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Effectiveness of a multimodal intervention to increase vaccination in obstetrics/gynecology settings

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ABSTRACT

Objective: To test the effectiveness of a multimodal intervention in obstetrics/gynecology (ob-gyn) clinics to increase uptake of influenza and tetanus-diphtheria-acellular pertussis (Tdap) vaccines in pregnant women and these vaccines plus human papillomavirus (HPV) vaccine in non-pregnant women.
Methods: A cluster randomized controlled trial among 9 private ob-gyn practices in Colorado from 9/2011 to 5/2014. The intervention consisted of: designation of immunization champions, staff/provider trainings, assistance with vaccine purchasing/management, identification of eligible patients, standing order implementation, chart review/feedback, and patient education materials. Control practices continued usual care. Primary outcomes were receipt of influenza and Tdap vaccines among pregnant women and these vaccines plus HPV vaccine among non-pregnant women, comparing a Baseline period (Year 0/Year 1) to Year 2, intervention versus control. With an estimated sample size of 32,590 per arm, there would be >80% power to detect a 10% difference between groups.
Results: In the Baseline period, 27% of pregnant women in both intervention and control practices received influenza vaccine. In Year 2, 29% of pregnant women in intervention practices received influenza vaccine versus 41% in control practices. In the Baseline period, 18% of pregnant women in intervention practices received Tdap vaccine versus 22% in control practices. Both intervention and control practices increased to 51% in Year 2, representing an increase of 33% for intervention practices and 29% for control practices, consistent with a change in Tdap recommendations. Relatively few HPV, influenza or Tdap vaccines (≤6% of eligible patients) were given to non-pregnant patients in either intervention or control practices at any time during the study.
Conclusion: In this cluster randomized trial designed to increase vaccination uptake, both intervention and control practices showed improved vaccination of pregnant but not non-pregnant patients. Future work should focus on tailoring evidence-based immunization practices or developing new approaches to specifically fit busy ob-gyn offices.

1. Introduction

Obstetrician/gynecologists (ob-gyns) have the potential to play a critical role as vaccinators of both pregnant and non-pregnant women. Pregnant women have an increased risk of severe complications from influenza [1–4], and their newborns are at increased risk of severe illness and death from both influenza [5–7] and pertussis [8,9]. Influenza and pertussis vaccination are now routinely recommended for all pregnant women [10,11]. There is growing evidence that these vaccines are both effective [12–19] and safe [20–26] when given in pregnancy. However, despite the promise of these vaccines for pregnant women, uptake remains suboptimal [27–30]. While some of the barriers to increased uptake of these vaccines appear to be related to patient concerns about their safety in pregnancy [31], there appear to be provider barriers as well. In a recent national survey, a substantial proportion of pregnant

Abbreviations: ACIP, Advisory Committee on Immunization Practices; VFC, Vaccines for Children; ACA, Affordable Care Act; ACOG, American College of Obstetricians and Gynecologists; Ob-gyn, obstetrician-gynecologist; CDC, Centers for Disease Control and Prevention; Tdap, tetanus diphtheria and acellular pertussis vaccine; HPV, human papillomavirus.

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women reported receiving neither a recommendation nor an offer for influenza vaccine from a provider, and these women were far less likely to receive influenza vaccine than those who received both a recommendation and an offer [27].

Vaccination in the ob-gyn setting is also important for non-pregnant women as many utilize an ob-gyn as their main source of medical care. The American College of Obstetricians and Gynecologists (ACOG) has guidelines for ob-gyns to deliver primary preventive care, including vaccinations [32]. ACOG also recommends that ob-gyns offer all ACIP recommended vaccines to their patients [33]. However, the number of vaccines recommended for adults has increased significantly in the last decade [34], and for many ob-gyns, vaccination is still a relatively new paradigm. For example, while the majority of ob-gyns were quick to begin delivery of human papillomavirus (HPV) vaccine upon its introduction in 2006 [35,36], prior to the pandemic influenza vaccine campaign in 2009, few ob-gyns delivered influenza vaccine [37,38]. Adult uptake of vaccines is suboptimal in general [39], and it is therefore critical to find ways to support all adult providers to vaccinate at every opportunity.

In light of these low vaccination rates among pregnant women and adults in general, and that many women using their ob-gyn as their sole source of medical care [40–42], we undertook an intervention to increase uptake of vaccines within the ob-gyn setting. Our objective was to test the effectiveness of a multimodal intervention focused on implementation of evidence-based strategies to increase vaccination uptake in ob-gyn offices on increasing rates of influenza and Tdap vaccines in pregnant women, and influenza, Tdap, and HPV vaccines in non-pregnant women.

2. Methods

2.1. Overview

Our objective was to test the effectiveness of a multimodal intervention focused on implementation of evidence-based strategies to increase vaccination uptake in ob-gyn offices on increasing rates of influenza and Tdap vaccines in pregnant women, and influenza, Tdap, and HPV vaccines in non-pregnant women.

This was a 2-armed, pragmatic cluster-randomized controlled trial among ob-gyn offices in Colorado from September 2011 to May 2014. Because this was a practice level intervention, randomization was clustered at the clinic level, and clinics were assigned in a 1:1 ratio. Vaccines of interest included influenza, Tdap, and HPV vaccines. Because women may have received the vaccines of interest outside of the ob-gyn office, and this information would not be captured within practice administrative data, we measured the primary vaccination outcomes of interest in two separate analyses: (1) from practice administrative data; and (2) from a series of office-based patient surveys. This study was approved by the Colorado Multiple Institutional Review Board and is registered with ClinicalTrials.gov (NCT01565135). The full trial protocol is available from the authors upon request.

