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Physician clinical decision support system prompts and administration of subsequent doses of HPV vaccine: A randomized clinical trial

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ABSTRACT

Background: HPV vaccine is effective in preventing several cancers and anogenital warts, yet rates of HPV vaccination series completion in the United States are low. A primary reason identified by parents for vaccinating children against HPV is a health care provider's recommendation. Although most clinicians embrace vaccine recommendations, they are not always carried out evenly and subsequent HPV vaccines are missed.

Methods: Using an electronic health records-based decision support system (CHICA) clinicians were randomized to either usual practice or to receive an automated reminder to recommend the 2nd or 3rd dose of HPV vaccine. The reminder was delivered to clinicians of all intervention group eligible adolescents who had already initiated the vaccine series. Logistic regression models with generalized estimating equations were used for data analysis.

Results: A total of 1285 clinical encounters were observed across 29 randomized pediatric providers over a 13-month time frame (50.7% control group, 49.3% intervention group). Overall, patients were 44.9% female, 59.4% Black, 22.1% Hispanic, and 48.8% were ages 11–12 yrs. Within the control group, 421 (64.7%) received a subsequent HPV vaccine, compared to 481 (75.9%) (OR: 1.72, (95% CI 1.35–2.19)). Adjusted analysis showed no difference between the groups (aOR 1.52 (95% CI 0.88–2.62)) or when examined by age (11-12yrs aOR 1.66, (95% CI 0.79–3.48)) and 13-17yrs (aOR 1.19, (95% CI 0.76–1.85)) or gender female (aOR 1.39 (95% CI 0.71–2.72)) and males (aOR 1.67 (95% CI 0.95–2.92)). When results were stratified by both age and gender, there was similarly no statistically significant effect between the two groups.

Conclusions: Automated physician reminders for subsequent 2nd and 3rd doses of HPV vaccination were used. Despite increased rates of vaccination in the intervention group, the differences did not reach the level of statistical significance. Future studies with multifaceted approaches may be needed to examine the efficacy of computer-based reminders.

Clinical Trial Registration: NCT02558803, "HPV Vaccination: Evaluation of Reminder Prompts for Doses 2 & 3".

Abbreviations: HPV, human papillomavirus; CDSS, clinical decision support system; ACIP, advisory committee on immunization practices; CHICA, child health improvement through computer automation; IIS, immunization information system; Tdap, tetanus diphtheria and acellular pertussis; GEE, generalized estimating equations; CHIRP, children and Hoosier immunization registry program.

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1. Introduction

Vaccination against human papillomavirus (HPV) has been shown to be extremely effective in preventing infection with viral strains most often associated with cervical, anogenital and oropharyngeal cancers, as well as genital warts [1,2]. One HPV vaccine is currently on the market in the U.S., the nonavalent vaccine, which protects against seven oncogenic HPV types and two low-risk types [3,4]. Guidelines regarding vaccination intervals and necessary frequency were recently updated in 2016 by the Advisory Committee on Immunization Practices (ACIP) to incorporate data that showed immunity was reached at earlier ages with 2 vaccine doses if they were administered prior to the age of 15 versus the originally recommended 3 dose series [5–7]. Thus, assuring the vaccine series is completed at an earlier age not only leads to higher immune responses but also overall less needed vaccines.

Because the human papillomavirus 9-valent (9vHPV) vaccine is preventative, the goal is to administer the vaccine series before the onset of sexual activity. However, the United States, in particular, has yet to achieve wide uptake for a variety of reasons [8]. This has resulted in low overall rates of vaccination in the United States with recent data showing only 53% of females and 44% of males completing the 3-dose vaccine series and with known differences geographically [9]. The rate of HPV vaccination is disappointing given the fact that other adolescent vaccines (e.g. Tetanus diphtheria and acellular pertussis (Tdap), Meningococcal) all have higher uptake. In order to realize benefits of HPV vaccination like herd immunity, a large portion of the population needs to be vaccinated [10].

Parents describe that one of the primary reasons they decided to vaccinate their children against HPV is when a health care provider recommends the vaccination, and the lack of recommendation leads to non-vaccination [11]. In order to improve vaccination rates, there have been intervention studies using clinical decision support tools to encourage and remind clinicians that a vaccine is due [12–15]. Clinical decision support system (CDSS) aids, in particular, are appealing because of their low cost and overall speed of implementation. Prior research on CDSS provides evidence they can be effective at encouraging preventative behaviors [16], including influenza and pneumococcal vaccine administration [17].

