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Impact of a clinical interventions bundle on uptake of HPV vaccine at an OB/GYN clinic

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Abstract

Introduction: HPV vaccine uptake is lowest among young adults. Little is known about the most effective way to decrease missed opportunities (MO) and increase uptake of the vaccine in this vulnerable population.

Objectives: To determine the impact of a clinical intervention bundle on the rate of MO and uptake of the vaccine among young adult women.

Methods: From 2/2014 to 7/2015, an intervention bundle (designating physician and nurse champions, pre-screening patients' charts, empowering nurses to recommend immunization, providing no-cost vaccinations, placing prompts in clinic note templates, eliminating requirement for pre-vaccination pregnancy test) was implemented at an urban, hospital-based OB/GYN clinic. Medical records were reviewed for all vaccine-eligible (non-pregnant, 11–26 years) women seen between 2/2013 and 9/2016. Impact of the bundled interventions on the monthly rates of MO and vaccine uptake was estimated by analyzing immunization trends with an interrupted time-series model using counterfactual comparison groups in order to control for pre-existing trends.

Results: There were 6,463 vaccine-eligible visits during our study period. The prevalence of women who had both completed and initiated the series was significantly higher, 20.3% and 29.7% respectively, in the last month, compared to their counterfactuals ($p < 0.01$). In the last

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Declarations of interest
None.

study month, the rate of MO was significantly lower than its counterfactual (19.73 per 100 encounters lower, $p < 0.01$). Hispanic women had attributable reductions in their rates of MO that were twice that of White women. Statistically significant attributable reductions were also seen among Spanish speakers, publicly insured, and uninsured women.

Conclusions: Implementation of this intervention bundle effectively reduced the monthly rate of MO and increased the prevalence of women who had initiated and completed the HPV vaccine series. The reduction of MO was most drastic among Hispanic, publicly insured and uninsured women compared to White and privately insured.

Keywords

HPV; Papillomavirus; Vaccination; Rates; Immunization; Intervention; Uptake; Initiation; Completion

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) and leads to approximately 31,500 cases of anogenital and oropharyngeal cancers annually in the U. S. [1]. An efficacious vaccine that prevents infection from 9 HPV types responsible for over 80% of cervical cancers is available for females and males aged 9–26 years [2–4]. Despite its proven safety and efficacy [5], HPV immunization rates in the U.S. are low, particularly relative to other vaccines recommended for adolescents [6]. HPV vaccine initiation and completion also remain low for women 18–26 years-old [7–9]. Additionally, racial disparities exist. Despite their significantly higher cervical cancer burden [9–12], multiple studies have demonstrated lower rates of HPV vaccine initiation among Black and Hispanic women 19–26 years-old, compared to their White counterparts [7,8,13,14].

Interventions to improve HPV immunization in ambulatory settings have been well studied. Most interventions focus on vaccine uptake among adolescents through pediatric or school-based health centers [15–19]. Although early immunization before sexual exposure to HPV is ideal, most young adult women are seronegative to the majority of vaccine-type HPV strains, and therefore will benefit from the vaccine [20,21]. As long as adolescent vaccination rates remain suboptimal, efforts to immunize young adult women and eliminate missed opportunities (MO) to prevent HPV disease are critical. Studies including adult women are lacking, and even fewer have evaluated HPV vaccine interventions specifically within obstetrics and gynecology (OB/GYN) clinics where young female patients often exclusively seek medical care [22].

We therefore implemented a clinical intervention bundle with the aims of reducing MO to vaccinate and improving HPV immunization uptake among eligible patients at an urban, hospital-based OB/GYN clinic serving a diverse, low-income patient population.