2.2. Study sites

Thirteen ob-gyn practices from Colorado were initially recruited to participate (9 urban, 4 rural) (Fig. 1). Eligibility criteria for clinic participation included being in Colorado, being an obstetrics/gynecology practice, being willing to be randomized to intervention or control, and being willing to share practice data with the study team. After randomization, prior to initiation of the intervention, one urban intervention and one rural intervention practice withdrew from the study due to concerns of time commitment to the study. To avoid highly unbalanced arms, one rural practice was reallocated to the intervention arm as it was most similar in size and patient demographics to the rural practice that had withdrawn from the study. After the intervention was initiated, 1 urban control practice dissolved, and 1 urban control practice was deemed ineligible to participate by its parent corporation, so that the final study population included nine practices (6 urban, 3 rural).

2.3. Randomization

Practices were randomized using covariate-constrained randomization as described in detail in our prior work [43]. This method of randomization seeks to balance study arms on covariates deemed important to the primary outcome [44–47]. For this study, covariates included in the model included practice size (measured by provider full time equivalents [FTE]), deliveries per month, percent public insurance, and a novel measure we called the Immunization Delivery Score [43]. The Immunization Delivery Score consisted of a score assigned after a baseline assessment of vaccination activities, including stocking vaccine, tracking vaccination history, identifying eligible patients, patient education, use of standing orders, avoiding missed opportunities for vaccination, and use of reminder/recall. These activities were assessed for all three vaccines of interest (influenza, Tdap, and HPV).

The randomization allocation was determined *a priori* so that there would be 4 urban practices and 2 rural practices in each study arm in the final randomization. The study analyst created a list of all possible randomizations using SAS Proc IML. There were 420 possible randomizations with equal numbers of urban and rural practices in each group. Since the overall goal of covariate-constrained randomization is to provide balance between study arms, the top 10% of randomizations (i.e. those that provide the most balance on the chosen covariates) was determined. From this optimal set of possible randomizations, a single randomization was then randomly chosen by the computer. One urban practice of the original thirteen practices recruited was unable to provide data on the covariates of interest prior to randomization, so this practice was randomized using simple randomization (and was allocated to the control arm). Neither the practices nor the research team were blinded to the arm allocation.

2.4. Intervention overview

Through a series of meetings, participating intervention clinics were presented with best practices in immunization delivery and each selected intervention procedures they felt best suited to their specific clinic needs. Minimum interventions at each clinic included stocking each of the three vaccines of interest, offering the three vaccines, offering training on vaccination program 'best practices' to practice staff and designating an immunization champion to serve as a primary point of contact for their immunization program and liaison to study personnel. Immunization champions were compensated for their additional duties for the study. Standing orders for all women recommended to receive each vaccine were strongly encouraged at all clinics, with assistance from the study team for implementation [48,49]. Most clinics chose to pursue the implementation of standing orders for all vaccines and recommended populations (obstetrics and gynecology patients); however, a few clinics chose to implement less comprehensive immunization protocols due to unique considerations for their clinics [48].

2.5. Staff training

Each private clinic site was provided educational training for all staff involved in immunization delivery. These trainings consisted of best practices for delivering immunizations in ob-gyn settings