However, results from studies using clinician-focused interventions to improve HPV vaccination rates have been mixed, with some showing an improvement and others finding no differences [14–15,18]. Previous work done by our group has shown that, although clinicians and staff do not always perceive reminder prompts as being effective in changing outcomes, improvement has been seen in *initiating* the HPV vaccine series with clinician prompts [19–20]. Given the overall low rates of HPV vaccine series completion in the state of Indiana (only 37.6% of girls and 8.1% of boys complete the 3-dose series), we sought to study the efficacy of an intervention to improve subsequent HPV doses in an already established clinical decision support tool. The Child Health Improvement through Computer Automation (CHICA)—that was linked to a statewide immunization information system (IIS) to determine whether clinician prompts would increase delivery of 2nd or 3rd dose HPV vaccines when the patient had already initiated the series. We hypothesized that implementation of this intervention would be feasible and lead to increased uptake of subsequent doses of HPV vaccination in the intervention group compared to the usual practice control group. At the time of the study, the 2-dose recommendation by ACIP had not been issued.

2. Methods

To examine whether a CDSS could improve 2nd and 3rd dose vaccination against HPV, we conducted a randomized trial. The trial (Clinical Trial # NCT02558803) was approved by the Indiana University Institutional Review Board and the requirement for written consent was waived.

2.1. Setting

The study was conducted in 5 primary care clinical sites within Eskenazi Health, a large safety net health system serving Marion County, Indiana, which is home to the city of Indianapolis. Approximately 70% of the families treated at the Eskenazi Health clinics are covered by Medicaid, and nearly 50% are non-Hispanic black and one-third Hispanic. All five clinics in the study employ the CHICA CDSS, which has been a part of the clinical system since 2004. It is unique in several ways. In particular, it can communicate with the statewide IIS, Children and Hoosier Immunization Registry Program (CHIRP) operated by the Indiana State Department of Health; there is a prioritization scheme to assure reminders to clinicians are prioritized (i.e. a patient that indicates suicide ideation will list that first compared to the importance of smoking cessation); and CHICA also collects its data directly from families in the waiting room (on a tablet prior to a clinical visit) to expedite flow.

2.2. Randomization

Twenty-nine pediatric clinicians were randomized across two arms using a randomization list generated in R. [21] The control arm consisted of usual practice, where vaccination recommendations from the statewide IIS were manually obtained by nurses who looked them up in CHIRP. The intervention arm received automated CDSS reminders via CHICA to recommend the 2nd and 3rd doses of HPV vaccine for eligible male and female adolescents who had already initiated the vaccine series (Fig. 1).

2.3. Participants

All pediatric clinicians serving the five CHICA clinics were included in this study and any patient aged 11–17 years who had previously received a dose of the HPV vaccine and was presenting for a well-child visit was eligible. Patients seen more than once in the study period could have been eligible at each encounter. Providers were not aware of which group they had been assigned. Because the clinics are part of an academic medical organization, providers routinely participate in trials and pilot studies of new practices.

2.4. Study design

Any scheduled patient within the target age range was identified by CHICA and their eligibility for inclusion was verified by the automated checking of immunization records in CHIRP. If a patient had received a prior HPV vaccine and the appropriate interval had passed for the 2nd or 3rd dose to be delivered, clinicians in the intervention arm received a CHICA prompt to order the vaccine within the CHICA physician worksheet, which is used to set the

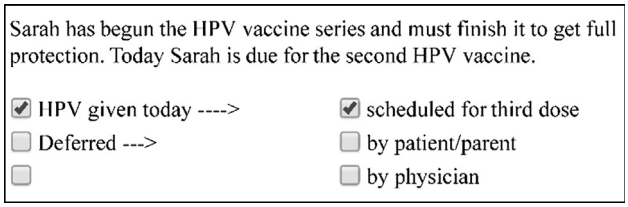

Fig. 1. Physician prompt.

agenda for a clinical encounter (see Fig. 1). The physician is able to document whether a vaccine was given or declined within the physician worksheet. However, to assure the accuracy of the primary outcome (vaccine delivery), fourteen days after an encounter, the CHIRP database was re-queried to determine if the HPV vaccine was delivered on the clinical encounter date and this was used as the primary outcome in analysis. Study recruitment was from July, 1 2015-May 17, 2016.

