $p < 0.05$ level.
⁺⁺Random effects model would not converge.
Bolded p-values indicate significance at $p < 0.05$ level. Abbreviations: RR, risk ratio; Tdap, tetanus, diphtheria, acellular pertussis; N/A, not applicable.

CHAPTER 6: MANUSCRIPT 2

Impact of a multi-component antenatal vaccine promotion package on improving knowledge, attitudes and beliefs about influenza and Tdap vaccination during pregnancy

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Abstract

Background: In the U.S., antenatal vaccination rates against seasonal influenza and pertussis are suboptimal; greater than 50% coverage has not been sustained for either the influenza vaccine or the tetanus, diphtheria and acellular pertussis (Tdap) vaccine. Understanding whether interventions designed to improve antenatal vaccine uptake change women's knowledge, attitudes and beliefs about vaccination is critical for advancing vaccine acceptance and coverage.

Purpose: To evaluate the effectiveness of a multi-component influenza and Tdap vaccine promotion package in changing women's knowledge, attitudes and beliefs towards antenatal vaccination.

Methods: From 2012 – 2013 a cluster-randomized trial was conducted in Georgia among 11 obstetric practices to test the effectiveness of a comprehensive vaccine promotion package on improving antenatal influenza and Tdap vaccine coverage. Participants included 325 unvaccinated pregnant women. Eleven measures aligned to 4 domains of the Health Beliefs Model were assessed among participants at baseline and again at follow-up 2 – 3 months post-partum. Generalized estimating equations accounting for clustering by practice were used to evaluate differences in proportions of women citing favorable responses to each measure between study groups at follow-up.

Results: Women enrolled in their third trimester had a significantly higher probability of asking their family members to get vaccinated to protect the infant if they were in the intervention group versus the control group (36% vs. 22%; risk ratio [RR] = 1.65, 95% confidence interval [CI]: 1.21, 2.26). A similar association was not observed among women enrolled prior to their third trimester (39% vs. 44%; RR = 0.93, 95% CI: 0.50, 1.73). Aside from this finding, there were no other significant differences at follow-up between study groups for the other behavioral measures.

Conclusions: While exposure to the intervention package may have raised awareness that vaccinating close family contacts can protect an infant, there is little evidence that exposure to the intervention package changed women's attitudes and beliefs towards antenatal vaccination. Future research of this nature should ensure adequate exposure to the intervention and specifically consider aspects of the study design including power to assess changes in secondary outcomes, discriminatory power of response options, and social desirability bias.

Introduction

In the U.S., neither seasonal influenza nor pertussis vaccination rates during pregnancy consistently exceed 50%.[57,58,121,133] Considerable research has sought to understand why women do not get vaccinated despite antenatal vaccination recommendations by the Centers for Disease Control and Prevention (CDC).[24,47] Reasons women have cited for not receiving antenatal vaccines include inadequate knowledge of the need for vaccination, lack of a provider recommendation, low perceptions of susceptibility to the diseases, safety concerns, and logistical or financial barriers to obtaining a vaccine.[21,82,132,134,135] While some of these reasons arise from barriers beyond a pregnant woman's control, others emanate from her own understanding or perception of the need for vaccination. With considerable amounts of evidence-based and non-evidence-based information on vaccination available to women, both legitimate and misguided concerns about vaccination have arisen.

In response to these reasons for not receiving antenatal vaccines, researchers are developing and evaluating interventions to increase vaccine uptake.[26,123] While improving vaccine coverage is the primary objective of these endeavors, a major upstream challenge to accomplishing this goal is changing women's knowledge, attitudes and beliefs about antenatal vaccines and the diseases against which they protect. This is especially true among women who may already be "vaccine hesitant," or reluctant to make immediate immunization decisions. While there was no effect in vaccination endpoints on account of exposure to the multi-component intervention package developed for the Emory MOMVAX study,[136] changes may have occurred in women's thoughts and attitudes towards vaccination. Using measures derived from the Health Beliefs Model and predictive of antenatal vaccination,[122] the aim of this study is to assess whether the MOMVAX intervention package affected women's knowledge, attitudes and beliefs towards antenatal influenza and tetanus, diphtheria and acellular pertussis (Tdap)

vaccination. Since the intervention package also included an introduction of the importance of childhood vaccination, we also seek to determine whether the package had any effect on women's likelihood of vaccinating her infant.

Methods

Data for these analyses were from the Emory MOMVAX Study. Detailed methods of the MOMVAX study design, recruitment strategy and intervention package components have been described elsewhere.[129] In summary, the MOMVAX study was a cluster-randomized trial conducted among 11 obstetric practices in Georgia from 2012 – 2013. We sought to evaluate the effectiveness of a comprehensive multi-component vaccine promotion package on improving influenza and Tdap vaccine receipt among pregnant women. The primary study outcomes were differences in likelihood of antenatal influenza and Tdap vaccination between study groups; secondary outcomes (presented here) included changes in knowledge, attitudes and beliefs towards antenatal vaccination between study groups.

Prior to randomization and patient recruitment, practices were pair-matched on 3 factors predictive of receipt: provision of the vaccines in-house, proportion of their patient population on Medicaid, and the estimated antenatal influenza vaccine coverage from the 2011 – 2012 influenza season. After randomization, intervention group practices were supplied the intervention package which consisted of practice-based components (promotional posters, educational brochures, lapel pins, and identification of an in-house vaccine champion), provider-based components (1-hour peer-to-peer educational training session and provider-to-patient talking points on influenza vaccination and Tdap vaccination), and a patient-level component (interactive iPad-based educational app). Maps to nearby pharmacies and health departments stocking influenza and/or Tdap vaccines were also provided to practices not offering one or both vaccines in-house as a

resource to distribute to patients. Control group practices maintained their standards of care regarding antenatal vaccine promotion for the duration of follow-up, receiving the intervention package at the conclusion of the study.

To assess changes in women's knowledge, attitudes and beliefs towards antenatal vaccination, 11 questions addressing 3 domains (perceived susceptibility, perceived severity, and perceived safety) of the Health Beliefs Model (HBM) were included on the study's baseline questionnaire and repeated on the study's follow-up questionnaire. [Table 6-1] Developed in 1966, the HBM model is one of the most widely used psychological constructs to predict and explain individuals' health-related behaviors, including intention to vaccinate.[78,79,137,138] Additional questions assessing their likelihood of receiving antenatal influenza and Tdap vaccines, likelihood of vaccinating their child, intention to ask family members and friends to get vaccinated and degree of vaccine hesitancy were also asked. The paper-based baseline questionnaire was administered upon enrollment following written informed consent; the follow-up questionnaire was administered over the phone or electronically 2 – 3 months post-partum.

Outcome measure analysis

For each of the 6 measures assessed on a 5-point Likert scale, responses were dichotomized into "favorable responses" and "unfavorable responses." [Table 6-1] Cut-points for these dichotomizations were based on the meaning of the scales' categories; for measures assessing perceived susceptibility and self-efficacy, responses of "Strongly agree (1)" and "Agree (2)" were combined and compared to responses of "Neutral/No opinion/Don't know (3)," "Disagree (4)," and "Strongly disagree (5)." For measures of perceived severity, responses of "Serious (4)" and "Very serious (5)" were combined and compared to responses of "Neutral/Don't know (3)," "Somewhat serious (2)," and "Not serious at all (1)."

The 4 measures assessed on 11-point Likert scales were analyzed in two ways. First, for the primary analyses, these questions were also dichotomized. Cut-points for these dichotomizations were scale-based; for the cues-to-action measures assessing intention to vaccinate, responses with scores of 9 or 10 were combined to indicate "strong willingness" and compared against responses with scores of 0 – 8. Similarly, responses with scores of 0 and 1 on the self-efficacy measure assessing general hesitancy towards antenatal vaccination were combined into a "not hesitant" category and combined against responses with scores of 2 – 10.

In addition to dichotomization, the four 11-point measures were also analyzed using ordinal logistic regression. This secondary analysis was conducted to determine whether exposure to the intervention package impacted knowledge, attitudes and beliefs across the spectrum of response options. For these analyzes, 3 categories of responses were created for each measure, grouping scores in the following manner: scores of 0 and 1, scores of 2 – 8, and scores of 9 and 10.

For all measures, the primary outcome was the risk ratio (RR) comparing proportions of favorable responses between study groups at follow-up. Additional practice or participant level covariates were added if imbalance across study groups was apparent at baseline. They were retained in the model if they changed the measure of effect by more than 10%. For the secondary analyses using ordinal logistic regression, the outcome for a given measure was the odds ratio (OR) comparing the odds of citing increasingly favorable responses between study groups.

Exploration of interactions

Anticipating that certain factors like prior awareness of Tdap vaccination or trimester of gestation at enrollment could modify the effectiveness of the intervention package on knowledge,

attitudes and beliefs, we explored interactions between study group and 1) reported knowledge of pertussis prior to engagement in this study, 2) prior awareness of Tdap vaccination prior to engagement in this study, and 3) trimester of gestation at enrollment for each measure. Due to the small sample size, each interaction was determined separately in the dichotomized models generated for the primary outcome analyses.

Statistical analyses

Risk ratios were calculated using log binomial regression employing generalized estimating equations (GEE) using PROC GENMOD in SAS version 9.3 (Cary, NC). For the interaction analyses, only interaction terms resulting in Wald test p-values < 0.05 were considered statistically significant. Ordinal logistic regression was also conducted using generalized estimating equations (GEE) in PROC GENMOD using a cumulative logit link function. The proportional odds assumption was tested using a score test followed by graphical verification of parallel slopes.[139] All models accounted for correlation among women recruited from the same practice by adjusting for practice of enrollment with a REPEATED statement and an independent working correlation structure.

Results

From December 2012 – April 2013, 1,876 women were approached from the 11 participating practices and 1,436 (77%) were screened for eligibility.[129] Of the 1,436 women screened, 388 (27%) were eligible. Of the pregnant women screened, 59% were ineligible because they had already received an influenza vaccine and 20% had already received a Tdap vaccine during their current pregnancy. Following declinations to enroll, incomplete enrollments

and withdrawals following enrollment, 325 (84%) of the eligible women were included in the study sample.

Table 6-2 shows the characteristics of the participants at baseline. Of the 325 participants, the mean age was 27.2 years, 154 (47%) identified as Caucasian/White, 305 (94%) were not Hispanic, 127 (39%) were high school/GED graduates, 185 (57%) had some type of health insurance, 160 (49%) saw a healthcare provider 1 – 4 times within the past year, 184 (57%) had not received a seasonal influenza vaccine in the past 5 years, 179 (55%) were enrolled from a practice stocking influenza vaccine, and 162 (50%) were enrolled from a practice stocking Tdap vaccine. Enrollment from a practice stocking Tdap vaccine was the only variable exhibiting a significant difference between intervention and control groups (40% vs. 60%; chi-square p – value = 0.0003).

Of the 325 women enrolled, 277 (85.2%) completed the follow-up questionnaire. Of these women, 271 (97.8%) completed the follow-up questionnaire by phone. Compared to the women who completed the follow-up questionnaire, women either refusing to take the questionnaire or lost to follow-up were younger (Mean age: 27.5 vs. 25.5, $p = 0.02$), less educated (Proportion having completed only high school or less: 70.8% vs. 42.9%, $p < 0.0001$) and more likely to be uninsured or on Medicaid (40.0% vs. 58.3%, $p = 0.02$). Of the 48 women who did not complete the follow-up questionnaire, equal proportions were from the intervention ($n = 24$) and control ($n = 24$) groups.

Between-group comparisons of outcome measures at baseline

At baseline, there were no significant differences in the proportions of women citing favorable responses for any of the 11 measures between study groups. [Table 6-3] Across both study groups, greater than 90% of women perceived pertussis as serious or very serious for an

infant within the first 6 months of life. Compared to perceptions of pertussis severity during infancy, perceptions of influenza severity during infancy were only slightly lower (Intervention group: 93.2% perceiving pertussis as serious vs. 88.8% perceiving influenza as serious; Control group: 92.0% perceiving pertussis as serious vs. 86.4% perceiving influenza as serious). Women also perceived pertussis as more severe during pregnancy than influenza, yet only about one-quarter of women perceived antenatal influenza vaccination as safe (26.4% in intervention group and 24.1% in control group). Similarly, only 36.9% of women in the intervention group and 34.6% of women in the control group reported not being hesitant about getting recommended antenatal vaccinations.

In terms of willingness to receive antenatal influenza and/or Tdap vaccines during pregnancy, women across both groups were reticent with only 16.3% and 11.6% indicating a strong willingness to receive a Tdap vaccine in the intervention and control groups respectively, and 10.6% and 6.7% indicating a strong willingness to receive an influenza vaccine. In contrast, 80% across both study groups indicated a strong willingness to get their infant vaccinated with all recommended childhood vaccines.

Primary analyses – log binomial regression

No significant differences were observed for any of the 11 measures at follow-up. While not reaching statistical significance, the imbalance between study groups at baseline for the measures of willingness to receive antenatal influenza or Tdap vaccines may be meaningful; however, adjustment for the baseline values of these measures did not attenuate the effect estimates by more than 10% (adjusted risk ratio [aRR] for likelihood of influenza vaccine receipt: 1.14, 95% confidence interval [CI]: 0.81, 1.61; aRR for likelihood of Tdap vaccine receipt: 1.15, 95% CI: 0.86, 1.54). Similarly, adjustment for enrollment from practices stocking Tdap did not

change any of the risk ratios for the pertussis, Tdap or general vaccination-related measures by more than 10% (data not shown).

Secondary analyses – ordinal logistic regression

Results from analyzing each of the 11-point Likert scales using ordinal logistic regression also demonstrated no significant associations between study group and likelihood of increasingly favorable attitudes towards antenatal vaccination or childhood vaccination. [Table 6-4] As observed in the dichotomized results for the measures assessing likelihood of antenatal vaccine receipt, the unadjusted ORs comparing proportions of women citing a strong likelihood of receipt demonstrate slight imbalance favoring the intervention group at baseline; adjusting for the baseline values of these measures in each model again attenuated the effect estimates (antenatal influenza vaccination: unadjusted OR = 1.35, 95% CI: 0.76, 2.39 vs. baseline-adjusted OR = 1.27, 95% CI: 0.75, 2.15; antenatal Tdap vaccination: unadjusted OR = 1.17, 95% CI: 0.55, 2.49 vs. baseline-adjusted OR = 1.13, 95% CI: 1.13, 95% CI: 0.55, 2.33).

Interaction analyses

Of the 277 women completing the follow-up questionnaire, 250 (90.3%) and 205 (74.0%) had heard of pertussis and Tdap, respectively before participating in this study. Neither prior awareness of pertussis nor of the Tdap vaccination to protect against pertussis had significant impacts on the associations between study group and any of the 6 measures related to pertussis, Tdap vaccination or general vaccination (data not shown).

For analyses exploring interactions between study group and trimester of gestation at enrollment for each of the 11 measures at follow-up, only the model for perception of seriousness of pertussis to the newborn failed to converge. Only the interaction between study group and trimester at enrollment was significant for asking close family members to vaccinate. Women

enrolled in their third trimester were significantly more likely to ask their family members to get vaccinated if they were in the intervention group versus the control group (36% vs. 22%; RR = 1.65, 95% CI: 1.21, 2.26), whereas no difference by study group was observed among women enrolled before their third trimester (39% vs. 44%; RR = 0.93, 95% CI: 0.50, 1.73).

Discussion

Aside from evidence suggesting exposure to the intervention package may have persuaded more women in their third trimester to request their family members get vaccinated to protect the infant, results suggest that the MOMVAX study intervention package had no other significant effects on women's knowledge, attitudes and beliefs about influenza, pertussis and associated vaccinations during pregnancy. It also had no apparent impact on women's attitudes towards childhood vaccination. Observational findings, however, emphasize substantial hesitancy on behalf of these women regarding antenatal vaccination, and specifically of the safety of antenatal influenza vaccination.[129] While the vast majority of women seemed to understand the severity of influenza and pertussis to themselves and their infants, more than 60% were hesitant about antenatal vaccination and 70% either perceived the influenza vaccine as risky during pregnancy or were unsure of its safety. Congruent with other studies reporting similar uncertainties,[57,76,82,140] these results again underscore the importance of finding why this disconnect persists and closing this knowledge gap especially as increasing numbers of studies are finding no increased risk for severe adverse events following antenatal vaccination.[65,67,98,99]

There are multiple factors to consider when deciphering these primarily null findings. First, no findings presented here suggest the intervention package had a detrimental effect on knowledge, attitudes and beliefs towards vaccination. This is important in light of recent research

by Nyhan, *et. al.* that found that provision of pro-vaccine messages can reduce intent to vaccinate, especially among individuals with unfavorable attitudes towards vaccination.[114] Nyhan identified that among parents with the least favorable attitudes towards vaccination, provision of information debunking links between MMR vaccination and autism significantly reduced intentions to vaccinate their children with an MMR vaccine (aOR: 0.36, 95% CI: 0.20–0.64).

By virtue of the timing of participant recruitment for the MOMVAX study (December – April), the women included in this study were likely more vaccine reticent than typical pregnant women. Since women had to have been unvaccinated against both seasonal influenza and pertussis to be eligible for enrollment, women more accepting of vaccinations would likely have already been vaccinated against influenza by initiation of recruitment.

Testing message frames was a unique contribution of our study. Based on our formative research examining preferences among pregnant women regarding how messages about antenatal vaccination are framed (i.e. "gain-framed" messages emphasizing the positive benefits of vaccination versus "loss-framed" messages emphasizing the risks or dangers of not vaccinating),[126] we specifically incorporated primarily gain-framed messaging in our intervention materials. This difference in message framing may have prevented the negative reaction that was observed after exposure to the loss-framed messages included in Nyhan's intervention.