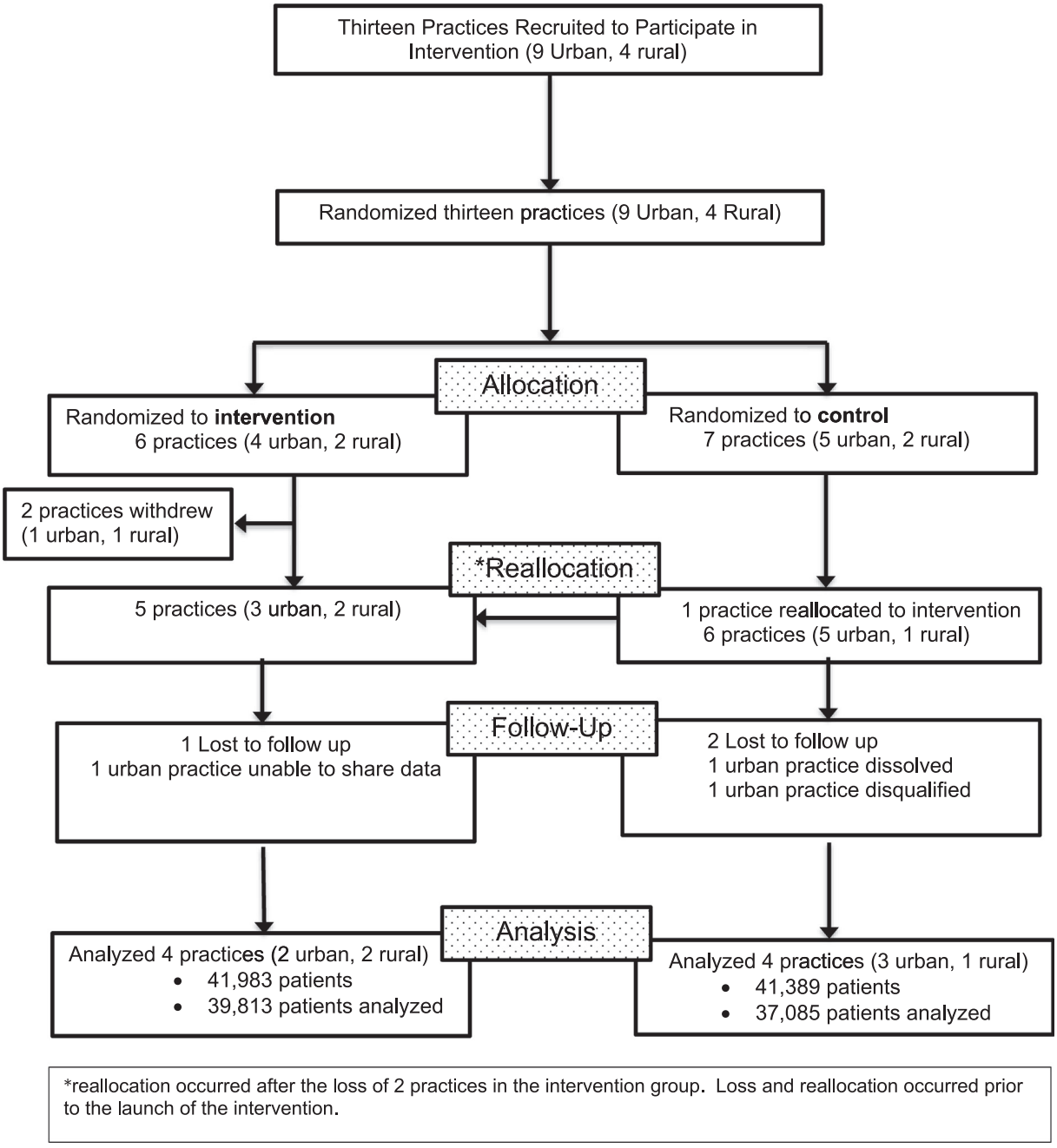

Fig. 1. Consolidated Standards of Reporting Trials Diagram of Multimodal Intervention to Increase Uptake of Vaccinations in Obstetrics and Gynecology Practices.

and use of standing orders, including how to identify eligible patients, collect immunization history for patients presenting for care, providing patient education, referring patient questions and concerns to providers, and delivering the vaccines. Each training was delivered by an immunization nurse from the state health department and trained study staff; clinic decision-makers attended to ensure consistency between the trainings and the policies of each clinic. Trainings were tailored to the interventions chosen for implementation by each office. Staff attending trainings took part in interactive post-training evaluations to assess their learning and clarify outstanding questions about immunization delivery in their clinics.

The clinics also provided educational trainings for their medical assistants and nursing staff each time they implemented a policy or procedure change: first, when standing orders were introduced for influenza, Tdap and HPV vaccines in ob-gyn clinics and second, when Tdap standing orders were updated to recommend Tdap during every pregnancy. Following these trainings, the study team continued monthly meetings with clinic study champions to help ensure the intended outcomes of each training were implemented, offering educational materials for review and reference as needed.

We contracted with an experienced pediatric office manager as a consultant to the project to work with the study practices to assist with managing vaccine inventory, billing for vaccine payment and administration fees, and general guidance on managing an immunization program. The consultant met with office managers at each of the intervention clinics and was available for consultation following the meeting throughout the baseline period of study.

2.6. Standing order implementation

Standing orders and the individual aspects of each (identify eligible patients, collect immunization history for patients presenting for care, providing patient education, referring patient questions and concerns to providers, and delivering the vaccines before patients see a provider) were implemented over a year and a half at the participating clinics. Once each clinic decided which vaccines and the extent of standing orders they wanted to implement, study staff worked with immunization champions and administrators at each clinic to develop protocols, draft standing orders, and implement standing order procedures. Study staff met regularly with immunization champions to troubleshoot challenges and implement solutions throughout the intervention period.

2.7. Survey administration

Surveys regarding vaccination status were administered in clinic waiting rooms for all women presenting for care to each clinic from June through August of 2012, 2013, and 2014. Office staff were instructed to hand these surveys out to every patient who had not previously filled one out for that particular summer. Because there was no way to obtain a denominator for how many patients were seen in these periods, this is considered a convenience sample. We received 6,143 surveys in 2012, 5,689 in 2013, and 6,560 in 2014.

2.8. Analytic methods

All female patients with a record of care between September 6, 2011 and May 31, 2014 and were between the ages of 15 and 100 years on the encounter date, were extracted from the administrative data of participating practices. One of the intervention practices was unable to share their data at the end of study, so that in the final analysis, 4 intervention and 4 control practices were included.

2.8.1. Study periods

The study period was divided into 2 periods: (1) a Baseline Period, September 6, 2011 –September 5, 2013; and (2) a Post-intervention Period, September 6, 2013 – May 31, 2014, which corresponded to a pre-specified trial stop date based on project budget and feasibility. Fig. 2 shows these periods along with the timing of the changing Tdap recommendations during the study period.

2.8.2. Outcomes

For each patient selected into these periods, the presence or absence of the three vaccinations, influenza, HPV and Tdap were the primary outcomes and all analyses were planned a priori to be stratified by obstetric vs. gynecologic visits. Records were assessed for influenza vaccine during the influenza season, which was defined as September 1st to March 31st of the following year. Instances of influenza vaccination were identified using 20 influenza vaccine CPT codes. Subjects for this outcome were limited to those with encounters during that time.

Instances of HPV vaccination were determined by CPT codes 90,649 and 90650, and were limited to those subjects that were between the ages of 15 and 26. Individuals were only assessed for HPV up to the year of receipt, and were excluded from subsequent years.

Tdap vaccinations were identified with CPT 90,715 which occurred on or after October 21, 2011.