2. Methods

2.1. Intervention bundle elements

Bundle elements were implemented from 2/1/14–7/31/15 (see Fig. 1) and were selected from intervention strategies that have proven effective in other clinical settings [23,24]. Prior research from our clinic found MO for HPV immunization were most common during nursing visits for depot medroxyprogesterone acetate injections and STI screening [25]. Thus, on 2/1/14, we began educating nurses on HPV vaccine and training them to pre-screen charts for vaccine eligibility among patients scheduled for nursing visits so vaccine orders could be placed in advance. Through this education and training, nurses were empowered to knowledgeably recommend the vaccine to eligible patients, developed the confidence to answer vaccine-related questions from patients, and were authorized to vaccinate appropriate patients without direct clinician involvement. Furthermore, we designated physician and nurse champions responsible for actively promoting HPV immunization at staff meetings [26,27].

On 8/1/14, the clinic Care Coordinator began reviewing charts for *all* age-eligible patients before their appointments with clinicians, and began annotating their electronic medical records (EMR) problem list and appointment note to alert clinicians to the need for HPV immunization.

Each HPV vaccine dose can cost \$150–\$200, creating a significant immunization barrier for un- or underinsured patients [8,28,29]. Thus, on 11/1/14, in collaboration with hospital pharmacy, we introduced Merck's Financial Assistance Program (MFAP) to provide free immunization to uninsured patients 19–26 years old.

Studies have also shown that in primary care clinics, EMR-generated provider prompts significantly increase vaccine initiation in adolescents and young adults [30,31]. Consequently, on 3/1/15, an EMR-generated prompt was added to note templates, reminding providers to screen patients for vaccine eligibility.

HPV vaccination is currently not recommended during pregnancy. Many providers thus require a pregnancy test before immunization [32]. The vaccine, however, is not associated with adverse maternal or fetal outcomes, and the CDC's Advisory Committee on Immunization Practices (ACIP) does not recommend a pregnancy test before immunization [21]. Therefore, on 6/1/15, we eliminated the pre-immunization pregnancy test requirement.

2.2. Data collection

Demographic and immunization data were collected for all 11–26 year-old females seen at our clinic from 2/1/13–9/30/16, including 12 months pre- and 15 months post-implementation of the intervention bundle. Pregnant patients were not vaccine-eligible and were excluded.

2.3. Data validation

Data were extracted from patients' medical records electronically by Yale's Joint Data Analytics team. Data were validated by first reviewing a random sample (10%) of medical

records of all women who had a visit during each study year. Clinic schedules were also audited to identify all women seen on the first clinic day of each month and verify that no visits were missed during data extraction. No inaccuracies were identified.

2.4. Study definitions

A missed opportunity was defined as a vaccine-eligible visit when the patient was due for an HPV vaccine dose but none was administered. Vaccine eligibility was determined by CDC/ACIP guidelines [3]. A vaccine-eligible visit was any visit where the patient was 11–26 years old, non-pregnant, and under-immunized (previously received 0, 1 or 2 doses of the HPV vaccine). If the patient had received a dose of the vaccine prior to the visit, the patient was considered ineligible for another dose until at least 8 weeks after the first dose, 12 weeks after the 2nd dose, and with 24 weeks between 1st and 3rd dose. The monthly rate of MO was calculated as the ratio of MO to the total number of vaccine-eligible visits every month.

Monthly vaccine uptake was determined by identifying the vaccine status of each woman on her last visit of each month. Women who had a visit and had received 1 dose by their last visit of the month were considered to have “initiated the series”. Women were considered to have “completed the series” if they had received 3 doses by their last visit of the month. The monthly prevalence of women who had initiated and completed the series was calculated as the ratio of the total number of women who had 1 visit in a given month and had initiated or completed the series, respectively, over the total number of women 11–26 years old who had at least one non-pregnancy related visit that month. The pre-implementation period included any visit from 1/31/13 – 1/31/14. The post-implementation period included any visit from 2/1/14 – 9/30/16.