The physician prompt was incorporated into the CHICA software and links to the state vaccine database were established and tested prior to implementation in July 2015. There was no notification or orientation to the change in the CDSS system for clinic staff or physicians because these type of changes are common for the end-users and we did not want to risk contamination between the groups. However, changes in the CDSS system are common and this change did not affect clinic flow in any noticeable way. Weekly technical meetings were held by the research team throughout the study period for the CDSS system and there were no issues with this prompt implementation throughout the study period.

In designing this trial, we originally estimated that with 30 physicians, a total of 1430 participants (1000 females, 430 males) we would be able to achieve 90% power to detect a 13% change in the vaccination rates within each group.

2.5. Data analysis

Demographic data of all participants were collected and summarized by treatment group. Our primary outcome was whether a subsequent dose of HPV vaccine was delivered when indicated. Secondary outcomes including examining the effect of the intervention on different genders and age groups of patients. To account for the potential clustering effect of healthcare provider, we performed logistic regression analysis of the HPV vaccine uptake data with generalized estimating equations (GEE), which help to accommodate the within-provider correlations. We also adjusted for the effects of patient race, gender and age as covariates in the GEE models. Furthermore, we stratified the data by gender and age, and then conducted the same analysis in each stratum. All analyses were performed using SAS Version 9.3 (Cary, North Carolina), and p-values less than 0.05 were considered statistically significant.

3. Results

Of the 29 clinicians, 14 were randomized to the control group and 15 to the intervention group. Descriptive statistics across and within each study arm are summarized in Table 1. Over the study period, each arm saw approximately the same number of vaccine-due encounters (Control: 651 (50.7%), Intervention: 634 (49.3%)), with the intervention group seeing slightly more females (48.9% vs. 41.0%). Of the patient encounters, 695 (54.1%) received a 2nd dose and 590 (45.9%) received a 3rd or higher HPV dose. The breakdown by age also shows that approximately half the patients were between the ages of 11–12 yrs. (n = 627, 48.8%) and the remaining were 13–17 yrs. (n = 658, 51.2%). The control group had older patients with more self-identified black patients, compared to the intervention group that had more self-identified Hispanic patients. Additional patient demographics are described in Table 1.

Vaccine uptakes in patients seen by the same provider were correlated; the estimated intra-cluster correlation (ICC) was 0.2, indicating a moderate level of correlation. Given the ICC value, the study was not powered sufficiently to detect differences between the groups. However, we did examine whether vaccine rates improved. Rates of receipt of a due subsequent HPV vaccination for the control group were 64.7% and the intervention group was 75.9%, for an unadjusted OR of 1.52 (96% CI 1.35–2.19).

Adjusted analysis, controlling for clustering by provider, found no difference in receipt of 2nd or 3rd doses of HPV between the control and intervention groups (aOR 1.52, 95% CI 0.88–2.62). When the results were stratified by age, there was similarly no effect of the intervention (11-12yrs aOR 1.66 (95% CI 0.79–3.48) and 13-17yrs (aOR 1.19 (95% CI 0.76–1.85)) (Table 2). We further stratified results by age and gender to determine whether an effect was present within different subcategories, and there was no intervention effect found (Table 3).

Table 1
Characteristics across trial arms and overall.

	Total n (%)	Control n (%)	Prompt n (%)
Health Center Providers	29	14 (48.3)	15 (51.7)
Patient Encounters	1285	651 (50.7)	634 (49.3)
Female	577 (44.9)	267 (41.0)	310 (48.9)
Race/Ethnicity			
Black	763 (59.4)	463 (71.1)	300 (47.3)
White	91 (7.1)	60 (9.2)	31 (4.9)
Hispanic	284 (22.1)	64 (9.8)	220 (34.7)
Other/Unknown	135 (10.5)	55 (8.4)	80 (12.6)
Missing value	12 (0.1)	9 (1.4)	3 (0.5)
Ages 11–12 yrs	627 (48.8)	252 (38.7)	375 (59.1)
Ages 13–17 yrs	658 (51.2)	399 (61.3)	259 (40.9)

Table 2
Receipt of subsequent doses of HPV vaccine stratified by age and gender.