2.8.3. Covariates

Patient age was calculated as of the beginning of each study year (September 6). Patient insurance was also assessed each year at the last observed encounter, and was classified as public, private or other. In addition to intervention status, there was one cluster level effect of geography based on the location of the practice and classified to rural or urban [50].

Codes related to obstetric care were searched for within each study year. If at least one record of OB care was observed in a year then the individual was considered to be an OB patient in that study year. In order to measure the type of care provided across practices visits were classified into prevention, problem, vaccination, and other categories.

2.8.4. Sample size and power calculations

To get an idea of the potential power, available methods appropriate to a cluster-randomized trial were used for testing the hypothesis that a sustainable intervention to promote immunization rates in obstetrician-gynecologist practices would result in greater increases in vaccination uptake among women needing vaccines compared to a usual care condition [51]. The study was powered to detect a clinically meaningful difference between the intervention and usual care arms, within practice type. In the 13 practices to be randomized, we estimated a population of 86,907 patients present for care per year. Based on data from the National Health Interview Survey, in 2009 less than 10% of women had received Tdap, less than 25% had received influenza, and less than 20% of 19–26 year olds had received any HPV vaccines [52]. For the purposes of power calculations we conservatively assumed that only 25% of our populations would have received any single one of these vaccines. Assuming the minimum sample size would be 75% of our population, we estimated we would have a sample size of 32,590 per group. Because of the potential clustering of patients with similar characteristics within practices, power and sample size calculations were adjusted using an intra-class correlation (ICC). If the ICC is 0.02, similar to what we've observed in other immunization studies, using an alpha of 0.05, there would be 81% power to detect a 10% difference between groups. Among pregnant women, with an average of 389 patients per practice, on average, and an ICC of 0.02, this sample size would provide 83% power to detect a 10% difference between groups.

For in-office surveys we would expect approximately 800 completed surveys per practice. Among these completed surveys we expected a sample size of approximately 1,755 completed surveys

Fig. 2. Timing of Vaccination Recommendations for Pregnant Women in Relation to Study Periods. Abbreviations: ACIP, Advisory Committee on Immunization Practices; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; ACOG, American College of Obstetricians and Gynecologists.

from patients eligible for one or more vaccines with approximately 877 per group. We anticipated a similar sample size for completed follow-up surveys resulting from the 800 completed in-office surveys. For an ICC of 0.02, we calculated >80% power to detect a 10 percentage point difference between groups.

2.8.5. Statistical analysis

All study variables were analyzed descriptively. Means and standard deviations were computed for continuous measures, while counts and percentages were calculated for nominal measures.

Tests of treatment and covariates against outcomes were computed using separate multilevel log-binomial models for each vaccination outcome. Clustering was adjusted for at the patient and practice level, with patients being nested within practices. To adjust for the small number of clusters an empirical variance estimate, with small sample adjustment was computed [53]. Degrees of freedom were computed by the between-within method for all tests [54–56].

The main test of interest was the improvement of intervention clinics relative to control and was assessed using an intervention by time (Post-intervention Period versus Baseline Period) interaction effect. Univariable tests were performed for each outcome on intervention by time, rural/urban, insurance type and patient age. The final model included all covariates to determine the adjusted effect of intervention and time.

The analyses described were performed for each vaccination outcome and in both the OB and GYN samples separately. Since HPV vaccine is not recommended in pregnancy, this outcome was not tested among the OB sample. Sensitivity analyses were performed estimating all three study years separately as well as collapsing Years Two and Three. Results were not meaningfully different. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

2.8.6. Survey analysis

For the analysis of the survey data, modeling was carried out in the same way as described for the main analysis with 3 exceptions. First, subject identifiers were not recorded for the survey, so it was not possible to add a patient level random effect. Second, the models only included the practice random effect, study year, the intervention indicator and the interaction between year and intervention. Lastly, the simplified model allowed the estimation of risk differences. All survey comparisons were done with respondents answering either yes or no, with an additional sensitivity analysis of considering responses of 'I don't know' considered to be a 'no' response. Questions were analyzed separately in pregnant and non-pregnant patients, where applicable. Subjects were considered vaccinated against influenza if they reported having received "Flu vaccine this past flu season". A sub-analysis was carried out among pregnant women who reported a due date that placed them with date of last menstrual period prior to December 31st of the previous year. Analysis of Tdap vaccination was carried out on two separate questions. First, for those responding affirmatively to having received a tetanus vaccine in the last 5 years and also endorsing that the vaccine included protection against pertussis: "did the tetanus vaccine you received also protect against pertussis?". Secondly, in the years after baseline an additional question became available "<TdaP in pregnancy>". Since this vaccine is generally given late in pregnancy, this analysis only included women with pregnancies within 6 weeks of the reported due date. Finally, the rate of reporting at least one dose of HPV vaccine was assessed among women reporting not currently pregnant and less than 27 years old at the time of the survey.

3. Results

3.1. Practice, patient and visit characteristics

Practice characteristics by study arm are shown in Table 1. Patient and visit characteristics by study arm are shown in Table 2. Due to large sample sizes, there were statistically significant differences between intervention and control practices for all characteristics examined. Several characteristics had large proportions of missing data (marital status, race/ethnicity, language preference). In general, though, differences were not large between study arms for known data. Regarding visit characteristics, about half of visits in both arms were obstetrical visits and half gynecologic. There were few 'vaccine only' visits. Obstetrical patients in intervention practices had a mean of 14.6 visits versus 13.6 in control practices.

Table 1
Practice Characteristics by Study arm (ranges).