2.5. Statistical analysis

We conducted a descriptive analysis of sociodemographic variables to characterize the overall population (all women 11–26 years-old who had at least one non-pregnancy related visit during each study period). Logistic regression models were used to determine differences in the study population between the pre- and post-implementation periods. Categories with statistically significant p-values (< 0.05) on simple logistic regression were included in multivariate logistic regression models.

We estimated the impact of the bundled interventions on the monthly rates of MO and vaccine uptake by analyzing trends with an interrupted time-series (ITS) model. This model fits the monthly outcomes of interest to an ordinary least-squares regression model including a linear trend, an indicator variable for the post-intervention period, and Fourier terms (sine and cosine functions) to control for seasonality [33]. For these models, we used Newey-West standard errors and a first-order autoregressive function [34]. For comparison, counterfactual outcomes were calculated to predict the rates of MO and prevalence of vaccine uptake during the post-implementation period had the interventions not been introduced. Counterfactuals were predicted by carrying forward the pre-implementation trend estimates to the last month of observation, allowing estimation of the changes in rates of MO and vaccine uptake that may have occurred as a consequence of the intervention while

accounting for pre-existing trends. Absolute reduction in the rates of MO were calculated by averaging the rate of MO from the first 3 months and subtracting the same rate from the last 3 months of the study. The attributable reduction in MO was similarly calculated but rather than averaging the first 3 months we used the average of the predicted last 3 counterfactual months. This allowed us to estimate the reduction of MO at the end of the study accounting for pre-existing trends. Sensitivity analyses were conducted using the leave-one-out cross validation (LOOCV) approach [35].

In a stratified analysis, we assessed the relative impact of our interventions on the rate of MO by race, language, and insurance. This was done by creating similar ITS models where the outcome was the ratio of MO among women in a specific subgroup to the total number of vaccine-eligible women belonging to that same subgroup who had a visit that month. Data were analyzed using Stata 12.0 (StataCorp, College Station, TX). The Yale University institutional review board approved this protocol.

3. Results

There were 28,854 clinic visits from 2/1/13–10/31/16 by women 11–26 years old, of which 18,647 were pregnancy-related and were excluded. Of the 10,207 non-pregnancy related visits, 2336 were completed during the pre-implementation period by 1176 women and 7871 during the post-implementation period by 2764 women. Table 1 summarizes the characteristics of all women who completed at least one non-pregnancy related visit during each study period.

Overall, 1495 vaccine doses were administered during the study period; 998 (66.8%) were administered either at the clinic or within 30 days after a clinic visit (i.e., at another clinic site). The changes in the prevalence of vaccine uptake (women who initiated and completed the series) by implementation period including counterfactuals are shown in Fig. 2. In the first month of the pre-implementation period, 16.7% of women who had 1 visit had completed the series and 33.9% had initiated it. In the subsequent months of the pre-implementation period, the prevalence of completion and initiation increased at a slow rate of 0.34% and 0.25% per month, respectively (Table 2). Post-implementation, there was a statistically significant change in the trend of women who had both completed and initiated the series, with a monthly rate of rise that was 2.71 and 3.76 times higher than the pre-implementation trend, respectively (Table 2). The proportion of women in the last month of the study who had completed or initiated the series was more than double the proportion of women who had completed or initiated the series in the first month (48.5% vs 16.7%, 73.3% vs 33.9%, respectively; $p < 0.01$). Had the bundled intervention not been implemented, at the end of the study period, our models predict that the prevalence of women who had completed and initiated the series would have been 20.3% and 29.7% lower, respectively ($p < 0.01$).