Secondly, women may not have been exposed to the intervention messages and materials in repeated doses over an extended period of time. Research examining changes in knowledge, attitudes and beliefs about health-related behaviors suggest routine, extended exposure to an intervention is more effective than brief or single exposures.[141] If a woman was enrolled in her second or third trimester of pregnancy, she may have only been exposed to certain elements of the intervention package (e.g., the poster, brochure) a few times. Working under the assumption that women enrolled in their first trimester of gestation would have been exposed to the

intervention package materials more times, we attempted to assess the effect of duration of exposure on the impact of the intervention package. While we found no associations between presumably more exposures to the package and the effectiveness of the package, this analysis could not take other factors into account like the impact of early refusal. If a woman declined vaccination at one visit early in her pregnancy, subsequent discussion of antenatal vaccination and exposure to intervention components like the educational brochure or iPad-tutorial may not have been reinitiated. Since the only significant interaction between trimester at enrollment and study group was among women in their third trimester for requesting family members to vaccinate, this finding may suggest that targeted exposure at the appropriate time in gestation may be as impactful as repeated or continuous exposures throughout pregnancy.

Often called "cocooning," vaccinating close family members and caregivers of an infant is a strategy used to protect an immunologically naïve newborn from contracting diseases, and this method has been promoted heavily for pertussis.[142] Since providers are encouraged to vaccinate women against pertussis in the third trimester of pregnancy, this finding is congruent with that timeframe. Furthermore, since explicit promotion of vaccinating family members was included in multiple intervention package components including the provider-to-patient talking points for Tdap, the educational brochure, and the iPad-based educational app, exposure to these components may have facilitated requests of family members to consider vaccination.

Another factor to consider when deciphering these findings is the high proportion of women providing favorable responses to many of the measures, even at baseline. Based on the low antenatal vaccination rates against both influenza and pertussis among these women, the high proportions of women perceiving influenza and pertussis as serious seem counterintuitive. However, two possible explanations for these high proportions include 1) poor discriminatory power of the questions' response options for discerning meaningful variability in attitudes and 2)

social desirability bias. While the Likert-scaled questions used in this study to correlate women's beliefs with specific psychosocial domains of the Health Beliefs Model were based on similar questions used to evaluate attitudes towards vaccination in other studies, those studies have primarily been about childhood vaccination, not maternal vaccination.[143] There is the possibility that these types of questions may need to be refined for their utility among expectant mothers. Probably more influential however was social desirability bias, and women not wanting to indicate disagreement to statements that would make them appear negligent or ignorant of matters related to their health or their infant's health. Perceived pressure to respond favorably may have impacted the follow-up questionnaire more than the baseline questionnaire since participants were responding directly to a study team member over the phone; compared to the analogous proportions at baseline, favorable response proportions were higher at follow-up across both study groups for 8 of the 11 measures.

This study has some important limitations. First, since the study was designed to detect differences in antenatal vaccine receipt, we likely lacked the sample size necessary to detect significant changes in measures of knowledge, attitudes and beliefs. Given the high prevalence of favorable responses to many of the measures at baseline, studies with larger sample sizes would likely be necessary to detect meaningful improvements. To the extent this small study can serve as a pilot for future research, however, these results can serve as useful signals for larger studies.

Secondly, considerable numbers of intervention group women did not recall seeing some of the educational components of the intervention package. For example, of the 137 intervention group women who completed the follow-up questionnaire, only 60 (43.8%) recalled seeing the educational brochure and 10 (7.3%) recalled seeing the iPad-based educational app.[136] Since components like the brochure and the interactive iPad-based tutorial were highly educational, lack of exposure to these items likely diluted the package's overall effectiveness on improving

knowledge or changing attitudes. Future studies evaluating interventions in a clinical setting should ensure exposure to all components of the intervention and assess exposure in ways that mitigate recall bias, such as routinely collecting data from clinical personnel on their experiences utilizing intervention materials.

In terms of analyses, dichotomization is not an ideal way to analyze data collected from questions assessed on Likert scales. Cut-points can seem subjective and subtle changes in proportions between individual response categories can be missed. For 5 of the 6 measures of disease severity and susceptibility, the data were so heavily skewed towards the favorable responses that we lacked sufficient numbers of observations in the less favorable response categories to use more appropriate techniques like ordinal logistic regression. Since data for 3 of the 4 measures assessed via 11-point Likert scales were not as severely skewed to one end of the response spectrum, we did conduct ordinal logistic regression for the 11-point Likert scale measures in order to more accurately assess the impact of the intervention across the range of possible responses. The results of these analyses were congruent with the dichotomous analyses and were presented secondarily because the odds ratios obtained from these analyses over exaggerated the true risk ratios since the outcomes of interest were not rare.[139] Despite these limitations, the follow-up rate for this study was high, and while the women who were lost to follow-up were meaningfully different from those who completed follow-up, their loss was equivalent across study groups.

As the first known study to scientifically evaluate a multi-component antenatal vaccine promotion package in the obstetric setting in the southeastern U.S., it serves as an important foundation for future research examining the ability of clinical interventions to change knowledge, attitudes and beliefs about antenatal vaccination. While the primary endpoint of promoting antenatal vaccination is actual vaccine receipt before delivery, understanding the

degree to which any intervention also improves women's underlying knowledge of the importance of vaccination is useful. As evidenced by the considerable proportions of women in this study expressing hesitancy about antenatal vaccination – despite perceptions of high disease severity and after exposure to an education-based intervention package addressing vaccine safety and efficacy - future research should explicitly explore reasons for this disconnect. Quantifying interventions' abilities to affect knowledge will help guide development of more robust, sustainable tools that can result in more informed vaccine-related decision making for women even beyond their current pregnancy.

Table 6-1. Questions on MOMVAX study questionnaires assessing knowledge, attitudes and beliefs about influenza and pertussis infection and associated vaccinations

Health Belief Domain	Question on baseline questionnaire	Question on postpartum follow-up questionnaire	Response options[a]
Perceived susceptibility (to self)	*(Please indicate level of agreement with this statement):* The flu is a concern for pregnant women.	*(Please indicate level of agreement with this statement):* The flu is a concern for pregnant women.	Strongly agree (1)* Agree (2)* Neutral/No opinion (3) Disagree (4) Strongly disagree (5) Don't know (3)
Perceived severity (to self)	How serious do you think it would be if you got influenza (the flu) while pregnant?	If you got pregnant again, how serious do you think it would be if you got influenza (the flu) while pregnant?	Not serious at all (1) Somewhat serious (2) Neutral (3) Serious (4)* Very serious (5)* Don't know (3)
	How serious do you think it would be if you got pertussis (whooping cough) while pregnant?	If you got pregnant again, how serious do you think it would be if you got pertussis (whooping cough) while pregnant?	
Perceived severity (to infant)	After delivery, how serious do you think it would be if your newborn baby got influenza (the flu) within their first 6 months?	How serious do you think it would be if your newborn baby got influenza (the flu) within their first 6 months?	
	After delivery, how serious do you think it would be if your newborn baby got pertussis (whooping cough) within their first 6 months?	How serious do you think it would be if your newborn baby got pertussis (whooping cough) within their first 6 months?	
Perceived safety	*(Please indicate level of agreement with this statement):* Getting a flu vaccine while pregnant seems risky.	*(Please indicate level of agreement with this statement):* Getting a flu vaccine while pregnant seems risky.	Strongly agree (1) Agree (2) Neutral/No opinion (3) Disagree (4)* Strongly disagree (5)* Don't know (3)
Likelihood of vaccinating self	On a scale of 0 (definitely not) to 10 (definitely so), please rank your likelihood of getting a flu shot during this pregnancy.	On a scale of 0 (definitely not) to 10 (definitely so), please rank your likelihood of getting a flu shot during your next pregnancy.	0 (Definitely not) – 10 (Definitely so)[†]
	On a scale of 0 (definitely not) to 10 (definitely so), please rank your likelihood of getting a Tdap shot during this pregnancy.	On a scale of 0 (definitely not) to 10 (definitely so), please rank your likelihood of getting a Tdap shot during your next pregnancy.	
Likelihood of vaccinating infant	On a scale of 0 (definitely will not) to 10 (definitely will), please rank the likelihood you will get your baby vaccinated with all recommended childhood vaccines.	On a scale of 0 (definitely will not) to 10 (definitely will), please rank the likelihood you will get your baby vaccinated with all recommended childhood vaccines.	0 (Definitely will not) – 10 (Definitely will)[†]
Intention to promote cocooning	Have you ever considered asking close family members to get a vaccine(s) (e.g. a flu shot or a Tdap shot) to help protect your newborn from infectious diseases?	During your most recent pregnancy, do you recall asking close family members to get a vaccine(s) (e.g. a flu shot or a Tdap shot) to help protect your newborn from infectious diseases?	Yes* No Don't know
Degree of vaccine hesitancy	On a scale of 0 (not hesitant) to 10 (very hesitant), how hesitant are you about getting shots your doctor recommends that you get during pregnancy?	On a scale of 0 (not hesitant) to 10 (very hesitant), how hesitant are you about getting shots your doctor recommends that you get during pregnancy?	0 (Not hesitant) – 10 (very hesitant)[‡]

[a]Numeric values provided in parentheses after response options for susceptibility, severity and self-efficacy measures were added after questionnaire administration for analysis purposes.
*Indicates favorable response options.
[†]Responses of 9 – 10 considered favorable.
[‡]Responses of 0 – 1 considered favorable.

Table 6-2. Participant characteristics by MOMVAX study group

Maternal characteristic	Study group; no. (%) Intervention (n = 161)	Control (n = 164)
Age at enrollment[a]	26.9 (5.2)	27.5 (6.0)
Race		
Caucasian/White	78 (48)	76 (46)
African American/Black	64 (40)	69 (42)
Asian	2 (1)	5 (3)
Other or missing	17 (11)	14 (9)
Ethnicity		
Hispanic	12 (7)	8 (5)
Non-Hispanic or missing	149 (93)	156 (95)
Parity (number of current children)[a]	1.0 (1.1)	1.1 (1.2)
Education		
< High school graduate/GED	9 (6)	16 (10)
High school graduate or GED test	69 (43)	58 (36)
Technical/vocational/Associates	32 (20)	41 (25)
Bachelor's degree or higher	51 (32)	47 (29)
Health insurance[b]		
Health insurance	19 (12)	25 (15)
Any private insurance	68 (42)	73 (45)
Medicaid or no insurance	73 (45)	65 (40)
Missing	1 (1)	1 (0)
Number of times treated by a healthcare provider in the past year		
0 times	67 (42)	73 (45)
1 – 4 times	84 (52)	76 (46)
5+ times	7 (4)	13 (8)
Don't know	2 (1)	2 (1)
Previous receipt of seasonal influenza vaccine in past 5 years		
0 times	91 (57)	93 (57)
1 time	27 (17)	33 (20)
2 - 4 times	28 (17)	24 (15)
5 times	6 (4)	5 (3)
Don't know	9 (6)	9 (5)
Trimester at enrollment		
First trimester (< 13 weeks gestation)	37 (23)	40 (25)
Second trimester (13 - 25 weeks gestation)	47 (29)	36 (22)
Third trimester (> 25 weeks gestation)	77 (48)	87 (53)
Enrolled from a practice stocking influenza vaccine	81 (50)	98 (60)
Enrolled from a practice stocking Tdap	64 (40)	98 (60)

[a]Mean (standard deviation)

[b]Initial question received by the first 50 participants regarding health insurance asked "Do you have health insurance?" Upon noting confusion on behalf of participants, the questionnaire was amended to include 2 questions: "Do you currently have private health insurance?" and "Are you currently covered by Medicaid?"

Table 6-3. Differences in proportions of women citing favorable responses to measures of knowledge, attitudes and beliefs about antenatal and childhood vaccination at baseline and follow-up, Emory MOMVAX Study

Measure of Knowledge, Attitude or Belief	Intervention group		Control group			Intervention effect
	Baseline (n =161)[a]	Follow-up (n=137)[a]	Baseline (n=164)[a]	Follow-up (n=140)[a]	p-values for between-group differences at baseline[b]	RR comparing intervention to control groups at follow-up[c]
Dichotomized 5-point Likert scale measures						
Perceives pertussis as serious or very serious for infant	93.2%	96.3%	92.0%	96.3%	0.63	1.00 (0.96, 1.04)
Perceives influenza as serious or very serious for infant	88.8%	92.6%	86.4%	94.1%	0.09	0.98 (0.93, 1.04)
Perceives pertussis as serious or very serious during pregnancy	82.3%	77.4%	80.1%	81.4%	0.64	0.95 (0.80, 1.12)
Agrees or strongly agrees that influenza is a concern for pregnant women	81.9%	83.9%	82.7%	85.0%	0.74	0.98 (0.90, 1.06)
Perceives influenza as serious or very serious during pregnancy	75.8%	73.0%	72.6%	70.0%	0.36	1.04 (0.88, 1.23)
Disagrees or strongly disagrees that antenatal vaccination seems risky	26.4%	29.9%	24.1%	30.2%	0.64	0.99 (0.64, 1.54)
Dichotomous measure						
Asks family members to get vaccinated to protect newborn	41.0%	37.2%	34.4%	32.4%	0.06	1.21 (0.74, 1.96)

Dichotomized 11-point Likert scale measures						
Indicates a strong willingness (scores of 9 - 10) to vaccinate their infant with recommended vaccines	80.1%	87.4%	78.8%	86.0%	0.78	1.01 (0.92, 1.11)
Indicates a strong willingness (scores of 9 - 10) to receive a Tdap vaccine during pregnancy	16.3%	53.3%	11.6%	45.0%	0.24	1.18 (0.81, 1.70)
Indicates a strong willingness (scores of 9 - 10) to receive an influenza vaccine during pregnancy	10.6%	39.4%	6.7%	32.1%	0.11	1.23 (0.78, 1.92)
Not hesitant (scores of 0 - 1) about getting recommended antenatal vaccines	36.9%	42.3%	34.6%	39.3%	0.65	1.05 (0.81, 1.37)

[a]For some measures, group counts varied slightly from these overall totals.
[b]As determined by score test comparing differences in PROC GENMOD accounting for clustering by practice.
[c]All models adjusted for clustering by practice.

Table 6-4. Intervention effects (odds ratios and 95% confidence intervals) on knowledge, attitudes and beliefs about antenatal vaccination among pregnant women in Georgia, estimated by ordinal regression

	Likelihood of getting an antenatal influenza vaccine	Likelihood of getting an antenatal Tdap vaccine	Likelihood of vaccinating infant	Hesitancy about getting vaccines during pregnancy
BASELINE				
Unadjusted OR	1.24 (0.76, 2.01)	1.18 (0.84, 1.67)	1.07 (0.59, 1.93)	0.96 (0.60, 1.52)
FOLLOW-UP				
Unadjusted OR	1.35 (0.76, 2.39)	1.17 (0.55, 2.49)	1.09 (0.55, 2.19)	1.01 (0.72, 1.40)
OR adjusted for baseline value of measure	1.27 (0.75, 2.15)	1.13 (0.55, 2.33)	---	---

CHAPTER 7: MANUSCRIPT 3

Trends in reasons for non-receipt of influenza vaccination during pregnancy in Georgia

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Abstract

Background: Considerable research has identified barriers to antenatal influenza vaccination, yet no research has explored how reasons for non-receipt have changed over time.

Purpose: To examine trends in reasons for non-receipt of influenza vaccination during pregnancy to reveal areas of improvement in antenatal vaccine promotion in the post-H1N1 era.

Methods: Serial cross-sectional analyses using 8 years of data from the Georgia Pregnancy Risk Assessment Monitoring Survey (PRAMS) were conducted. Weighted logistic regression was used to examine linear trends in the prevalence of citing reasons for non-receipt over time. Interaction models were used to identify differential changes in trends by maternal characteristics including age, education, race/ethnicity, insurance status and urban/rural residence.

Results: The study sample included 8,300 women in Georgia who reported no influenza vaccination during or immediately before pregnancy. Proportions of women citing "doctor didn't mention vaccination," "in first trimester during influenza season," and "not pregnant during influenza season" decreased significantly between 2004 and 2011 (Doctor didn't mention: 48.0% vs. 27.1%, test for trend $p < 0.001$; in first trimester: 26.8% vs. 16.3%, test for trend $p < 0.001$; not influenza season: 24.2% vs. 12.7%, test for trend $p = 0.001$). Safety concerns increased significantly over 2004 proportions in 2010 (concern about side effects for me: 40.2% vs. 28.5%, prevalence ratio (PR): 1.41, 95% confidence interval (CI): 1.16, 1.71; concern about harming my

baby: 38.9% vs. 31.0%, PR=1.26, 95% CI: 1.04, 1.53) and 2011 (concern about side effects for me: 39.0% vs. 28.5%, PR=1.37, 95% CI: 1.13, 1.65; concern about harming my baby: 38.8% vs. 31.0%, PR=1.25, 95% CI: 1.04, 1.50). Compared to women of other races, more Hispanic women cited concern about harming their baby following the 2009/2010 H1N1 pandemic; in 2011, they remained significantly more concerned about harming the baby than non-Hispanic white women (63% vs. 35%; adjusted PR = 1.79, 95% CI: 1.23, 2.61).

Conclusion: Examining trends in reasons for non-receipt of antenatal influenza vaccination reflect successes related to clinical vaccine promotion and areas for further improvement. By highlighting differential impacts of the 2009/2010 H1N1 pandemic on women of different demographics, we reveal opportunities for further research into the necessity of tailoring vaccine promotion efforts to specific types of women.