	Intervention	Control
Practice Characteristics	median (min, max)	median (min, max)
Urban clinics, n	3	1
Rural clinics, n	2	3
Patients, n	41,983	41,389
Provider FTE, n*	4 (2–19.4)	6 (5–9.2)
Deliveries per month, n	41 (15–125)	51 (15–78)
Medicaid, %*	16% (4%–42%)	6% (3%–32%)
Immunization Delivery Score, n	17 (8–20)	20 (13–25)

Abbreviations: FTE, full time equivalent.
* data missing from one intervention practice

Table 2
Study Population by Arm, Sept 2011 – May 2014.

Patient Characteristics		Intervention	Control
		n = 39,813	n = 37,085
Age at most recent visit	mean (sd)	41 (14.9)	38 (12.9)
Marital Status	n (%)		
Married/coupled		24,864 (62.5)	13,057 (35.2)
Other		12,438 (31.2)	9,479 (25.6)
Unknown		2,511 (6.3)	14,549 (39.2)
Insurance (at most recent visit)	n (%)		
Public		5,266 (13.2)	4,701 (12.7)
Private		32,702 (82.1)	32,174 (86.8)
Other		1,845 (4.6)	210 (0.6)
Patient Type	n (%)		
GYN, only		32,133 (80.7)	28,609 (77.1)
OB, only		1,423 (3.6)	2,289 (6.2)
OB & GYN during study		6,257 (15.7)	6,187 (16.7)
Race/ethnicity	n (%)		
White, non-Hispanic		11,928 (30)	12,549 (33.8)
Black, non-Hispanic		89 (0.2)	1,395 (3.8)
Hispanic		1,541 (3.9)	3,857 (10.4)
Other		867 (2.2)	1,580 (4.3)
Unknown		25,388 (63.8)	17,704 (47.7)
Language	n (%)		
English		10,661 (26.8)	10,660 (28.7)
Spanish		243 (0.6)	200 (0.5)
Other		485 (1.2)	319 (0.9)
Unknown		28,424 (71.4)	25,906 (69.9)
Visit Characteristics			
Total visits	n (%)	211,168	196,163
Total OB visits		93,000 (44)	92,285 (47)
Total GYN visits		118,168 (56)	103,878 (53)
Visit Focus	n (%)		
Prevention		95,558 (45.3)	93,728 (47.8)
Problem		64,685 (30.6)	58,185 (29.7)
Vaccination		889 (0.4)	1,708 (0.9)
Other		50,036 (23.7)	42,542 (21.7)
Mean visits per GYN patient		3.1	2.8
Mean visits per OB patient		14.6	13.6

Abbreviations: GYN, gynecologic; OB, obstetric.

Gynecologic patients in intervention practices had a mean of 3.1 visits versus 2.8 in control practices.

3.2. Vaccination uptake: pregnant patients

3.2.1. Influenza vaccine

There were not significant differences between intervention and control arms for uptake of influenza vaccine among pregnant women, with both study arms increasing their uptake. Based on administrative data, in the Baseline Period, 27% of eligible pregnant women in both intervention and control practices had received influenza vaccine. In the Post-intervention Period, 29% of pregnant women in intervention practices received influenza vaccine versus 41% in control practices, representing an increase of 2% in intervention practices and 14% in control practices ($p = 0.15$) (Table 3).

After adjustment, these changes represented risk ratios of 1.14 (95% CI, 0.95–1.37) and 1.45 (95% CI, 1.05–1.99) for intervention and control practices, respectively, and 0.79 (95% CI, 0.55–1.14) for intervention versus control (Fig. 3 and Table 5).

Results from the patient survey data were similar, although the reported rates of uptake were higher than what was found in administrative data (Table 4). In the Baseline Period, 46% of pregnant women in intervention practices and 39% of pregnant women in control practices reported influenza vaccine receipt. In the Post-intervention Period, 48% of women in intervention practices and 50% of women in control practices reported influenza vaccine receipt, representing an increase of 2% in intervention practices and 11% in control practices ($p = 0.43$).

3.2.2. Pregnant Patients, Tdap vaccine

There were not significant differences in uptake of Tdap vaccine in intervention practices compared to control practices (Table 3). In the Baseline Period, 18% of pregnant women in intervention practices received Tdap vaccine versus 22% in control practices. Not surprisingly given the change in recommendations during the study period, these proportions increased dramatically in both arms during year three of the study period. Both intervention and control practices increased to 51% in the Post-Intervention Period, representing an increase of 33% for intervention practices and 29% for control practices. After adjustment, this translated to risk ratios of 2.88 (95% CI, 1.86–4.47) and 2.19 (95% CI, 1.44–3.32) for intervention and control, respectively, and 1.32 (95% CI, 0.72–2.41) for intervention versus control (Fig. 3 and Table 5).

Because the questions in the patient survey differed in the years of the study based on the change in Tdap recommendations, statistical comparisons are not possible (Table 4). Among eligible respondents (pregnant women $\geq$ 34 weeks gestation), in the intervention practices in the Baseline Period, 56% reported receiving Tdap vaccine during pregnancy compared to 72% in the Post-intervention Period. In control practices, 42% reported Tdap receipt during pregnancy in the Baseline Period compared to 59% in the Post-intervention Period.

3.3. Vaccination Uptake: Non-Pregnant patients

3.3.1. Influenza vaccine

Relatively few influenza vaccines were given to non-pregnant patients in either intervention or control practices in either the Baseline Period or the Post-intervention Period (Table 3). In the Baseline Period, 1% of women in intervention practices and 4% of women in control practices had records of influenza vaccination in administrative data during influenza vaccination season. This was essentially unchanged at the end of the study period with 1% of women and 5% of women in intervention and control practices, respectively, having recorded influenza vaccine receipt in administrative data.