	Group Assignment		Adjusted Odds Ratio (95% CI)
	Control* (n = 651)	Prompt (n = 634)	
Received HPV Vaccine	421 (64.7)	481 (75.9)	1.52 (0.88–2.62)**
11–12 yrs	159 (63.1)	301 (80.3)	1.66 (0.79–3.48)¥
13–17 yrs	262 (65.7)	180 (69.5)	1.19 (0.76–1.85)¥
Females	176 (65.9)	233 (75.2)	1.39 (0.71–2.72)±
Males	245 (63.8)	248 (76.5)	1.67 (0.95–2.92)±

* Reference Group.
** Analysis accounted for clustering by health care provider and adjusted for age, gender and race.
¥ Analysis accounted for clustering by health care provider and adjusted for race and gender.
± Analysis accounted for clustering by health care provider and adjusted for race and age.

Table 3
Receipt of subsequent doses of HPV vaccine by gender, stratified by age.

HPV Vaccine Received by Males, Stratified by Age

	Group Assignment		Adjusted Odds Ratio** (95% CI)
	Control* (n = 384)	Prompt (n = 324)	
11–12 yrs	84 (58.7)	155 (79.1)	1.77 (0.80–3.90)
13–17 yrs	161(66.8)	93 (72.7)	1.45 (0.93–2.28)

HPV Vaccine Received by Females, Stratified by Age

	Group Assignment		Adjusted Odds Ratio** (95% CI)
	Control* (n = 267)	Prompt (n = 310)	
11–12 yrs	75 (68.8)	146 (81.6)	1.71 (0.75–3.88)
13–17 yrs	101 (63.9)	87 (67.2)	1.06 (0.55–2.07)

* Reference Group.
** Analysis accounted for clustering by health care provider and adjusted for race.

4. Discussion

A randomized trial to test the effect of a clinician CDS prompt for 2nd and/or 3rd doses of the HPV vaccine using an already established CDSS demonstrated that while implementing a prevention reminder is possible, it may not make a significant impact on vaccine uptake. Although the intervention arm of the trial did have a higher uptake of the 2nd and 3rd dose, the effect of correlation amongst patients seen by the same provider led to insufficient power to detect a significant difference. Despite the statistical results, the trial adds evidence to the growing body of literature on CDS prompts to improve HPV vaccination rates, and the study has implications for the broader field of informatics that examines the effect of technologies like CDSS on clinical processes and health outcomes.

The current study adds to the existing literature on interventions that target improving HPV vaccination rates. A recent systematic review by Francis et al. examined communication technologies, including CDS prompts, to determine which set of interventions might impact HPV vaccination rates. [12] The 12 studies examined in the review used technologies targeted at providers, parents and adolescents, or a combination of these groups. With respect to providers, prior studies have been mixed where half found no difference in HPV vaccination rates post-intervention [12,14,15,18,20]. These studies, like this one, have generally employed CDS prompts randomized at the provider level. Furthermore, while some prior studies have found statistically significant increases in HPV vaccine uptake, the effect size of the CDS intervention was relatively small [20,22–24].

With respect to interventions that target parents and adolescents directly, the review concluded that most of these interventions improved HPV vaccination uptake [12]. However, the methods employed in these studies were generally weak with many lacking a control group. Furthermore, few of these studies took place within a typical outpatient clinic setting. Overall, interventions focused on targeting parents were generally successful. Those targeting patients and providers showed mixed results and seem to suggest that multiple targets and technologies have potential to increase rates [12].

There has only been one previous study designed with a clinician-only focused intervention, and those results were mixed [14]. Because our CDSS system is already part of the clinical culture, implementation of this clinician prompt was relatively easy and did not change clinicians' workflow. Our CDSS system is also unique because of its link to the state-wide vaccine registry (CHIRP) and the communication that is possible between the two systems. The review by Francis et al. and prior studies, in light of this trial, suggest that a provider-only CDS intervention alone may not be sufficient and that more rigorous, and larger, trials are warranted to improve HPV vaccine uptake.