Of the 10,207 non-pregnancy related visits, 2969 (31.5%) were not vaccine-eligible, either because the patient had previously completed the series (74.4%), or because not enough time had passed since administration of the previous dose (25.6%). Overall, there were 6463 vaccine-eligible visits during the study period. The trends in the rate of MO by

implementation period are shown in Fig. 3. The rate of MO decreased from the first month of the pre-implementation period to the last month of the postimplementation period by 26.4 per 100 encounters (Table 3). In the 5 months after introduction of the first interventions, the rate of MO plummeted (from 96.5 to 82.2 per 100 encounters). In addition, the rate of decline during the post-implementation period was 4 times faster than the pre-implementation trend (-0.44 vs -0.11 per 100 encounters/month, $p < 0.02$). In the last month of the study period, the observed rate of MO per month was significantly lower than the predicted rate of MO had no intervention taken place (19.73 per 100 encounters lower, $p < 0.01$). Sensitivity analysis showed less than 4% difference on the root mean squared errors between these models using the LOOCV approach. The monthly trends of MO by race, language and insurance are summarized in Table 3. There were statistically significant attributable reductions in the rates of MO among Hispanic women, who had a reduction of 24.36 per 100 encounters, a reduction that was 2.2 times higher than that of White women. Similarly, the bundled intervention had a significant attributable reduction among Spanish speakers and publicly insured and uninsured women.

4. Discussion

This study demonstrates the impact of implementing an evidence-based multi-component interventions bundle that successfully reduced MO and increased HPV vaccine uptake in a low resource OB/GYN clinic serving predominantly low-income, black, and Hispanic women.

Our study is unique, when compared to other vaccine intervention studies. Many prior studies have focused on efforts to increase uptake through educational campaigns, patient/parent reminder/recall systems, or improving provider education or incentives to recommend the vaccine [18,19,31,36–47]. Generally, however, multi-component (rather than single-method) interventions have been consistently associated with the most significant increases in HPV vaccine uptake [48,49]. Building on this evidence, our study utilized an intervention bundle that was sequentially introduced. Our bundle was multidimensional, involving the full scope of clinic staff, collaboration with the hospital pharmacy, and changes to clinical policies and work flow, including reminders for providers, empowering nurses and eliminating barriers to administration. We implemented practical interventions with proven efficacy based on previous research findings. By serially implementing each intervention, we introduced changes organically, thereby minimizing disruptions to clinic flow and not overwhelming staff with new requirements.

In a recent systematic review of all intervention studies aimed at increasing HPV vaccine uptake [43], the studies with the largest increases in vaccine initiation were either “environmental approaches” (i.e., school-based programs) or multi-component intervention studies that combined patient and provider education and reminders, and practice modifications. Most studies lacked a control group and nearly all lacked data on race/ethnicity or socioeconomic status. These interventions reported increases in vaccine initiation that ranged from 4 to 50% [15,30,41,50]. Our results compare favorably to these studies. At the end of our study, the proportion of women who had initiated the series was 29.7% higher than its respective counterfactual. The study in the systematic review that reported the

largest improvements in uptake was limited by a small sample size and by use of historical controls, which risks overestimation of the actual benefit of an intervention as it does not account for pre-existing increasing trends in vaccine uptake [15].

Several studies suggest that a primary reason for suboptimal HPV vaccination rates in the U.S. is missed opportunities to recommend and administer the vaccine [51]. Dunne et al. demonstrated that over 50% of adolescents had at least one missed opportunity for HPV vaccination while another vaccine was administered [52]. Our first interventions capitalized on these MO by targeting visits where women were scheduled to receive another injectable medication. These first interventions were likely the most effective in our study as nearly half of the attributable reduction of MO occurred during the first 5 months post-intervention before introduction of the second set of interventions. Each intervention in our study was targeted, required few resources, and capitalized on opportunities to offer the vaccine to eligible patients. For example, empowering nurses to recommend the vaccine during contraception or STI screening visits, where discussions of sexual health and prevention are common, provided a practical way to decrease frequently encountered MO.