Self-reported influenza vaccination rates were much higher than those found in administrative data, with 46% of women in intervention practices and 49% in control practices reporting influenza vaccine receipt in the Baseline Period (Table 4). At the end of the intervention period, 47% of women in intervention practices and 55% in control practices reported influenza vaccine receipt ($p = 0.39$).

Table 3
Vaccination Uptake by Study Arm for Influenza, Tdap, and HPV Vaccines.

		Intervention			Control			Difference in % vaccinated
		# vaccines given	# women eligible	% uptake	# vaccines given	# women eligible	% uptake	(I % –C % vaccinated)
Pre Period	**OB**							
	Flu	1,594	5,989	27%	1,150	4,234	27%	−1%
	Tdap	1,167	6,623	18%	1,474	6,633	22%	−5%
	Gyn							
	Flu	254	30,279	1%	574	13,715	4%	−3%
	Tdap	337	42,787	1%	152	33,319	0%	0%
	HPV	270	7,758	3%	378	6,266	6%	−3%
Post Period	**OB**							
	Flu	660	2,249	29%	775	1,900	41%	−11%
	Tdap	1,161	2,280	51%	1,364	2,637	51%	0%
	Gyn							
	Flu	161	11,822	1%	370	6,875	5%	−4%
	Tdap	208	14,344	1%	66	13,823	0%	1%
	HPV	70	1,963	4%	99	2,170	5%	−1%
Change in % uptake (post-pre)	**OB**							
	Flu			3%			14%	−11%
	Tdap			33%			29%	4%
	Gyn							
	Flu			1%			1%	−1%
	Tdap			1%			0%	1%
	HPV			0%			−1%	2%

Abbreviations: OB, obstetric patients; Gyn, gynecologic patients; Flu, influenza; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; HPV, human papillomavirus vaccine; I, intervention; C,

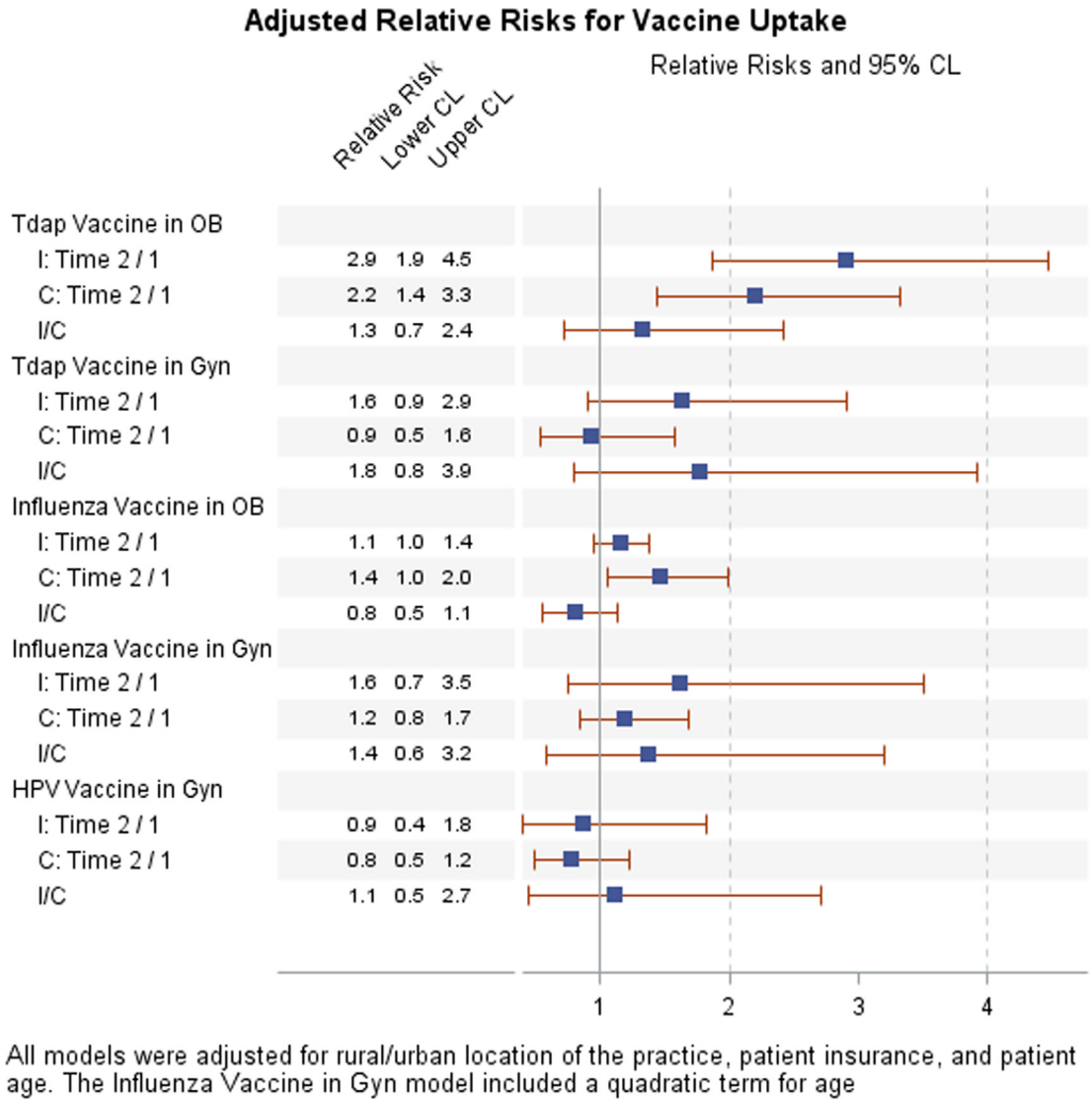

Fig. 3. Abbreviations: CL, confidence limit; I, intervention; C, control; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; OB, obstetrical patients; Gyn, gynecology patients; HPV, human papillomavirus.