Introduction

Influenza vaccination has been recommended for all pregnant women regardless of trimester since 2004.[47] Despite research demonstrating increased risks of hospitalization and death from influenza-related complications, achieving high vaccination rates among this population has been challenging.[5,144,145] Considerable research has explored why women do not get vaccinated, and reasons for non-receipt range from concerns about the safety of the vaccine to perceptions of not being susceptible to influenza.[70,122,132,140,146] Additional reasons like an inadequate knowledge of the benefits of antenatal vaccination and lack of a provider's recommendation for the vaccine have highlighted clear education-related gaps and opportunities for intervention.[21,87] Initiatives fostering clinical promotion of antenatal vaccination have resulted in increases in antenatal vaccination rates,[27] and with the 2009/2010 H1N1 pandemic amplifying awareness of maternal vulnerability and the need for protection, national antenatal influenza vaccination coverage estimates increased from 35% in 2008-2009 to nearly 50% in 2009-2010.[124,147]

Since the H1N1 pandemic, however, antenatal vaccination rates have plateaued. National antenatal coverage estimates for the 5 influenza seasons following the pandemic have remained around 50%.[56-58] While studies have explored trends in antenatal vaccine coverage rates,[146-149] no research has explored temporal changes in reasons women cite for not getting vaccinated during pregnancy. Valuable insights may be garnered from exploring these trends; for example, changes in reasons for non-receipt could identify contemporary gaps that could guide development of interventions aimed at improving vaccine coverage in the post-H1N1 era. Using 8 years of data from the Georgia Pregnancy Risk Assessment and Monitoring (PRAMS) survey, this study identifies prevalence trends in reasons women cite for not receiving an influenza vaccination

during pregnancy, determines whether these trends differ by certain maternal characteristics, and assesses any influence the 2009/2010 H1N1 pandemic may have had on the non-receipt profile.

Methods

Data are from the Georgia Pregnancy Risk Assessment and Monitoring (PRAMS) survey. PRAMS is a collaboration between the Centers for Disease Control and Prevention (CDC) and participating health departments that collects population-based, state-specific information on women's experiences and behaviors before, during, and after pregnancy.[150] Participants' responses are linked to their infants' birth certificates, so data collected through PRAMS supplements information recorded on birth certificates. The survey employs a stratified random sampling method among all women in a given state 2 – 6 months post-partum. From 2004 – 2008, PRAMS required a response rate of ≥ 70% to release the data; from 2009 – 2011, they required ≥ 65% response rate.

To account for oversampling of women of certain races, from certain counties and having infants with low birth weights, data from each year were weighted according to the oversampling strategy used for that year. Weights were calculated and provided by the Georgia Department of Public Health.

To explore temporal trends in the prevalence of reasons cited for non-receipt, a serial cross-sectional approach was taken to examine changes in the annual proportions of women citing specific reasons for non-receipt of influenza vaccination during pregnancy. Only women who indicated not receiving an influenza vaccination during their most recent pregnancy were instructed to answer the question "What were your reasons for not getting a flu vaccination during your most recent pregnancy?" Response choices included: "My doctor didn't mention

anything about a flu vaccination during pregnancy," "I was worried about side effects of the flu vaccination for me," "I was worried that the flu vaccination might harm my baby," "I wasn't pregnant during the flu season (November – February)," "I was in my first trimester during the flu season (November – February)," "I don't normally get a flu vaccination," and "Other (please specify." For each response choice, women were instructed to circle "Yes" if the reason applied to them or "No" if it did not. Thus, women could report multiple reasons for why they were not vaccinated. Thirty-nine women who did not answer the question about influenza vaccine receipt but answered any or all of the questions about reasons for non-receipt were recoded as not having received an influenza vaccine during pregnancy. Linear trends in the prevalence of citing certain reasons for non-receipt were determined by combining data from all years and modeled using weighted logistic regression with an ordinal variable for survey year. We also modeled year as an independent categorical variable to compare proportions of reasons for non-receipt between years.

To assess bivariate associations between maternal characteristics and reasons for non-receipt over time, the following maternal characteristics were assessed: age (≤19, 20 – 24, 25 – 29, 30 – 34, ≥35), education attained (<12 years, 12 years, >12 years), race/ethnicity (non-Hispanic white, non-Hispanic black, non-Hispanic Asian/other, Hispanic), prenatal insurance status (Medicaid/No private insurance, At least some private/military insurance, None), and urban/rural residence. If no information was provided about prenatal insurance coverage, insurance status at delivery was substituted as a proxy for prenatal insurance coverage. Reasons for non-receipt exhibiting a linear association between annual prevalence and time were modeled using weighted logistic regression with a variable for the characteristic, an ordinal variable for year and a (characteristic x year) interaction term. For reasons not demonstrating a linear association between annual prevalence and time, dummy variables for each year were included so as to examine individual interactions between each year and a given maternal characteristic. Any

model for which the (characteristic x year) interaction term resulted in a statistically significant Wald-test was considered to have significant differences in the trends of citing that reason across levels of the maternal characteristic.

To determine the impact of the 2009/2010 H1N1 influenza pandemic on the non-receipt profile, we re-ran each of the aforementioned weighted logistic regression models exploring associations between each maternal characteristic and each reason for non-receipt with a dummy variable for pandemic. While we retained an ordinal variable for year in each model to account for secular trends in citing a given reason for non-receipt, we substituted the (characteristic x year) interaction term for a (characteristic x pandemic) interaction term. Women who gave birth before 09/01/2009 were considered as pregnant pre-pandemic; women who gave birth on or after this date were considered as pregnant during or post-pandemic. While pandemic vaccines did not become available in Georgia until mid to late October 2009, the 2009/2010 seasonal vaccine was available by September. Women giving birth in the interval of time between seasonal vaccine availability and pandemic vaccine availability would not have had the opportunity to receive the H1N1 vaccine, but the publicity around H1N1 influenza over summer 2009 could have influenced their decision to also receive the seasonal vaccine. The 47% median coverage rate for seasonal influenza vaccination among pregnant women during the 2009/2010 compared to 35% coverage during the 2008/2009 season supports this hypothesis.[19] For any model in which the (characteristic x pandemic) interaction term resulted in a significant Wald-test, the pandemic was considered to have significant differential effects across levels of the maternal characteristic on the proportions of women citing that reason for non-receipt.

Finally, to ascertain each maternal characteristic's association with each reason for non-receipt, we limited analyses to 2011 data in order to reflect the most current state of these associations given contemporary societal and policy contexts surrounding maternal influenza

vaccination. All 5 maternal characteristics were included in each weighted logistic regression model for each reason for non-receipt.

Results of all weighted logistic regression models are reported as prevalence ratios and 95% confidence intervals unless otherwise noted. In interaction models, Wald test p-values assessing the significance of interaction terms were adjusted using the Holm-Bonferroni correction to account for multiple hypothesis tests run on the data.[151] SAS version 9.3 (Cary, NC) and SAS-callable SUDAAN version 11.0.1 (Research Triangle Park, NC) were used to conduct analyses accounting for the complex survey design and to generate prevalence ratios using predicted marginal proportions.

Results

The study sample consisted of 8,300 women who did not receive an influenza vaccination immediately before or during pregnancy between 2004 – 2011. The distributions of women by age and education level did not vary significantly over these 8 years; however, compared to other years, the proportions of Hispanic women were greater in 2008 and 2009, the proportion of women citing no insurance was higher in 2008, and the proportion of women living in rural areas was higher in 2007. [Table 7-1]

Between 2004 – 2011, the proportion of women not receiving an antenatal influenza vaccine decreased over time (88.9% in 2004 vs. 64.2% in 2011, test for trend $p < 0.001$). [Figure 7-1] Of the total sample, 7,983 (96.2%) provided at least one reason why she did not receive an influenza vaccine during pregnancy. Despite the significant decreases in unvaccinated women during this time period, the most frequently cited reason for non-receipt across all years was "I

don't normally get a flu vaccine." [Figure 7-2F] Among women citing this reason, 34% cited no additional reason.

The prevalence of women citing that their doctor didn't mention vaccination, that they were in their first trimester, and that they were not pregnant during influenza season all decreased significantly over time (Doctor didn't mention: 48.0% in 2004 vs. 27.1% in 2011, test for trend $p < 0.001$; In first trimester: 26.8% in 2004 vs. 16.3% in 2011, test for trend $p < 0.001$; not influenza season 24.2% in 2004 vs. 12.7% in 2011, test for trend $p = 0.001$). [Figure 7-2A –7-2C] The proportion of women citing concern about side effects for themselves and concern about harming their baby declined or remained relatively stable through 2009 then increased significantly over 2004 proportions in 2010 (Concern about side effects for me: 40.2% vs. 28.5%, PR=1.41, 95% CI: 1.16, 1.71; concern about about harming my baby: 38.9% vs. 31.0%, PR=1.26, 95% CI: 1.04, 1.53) and 2011 (Concern about side effects for me: 39.0% vs. 28.5%, PR=1.37, 95% CI: 1.13, 1.65; concern about harming my baby: 38.8% vs. 31.0%, PR=1.25, 95% CI: 1.04, 1.50). [Figure 7-2D – 7-2E]

Of the three reasons for non-receipt whose yearly proportions showed a linear decrease over time, two interaction models produced significant (year x maternal characteristic) interactions. For citing "in my first trimester during flu season," Hispanic women went from being the least likely racial/ethnic group to cite this reason in 2004 to the most likely group in 2011, while proportions of both non-Hispanic black and non-Hispanic white women citing this reason decreased over time. [Figure 7-3a] For citing "not pregnant during influenza season," uninsured women started citing this reason more beginning in 2009 than privately-insure women or women on Medicaid. [Figure 7-3b]

Of the two reasons for non-receipt whose yearly proportions showed a U-shaped association with time, only the interaction model examining an association between race/ethnicity and citing concern about harming my baby showed significant heterogeneity across years. [Figure 7-3c] Beginning in 2009, Hispanic women started becoming more likely to cite concern about harming the baby than women of other races, with the interaction term between Hispanic race and year becoming highly significant in 2011 ($p = 0.008$).

Of models exploring interactions between selected maternal characteristics and the 2009/2010 H1N1 pandemic, only the model examining an association between insurance status and citing doctor did not mention vaccination exhibited significant interaction between insurance status and the pandemic ($p = 0.005$). Compared to women with at least some private health insurance, women without any insurance were more likely to cite their doctor not mentioning vaccination after the pandemic than before (Pre- vs. post-pandemic prevalances for insured women: 45% vs. 37%; pre vs. post-pandemic prevalences for women without insurance: 35% vs. 50%). Eight other models contained a significant interaction term between a given maternal characteristic and the pandemic dummy variable prior to the Holm-Bonferroni correction. Data from these models are presented in Supplementary Table 7-A. Note that no models testing differential impacts of the pandemic by levels of the five selected maternal characteristics were significant for citing "worried about side effects for me" or "I don't normally get an influenza vaccine" (data not shown).

In 2011, women less than 20 years old were more likely to cite that their doctor did not mention flu vaccination than women aged 25 – 29 years old (PR = 1.71, 95% CI: 1.10, 2.67). [Table 7-4] Non-Hispanic Asian/other women were over twice as likely to cite the doctor did not mention vaccination than non-Hispanic white women (PR = 2.03, 95% CI: 1.03, 3.99). Significantly more Hispanic women cited concern about harming their baby than non-Hispanic

white women (PR = 1.79, 95% CI: 1.23, 2.61), and women aged 20 – 24 were significantly less likely than 25 – 29 year olds to cite that they were not pregnant during influenza season (PR = 0.35, 95% CI: 0.13, 0.95).

Discussion

The number of women in Georgia who declined flu vaccination during pregnancy declined significantly between 2004 – 2011, and the reasons women cited for not getting vaccinated changed between 2004 – 2011. The prevalence of citing "doctor did not mention vaccination" declined steadily over time, presumably as more obstetricians and women became familiar with the recommendation to promote and receive this vaccine during pregnancy. Likewise, a similar decline is observed in the proportions of women citing their first trimester as a reason for non-receipt, a finding which not only aligns with the 2004 endorsement of the safety of the influenza vaccine during any trimester,[47] but with concomitant increases in coverage among women in their first trimester of pregnancy.[148] From a public health policy perspective these trends are positive as they likely reflect successful efforts to increase provider-patient discussions of antenatal influenza vaccination and awareness of the vaccine's safety. But in the post-H1N1 era as public health practitioners and vaccine advocates aim to surpass 50% antenatal influenza vaccine coverage, it is worth exploring these trends in more depth to identify potential areas for improvement in antenatal vaccine promotion.

Across all years, the most frequently cited reason for non-receipt was "I don't normally get an influenza vaccine." Numerous studies have identified a correlation between prior seasonal influenza vaccine receipt and antenatal receipt, and the predominance of this reason across time support these findings.[140] With over one-third of the women citing this reason not citing any

additional reason, delving deeper into why these women do not normally get a seasonal influenza vaccine will be an important step towards identifying effective interventions. Reasons like believing influenza vaccines are ineffective or perceiving themselves as unsusceptible to influenza are two examples of other reasons frequently cited, and their absence as explicit response options on the Georgia PRAMS survey may have inadvertently discouraged contribution of these reasons. These response choices were subsequently added to Georgia PRAMS beginning in 2012.

The 2009/2010 pandemic appears to have had a considerable impact on the non-receipt profile, most notably on citing concerns about vaccine safety. Prior to the pandemic, the prevalence of citing concern about side effects for me and concern about harming the baby rarely exceeded 30%. The prevalence of each of these reasons increased significantly after the pandemic, reaching or approaching 40%. While concern about harming the baby increased across all racial/ethnic groups following the pandemic, the increase was highly significant for Hispanic women, resulting in a post-pandemic prevalence of 50% that remained significantly greater than that of non-Hispanic white women even into 2011. Similarly, while the prevalence of citing doctor did not mention vaccination continued to decline after the pandemic, declines were only significant among non-Hispanic whites and those privately insured. The proportion of uninsured women citing this reason rose compared to women with public or private coverage. These differential impacts of the 2009/2010 pandemic corroborate findings from other studies,[85] and lend important insights into how women of different backgrounds recalled or perceived influenza vaccination after the 2009/2010 pandemic. Exploring and understanding the underlying reasons for these differences will be important to developing targeted, evidence-based messaging following similar pandemic events affecting pregnant women.

While examining trends in reasons for non-receipt is useful for identifying ways in which high-profile vaccine-related events like pandemics can affect these reasons, focusing on the most current non-receipt profile offers its own important insights. Analysis of 2011 data again reveals the elevated concern about harming the baby on the part of Hispanic women. It also suggests that the youngest women and Non-Hispanic Asian/other women are not recalling doctors mentioning influenza vaccination. Rectifying these differences could mean calling physicians' attention to these findings, and reiterating the importance of promoting influenza vaccination to all pregnant women regardless of demographics. However, they could reflect a need for more targeted, evidence-based communication strategies physicians can use when discussing antenatal vaccination with Hispanic women, Asian women or teenage mothers. More research is necessary to further understand and address the root causes of these observations.

This study has some important limitations. First, the PRAMS questionnaire only asks women who did not receive an influenza vaccine more detailed follow-up questions on reasons for non-receipt. While non-receivers are the most important group to focus on for the purpose of public health intervention, understanding why the women who got vaccinated chose to do so is also important in terms of identifying influential factors. Additionally, it is possible that some of the women who chose to vaccinate still had reservations about vaccination. Without analogous data on concerns from the vaccinated women, we were unable to determine the proportion of total women who may actually have had concerns.

While the results are most generalizable to the state of Georgia, we do not have reason to believe that pregnant women in Georgia are dramatically different from pregnant women in most other states. It should be noted though that states can vary on issues around vaccine acceptance, so caution should still be taken in extrapolating findings from this study to other populations. Since PRAMS is a yearly cross-sectional study, inferences can only be drawn on associations

between maternal characteristics and reasons for non-receipt and not causality. Moreover, at the time of this analysis, 2012 PRAMS data was not yet available, so we had only 2 influenza seasons of data following the H1N1 influenza pandemic to analyze. Including additional years of data following the 2009/2010 H1N1 pandemic will be beneficial in confirming any changes in trends potentially associated with the pandemic.

It is important to note that from December 2009 – December 2010, Georgia PRAMS added H1N1-vaccine related supplementary questions to the end of the standard questionnaire, however, we only used women's responses to the first standard influenza vaccination questions for our analyses. While the supplement included questions differentiating between receipt of the 2009/2010 H1N1 pandemic vaccine and the 2009/2010 seasonal influenza vaccine, the supplementary questions appeared at the very end of the questionnaire well after a woman responded to the standard questions on antenatal influenza vaccine receipt. Since our primary purpose was to understand trends in non-receipt among women who did not receive any antenatal influenza vaccinations, and the standard questions were not specific to either vaccine, we assumed women answered the standard questions considering their receipt of either, both or neither vaccine.

As the first study to use PRAMS survey data to examine changes in reasons for non-receipt of antenatal influenza vaccination over time, we can visualize both successes related to clinical vaccine promotion as well as areas for further improvement. Consistent declines in the number of women citing reasons like their doctor did not mention vaccination and being in their first trimester during influenza season indicate substantial progress in overcoming knowledge gaps once identified as major barriers antenatal vaccine uptake. But a more nuanced view reveals how these trends can differ by race, insurance status, or maternal age, and how they can suddenly be altered by high-profile health-related events like the 2009/2010 influenza pandemic. Using

trend data to identify these types of disparities or confirm findings from other cross-sectional surveys exploring reasons for non-receipt can refine vaccine promotion efforts. As new, targeted vaccine promotion efforts are adopted and as more years of PRAMS data are collected, we can continue to track progress towards increasing antenatal coverage and more effectively address reasons for non-receipt as they arise.