Although not significant, the results do show an improvement in HPV series completion. A more than 10% increase was observed in the intervention arm, and this effect was consistent in the subgroup of those aged 11–12 years, females, and males. This is an important piece now that updated ACIP guidelines require only 2 doses for immunization, compared to 3 total doses if older than 15 years. The CDS prompts, therefore, do appear to influence provider behavior and awareness of a patient's vaccine status in the younger subgroups.

This finding is similar to that of a recent study by Dixon et al. where a CDS prompt was tested in similar settings to effect initiation of the HPV vaccine series [25]. The prior study interviewed pediatric providers about their awareness of the CDS prompts. Most providers were aware of the prompts, but they did not perceive them to have influenced their behavior. Yet the trial in which these providers participated found statistically significant increases in HPV series initiation in the control (45%) versus intervention (62%) arms (aOR = 2.76, 95% CI 1.07–7.14) [20]. Like the prior study, the clinicians in this trial appear to be influenced even if the difference was not as striking as the one measured in the trial on vaccine initiation. However, provider prompt fatigue is something to be balanced with which prompts are chosen to be incorporated into the EMR [26–28].

Also noteworthy about the results is that the control group rates of vaccine updated are more than twice the population rates for Indiana. Whereas the Indiana statewide HPV series completion rates, measured by the IIS, are 37.6% for girls and 8.1% for boys, the 2nd and 3rd dose uptake among the control group in this trial was 65.9 for girls and 68.3% for boys. Therefore the clinics at Eskenazi Health were already successful in vaccinating their patient population prior to the trial. Therefore future studies to nudge clinicians to recommend the HPV vaccine might be best conducted in mixed clinical environments with respect to low, moderate, and high rates of vaccination prior to introduction of the CDS prompts.

There are several limitations in this study to note. First, the final enrollment was close to but did not reach the designed target numbers that were estimated under the assumption of weak intra-class correlation. The higher than expected intra-class correlation determined after study completion led to a loss of power to detect difference between the groups. Given the magnitudes of the estimated effects, it is likely with more participating clinicians and children under their care one would be able to detect significant differences between the 2 groups. Therefore, the negative trial results could be a consequence of the insufficient sample size or a true lack of intervention effect. Second, because a true baseline vaccine rates for the clinicians was unknown, it is possible that the randomization by physician was unbalanced. Thirdly, the unique link between the state vaccine registry, the CHICA system and our EMR is no necessarily available or feasible in other clinical settings. Until it is available more widely in other practice settings, our study methods are not completely generalizable. However, this study took place within one of the largest clinical systems within our state and serves a population in need of improved healthcare access and outcomes. Finally, the reminder prompts only occurred when patients presented for well-child visits and thus there might have been missed opportunities to provide HPV vaccine reminders at urgent visits. One report estimates that if every missed opportunity was used to deliver HPV vaccines, we could achieve close to a 90% rate of vaccination [29].

The importance of completing the HPV vaccine series in a timely manner is clear to assure protection before the onset of sexual activity and improve immunity effects through younger vaccination. CDSS reminder prompts focused on clinicians is a promising intervention that is relatively easy to implement in those practices where EMR prompts are already utilized. Despite the limitations, our study provides evidence that linking to a statewide IIS and using CDSS reminder prompts to increase additional delivery of HPV vaccines once the series has been started is feasible. Additional studies in diverse clinical settings with more participants to provide adequate power are needed to determine the effect of CDS prompts. This leads to accumulated evidence that simple prompts may not be sufficient and that a combination of interventions may be needed to target providers along with parents and adolescents.

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Declaration of Competing Interest

Gregory Zimet has been an investigator on investigator-initiated research funded by Merck and Roche, received travel funding from Merck to present research at a scientific conference, and received an honorarium for participation in an adolescent immunization initiative meeting. Brianna Lindsay was an employee of Merck & Co., Inc at the time this research study was conducted. The Child Health Improvement through Computer Automation (CHICA) system is the intellectual property of Indiana University. Stephen Downs and Tammy Dugan are cofounders of Digital Health Solutions, LLC, a company created to license and market CHICA. Tracey Wilkinson, Brian Dixon, Shan Xiao, Wanzhu Tu, and Meena Sheley have no potential conflicts of interest to report.

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