3.3.2. Tdap vaccine

Similar to influenza vaccination, very few Tdap vaccines were administered to non-pregnant patients in either intervention or control practices in the Baseline Period or the Post-intervention Period (all about 1% of the total eligible population) (Table 3). After adjustment, these changes remained non-significant (Fig. 3 and Table 5).

Self-reported Tdap vaccination rates were higher, with 23% of women in intervention practices and 25% of women in control practices reporting Tdap receipt in the last five years in the Baseline Period, with both intervention and control practices increasing by 5% to 28% and 30%, respectively, in the Post-intervention Period (Table 4).

3.3.3. HPV vaccine

There were also relatively few HPV vaccines administered in these practices (Table 3). In the Baseline Period, 3% of eligible women in intervention practices and 6% of eligible women in control practices received $\geq$ 1 HPV vaccine, with 4% and 5% of eligible women in intervention and control practices, respectively having record of HPV vaccination at the end of the intervention period. Adjusting for potential confounders did not change these results (Fig. 3 and Table 5).

Self-reported receipt of $\geq$1 HPV vaccine was much higher than those found in administrative data, with 56% of women in intervention practices and 57% in control practices reporting a history of HPV vaccination in the baseline Years 0 and 1 (Table 4). At the end of the intervention period, these had increased by 4% in intervention practices and 4% in control practices to 60% and 62%, respectively ($p = 0.97$).

4. Discussion

We report the results of a large, cluster-randomized trial of an intense, multimodal intervention to increase uptake of vaccines in ob-gyn offices. This study essentially had a null finding, as there were no significant improvements in vaccine uptake among intervention practices versus controls. Despite the lack of effect of the intervention, there are several findings from this study that are important to consider as the role of the ob-gyn as vaccinator evolves. If nothing else, this study is an illustrative example of the difficulties ob-gyn providers have in achieving the goals set out by ACOG to be vaccinators.

One of the most important findings from our study was the almost complete lack of vaccination in non-pregnant patients. These were practices who agreed upon recruitment to the study

Table 4
Self-Reported Vaccination Uptake by Study Arm.

		Intervention			Control			Difference in % uptake	P-value
		vaccines given, n	womeneligible, n	% uptake	vaccines given, n	women eligible, n	% uptake	(Intv. % uptake – Cont. % uptake)	
Pre Period	**OB**								
	Flu with LMP prior Dec. 31	360	674	53%	322	726	44%	9%	0.42
	Tdap and within 6 weeks of due date	91	163	56%	70	165	42%	13%	0.22
	Gyn								
	Flu	2,085	4,506	46%	1,839	3,739	49%	−4%	0.19
	Tdap, last 5 years	1,009	4,367	23%	898	3,635	25%	−2%	0.50
	HPV	517	927	56%	488	853	57%	−1%	0.90
Post Period	**OB**								
	Flu with LMP prior Dec. 31	185	304	61%	335	574	58%	2%	0.86
	Tdap and within 6 weeks of due date	102	141	72%	143	241	59%	13%	0.35
	Gyn								
	Flu	993	2,103	47%	1,239	2,267	55%	−7%	0.13
	Tdap, last 5 years	573	2,030	28%	659	2,207	30%	−2%	0.70
	HPV	267	447	60%	302	491	62%	−2%	0.88
Change in % uptake (post-pre)	**OB**								
	Flu with LMP prior Dec. 31			7%			14%	−7%	0.56
	Tdap and within 6 weeks of due date			17%			17%	0%	0.97
	Gyn								
	Flu			2%			5%	−4%	0.39
	Tdap, last 5 years			5%			5%	0%	0.99
	HPV			4%			4%	0%	0.97

Abbreviations: OB, obstetric patients; Gyn, gynecologic patients; Flu, influenza; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; HPV, human papillomavirus vaccine; I, intervention; C, control.

Table 5
Risk Ratios and 95% confidence intervals.

	Year 2 VS baseline and year1		
	Intervention	Control	I/C
OB			
Tdap Vaccine	2.88 (1.86–4.47)	2.19 (1.44–3.32)	1.32 (0.72–2.41)
Influenza Vaccine	1.14 (0.95–1.37)	1.45 (1.05–1.99)	0.79 (0.55–1.14)
Gyn			
Tdap Vaccine	1.62 (0.90–2.91)	0.92 (0.54–1.58)	1.76 (0.79–3.91)
Influenza Vaccine	1.61 (0.74–3.50)	1.18 (0.83–1.68)	1.36 (0.58–3.20)
HPV Vaccine	0.85 (0.40–1.83)	0.77 (0.48–1.23)	1.10 (0.45–2.71)

Abbreviations: OB, obstetric patients; Gyn, gynecologic patients; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; HPV, human papillomavirus vaccine; I, intervention; C, control.

to vaccinate all of their eligible patients – both pregnant and non-pregnant – if randomized to the intervention arm. Despite this though, the practices, intervention and control, made vaccination of these non-pregnant patients a lower priority than vaccination of pregnant patients. This finding has important implications, as there are many women who either consider their ob-gyn provider to be their primary care provider or functionally use them as such [40–42]. If ob-gyn providers do not vaccinate these women, it is unlikely that they will be vaccinated elsewhere.