Table 7-1. Weighted distributions of maternal characteristics by year among women indicating no influenza vaccine receipt during or immediately before pregnancy, Georgia PRAMS, 2004 - 2011

	Survey year								
	2004 ***(n = 1,384)*** ***No. (%)***	**2005** ***(n = 1,476)*** ***No. (%)***	**2006** ***(n = 1,661)*** ***No. (%)***	**2007** ***(n = 584)*** ***No. (%)***	**2008** ***(n = 802)*** ***No. (%)***	**2009** ***(n = 604)*** ***No. (%)***	**2010** ***(n = 709)*** ***No. (%)***	**2011** ***(n = 1,078)*** ***No. (%)***	**p[a]**
Maternal age (yr)									0.81
≤19	158 (9.5)	191 (10.6)	210 (11.8)	71 (12.6)	86 (11.4)	94 (14.2)	99 (10.7)	356 (11.8)	
20-24	378 (26.7)	430 (29.5)	464 (29.1)	153 (26.3)	235 (28.2)	178 (30.1)	220 (29.9)	237 (28.5)	
25-29	368 (27.6)	373 (26.5)	443 (26.9)	137 (26.7)	217 (28.4)	147 (25.7)	176 (25.0)	226 (30.9)	
30-34	281 (21.2)	321 (23.1)	334 (20.1)	126 (20.3)	148 (19.8)	121 (19.3)	146 (24.2)	156 (18.6)	
≥35	199 (15.0)	161 (10.3)	210 (12.1)	97 (14.2)	116 (12.2)	64 (10.7)	68 (10.2)	103 (10.2)	
Missing	0	0	0	0	0	0	0	0	
Maternal education									0.52
<12 years	269 (22.7)	313 (22.9)	225 (15.9)	103 (17.4)	149 (22.3)	119 (21.4)	146 (19.7)	295 (19.7)	
12 years	441 (29.8)	488 (32.4)	529 (35.5)	210 (36.2)	259 (32.5)	181 (34.4)	237 (35.3)	363 (33.6)	
>12 years	650 (47.6)	644 (44.7)	746 (48.6)	250 (46.4)	364 (45.2)	270 (44.2)	311 (45.1)	383 (46.7)	
Missing	24	31	161	21	30	34	15	37	
Race/Ethnicity									**<0.0001**
Non-Hispanic white	523 (51.6)	531 (50.9)	608 (49.6)	230 (49.3)	277 (39.8)	215 (41.6)	279 (43.1)	464 (49.9)	
Non-Hispanic black	690 (31.5)	768 (33.1)	847 (33.8)	257 (29.8)	292 (29.1)	259 (33.5)	342 (36.7)	457 (32.8)	
Non-Hispanic Asian/other	36 (1.9)	43 (3.1)	40 (3.5)	23 (6.1)	111 (11.1)	31 (4.8)	27 (6.3)	35 (3.6)	
Hispanic	117 (15.0)	118 (12.9)	140 (13.1)	63 (14.8)	106 (20.0)	84 (20.1)	56 (13.9)	108 (13.6)	
Missing	18	16	26	11	16	15	5	14	
Prenatal insurance status									**0.004**
Medicaid/No private	692 (45.0)	781 (46.4)	863 (48.3)	281 (42.0)	391 (45.6)	306 (51.5)	413 (52.8)	699 (56.3)	
At least some private	631 (47.8)	618 (46.1)	696 (43.8)	254 (48.1)	336 (41.6)	244 (39.8)	234 (36.9)	300 (35.9)	
None	55 (7.2)	69 (7.5)	98 (7.9)	46 (9.9)	69 (12.7)	34 (8.6)	43 (10.3)	61 (7.9)	
Missing	6	8	4	3	6	20	19	18	

Urban/rural residence									
Urban	1000	985	730	388	642	384	432	685	
	(68.7)	(69.6)	(68.7)	(59.2)	(73.6)	(75.5)	(69.9)	(70.9)	**0.0001**
Rural	384	404	335	196	160	220	277	393	
	(31.3)	(30.4)	(31.3)	(40.8)	(26.4)	(24.5)	(30.1)	(29.1)	
Missing	87	596	0	0	0	0	0	0	

Sample sizes reflect actual frequencies; percentages are weighted, unadjusted estimates.
[a]p-values are based on Rao-Scott $\chi 2$ tests of the weighted percentages. Bolded p-values indicate significance at the 0.05 level

Figure 7-1. Proportions of women in Georgia who reported not receiving an influenza vaccine immediately before or during pregnancy, Georgia PRAMS, 2004 – 2011

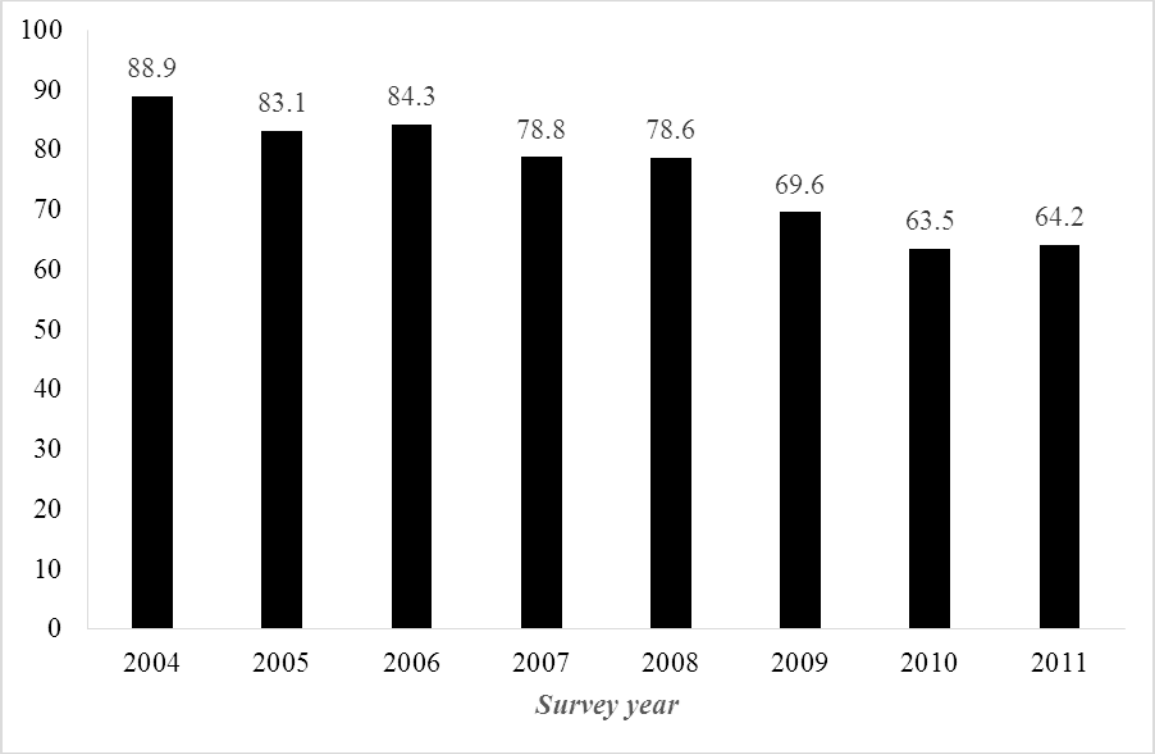
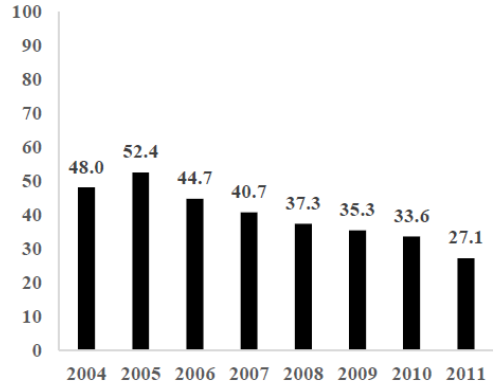
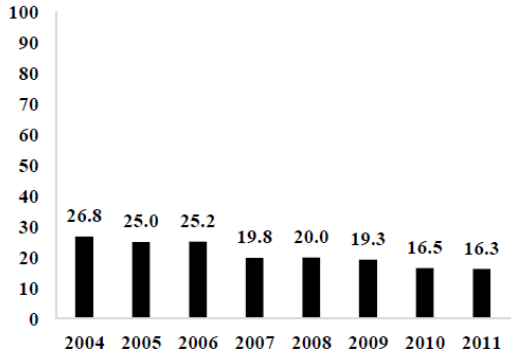


Figure 7-2. Trends in prevalence of reasons cited for not receiving an influenza vaccination during pregnancy, Georgia PRAMS, 2004 – 2011

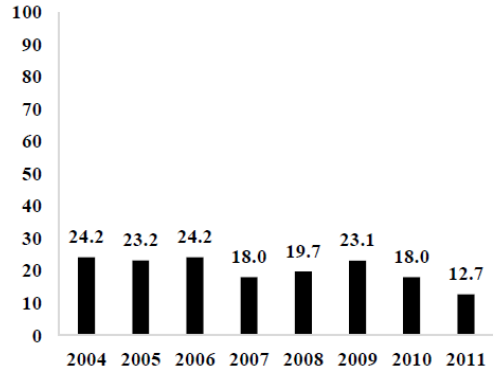
A. Doctor did not mention influenza vaccination



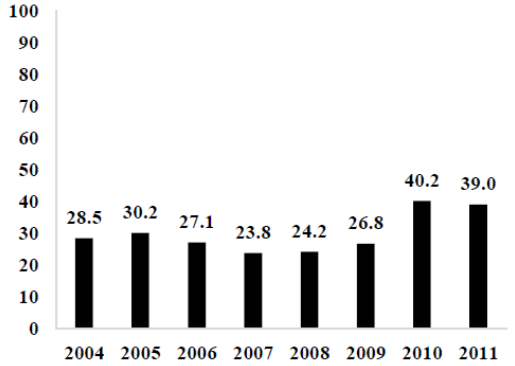
B. In first trimester during influenza season (November – February)



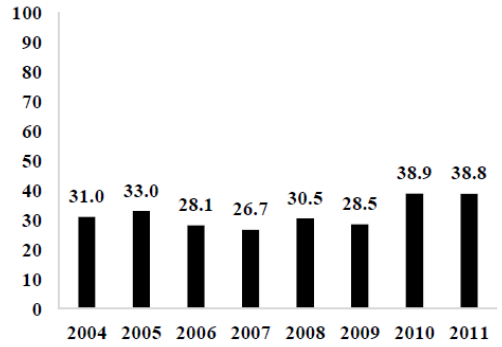
C. Was not pregnant during influenza season (November – February)



D. Worried about side effects of vaccination for me



E. Worried about harming the baby



F. Do not normally get an influenza vaccine

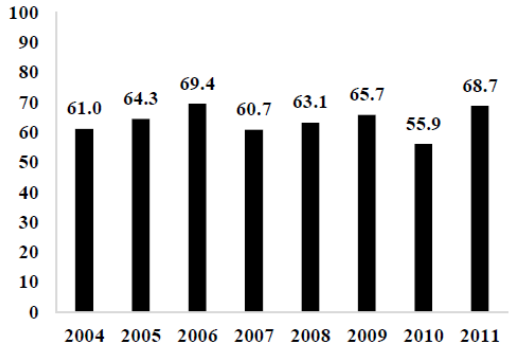
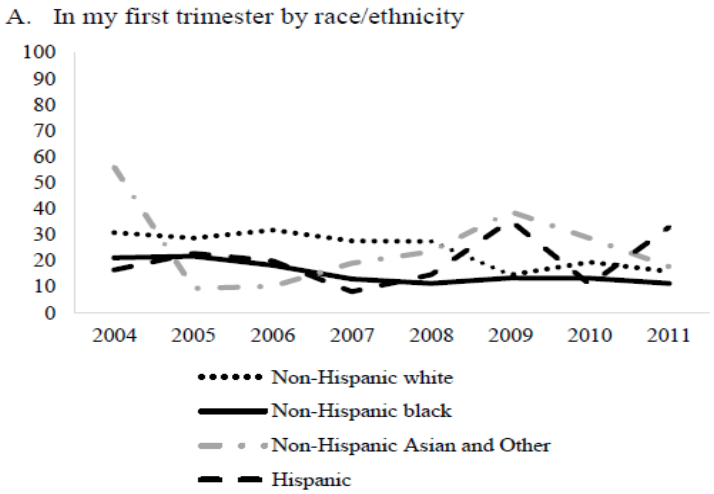
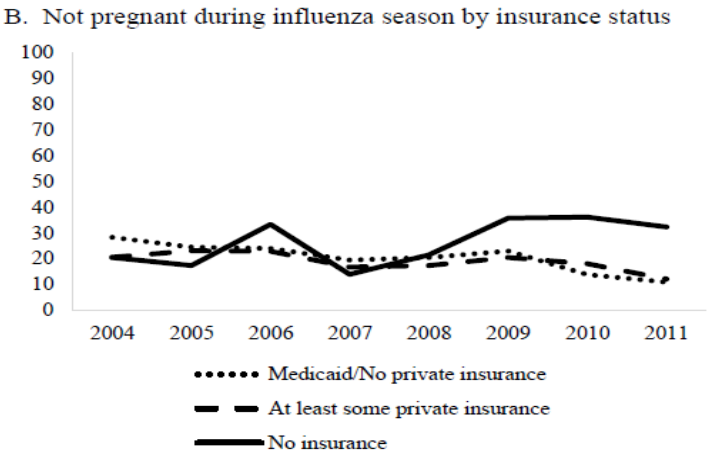


Figure 7-3. Trends in the prevalence of citing A) in my first trimester by race/ethnicity, B) not pregnant during influenza season and insurance status, and C) concerned about harming my baby by race/ethnicity, Georgia PRAMS, 2004 - 2011





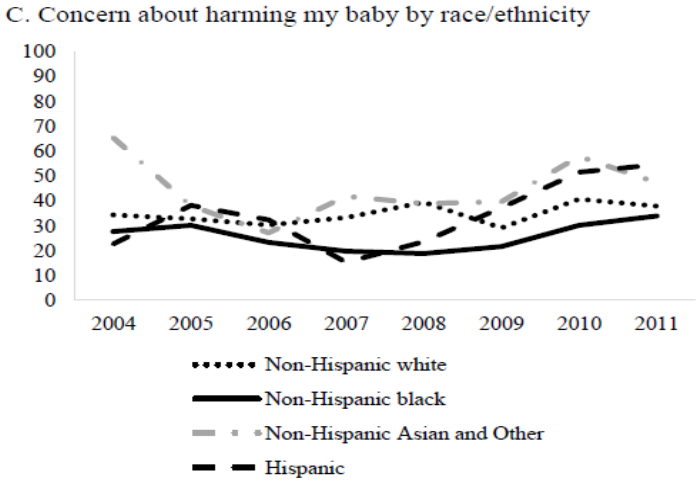


Table 7-2. Associations between maternal characteristics and reasons cited for non-receipt of influenza vaccination during pregnancy, multivariate model, Georgia PRAMS, 2011

Characteristics	Doctor didn't mention flu vaccination during pregnancy	Worried about side effects of the flu vaccine for me	Worried the vaccine might harm baby	Wasn't pregnant during flu season (Nov. – Feb.)	In first trimester during flu season	Don't normally get a flu vaccination
Maternal age (years)	*Adjusted PR (95%CI)*					
<20	**1.73 (1.11, 2.70)**	0.88 (0.59, 1.30)	1.04 (0.72, 1.51)	0.75 (0.39, 1.43)	0.91 (0.49, 1.67)	0.85 (0.68, 1.06)
20-24	1.17 (0.68, 2.02)	0.97 (0.63, 1.49)	1.01 (0.66, 1.58)	**0.35 (0.13, 0.95)**	0.65 (0.27, 1.45)	0.94 (0.75, 1.18)
25-29	ref	ref	ref	ref	ref	ref
30-34	1.01 (0.53, 1.93)	1.02 (0.67, 1.56)	1.16 (0.75, 1.80)	0.70 (0.31, 1.58)	1.16 (0.57, 2.37)	0.96 (0.76, 1.21)
≥35	1.00 (0.42, 2.41)	1.20 (0.74, 1.97)	1.53 (0.99, 2.37)	0.62 (0.18, 2.20)	0.32 (0.07, 1.40)	0.82 (0.58, 1.17)
Maternal education						
<12 years	0.82 (0.44, 1.55)	0.66 (0.39, 1.11)	0.71 (0.44, 1.13)	2.04 (0.86, 4.86)	1.48 (0.65, 3.39)	0.97 (0.75, 1.25)
12 years	1.17 (0.73, 1.88)	0.84 (0.58, 1.20)	1.06 (0.76, 1.49)	1.22 (0.51, 2.94)	1.71 (0.86, 3.39)	0.96 (0.79, 1.18)
>12 years	ref	ref	ref	ref	ref	ref
Race/Ethnicity						
Non-Hispanic white	ref	ref	ref	ref	ref	ref
Non-Hispanic black	1.16 (0.72, 1.86)	0.95 (0.66, 1.36)	1.05 (0.73, 1.50)	0.86 (0.47, 1.58)	0.77 (0.39, 1.49)	0.93 (0.78, 1.11)
Non-Hispanic Asian/other	**2.03 (1.03, 3.99)**	1.02 (0.52, 2.02)	1.19 (0.62, 2.30)	1.04 (0.28, 3.82)	1.03 (0.30, 3.52)	0.85 (0.50, 1.45)
Hispanic	1.47 (0.76, 2.83)	1.33 (0.87, 2.05)	**1.79 (1.23, 2.61)**	0.62 (0.22, 1.76)	1.31 (0.62, 2.77)	0.73 (0.50, 1.07)
Prenatal insurance status						
Medicaid/No private	0.94 (0.55, 1.60)	0.70 (0.48, 1.02)	0.73 (0.50, 1.06)	0.78 (0.34, 1.79)	0.79 (0.37, 1.68)	1.05 (0.84, 1.31)
At least some private	ref	ref	ref	ref	ref	ref
None	1.38 (0.61, 3.08)	0.92 (0.49, 1.71)	0.85 (0.46, 1.58)	2.31 (0.78, 6.82)	1.51 (0.59, 3.87)	1.14 (0.83, 1.56)
Urban/rural residence						
Urban	ref	ref	ref	ref	ref	ref
Rural	1.29 (0.85, 1.94)	1.08 (0.78, 1.49)	1.11 (0.82, 1.51)	1.70 (0.93, 3.10)	0.84 (0.47, 1.52)	1.04 (0.88, 1.24)

Bold values indicate significance of 95% CI. Models for each reason for non-receipt were adjusted for all the variables in the table.