Racial and socioeconomic disparities exist in HPV vaccine coverage and in cervical cancer. Few studies, however, have described the impact of specific vaccine interventions on reducing these disparities. Since our clinic serves a predominantly low-income, minority population, we could analyze the impact of our interventions by race/ethnicity, insurance and language. We found that although all racial/ethnic subgroups had both absolute and attributable declines in MO, only Hispanic women had statistically significant attributable reduction that would not have been observed in the absence of our bundled interventions. Similarly, Spanish speaking women had a steeper statistically significant attributable decline in MO compared to English speakers. This finding may be due, in part, to the MFAP, which increased vaccine access to uninsured patients, who in our clinic are more often Hispanic women. Likewise, publicly insured and uninsured women had a steeper reduction in MO compared to privately insured women. This suggests that our bundled interventions can be used as a strategy to reduce racial and socioeconomic disparities in MO and potentially eliminate disparities in HPV vaccination.

Despite these strengths, our study had some limitations. First, our study was retrospective and required complete and accurate input of clinical information into each patient's EMR. Secondly, this was a single-center study, therefore a vaccine dose that was administered by a provider who does not utilize our EMR or has not shared records with us may have been missed. This potential bias may lead to underestimation of the intervention's impact. The data were also limited by the dynamic nature of inputs into the EMR for variables that may have changed between the time of a clinic visit and the time of data extraction such as patient's religion, marital status or language. Additionally, our study was not randomized and lacked a contemporaneous control clinic, thus limiting the generalizability of our findings. This limitation was mitigated by our use of counterfactual predictions that account for pre-existing trends of MO and immunization rates. However, our counterfactual models assume that, apart from our interventions, there were no systemic or extraneous influences during the study period (i.e., increased media attention or public health interventions) that might have independently increased HPV vaccine coverage in our community. Therefore,

despite our efforts to adjust for confounding, further research is required and our findings must be interpreted with some caution.

Finally, though these interventions were feasible in our clinic, other clinics may lack the capacity to implement the entire intervention bundle, and in fact, all of the components may be unnecessary. Indeed, our first set of interventions alone had the greatest impact on reducing MO for HPV vaccination. Thus, clinics with fewer resources may find it more practical to focus on a few specific interventions.

5. Conclusions

This study analyzed the impact of an HPV vaccine intervention bundle sequentially introduced at an OB/GYN clinic that serves predominantly low-income women of color. These interventions effectively reduced the monthly rate of MO by 19.8 per 100 encounters, and increased the prevalence of women who had initiated and completed the HPV vaccine series by 29.7% and 20.3%, respectively. The reduction of MO was greatest among Hispanic, publicly insured and uninsured women compared to White and privately insured. Our results suggest that implementing similar interventions within other low-resource clinics serving low-income minority women, can potentially increase HPV vaccine uptake, as well as eliminate racial and socioeconomic disparities in this high-risk population.

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Fig. 1.
Timeline depicting the introduction of each intervention bundle element from February 2014 to July 2015.

Fig. 2.
Time series of HPV vaccine uptake by month pre- and post-Implementation of the bundled interventions.

Fig. 3.
Time series of the rate of missed opportunities by month pre- and post-implementation of the bundled interventions.

Characteristics of all women with a non-pregnancy associated encounter by study period