There is also an important lesson to be learned from the lack of effectiveness we found with our study. Our intervention consisted primarily of implementing – or attempting to implement – evidence-based strategies for increasing vaccination uptake in ob-gyn settings, given the relatively new paradigm of vaccination in this setting. It is important to note that these evidence-based strategies were developed in other clinical settings, such as pediatric or family medicine practices [57]. For example, in a recent effectiveness review by the US Community Preventive Services Task Force on the use of standing orders to promote vaccination uptake, of 35 included studies, none was performed in an ob-gyn setting [58]. The competing demands present in ob-gyn offices are different than those in pediatric or family medicine offices. The fact that we were not able to show an effect suggests that perhaps these strategies are not well-suited to ob-gyn offices, or at least need adaptation to be effective. For example, in a qualitative evaluation of standing orders that was part of this study, we reported on the facilitators and barriers to implementation of standing orders with our participating practices [48]. Further evaluation of the use of standing orders, as well as evaluation of other evidence-based strategies, such as chart review and feedback [59] and reminder/recall [57,60], in the ob-gyn setting, are warranted. Novel interventions specific to the ob-gyn setting may be needed as well.

We are not the first group to find lack of effectiveness with an immunization intervention in the ob-gyn setting. Moniz et al tested the effectiveness of text messaging to improve uptake of influenza vaccine in a primarily inner-city African-American population of pregnant women, and showed no improvement, despite the fact that text messaging has been shown to increase influenza vaccine uptake in other populations [61]. Similarly, Stockwell et al studied text messaging for influenza vaccination in pregnancy, and while they were able to show a statistically significant difference in certain subgroups, the overall difference in uptake between arms was only 2% (47% versus 49%), and was not significant [61]. In a study similar to ours but smaller and only focused on pregnancy, Chamberlain et al worked with ob-gyn practices in Georgia on a multimodal intervention that included designation of an immunization champion, informational materials, and provider and staff education [62]. The study, which also included a patient-level iPad-based intervention, failed to show any improvement in

uptake of either Tdap or influenza vaccine. These negative studies reiterate one of the primary implications of our study: we may need to 'start from scratch' in determining what techniques work best for improving vaccine uptake in the ob-gyn setting.

The rates of vaccination uptake we gathered from administrative data were much lower than those reported in our patient surveys. We expected some difference in these data sources, but were surprised by the magnitude of the difference. We are unable to ascertain from our study to what degree this reflects women being vaccinated elsewhere versus incomplete recording of vaccination within the offices themselves, but suggests that many women are vaccinated outside of the ob-gyn setting. If this is the case, it will be important for ob-gyn offices to find ways to accurately capture this information in the medical record, which does not appear to be currently the case based on other data we collected in this study (manuscript under review). These findings can inform future immunization delivery projects in ob-gyn settings: multiple sources may be needed for vaccination outcome data. Colorado does not have mandatory reporting of immunizations to its immunization information system (CIIS), and relatively few adult vaccines are captured in CIIS. States that have such a requirement would likely have more accurate vaccination data.

This study had several limitations. It was limited to one state, our study population was relatively homogenous, with non-Hispanic whites over-represented, and there was a great deal of missing race/ethnicity data. Practices that agreed to participate may have been more pro-vaccine than practices that declined. There may also have been a Hawthorne effect, as recruiting practices to participate required meeting with the practices prior to randomization and discussing the importance of vaccination. Also, although we attempted to account for missing data and vaccines received outside the ob-gyn office by using self-reported vaccination status, both sources of our vaccine data are subject to their own limitations, such as recall and response bias in the case of the surveys [63] We also conducted this study in a period when there important secular trends related to vaccination uptake taking place, both for influenza and Tdap. Although we attempted to account for this through a randomized design, the magnitude of changes in vaccination uptake due to secular trends may have overshadowed any potential impact of the intervention. Finally, this study exemplifies the difficulties of conducting pragmatic trials within private practices in a changing healthcare environment, with thirteen practices randomized and only eight able to be fully analyzed at the end of the study.

4.1. Conclusion

This was a large, well-funded, labor-intense randomized controlled trial within ob-gyn offices that failed to show an effect on vaccination rates among both pregnant and non-pregnant patients. Two major lessons can be learned from this trial: first, despite recommendations from CDC and ACOG to vaccinate at every opportunity, ob-gyn physicians appear to be still focused almost exclusively on vaccines in pregnancy; future work should explore sustainable solutions to address this unmet need within ob-gyn practices. Second, future work should also focus on developing and testing uniquely tailored interventions within ob-gyn settings to increase vaccination uptake, as the tried-and-true evidence-based approaches developed in other primary care settings do not appear to be easily applied to ob-gyn settings.

5. Prior presentations

Portions of this paper were presented at the Infectious Diseases Society for Obstetrics and Gynecology annual meeting (Park City, UT, Aug 10–12, 2017), the National Immunization Conference (Atlanta, GA, May 15–17, 2018), and IDWeek (San Diego, CA, Oct 4–8, 2017).

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8. Clinical trial registration

ClinicalTrials.gov, www.clinicaltrials.gov, NCT01565135.

Declaration of Competing Interest

No authors have conflicts of interest to disclose.

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