Abbreviations: PRAMS (Pregnancy Risk Assessment Monitoring System), PR (prevalence ratio), CI (confidence interval), ref (referent)

Supplementary Table 7-A. Prevalence differences in reasons cited for non-receipt of antenatal influenza vaccines after versus before 2009/2010 H1N1 influenza pandemic by maternal characteristic, Georgia PRAMS, 2004 - 2011

	Prevalence pre-pandemic	Prevalence post-pandemic	Prevalence difference	*P-value*	Difference in differences	*P-value*
Doctor didn't mention vaccination						
Race/Ethnicity						
Non-Hispanic white	0.46	0.34	**-0.13**	**0.004**	ref	
Non-Hispanic black	0.37	0.36	-0.01	0.79	0.11	0.02
Non-Hispanic Asian/other	0.42	0.46	0.04	0.71	0.17	0.14
Hispanic	0.39	0.42	0.03	0.71	0.15	0.04
Insurance status						
Medicaid/No private	0.45	0.37	-0.08	0.07	0.04	0.43
At least some private	0.40	0.29	**-0.11**	**0.009**	ref	
None	0.35	0.50	0.14	0.10	**0.25**	**0.005**
Worried about harming the baby						
Race/Ethnicity						
Non-Hispanic white	0.33	0.38	0.05	0.25	ref	
Non-Hispanic black	0.23	0.32	0.09	0.03	0.04	0.37
Non-Hispanic Asian/other	0.41	0.49	0.09	0.42	0.04	0.73
Hispanic	0.28	0.50	**0.23**	**0.0008**	0.18	0.01
Not pregnant during influenza season						
Maternal age						
≤19	0.25	0.24	-0.01	0.85	-0.09	0.16
20-24	0.22	0.16	-0.06	0.14	-0.14	0.007
25-29	0.18	0.26	0.08	0.09	ref	
30-34	0.19	0.26	0.07	0.20	-0.01	0.86
≥35	0.18	0.22	0.05	0.48	-0.03	0.64
Race/Ethnicity						
Non-Hispanic white	0.20	0.20	0.00	0.93	ref	
Non-Hispanic black	0.19	0.17	-0.02	0.54	-0.03	0.52
Non-Hispanic Asian/other	0.25	0.36	0.11	0.30	0.11	0.32
Hispanic	0.22	0.40	0.18	**0.01**	0.18	0.01
Insurance status						
Medicaid/No private	0.22	0.17	-0.04	0.20	-0.11	0.01
At least some private	0.18	0.24	0.06	0.13	ref	
None	0.21	0.45	**0.23**	**0.007**	0.17	0.05
Urban/rural residence						
Urban	0.20	0.20	-0.00	0.92	ref	
Rural	0.20	0.28	0.09	0.07	0.09	0.046

In my first trimester during influenza season						
Race/Ethnicity						
Non-Hispanic white	0.27	0.18	-0.09	**0.01**	ref	
Non-Hispanic black	0.17	0.12	-0.04	0.14	0.05	0.23
Non-Hispanic Asian/other	0.25	0.24	0.00	0.96	0.09	0.39
Hispanic	0.19	0.27	0.09	0.18	0.18	0.007
Insurance status						
Medicaid/No private	0.19	0.15	-0.04	0.21	0.03	0.42
At least some private	0.27	0.20	-0.07	0.08	ref	
None	0.16	0.28	0.12	0.12	0.19	0.02

All models adjusted for year. P-values that are bolded are significant at 0.05 threshold after application of the Holm-Bonferroni correction.

CHAPTER 8: CONCLUSIONS AND FUTURE DIRECTIONS

In the two studies related to the evaluation of the multi-component intervention package of the MOMVAX study, we found no significant impacts of the package on either antenatal influenza or Tdap vaccine receipt or improvements in knowledge, attitudes and beliefs towards vaccination. There was some evidence that the package influenced post-partum Tdap vaccine receipt, but the 14% absolute difference observed between intervention and control groups for the outcome of any Tdap vaccine receipt (antenatal or post-partum) should be interpreted cautiously since the significance of the difference was eliminated after correlation by practice was taken into account. Similarly, while explorations of effect modification by trimester of gestation at enrollment suggested that exposure to the intervention package had a more profound effect on women in their third trimester than women enrolled earlier in their pregnancies, this association should be explored further in future studies.

While the results of the first two studies were null, results of our third study examining trends in reasons for non-receipt of antenatal influenza vaccination over time among women in Georgia revealed interesting changes in reasons for non-receipt between 2004 – 2011. The proportions of women citing that their doctor didn't mention vaccination, that they were in their first trimester during influenza season or that they were not pregnant during influenza season all declined significantly over time. In contrast, while the proportions of women citing safety concerns either for themselves or their fetuses either declined or remained stable between 2004 – 2009, they increased significantly over 2004 proportions beginning in 2010, presumably on account of the 2009/2010 H1N1 influenza pandemic. Moreover, analyses stratifying by race/ethnicity and insurance status revealed that Hispanic women became the racial/ethnic group most concerned about harming their baby after the 2009/2010 H1N1 pandemic and that the proportion of uninsured women citing "doctor didn't mention influenza vaccination" rose

significantly after the pandemic and in comparison to women with public or private coverage. These findings illustrate that while achievements have been made in regards to encouraging discussion of antenatal vaccination within the obstetric setting, more work is needed not only to continue the progress set in motion prior to the H1N1 pandemic, but to potentially address and rectify disparities or anxieties created by the pandemic itself.

When considering the combined impacts of these studies on the field of public health, it is important to put them in context. To our knowledge, the MOMVAX study was the first study to scientifically evaluate a multi-component intervention package on improving antenatal vaccination rates against influenza and pertussis. While interventions to improve vaccination rates in pediatric clinics have been evaluated through clinical trials, there is a dearth of analogous research in the obstetric setting. While the MOMVAX study had its limitations, largely influenced by its small sample size, recruitment timeline and inclusion of practices not offering one or both vaccines in-house, it joins a small, but growing number of studies beginning to apply the scientific method to interventions hypothesized to improve antenatal vaccine uptake.[25-27] As Nyhan revealed in his 2014 paper presenting results from a trial testing the effectiveness of messages aimed at correcting myths about a correlation between MMR vaccination and autism, well-intentioned messaging intended to correct misconceptions can backfire, reducing the likelihood of vaccination among the most vaccine reticent individuals.[114] The greatest lessons from Nyhan's research were the assertion that applying experimental rigor to interventions aimed at improving vaccine acceptance is imperative and that interventions can have variable impacts based upon a person's underlying perceptions of or attitudes towards vaccination. The MOMVAX study contributes to the literature in both of these critical ways: by evaluating an evidenced-based intervention package in a well-designed clinical trial and doing so among a population of women likely to have been more vaccine reticent than the typical pregnant woman.

Since the MOMVAX study was small with only 5 obstetric practices per study group and 325 participants, we lacked power for some of the more nuanced analyses like determining impacts of individual components of the intervention package on our outcomes of interest or potential synergies between a doctor's recommendation and any of the physical components of the package. Despite insufficient power for these analyses, we explored these types of associations anyway, and we presented our findings where possible. Our rationale for this approach was to be as informative to future studies as possible; research in this arena needs to be conducted until we find the interventions, messages or approaches that are effective in encouraging women to get vaccinated. To the extent this study can assist researchers by providing "signals" potentially worthy of more formal attention in larger trials, it should. A good example is the need to delve deeper into understanding why such a drastic disconnect seems to exist between women's perceptions of severity of influenza and pertussis and their willingness to protect themselves (and their infants) against these diseases through antenatal vaccination. From these studies, it is apparent there are concerns about vaccine safety. But are the safety concerns mostly in regards to themselves, their fetuses or both? And do women (and potentially obstetric care providers) need to be educated more on the process by which a national vaccine recommendation is made, emphasizing the processes by which safety and effectiveness are evaluated? Knowing the answers to these questions will be invaluable to building confidence in the vaccines and hopefully in improving uptake.

From a study design perspective, future trials should be larger (incorporating at least 6 practices per study group if utilizing the cluster-randomized design), should be powered to adequately assess differential impacts by women's baseline attitudes towards vaccination, and should incorporate a detailed intervention adoption plan to periodically assess practices' implementation of each component of the intervention for the duration of follow-up. Quantifying and rectifying any lack of participant exposure to the intervention on account of barriers on the

practitioners' part are critical not only to a study's internal validity, but to the eventual clinical practicality of the intervention beyond an academic study. Additionally, while the intervention package created for the MOMVAX study included practice-, provider-, and patient-focused components, it lacked provider-level components like vaccination rate feedback, standing vaccine orders, and automatic vaccination reminders in electronic medical records systems proven to be impactful in pediatric and obstetric settings.[87,88] Future studies assessing interventions to improve antenatal vaccine uptake should consider integrating these components into their packages as well.

Since the MOMVAX study was conducted in Georgia, its generalizability is most appropriate for women in Georgia. However, extending the results and lessons learned from this study to obstetric populations in most other states is not entirely unadvisable; we have no reason to believe pregnant women in Georgia are vastly different from pregnant women in other states. Likewise, while results from analysis of the Georgia PRAMS data most appropriately complement the results of the MOMVAX study, findings derived from the PRAMS data have relevance to obstetric populations beyond Georgia. While many studies have explored reasons why women have not chosen to vaccinate during pregnancy, no studies have explored whether and how these reasons have changed over time. Since Georgia had been collecting data on influenza vaccine non-receipt since 2004, we were able to use publicly available data to uncover how trends in certain reasons have declined over time and how others have increased subsequent to the 2009/2010 H1N1 influenza pandemic. While the significant declines in reasons like "doctor didn't mention vaccination" and "in my first trimester during pregnancy" likely reflect increasing frequency of provider-initiated conversations and diffusion of education about antenatal vaccination, they signal the need to now focus on improving providers' messaging. Between 2004 and now, whatever discussions have taken place between providers and pregnant women about antenatal influenza vaccination have only gotten us to 50% coverage. Additionally,

analyses from these PRAMS data also revealed that safety concerns rose dramatically after the 2009/2010 H1N1 pandemic, and most notably among Hispanic women. Supplying providers with ample data on vaccine safety and providing evidenced-based talking points that specifically address safety concerns---and potentially in culturally-sensitive ways---may be one of the most impactful interventions to examine in future studies. While we can recognize and laud the achievements made this far in promoting influenza vaccination during pregnancy, it is important to keep going, especially since more vaccines against pathogens like group B streptococcus (GBS) and respiratory syncytial virus (RSV) are currently being studied for use during pregnancy.[134]

Anticipating the number of vaccines recommended during pregnancy to increase, normalizing vaccination within obstetric care is becoming increasingly important. However, for obstetric practices, starting or expanding a vaccination program is not without challenges. Purchasing vaccine can be a financial liability, especially if doses go unused. Storing vaccine appropriately also requires resources and space. Reimbursement for administration of vaccines during pregnancy can also vary, especially for patients without private insurance. Because of these barriers, we found that practices serving lower socio-economic populations or populations more likely to be vaccine reticent (e.g. African Americans) often chose not to supply influenza and/or Tdap vaccines in-house. For the MOMVAX study, this posed one of the greatest challenges to our study design: whether or not to include practices in the study that did not already stock vaccines in-house. In planning the study and enrolling practices, we realized that limiting eligibility to practices that already stocked vaccines would in turn limit our sample to practices serving higher socio-economic patient populations and already having antenatal vaccination rates above the state average of about 30% coverage. We would therefore miss the opportunity to evaluate the package among certain demographics of women, some of whom previous research has suggested can be harder to vaccinate. Despite understanding that practices

not already offering vaccines in-house inherently assume the greatest barrier to vaccine promotion by not being able to immediately provide the vaccine(s) they are endorsing,[152] we decided to include them in our study and control for this confounder by matching on this practice-level characteristic prior to randomization. We found that not already having a vaccine program was not a barrier to practices' interest in participating; many wanted to promote the vaccines and encourage their patients to seek out vaccination, even if they had not yet made the financial commitment to initiate a vaccine program. Additionally, since the recommendation to administer Tdap at every pregnancy was so new at the time our study started, many practices had not yet started stocking Tdap for routine obstetric care. We felt that if the package could be effective despite stocking the vaccines in house, it could immediately be adopted by practices regardless of whether they supplied the vaccines yet or not.

For researchers considering future studies of this nature, considering whether to make provision of vaccines in-house an eligibility criterion is an important decision. From a public health standpoint, a future in which all obstetric care providers supply all recommended antenatal vaccines can and should be the goal. But achieving this new norm will take time, especially among practices serving primarily uninsured patients or certain demographics of women who are known to be more reluctant to receive certain vaccines. For the immediate future, it will remain important for researchers to realize that by excluding practices that do not already stock vaccines from trials testing interventions to improve vaccine coverage, they will be missing opportunities to promote vaccination among potentially important groups of women.

Taken together, the research presented in this dissertation contributes not only to the growing knowledge base on the challenging topic of antenatal vaccination, but to a national immunization priority set in motion in 2014 by the National Vaccine Advisory Committee (NVAC).[19] Through NVAC's extensive review of the current state of maternal immunization

and identification of gaps and barriers to executing the current antenatal vaccine recommendations, NVAC made 5 key recommendations on ways to improve maternal vaccination to U.S. Assistant Secretary for Health. These recommendations included enhancing communication to address safety and effectiveness of antenatal immunizations, maximizing provider recommendation and administration efforts, improving financing for immunization services, increasing the use of electronic health records and immunization information system among obstetricians, and addressing current vaccine liability laws to assist instead of hamper vaccine uptake. By scientifically evaluating an evidence-based intervention package to improve antenatal vaccination and examining trends in reasons for non-receipt of antenatal influenza vaccination over time, this dissertation addresses at least the first two of these important national priorities and pushes the science forward to finding clinical interventions that truly do improve knowledge about antenatal vaccination and push national coverage rates closer to 100%.

APPENDECES

Appendix A – A priori rules for determining influenza and Tdap vaccination status in Emory MOMVAX study

1. Data obtained from the Georgia Registry for Immunization Transactions and Services (GRITS) was only used to increase sensitivity of the outcome. Lack of a record in GRITS did not override results of an obstetric chart review or acceptable self-report indicating vaccine receipt before the expected date of delivery.

2. For practices offering vaccine in-house, obstetric chart reviews were used to increase sensitivity as well as specificity of the outcome. If a woman appeared to remain a patient of the enrolling practice through the duration of her pregnancy, results of obstetric chart reviews:
    a. Determined the antenatal vaccination status of women lost to follow-up
    b. Determined the antenatal vaccination status of women who reported "don't know" to questions about antenatal vaccine receipt on the post-partum follow-up survey
    c. Took precedence over self-reported non-receipt if the chart review indicated receipt before the date of delivery
    d. Took precedence over self-reported antenatal vaccine receipt UNLESS:
        i. There was evidence that a woman moved residences during follow-up
        ii. There was evidence a woman may have received prenatal care from providers outside of the practice of enrollment
        iii. A woman appeared lost to follow-up by the practice of enrollment before delivery

3. If self-reported vaccination status as obtained through the post-partum follow-up survey was the only method of determining antenatal vaccine receipt (i.e. a woman did not authorize release of her medical records or the enrolling practice did not offer the vaccine and there was no positive record in GRITS), the woman's report was accepted as truth EXCEPT:
    a. When a woman enrolled from a practice not providing the vaccine in house reported receiving the vaccine at her OB/GYN's office without evidence of relocation, ceasing prenatal care at the enrolling practice or receiving prenatal care outside of the enrolling practice

4. Antenatal vaccination status was deemed unknown if a woman was enrolled from a practice that did not offer the vaccine and she was either lost to follow-up or did not know her antenatal vaccination status at the time of the follow-up survey and there was no record in GRITS.

5. Postnatal Tdap receipt was defined as receipt of a Tdap vaccination in the hospital after delivery and was only assessed via self-report on the follow-up survey.

Appendix B – MOMVAX Study Baseline Questionnaire

Name:_____ **PID:**_____

Section 1. Healthcare and flu experience

Protecting Pregnant Women in GA from Infectious Diseases

Emory University Study - Baseline Participant Survey

Protecting you and your baby against infectious diseases both during pregnancy and after birth is important. Your OB/GYN practice is exploring ways to improve the protection of its pregnant patients and their babies. First, we'd like to know a little bit about your knowledge, attitudes and beliefs about infectious diseases during pregnancy. Please fill out the following short questionnaire.

1) **Do you consider your OB/GYN to be your primary care doctor?**
   a) _____Yes
   b) _____No
   c) _____Don't know

2) **In the past year, approximately how many times have you been treated for an illness or condition by a healthcare provider?**
   a) _____0 times
   b) _____1-4 times
   c) _____5-9 times
   d) _____10 times or more
   e) _____Don't know

3) **Do you currently have private health insurance?**
   a) _____Yes
   b) _____No
   c) _____Don't know

4) **Are you currently covered by Medicaid?**
   a) _____Yes
   b) _____No
   c) _____Don't know

5) **Which vaccine(s) have you received in an OB/GYN doctor's office before? (Check all that apply.)**
   a) _____Seasonal influenza (flu) shot
   b) _____H1N1 pandemic influenza (flu) shot
   c) _____HPV vaccine
   d) _____Tetanus or pertussis vaccine (e.g. Td or Tdap)
   e) _____Other
   f) _____I don't remember
   g) _____I have never received a vaccine in an OB/GYN doctor's office before

6) In the past five years, how often have you received a seasonal flu shot?

a) _____5 times (e.g., every year: 2007, 2008, 2009, 2010, 2011)
b) _____2-4 times
c) _____1 time
d) _____0 times
e) _____Don't know

7) Where did you get your last flu shot?

a) _____Primary-care doctor's office
b) _____OB/GYN doctor's office
c) _____Community/Public health clinic
d) _____Storefront clinic (i.e. CVS, RiteAid, Walgreen's)
e) _____Hospital
f) _____School health clinic
g) _____At work/worksite health clinic
h) _____Other (specify)_____
i) _____Don't know
j) _____I did not get a flu shot

Section 2: Protection during pregnancy

8) On a scale of 0 (definitely not) to 10 (definitely so), please rank how likely it is that you could get the flu while pregnant? (Circle one number.)

0 1 2 3 4 5 6 7 8 9 10

Definitely not Definitely So

How serious do you think it would be if you got the following illnesses while pregnant? (Mark best answer for each illness listed.)

