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

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Improving influenza and Tdap vaccination during pregnancy: A cluster-randomized trial of a multi-component antenatal vaccine promotion package in late influenza season

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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 factor most strongly associated with 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 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.

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1. 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 [1–6]. Pregnant women are strongly encouraged to receive an influenza vaccine anytime during pregnancy [7]. 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 [8]. 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 [9,10]. 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 [11,12]. Since 2012, the Centers for Disease Control and Prevention (CDC) has recommended antenatal Tdap vaccination during every pregnancy [13].

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 [14,15]. 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% [16–18].

Substantial research has explored facilitators and barriers to vaccinating pregnant women, especially against influenza [19–22]. 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 [23–25]. 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 [26–29]. Few studies have examined the impact of multi-component interventions on improving antenatal vaccination rates within the obstetric setting [30]. 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.

2. Methods

2.1. 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.

2.2. 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 [31]. 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.

2.3. 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.

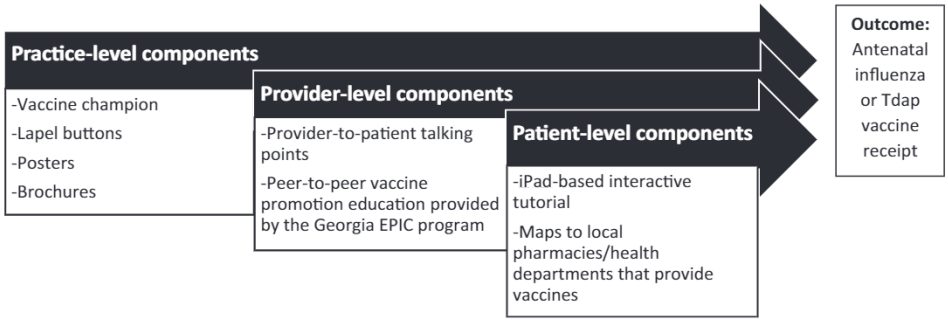
2.4. Intervention package

Practices randomized to the intervention group received all components of the package [Fig. 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 [32].

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 [29,30,33]. 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



Practice-level component descriptions	
Vaccine champion	A staff member identified by the practice to be the primary resource for vaccine-related information for allpractice 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.

Fig. 1. MOMVAX study P3 package components and descriptions.

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 [34].

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.

2.5. 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) [35]. A priori rules for determining final antenatal vaccination status are provided in the supplementary materials.

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.

2.6. 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

Table 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 2011–2012 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.

vaccine coverage [27,30,33,36]. 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 [37].

3. 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 1 and participant characteristics stratified by study group are provided in Table 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 [Fig. 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; $p < 0.0001$). 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 3] 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.

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 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).

3.1. 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

Table 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 (60)
Enrolled from a practice stocking Tdap vaccine	64 (40)	98 (60)	162 (55)
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 pertussis

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.

4. 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 [28]. 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