Table 1

	Pre-Implementation N = 1176		Post-Implementation N = 2764		p-value *	OR **	p-value **
Age, median (IQR), y	22	(20–25)	23	(20–25)	0.20	–	–
Race, No. (%)							
White	97	(8.2)	341	(12.3)	Reference	–	–
Hispanic	445	(37.8)	990	(35.8)	<0.01	0.69	<0.01
Black	554	(47.1)	1207	(43.7)	<0.01	0.61	<0.01
Other	13	(1.1)	32	(1.2)	0.30	0.60	0.45
Unknown	67	(5.7)	194	(7.0)	–	–	–
Religion, No. (%)							
Catholic	465	(39.5)	957	(34.6)	Reference	–	–
Protestant	228	(19.4)	534	(19.3)	0.18	–	–
Muslim	25	(2.1)	73	(2.6)	0.37	–	–
Other	15	(1.3)	56	(2.0)	0.12	–	–
No Religion	377	(32.1)	929	(33.6)	0.61	–	–
Unknown	66	(5.6)	215	(7.8)	–	–	–
Language, No. (%)							
English	998	(84.9)	2350	(85.0)	Reference	–	–
Spanish	160	(13.6)	321	(11.6)	0.12	1.06	0.64
Other	17	(1.4)	90	(3.3)	<0.01	2.41	0.04
Unknown	1	(0.1)	3	(0.1)	–	–	–
Marital Status, No. (%)							
Married	154	(13.1)	293	(10.6)	Reference	–	–
Single	999	(84.9)	2396	(86.7)	0.03	1.44	<0.01
Other	22	(1.9)	64	(2.3)	0.11	1.71	0.05
Unknown	1	(0.1)	11	(0.4)	–	–	–
Insurance, No. (%)							
Private	72	(6.1)	160	(5.8)	0.397	0.83	0.24
Public	936	(79.6)	2356	(85.2)	Reference	–	–
Uninsured	168	(14.3)	248	(9.0)	<0.01	0.57	<0.01

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+Other Race: American Indian, Asian and Native Hawaiian.
Other language: Arabic, Turkish, Chinese, Farsi, French, Pashto, Serbian, Sign, Swahili, Tigrinya, Vietnamese and Hindi.
* p-value estimated using simple logistic regression where the outcome equals one if the encounter is in the post-implementation period.
** Odds Ratio determined using multivariate logistic regression adjusting for race, language, marital status and insurance.

Table 2

Monthly trends of HPV vaccine uptake pre-and post-implementation

	Pre-implementation		Post-implementation		Ratio [‡]	p-value
	Trend [*]	95%CI	Trend [*]	95%CI		
Vaccine uptake						
Completed series	0.34%	0.17–0.51%	0.92%	0.85–0.99%	2.71	<0.01
Initiated series	0.25%	–0.16 to 0.66%	0.94%	0.78–1.09%	3.76	0.01

^{*} The trend is the average difference in uptake between any 2 given months during each intervention period.

[‡] Trend ratio: trend post-implementation over the trend pre-implementation.

Table 3

Reduction in the rate of missed opportunities, overall and by sociodemographics.

Mean rate per 100 encounters							
	Pre-implementation		Post-implementation		Counterfactual*	Absolute reduction	Attributable reduction
	Rate*	Trend	Rate*	Trend			
Missed opportunities	97.49	-0.11	71.05	-0.44	90.78	26.44	19.73
Race							
Hispanic	98.15	-0.04	69.94	-0.46	94.30	28.21	24.36
White	100.00	-0.33	69.36	-0.64	80.70	30.64	11.34
Black	97.07	-0.34	75.04	-0.32	82.55	22.02	7.51
Other	100.00	0.00	60.00	-1.64	100.00	40.00	40.00
Language							
English	97.20	-0.19	73.78	-0.34	87.68	23.42	13.90
Spanish	100.00	0.00	62.58	-0.96	98.07	37.42	35.49
Other	100.00	0.00	56.94	-1.06	100.00	43.06	43.06
Insurance							
Private	93.33	-0.15	84.84	-0.36	87.87	8.49	3.03
Public	97.11	-0.08	70.92	-0.39	91.72	26.19	20.80
Uninsured	100.00	0.09	58.97	-0.96	100.00	41.03	41.03

+ Other Race: American Indian, Asian and Native Hawaiian.

Other language: Arabic, Turkish, Chinese, Farsi, French, Pashto, Serbian, Sign, Swahili, Tigrinya, Vietnamese, and Hindi.

Absolute Reduction = (average rate observed during last 3 months) – (average rate observed during first 3 months).

Attributable Reduction = (counterfactual rate of last 3 months) – (observed rate of last 3 months).

* Average of first or last 3 months respectively for the pre- and post-implementation periods.