	Not serious at all	Somewhat serious	Neutral	Serious	Very serious	Don't know
9) A cold	□	□	□	□	□	□
10) A stomach virus	□	□	□	□	□	□

11) Influenza (the flu)	□	□	□	□	□	□
12) Pertussis (whooping cough)	□	□	□	□	□	□

On a scale of 0 (Definitely not) to 10 (Definitely so), please rank <u>your likelihood</u> of getting the following shots during this pregnancy. (Circle one best answer for each vaccine).

13) Flu shot:

0 1 2 3 4 5 6 7 8 9 10

Definitely not Definitely So

14) Tdap shot [Protects against tetanus, diphtheria, and pertussis (whooping cough)]:

0 1 2 3 4 5 6 7 8 9 10

Definitely not Definitely So

15) On a scale of 0 (not hesitant) to 10 (very hesitant), how hesitant are you about getting shots your doctor recommends that you get during pregnancy? (Circle best answer.)

0 1 2 3 4 5 6 7 8 9 10

Not hesitant Very hesitant

For the following questions, please mark the appropriate box for each question to indicate how much you agree with each statement (1 = 'Strongly Agree,' 5 = 'Strongly Disagree').

	1 Strongly agree	**2** Agree	**3** Neutral/ No Opinion	**4** Disagree	**5** Strongly Disagree
16) Most people in my community have already gotten or will get the flu shot this flu season.	□	□	□	□	□
17) The flu is a concern for pregnant women.	□	□	□	□	□

18) Getting a flu vaccine while pregnant seems risky.	□	□	□	□	□

Section 3: Protecting your fetus and baby from infectious diseases

19) Have you ever considered asking close family members to get a vaccine(s) (e.g. a flu shot or a Tdap shot) to help protect your newborn from infectious diseases?

a) _____Yes
b) _____No
c) _____Don't know

After delivery, how serious do you think it would be if your newborn baby got any of the following illnesses within their first 6 months? (Mark best answer for each illness listed.)

	Not serious at all	Somewhat serious	Neutral	Serious	Very serious	Don't know
20) A cold	□	□	□	□	□	□
21) A stomach virus	□	□	□	□	□	□
22) Influenza (the flu)	□	□	□	□	□	□
23) Pertussis (whooping cough)	□	□	□	□	□	□

24) On a scale of 0 (definitely will not) to 10 (definitely will), please rank the likelihood you will get your baby vaccinated with all recommended childhood vaccines. (Circle best answer.)

0 1 2 3 4 5 6 7 8 9 10

Definitely will not Definitely will

Section 4: Participant Demographics

25) How old are you? _____ years old

26) What is the highest level of school that you have completed?

a) _____K-8 grade
b) _____9-11 grade
c) _____High school graduate/ GED
d) _____Technical/ Vocational or Associates
e) _____Bachelor degree
f) _____Master's degree
g) _____Doctorate

27) How would you describe your ethnic background?

a) _____African American/ Black
b) _____Hispanic/ Latino/ Chicano
c) _____Caucasian/ White
d) _____Other. Please specify _____

28) How many children do you currently have (not including your current pregnancy)?

a) _____0
b) _____1
c) _____2
d) _____3
e) _____4
f) _____5
g) _____6+

Thank you!

Appendix C – MOMVAX study post-partum follow-up questionnaire

Protecting Pregnant Women in GA from Infectious Diseases

Emory University Study – Follow-up Participant Survey

This follow-up survey will be administered over the phone to participants who enrolled in the MOMVAX study between 12/11/12 – XX/XX/13 and completed the baseline questionnaire upon enrollment. This survey will be administered to each participant 2 – 3 months after the expected delivery date provided by participants on the contact information sheet completed at enrollment.

Name:_____ PID:_____

Below is a script to use when calling:

Hello, this is _____calling from Emory University in Atlanta, GA. We are trying to reach _____. Is this she? (If yes:) You enrolled in a study with us while at your OB/GYN office when you were pregnant and we are calling with the follow-up survey that will complete your role in the study. Upon completion of this survey, you will be sent a $25 gift card to either Target or Walmart. This survey should only take about 20 minutes; can we ask you the follow-up questions at this time?

-If no: When would be the best time to call you? _____

-If yes: OK, great. Just so you know, everything we talk about will be kept confidential and will not be shared with anyone outside of our research team. OK? We will make sure that the information is only used for scientific purposes. You can also decide to stop participating at any time. Do you have any questions?

Instructions: Please answer the following questions honestly and to the best of your ability. Unless I tell you otherwise, all of the questions I will ask have to do with your most recent pregnancy.

Section 1. Pregnancy and Baby Health Outcomes

INTERVIEWER READS: "In this first section, I will ask some general questions about your most recent pregnancy and bab(ies)".

1. **In your most recent pregnancy, did you experience any complications during your pregnancy or during delivery? This can include pre-eclampsia (which is high blood pressure), bleeding, miscarriage, or stillbirth.**
   a. _____No
   b. _____Yes*
   c. _____Don't know

   In general terms, what was the complication(s)? *(& how far along in pregnancy):

   _____
   ___

[NOTES TO INTERVIEWER: If the participant experienced a miscarriage, spontaneous abortion, or stillbirth, offer condolences: "Oh no, I am sorry to hear about your loss. Would you feel comfortable continuing, or would you like to stop? I am happy to do whatever you are comfortable with."

If the participant experienced a miscarriage or spontaneous abortion (loss of a baby before 21 weeks gestation), and is willing to continue, proceed to Question 10. SKIP QUESTIONS 33, and 44 – 47.

If the participant experienced a stillbirth (loss of a baby after 21 weeks gestation and up until delivery), and is willing continue, continue to ask questions below, but SKIP QUESTIONS 3, 8, 9, 33, 44 – 47.]

2. **In your most recent pregnancy, were you pregnant with a single baby or multiple babies like twins, triplets or more?**
   a. _____Single
   b. _____Twins
   c. _____Triplets
   d. _____Other: _____

3. **Is your bab(ies) alive now?**
   a. _____No *(Express condolence: "Oh no, I am so sorry to hear that. Would you feel comfortable continuing, or would you like to stop? I am happy to do whatever you are comfortable with.")*
   b. _____Yes
   c. _____Only certain ones (please specify):_____

4. **Is/are/were your new babie(s) a boy(s) or girl(s):**

   -child#1: [ ] Male/Boy [ ] Female/Girl

   -child #2: [ ] Male/Boy [ ] Female/Girl

   -child #3: [ ] Male/Boy [ ] Female/Girl

   -child #4: [ ] Male/Boy [ ] Female/Girl

5. **Was/were your babie(s) born** (INTERVIEWER NOTE: Read answer options aloud)**:**
   a. _____Pre-term *(before 37 weeks)*
   b. _____Term *(37-42 weeks)*
   c. _____Post-term *(over 42 wks)*
   d. _____Not sure / Don't know

6. **At how many <u>weeks</u> of pregnancy did you deliver your bab(ies)? _____weeks**

7. **How much did your babie(s) weigh at birth:**

   Child #1: _____ Child #2: _____

   Child #3: _____ Child#4: _____

   (Additional:
   _____)

   [ ] Don't know

8. **After your bab(ies) were born, was he or she put in an <u>intensive care unit</u>?**
   a. _____No
   b. _____Yes*
   c. _____Only certain ones (please specify):_____*
   d. _____Don't know

   ***For how many days? _____**

9. **Since birth, has/have your babie(s) experienced any <u>medical conditions</u> for which you have had to take him/her/them to the doctor?**

   a. _____No
   b. _____Yes*
   c. _____Don't know

   ***Could you briefly explain?**

Section 2. Healthcare and flu experience

INTERVIEWER READS: "In this second set of questions, I will ask about your experience with influenza, or the flu. The flu is a contagious disease caused by the influenza virus. It is a respiratory disease which affects your nose, throat and lungs. It can be spread through coughing, sneezing, or nasal secretions."

10. Did you get sick with the flu during your most recent pregnancy?

a. _____No [GO TO QUESTION 14]
b. _____Yes
c. _____Don't know [GO TO QUESTION 14]

11. How did you know it was the flu? (NOTE TO INTERVIEWER: read all answer choices to participant, asking "Yes" or "No" after each one you read so they can easily understand each response option and answer after each. Mark all that apply.)

a. _____The diagnosis was made by a doctor based on clinical signs and symptoms
b. _____The diagnosis was made by a doctor, confirmed by laboratory tests [NOTE TO INTERVIEWER: To clarify this response choice, you can say, "Was a cotton swab like a Q-tip put into your nose or possibly into your throat to test for the flu?"]
c. _____I thought I had it but I didn't visit a doctor
d. _____A friend or relative told me I had it
e. _____A pharmacist told me I had it
f. _____I got it from the flu shot
g. _____Other: _____
h. _____Don't know

12. What symptoms did you have? (NOTE TO INTERVIEWER: read all answer choices individually and mark all that apply.)

a. _____Cough
b. _____Runny nose
c. _____Sore throat
d. _____ Nasal congestion/"stuffy nose"
e. _____Itchy eyes
f. _____Fever or feeling feverish/chills
g. _____Muscle or body aches
h. _____Headache
i. _____Fatigue (very tired)
j. _____Vomiting
k. _____Diarrhea
l. _____Difficult breathing
m. _____None of the above
n. _____Other. Specify:
_____

13. Did you <u>need to be hospitalized</u> for the flu or flu-related complications?

a. _____No
b. _____Yes

If yes, please explain:

_____

14. Did anyone you were <u>living with or were in contact with 3 or more times per week</u> get the flu while you were pregnant?

a. _____No
b. _____Yes
c. _____Don't know

15. <u>During your most recent pregnancy</u>, did your OB/GYN or nurse midwife, recommend that you get the flu shot?

a. _____No
b. _____Yes
c. _____Don't know

16. <u>Prior to your most recent pregnancy</u>, did you get a flu shot during the previous year's flu season (2011-2012)?

a. _____No
b. _____Yes
c. _____Don't know

17. Did you get a flu shot <u>during your most recent pregnancy</u>?

a. _____No [GO TO QUESTION 20]
b. _____Yes
c. _____Don't know [GO TO QUESTION 21]

18. Where did you go to get the <u>flu shot</u>?

a. _____Primary-care doctor's office
b. _____Ob/GYN doctor's office
c. _____Community/public health clinic

d. _____Drug store, grocery store or retail chain (i.e., CVS, RiteAid, Walgreen's clinic, Kroger, Wal-Mart)
e. _____Hospital
f. _____Emergency Room
g. _____Prison clinic
h. _____School health clinic
i. _____Worksite health clinic
j. _____Other. Please specify _____
k. _____Don't remember

19. Did <u>anyone or anything</u> influence your decision to get a flu shot during pregnancy? For instance, your doctor, your friends, a celebrity or an organization like the CDC which is the Centers for Disease Control and Prevention? (NOTE TO INTERVIEWER: In the box provided, write out the reasons stated by the participant. Immediately after the interview, post-code the recorded response to this question according to the options provided below. Check all that apply based on the answer given. Do NOT read out response options below, but do prompt participant by asking "Any other reason?" to get at least 3 responses.)

a. _____It is recommended by *the President of the United States*
b. _____It is recommended by *my doctor*
c. _____It is recommended by *my school or my employer*
d. _____It was required by *my employer or school*
e. _____It is recommended by *my friends*
f. _____It is recommended by *a family member*
g. _____It is recommended by *my faith leader/my pastor*
h. _____It is recommended by *my herbalist/alternative medical therapist*
i. _____It is recommended by *a famous sports player or movie star*
j. _____It is recommended by Oprah
k. _____It is recommended by *the Centers for Disease Control and Prevention*
l. _____It is recommended by *the American College of Obstetricians and Gynecologists*\
m. _____I saw a TV commercial/advertisement/public service announcement for the flu shot
n. _____I heard a radio commercial/advertisement/public service announcement for the flu shot
o. _____ I saw a commercial/advertisement/public service announcement on the internet for the flu shot
p. _____I saw a billboard, banner or poster for the flu shot
q. _____I was incentivized by a store's promotion of a discount on my purchase if I got a flu shot.
r. _____Other: _____

20. What was the <u>most important reason</u> to you for getting a flu shot during pregnancy? (NOTES TO INTERVIEWER: This is an open ended question. Please type the participant's response in the box below.) <u>GO TO QUESTION 23 AFTER PARTICIPANT ANSWERS</u>.)

_____
_____
_____
___

For women who did *not* get the flu shot:

21. **What are the main reasons you decided not to get the flu shot?** (NOTE TO INTERVIEWER: In the box provided, write out the reasons stated by the participant. Immediately after the interview, post-code the recorded response to this question according to the options provided below. Check all that apply based on the answer given. Do NOT read out response options below, but do prompt participant by asking "Any other reason?" to get at least 3 responses.)

    a. _____I was concerned that the vaccine would weaken my immune system
    b. _____I feel that it is better for me to get the natural flu than get a vaccine
    c. _____I didn't think I was at risk for the flu
    d. _____I didn't think the flu was that dangerous for me
    e. _____I don't think the vaccine works or works well
    f. _____I don't take vaccines
    g. _____I am afraid of needles
    h. _____I was worried the vaccine would cause me or my baby harm (NOTE TO INTERVIEWER: IF THIS ANSWER CHOICE IS MENTIONED, ASK FOR MORE DETAIL WITH THESE PROMPTS:
        i. ____I believe the vaccine causes autism
        ii. ____I believe there is poison in the vaccine
        iii. ____Other reason(s):
        _____
        _____
        _____
    i. _____I have a moral or ethical objection to getting the vaccine
    j. _____I have a religious objection to getting the vaccine
    k. _____The vaccine was not recommended to me by my doctor (or by _____)
    l. _____It was too annoying or inconvenient to go get one
    m. _____It was too expensive
    n. _____I wanted to get a shot, but the place I went was out of flu shots
    o. _____I wanted to get a shot, but my doctor's office ran out of flu shots
    p. _____Other, please specify:_____

22. **Would you have been more likely to get a flu shot during your most recent pregnancy if your OB/GYN or nurse midwife had offered you the shot during a pregnancy visit?**

    a. _____No
    b. _____Yes
    c. _____No; they did offer me the shot
    d. _____Don't know

23. Is there anything else that would have convinced you to get a <u>flu shot</u> during your most recent pregnancy?

a. _____No
b. _____Yes*
c. _____Maybe/not sure*

***Please explain:**

_____

<u>Section 3. Tdap shot experience</u>

INTERVIWER READS: "In the next set of questions, I will ask you about pertussis and the Tdap shot. The Tdap shot protects you against 3 diseases: pertussis, tetanus and diphtheria. Pertussis is more commonly known as whooping cough, and is a bacterial disease that causes severe coughing spells which can lead to difficulty breathing, vomiting and disturbed sleep."

24. Before participation in this study, <u>had you heard of pertussis, or whooping cough</u>?

a. _____No
b. _____Yes
c. _____Don't know

25. Before participation in this study, <u>had you heard of the Tdap shot</u> to protect against whooping cough?

a. _____No
b. _____Yes
c. _____Don't know

26. <u>During your most recent pregnancy</u>, did your OB/GYN or nurse midwife, recommend that you get the <u>Tdap shot</u>?

a. _____No
b. _____Yes
c. _____Don't know

27. During your most recent pregnancy <u>but before you delivered your baby</u>, did you get a Tdap shot?

a. _____No [GO TO QUESTION 30]
b. _____Yes
c. _____Don't know [GO TO QUESTION 31]

Where did you go to get your <u>Tdap shot</u> when you were pregnant?

a. _____Primary-care doctor's office
b. _____Ob/GYN doctor's office
c. _____Community/public health clinic
d. _____Drug store, grocery store or retail chain (i.e., CVS, RiteAid, Walgreen's clinic, Kroger, Wal-Mart)
e. _____Hospital
f. _____Emergency Room
g. _____Prison clinic
h. _____School health clinic
i. _____Worksite health clinic
j. _____Other. Please specify _____
k. _____Don't remember

28. **Did <u>anyone or anything</u> influence your decision to get a Tdap shot during pregnancy? For instance, your doctor, your friends, a celebrity or an organization like the CDC which is the Centers for Disease Control and Prevention?** (NOTE TO INTERVIEWER: In the box provided, write out the reasons stated by the participant. Immediately after the interview, post-code the recorded response to this question according to the options provided below. Check all that apply based on the answer given. Do NOT read out response options below, but do prompt participant by asking "Any other reason?" to get at least 3 responses.)

a. _____It is recommended by *the President of the United States*
b. _____It is recommended by *my doctor*
c. _____It is recommended by *my school or my employer*
d. _____It was required by *my employer or school*
e. _____It is recommended by *my friends*
f. _____It is recommended by *a family member*
g. _____It is recommended by *my faith leader/my pastor*
h. _____It is recommended by *my herbalist/alternative medical therapist*
i. _____It is recommended by *a famous sports player or movie star*
j. _____It is recommended by Oprah
k. _____It is recommended by *the Centers for Disease Control and Prevention*
l. _____It is recommended by *the American College of Obstetricians and Gynecologists*\
m. _____I saw a TV commercial/advertisement/public service announcement for the Tdap shot
n. _____I heard a radio commercial/advertisement/public service announcement for the Tdap shot
o. _____ I saw a commercial/advertisement/public service announcement on the internet for the Tdap shot
p. _____I saw a billboard, banner or poster for the Tdap shot
q. _____I was incentivized by a store's promotion of a discount on my purchase if I got a Tdap shot.
r. _____Other: _____

29. What was the <u>most important reason</u> to you for getting a Tdap shot during pregnancy? (NOTES TO INTERVIEWER: This is an open ended question. Please type the participant's response in the box below. <u>GO TO QUESTION 33 AFTER PARTICIPANT ANSWERS</u>.)