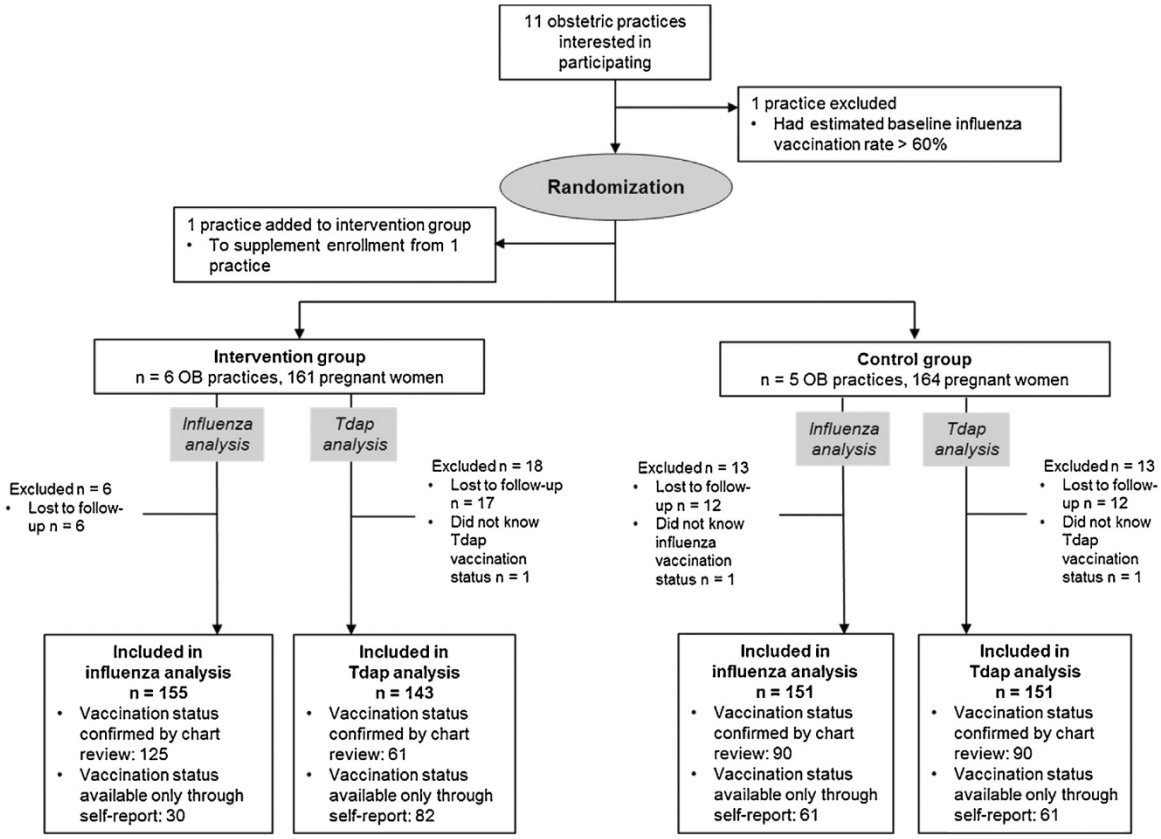


Fig. 2. Obstetric practice and participant enrollment for MOMVAX study.

influenza vaccine and 20% indicated having already received a Tdap vaccination [38]. 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 [13]. 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 to be a factor strongly associated with 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.

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. Additionally, we included practices that both stocked and did not stock vaccine despite the fact stocking vaccine in-house is a fundamental barrier to vaccine uptake [39–41]. Because the recommendation to administer Tdap at every pregnancy was so new at the time of study initiation and excluding practices not offering vaccines would have limited the diversity of patients included in our study sample, we chose to include practices not offering one or both vaccines and control for this important characteristic through the pair-matching process prior to randomization. While ensuring that every obstetric care provider stocks all recommended vaccines is the ultimate goal, research has shown that concerns over reimbursement, discomfort with discussions of vaccination with pregnant patients, vaccine safety and even perceptions of low disease incidence can inhibit providers' willingness to stock vaccine [42]. Despite these barriers, it remains important to test the effectiveness of interventions to increase antenatal vaccine

Table 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: control: 16/149 (10.7%) 11/151 (7.3%)				Intervention: control: 19/140 (13.6%) 13/151 (8.6%)				Intervention: control: 61/140 (43.6%) 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

Abbreviations: risk difference (RD); risk ratio (RR); confidence interval (CI); intracluster correlation coefficient (ICC); tetanus; diphtheria and acellular pertussis (Tdap).

[†] Generated using SAS PROC GENMOD and not accounting for clustered study design.

[‡] Random effect for practice is significant at $p < 0.05$ level.

Table 4
Associations between individual intervention package components and 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 ($n = 89$) No ($n = 48$)	16.9% 0.0%	**<0.01**	–[+]	–[+]	N/A				N/A			
Recollection of OB/GYN or midwife recommending antenatal Tdap vaccination	Yes ($n = 63$) No ($n = 73$)	N/A				25.4% 2.7%	**<0.01**	6.49[†] (1.55, 27.31)	**0.01**	65.1% 26.0%	**<0.01**	2.45 (1.54, 3.91)	**<0.01**
Recollection of poster about influenza and Tdap vaccination	Yes ($n = 93$) No ($n = 43$)	14.0% 4.7%	0.14	3.28 (0.77, 17.07)	0.11	10.8% 19.1%	0.27	0.89[†] (0.42, 1.88)	0.75	47.3% 38.1%	0.35	1.26 (0.82, 1.92)	0.29
Recollection of educational brochure about influenza and Tdap vaccination	Yes ($n = 60$) No ($n = 77$)	16.7% 6.5%	0.10	2.57 (0.92, 7.18)	0.07	18.6% 9.1%	0.13	1.87[†] (0.86, 4.02)	0.11	47.5% 41.6%	0.60	1.12[†] (0.79, 1.60)	0.52
Recollection of lapel buttons promoting vaccination worn by doctors and nurses	Yes ($n = 23$) No ($n = 114$)	21.7% 8.8%	0.13	2.49 (0.93, 6.67)	0.07	13.0% 13.3%	1.00	0.86[†] (0.31, 2.42)	0.78	65.2% 39.8%	**0.04**	1.60 (1.08, 2.37)	**0.02**
Recollection of iPad-based educational app	Yes ($n = 10$) No ($n = 127$)	30.0% 9.5%	0.08	3.17 (1.06, 9.53)	**0.04**	30.0% 11.9%	0.13	–[++]	–[++]	60.0% 42.9%	0.34	1.26[†] (0.76, 2.09)	0.37

Bolded p-values indicate significance at $p < 0.05$ level. Abbreviations: RR, risk ratio; Tdap, tetanus, diphtheria, acellular pertussis; N/A, not applicable.

[+] 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.

coverage, especially if the interventions are educational in nature and can serve to close knowledge gaps related to the importance of antenatal vaccination for both the providers and patients.

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 [43].

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 [44], this trial provides necessary research towards development of evidence-based interventions to improve vaccine coverage. By developing non-burdensome interventions 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%.

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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.05.048

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