_____

_____

_____

<u>For women who did *not* get a Tdap shot:</u>

30. What are the main reasons you decided <u>not</u> to get a Tdap shot during your pregnancy? (NOTE TO INTERVIEWER: In the box provided, write out the reasons stated by the participant. Immediately after the interview, post-code the recorded response to this question according to the options provided below. Check all that apply based on the answer given. Do NOT read out response options below, but do prompt participant by asking "Any other reason?" to get at least 3 responses.)

a. _____I was concerned that the vaccine would weaken my immune system
b. _____I feel that it is better for me to get tetanus, diphtheria, and/or pertussis (whooping cough) naturally than get a vaccine for them
c. _____I didn't know about the Tdap vaccine
d. _____I wasn't sure what the Tdap vaccine was for
e. _____I didn't think I was at risk for tetanus, diphtheria or pertussis (whooping cough)
f. _____I didn't think tetanus, diphtheria or pertussis (whooping cough) was that dangerous for me
g. _____I don't think the vaccine works
h. _____I don't take vaccines
i. _____I am afraid of needles
q. _____I was worried the vaccine would cause me or my baby harm (NOTE TO INTERVIEWER: IF THIS ANSWER CHOICE IS SELECTED, ASK FOR MORE DETAIL WITH THESE PROMPTS:
    i. ____I believe the vaccine causes autism
    ii. ____I believe there is poison in the vaccine
    iii. ____Other reason(s):
    _____
    _____
j. _____I have a moral or ethical objection to getting the vaccine
k. _____I have a religious objection to getting the vaccine
l. _____The vaccine was not recommended to me by my doctor (or by _____)
m. _____Too annoying or inconvenient to go get one
n. _____The Tdap shot was too expensive
o. _____I wanted to get a shot, but the place I went was out of Tdap shots
p. _____I wanted to get a shot, but my doctor's office ran out of Tdap shots
q. _____I got a Tdap shot after my last pregnancy, so I thought I didn't need another one.
r. _____I got a Tdap shot within the last 10 years, so I thought I didn't need another one.
s. _____Other, please (specify)_____

31. Would you have been more likely to get a Tdap shot during your last pregnancy if your OB/GYN or nurse midwife offered you the shot <u>during a pregnancy visit</u>?

a. _____No
b. _____Yes
c. _____No; they did offer me the shot
d. _____Don't know

32. Is there anything else that would have convinced you to get a <u>Tdap shot</u> during your most recent pregnancy?

a. _____No
b. _____Yes*
c. _____Maybe/not sure*

*Please explain:
_____

33. Did you get a Tdap shot for yourself when you were still in the hospital <u>after you delivered your baby</u>?

a. _____No
b. _____Yes
c. _____Don't know

Section 4: Protection during and after pregnancy

INTERVIEWER READS: "In the next set of questions, I will ask general questions about protection against infectious diseases during and after pregnancy."

If you got pregnant again, how serious do you think it would be if you got the following illnesses while pregnant? (NOTE TO INTERVIEWER: READ ALL ANSWER CHOICES AFTER STATING EACH ILLNESS.)

	Very serious	Serious	Neutral	Somewhat serious	Not serious at all	Don't know
34) Influenza (the flu)	□	□	□	□	□	□
35) Pertussis (whooping cough)	□	□	□	□	□	□

On a scale of 0 (Definitely not) to 10 (Definitely so), please rank your likelihood of getting the following shots during your next pregnancy. (Mark best answer for each vaccine).

36) Flu shot:

0 1 2 3 4 5 6 7 8 9 10

Definitely not Definitely So

❑ Refused to respond

37) Tdap shot (for pertussis, or whooping cough, tetanus, and diphtheria):

0 1 2 3 4 5 6 7 8 9 10

Definitely not Definitely So

❑ Refused to respond

16) On a scale of 0 (not hesitant) to 10 (very hesitant), how hesitant are you about getting shots your doctor recommends that you get during pregnancy? (NOTE TO INTERVIEWER: If someone asks what "hesitant" means or "what we mean by 'hesitant'," then say: "How *worried or reluctant* are you about getting shots your doctor recommends that you get during pregnancy?")

0 1 2 3 4 5 6 7 8 9 10

Not hesitant Very hesitant

❑ Refused to respond

Next, I'm going to read some statements to you, and for each one, please tell me how much you agree or disagree with each statement. (NOTE TO INTERVIEWER: READ ALL ANSWER CHOICES AFTER SAYING EACH STATEMENT.)

	Strongly agree	Agree	Neutral/ No Opinion	Disagree	Strongly Disagree	Don't Know
39) The flu is a concern for pregnant women.	□	□	□	□	□	□
40) Getting a flu vaccine while pregnant seems risky.	□	□	□	□	□	□
41) I wish my OB/GYN practice would provide me with more information about flu shots during pregnancy.	□	□	□	□	□	□
42) I wish my OB/GYN practice would provide me with more information about Tdap shots during pregnancy.	□	□	□	□	□	□

20) During your most recent pregnancy, do you recall asking close family members to get a vaccine(s) (e.g. a flu shot or a Tdap shot) to help protect your newborn from infectious diseases?

a) _____No
b) _____Yes
c) _____Don't know

How serious do you think it would be if your newborn baby gets either of the following illnesses within their first 6 months? (NOTE TO INTERVIEWER: READ ALL ANSWER CHOICES AFTER STATING EACH ILLNESS.)

	Very serious	Serious	Neutral	Somewhat serious	Not serious at all	Don't know
44) Influenza (the flu)	□	□	□	□	□	□
45) Pertussis (whooping cough)	□	□	□	□	□	□

27) On a scale of 0 (definitely will not) to 10 (definitely will), please rank the likelihood you will get your baby vaccinated with all recommended childhood vaccines. (Mark best answer.)

0 1 2 3 4 5 6 7 8 9 10

Definitely will not Definitely will

❑ Refused to respond

28) Like the Tdap shot for adults, the DTaP shot is given to babies for pertussis (which is whooping cough), tetanus and diphtheria. Has your bab(ies) gotten their first Dtap shot yet?

a) _____No
b) _____Yes
c) _____Maybe; my bab(ies) have received all shots recommended up until this point, but I am not certain about DTaP specifically
d) _____Don't know

Section 5: Intervention package component questions

INTERVIEWER READS: "In this final set of questions, I will ask you some questions about some things you may have seen at your OB/GYN's office during your last pregnancy."

29) During your last pregnancy, did you ever get a brochure from your OB/GYN practice about the flu and Tdap vaccines during pregnancy?

a) _____No
b) _____Yes
c) _____Don't know

30) During your last pregnancy, do you recall seeing any posters hung around your OB/GYN's office that talked about getting a flu shot and a Tdap shot during pregnancy?

a) _____No
b) _____Yes
c) _____Don't know

31) During your last pregnancy, do you recall seeing doctors and staff in your OB/GYN's office wearing lapel buttons that promoted vaccination during pregnancy?
(INTERVIEWER NOTE: If you get asked what a "lapel button" is, say, "A round pin worn on their white coat, uniform or scrubs?")

a) _____No
b) _____Yes
c) _____Don't know

32) During your last pregnancy, did you ever take an iPad-based educational app in your OB/GYN's office?

a) _____No (THANK YOU FOR TAKING OUR SURVEY! CONFIRM MAILING ADDRESS FOR RECEIPT OF SECOND GIFT CARD)
b) _____Yes (GO TO NEXT QUESTION)
c) _____Don't know (THANK YOU FOR TAKING OUR SURVEY! CONFIRM MAILING ADDRESS FOR RECEIPT OF SECOND GIFT CARD)

END OF SURVEY IF THEY DID NOT SEE IPAD TUTORIAL

33) Do you remember what this iPad-based educational app was about?

a) _____No

b) _____Yes, please describe: _____

c) _____Don't know

34) What did you <u>like</u> about this iPad-based app? Please describe:

_____
_____
_____
_____
_____

35) What did you <u>dislike</u> about this iPad-based app? Please describe:

_____
_____
_____
_____
_____

And then I have a few final questions about the iPad-based educational app. Please tell me whether you agree or disagree with the following statements.

	Agree	Disagree	Don't know/ Don't remember
36) I learned something from the iPad app about vaccines.			
37) The iPad app was too complex. I had a hard time understanding a lot of the content.			
38) I liked the moms' testimonies.			
39) I thought the moms' testimonies were too scary.			
40) I found the doctors' video explanations helpful.			
41) I found the doctors' video explanations boring.			
42) The iPad app influenced my decision to get a flu shot during pregnancy.			
43) The iPad app influenced my decision to get a Tdap shot during pregnancy.			

***INTERVIEWER READS:* "Thank you for taking this survey and participating in our study! We appreciate your time and participation. Please verify your current mailing address so we can mail you your second gift card":**

Mailing Address:_____
_____
_____

"Which type of gift card would you like?"

____$25 Walmart Card

_____$25 Target Card

"May we contact you for a future study about your infant's health care?"

a) _____No
b) _____Yes

POST SURVEY SECTION:

Interviewer Remarks:

_____
_____
_____
_____
_____

Appendix D – MOMVAX intervention package components

Promotional poster

Educational brochure

Why get vaccinated during pregnancy?

Getting vaccinated during pregnancy is the first way to start protecting your unborn baby from influenza (flu) and pertussis (whooping cough). While they cannot get sick with flu or whooping cough while in your womb, they can be negatively affected if you get sick.

It is important to know that by getting the flu and whooping cough shots during pregnancy, you protect yourself and your baby both before and after birth.

Your baby will get antibodies from you during pregnancy and afterwards through breastfeeding. Though these antibodies eventually go away, they help protect babies until they are old enough to be vaccinated themselves.

Flu is a concern every year, and pregnant women are at higher risk for complications from the flu than when they are not pregnant. If you catch the flu when you are pregnant, you are more likely to have trouble breathing and the illness can be worse than usual.

Whooping cough, or pertussis, is a growing concern for pregnant women and newborns. Outbreaks of whooping cough are becoming more common in the United States in part because people are not getting vaccinated. Babies get the sickest from whooping cough because their airways are so small that mucous can easily block their ability to breathe.

What is in the shots?

Flu shot: The seasonal flu shot that pregnant women receive contains killed parts of the influenza virus that have been purified. These particles are what your body's immune system uses to make the antibodies needed to protect you and your baby from getting the flu.

Whooping cough shot (Tdap): The shot which protects you against whooping cough is called the Tdap shot. This shot also provides protection against tetanus and diphtheria, two other harmful diseases caused by bacteria. The Tdap shot contains purified components from all three bacteria, and these components are what your immune system needs to make protective antibodies.

Did you know? By getting vaccinated and preventing yourself from getting the flu, you protect your fetus by lowering her risk of being born prematurely or being too small at birth.

Are the shots safe?

Yes. It is safe to get the flu shot and Tdap shot during pregnancy. Both the Centers for Disease Control and Prevention (CDC) and the American Congress of Obstetricians and Gynecologists (ACOG) recommend that pregnant women receive these shots during pregnancy. The most common side effects are mild, and include pain, redness or swelling at the site of the shot, mild fever, and tiredness. Hoarseness; sore, red or itchy eyes; and cough can sometimes happen after the flu shot.

Worse side effects like intense pain or serious allergic reactions are very rare.

When should I get the shots?

Flu shot: Any time during pregnancy, especially if you are pregnant during the flu season which runs from September – May.

Whooping cough shot (Tdap): It is best to get during your second or third trimester of pregnancy. This shot is available year round at most doctors' offices.

It is important to know that it is safe to get both shots during the same prenatal visit or at the same doctor's visit.

How can I protect my baby?

Getting these shots during pregnancy is the single best way to start protecting your baby as soon as possible, even before it is born. Because babies cannot get their first whooping cough shot until they are two months old, it is important to encourage family members and close friends to get the flu and Tdap shots too. By making sure everyone your newborn comes in contact with has their shots, you create a safe and healthy "cocoon" for her first vulnerable months of life.

What if I have more questions?

Please ask your doctor or nurse today if you have any questions about these shots. They will be happy to answer them or give you more information. You may also visit immunizationforwomen.org to find out more about these recommended vaccines.

Protect yourself. Protect your baby.
Get vaccinated during pregnancy!

Provider to patient talking points – influenza

Provider-to-Patient Talking Points: INFLUENZA VACCINATION DURING PREGNANCY

All women should receive the influenza vaccine during pregnancy. The influenza vaccination is an essential element of prenatal care as pregnant women are at an increased risk of serious illness and mortality due to influenza.

Primary influenza vaccine provider-to-patient talking points:

1. Getting your flu shot while pregnant is the **best way to protect your newborn**. The protective antibodies your immune system creates to the shot pass to your fetus through your placenta and umbilical cord. These antibodies are what help protect your vulnerable baby before they can get a flu shot at 6 months old.
2. Research has shown that **getting the flu shot during pregnancy can reduce your baby's risk of being premature or being born too small**, especially if you are pregnant during flu season.
3. **I strongly recommend that all my pregnant patients get the flu shot.** It is safe to receive during pregnancy, has been given to pregnant women for decades, and is the best way to protect both of you from the flu.

More safety-related talking points:

- The risks of getting sick from the flu are far greater for a pregnant woman and her baby than the possibility of having a complication or bad reaction from the shot itself.
- Only the inactivated influenza vaccine (i.e. the flu shot) is recommended during pregnancy. The nasal spray flu vaccine, which contains weakened, live influenza virus, is not recommended for pregnant women.
- It is safe for pregnant women to receive a vaccine with thimerosal. All single dose vials of influenza vaccine are thimerosal free, so if your practice only stocks single-dose vials, thimerosal is not a concern. Thimerosal, a mercury-containing preservative used in multidose vials, has not been shown to cause any adverse effects except for occasional local skin reactions.
- There is no scientific evidence that thimerosal-containing vaccines cause adverse effects in children born to women who received vaccines with thimerosal.

Remember: the most effective way to increase your vaccine acceptance rate is for you to directly recommend and provide the vaccine. Talk to your patients about the flu shot today.

References:

ACOG influenza vaccine script for providers:
http://www.immunizationforwomen.org/site/assets/docs/Laminated%20Card%20Imm%202012.pdf

Omer SB, Goodman D, Steinhoff MC, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Med 2011;8:e1000441.

Provider to patient talking points - Tdap

Provider-to-Patient Talking Points: TDAP VACCINATION DURING PREGNANCY

All women should receive the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine; this is particularly important for pregnant women because they are susceptible to acquiring pertussis (whooping cough), and newborns are at highest risk of having severe complications from pertussis.

Primary Tdap vaccine provider-to-patient talking points:

1. I strongly recommend that you receive a Tdap vaccine during pregnancy. The Tdap vaccine protects you and your baby from tetanus, diphtheria, and pertussis, which is whooping cough. **Newborns are the highest risk group for complications from whooping cough,** so getting a Tdap shot during pregnancy is the best way to protect both you and your baby.
2. Whooping cough cases, which have been increasing in the U.S., are worst for infants because their tiny airways get clogged from mucous and they cannot breathe. **Getting your Tdap shot during pregnancy gives your baby a head-start on protection.** The antibodies you create to the shot pass to your baby before birth and can protect him/her in their most vulnerable first months.
3. The Tdap vaccine is safe to receive at any point during pregnancy, but **I recommend getting it in your second or third trimester** so that your baby receives the most antibodies against whooping cough right before birth.

More safety-related talking points:

- The recommendation for pregnant women to receive the Tdap shot during pregnancy as opposed to immediately post-partum started in 2011. This change in the CDC recommendation was made after review of safety data from several sources including adverse event registries, pregnancy registries from vaccine manufacturers, and other research studies.
- Unvaccinated adolescents and adults, including adults aged 65 years and older, who will have contact with infants younger than 12 months of age should also receive a single dose of Tdap.

Remember: the most effective way to increase your vaccine acceptance rate is for you to directly recommend and provide the vaccine.
Talk to your patients about the Tdap shot today.

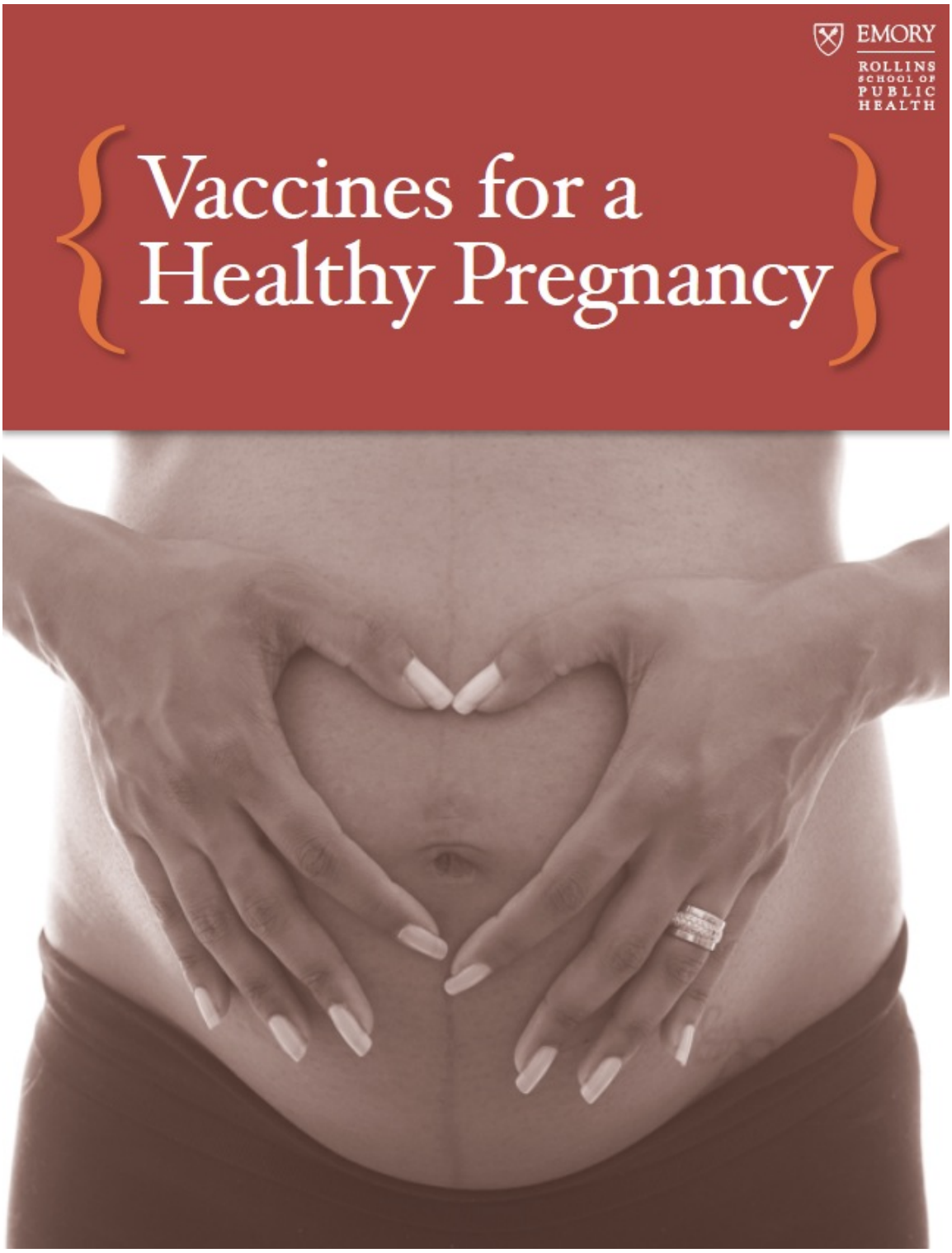
Reference:

ACOG Tdap vaccination script for providers:
http://www.immunizationforwomen.org/site/assets/docs/Phys%20Script%20TDAP%281%29.pdf

Lapel button designs

Emory PERRC MOMVAX "P3" Package: Physician/Staff Lapel Button Designs

Interactive iPad-based app (PDF version)



{Vaccines for a Healthy Pregnancy}

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH

I Introduction to Tutorial

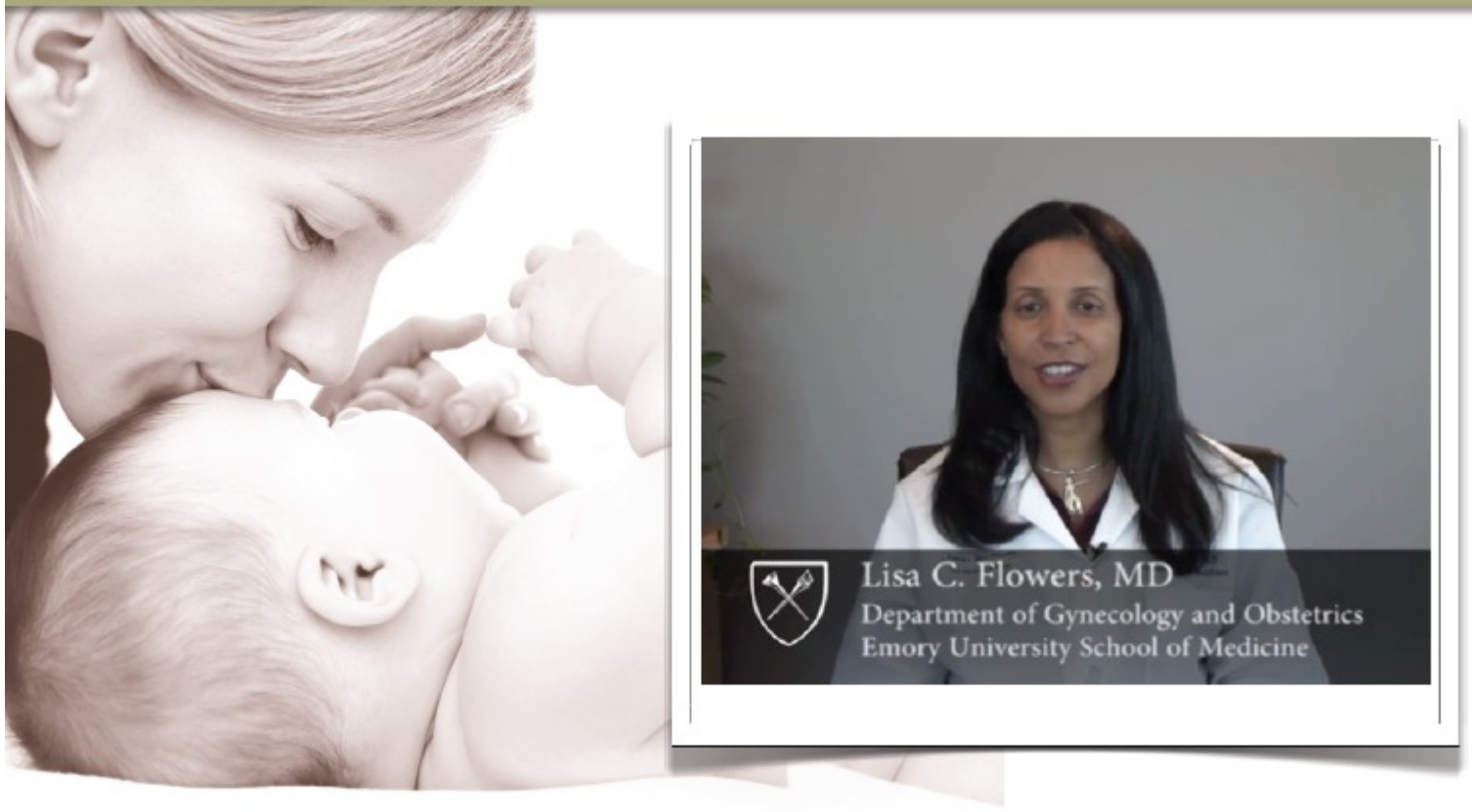
II About Flu and Whooping Cough

III Getting Vaccinated During Pregnancy: The Flu and Whooping Cough

IV Vaccine Safety During Pregnancy

V Vaccines for Your Baby

Introduction to Tutorial

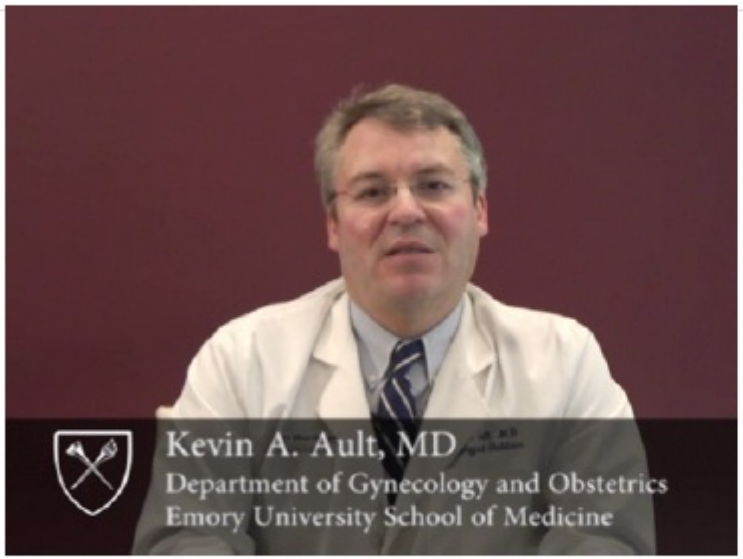


II About Flu and Whooping Cough

1 What are flu and whooping cough, and how do they affect pregnant women?

2 How can flu and whooping cough harm my baby?

1 What are flu and whooping cough, and how do they affect pregnant women?



Both Flu and whooping cough:

- Are highly contagious
- Affect your lungs, throat, nose and sinuses
- Flu can be more serious during pregnancy due to changes in your body and immune system

2 How can flu and whooping cough harm my baby?

Infants are at the **greatest risk** of severe complications from both flu and whooping cough, and here are **two personal stories** describing what can happen when a baby catches these diseases. These stories emphasize the importance of getting vaccinated against flu and whooping cough during pregnancy.

Influenza The Story of Baby Ian

Courtesy: Families Fighting Flu

Whooping Cough The Story of Baby Colin

Courtesy: Parents of Kids with Infectious Diseases (PKIDS)

III Getting Vaccinated During Pregnancy: The Flu and Whooping Cough Shots

1. Why do I need to get vaccinated for flu and whooping cough during pregnancy?
2. What shots should I get and when?
3. What if I have had a few prenatal visits already and my doctor has not offered me either shot?

1 Why do I need to get vaccinated for flu and whooping cough during pregnancy?

2 What shots should I get and when?

For the Flu:

To protect against flu, pregnant women should get the **inactivated flu shot**, not the nasal spray form of the vaccine. The sooner you get the shot, the better. CDC recommends that the flu shot can be given at any point during pregnancy. The flu season in the United States runs from September – May. Flu shots are often available by September, and in some cases even in August. Whether you are pregnant at any point during flu season, or are planning to have your baby during flu season, it is important to get your vaccine.

For Whooping Cough:

The **Tdap shot** is the vaccine which protects you from whooping cough. While it's safe to get Tdap any time during pregnancy, it's best to wait until your second or third trimester (20 weeks or later) to make sure your fetus gets the most antibodies it can right before birth.

Can I get both shots at the same visit?

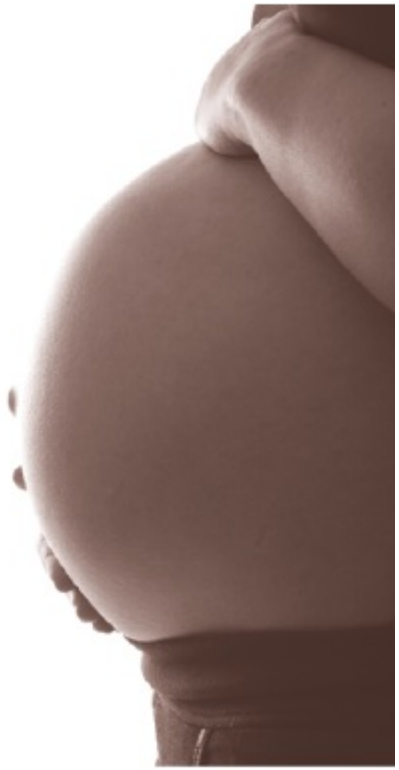
Yes! It is safe to both you and your fetus to get both shots at once.

3 What if I have had a few prenatal visits already and my doctor has not offered me either shot?

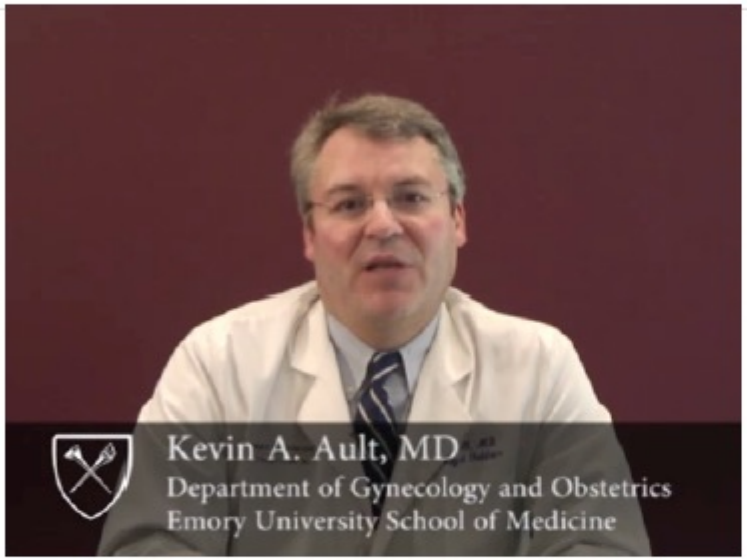
If your doctor has not explicitly offered or talked to you about the flu or Tdap shots, then you should ask about them. More and more OB/GYN practices are encouraging every patient---especially pregnant patients---to be up to date on their vaccines. Your doctor or nurse will be happy to answer your questions, address your concerns, give professional advice, and if possible, give you your shots!

IV Vaccine Safety During Pregnancy

1. Is it safe to receive the flu and whooping cough shots during pregnancy?
2. What is in each vaccine?
3. Are there any reasons I should not get either vaccine while pregnant?
4. How do I know the benefits of getting these shots outweigh the risks?
5. Are there any side effects to the vaccines I should know about?



1 Is it safe to receive the flu and whooping cough shots during pregnancy?



- Yes, both vaccines are safe and recommended during pregnancy
- There has been no observed increase in birth defects among babies born to moms who got the flu shot
- You cannot get the flu from the flu shot

2 What is in each vaccine?

Flu shot:

The flu shot that is recommended for pregnant moms is the inactivated flu shot that is given in your arm with a needle. This shot either contains **inactivated split flu virus parts** or **inactivated viral subunits**. It is these purified parts of the virus that your immune system recognizes and uses to make the antibodies needed to protect you from actually getting the flu.

The "nasal spray" version of the flu vaccine is not recommended during pregnancy because unlike the flu shot, this vaccine contains weakened live flu virus which has not been recommended for safe use in pregnant women.

Tdap:

The Tdap shot contains: **toxoids** from the tetanus and diphtheria bacteria, and **inactivated toxin** from the pertussis, or whooping cough, bacteria

The small doses of these toxoids are what your body needs to develop its immune defenses to the diseases themselves.

Do I need protection against tetanus and Diphtheria too?

You do. Tetanus, often referred to as "lock-jaw" is a bacterial disease which causes severe muscle spasms and stiffness. It can lead to severe cramping and tightening of muscles in the head and neck that result in an inability to open your mouth, swallow, or even breath.

Tetanus kills about 1 out of 5 people who are infected. Tetanus often enters the body through open wounds, so historically, it has been **a major concern for both mom and baby** during labor and delivery.

While not as severe as tetanus, **diphtheria is a bacterial disease** which can cause a thick membrane to cover the back of the throat. This can cause breathing problems, paralysis, heart failure, and even death.

The shots given to prevent both tetanus and diphtheria have been used safely for decades, and the Tdap vaccine which provides protection from tetanus, diphtheria and pertussis is **safe to get during pregnancy**.

3 Are there any reasons I should not get either vaccine while pregnant?

Sometimes there can be reasons for you to not get certain vaccines.

For Flu:

Before getting a flu shot, be sure to tell your doctor if:

- You have an allergy to eggs
- You have any other severe, life-threatening allergies
- You have ever had a severe reaction to the flu shot before
- You have ever had Guillian-Barre Syndrome (GBS)

Also, if you are moderately or severely ill when you try to get a flu shot, you should wait until you're healthy before getting the flu shot. You may want to reschedule getting your shot.

For Tdap:

Before getting a Tdap shot, be sure to tell your doctor if:

- You have had a life-threatening allergic reaction after getting a dose of any shot for tetanus, diphtheria or pertussis.
- You have a severe allergy to any component of a vaccine.
- You have had a coma or seizures within 7 days after a dose of DTP or DTaP which are two other vaccines similar to Tdap
- You have epilepsy or other nervous system problem
- You had severe swelling or severe pain after a previous dose of a vaccine for tetanus, diphtheria or pertussis.
- You have had Guillain Barre Syndrome.

If you are moderately to severely ill on the day you are supposed to receive a Tdap shot, you should usually wait until you get better before getting a Tdap shot.

4 How do I know the benefits of getting these shots outweigh the risks?

For my baby?

Studies have shown that getting vaccinated for flu during pregnancy can reduce the likelihood that your baby will be born prematurely or of low birth weight. By protecting yourself from getting sick, you increase the chances your baby stays healthy and is born on time.

Protective antibodies that you produce to the shots have been shown to pass from your blood to the baby through your placenta or umbilical cord. Antibodies also pass through breastmilk which is extremely important for protecting your newborn before they are able to get shots themselves. Babies cannot receive their first whooping cough vaccine until they are 2 months old, and they cannot receive a flu vaccine until they are at least 6 months old. **Protecting yourself through vaccination is the best way to protect your baby during their most vulnerable few months.**

Seeing a baby suffer from whooping cough is terrible. The babies struggle to breathe through bouts of terrible coughing. Doing whatever you can to prevent your newborn from getting sick with whooping cough is important.

For me?

Flu can be a very serious disease if you get it during pregnancy. When pregnant, you are more likely to go to the hospital with severe complications from the flu than if you catch the flu when you are not pregnant. The flu can make you very sick for many days, resulting in fever, difficulty breathing, and appetite loss. All of these things can take a toll on your strength, and you need all the strength and nutrients you can get to make sure your baby grows properly.

5 Are there any side effects to the vaccines I should know about?

Flu:

The most common and mild side effects from the flu shot are very minor. These include:

- soreness, redness & swelling at the shot site
- cough
- fever
- headache
- red/itchy eyes
- fatigue
- itching

If any of the side effects listed above occur, they will happen soon after you get the shot and last 1 – 2 days.

Severe problems are very rare, but include life-threatening allergic reactions that occur within minutes to hours of getting the flu shot.

Tdap:

For a Tdap shot, **mild side effects** that are noticeable, but don't interfere with activities include:

- Pain, redness, or swelling at the injection site
- Mild fever of at least 100.4° F (about 1 out of 100 adults)
- Headache (about 3 in 10 adults)
- Tiredness (about 1 in 4 adults)
- Nausea, vomiting, diarrhea, stomach ache (about 1 in 10 adults)
- Chills, body aches, sore joints, rash, or swollen glands. (uncommon)

Moderate side effects that may interfere with activities include:

- Pain at the site of the shot (about 1 in 100 adults)
- Redness or swelling (about 1 in 25 adults)
- Fever over 102° F (about 1 in 250 adults)
- Headache (about 1 in 300)
- Nausea, vomiting, diarrhea, stomach ache (about 1 in 100 adults)
- Excessive swelling of the arm where shot was given (up to about 3 in 100)

Severe problems that may require medical attention include:

- Swelling, severe pain, bleeding and redness in arm where shot was given (rare).

What if I have a severe reaction?

Know that severe reactions are extremely rare. If they weren't, doctors would not recommend women get these vaccines at all.

Severe allergic reactions to either vaccine would occur within a few minutes of either shot. Signs to look out for are difficulty breathing, weakness, hoarseness or wheezing, a fast heart beat, hives, dizziness, paleness, or swelling of the throat.

If you experience any of the above, call your doctor immediately or come in right away. Try to record the date and time of the unusual condition.

V Vaccines for Your Baby

1 Introduction to childhood vaccines

2 Where can I find more information on childhood vaccines?

Thank you

Thank you for taking the time to learn more about the flu, whooping cough, and the importance of getting vaccinated during pregnancy. For further information, please send inquiries to momvax@emory.edu.

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