An Educational Intervention to Improve HPV Vaccination: A Cluster Randomized Trial

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Short Title: A Video Intervention for HPV Vaccination

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Abbreviations: HPV, Human Papillomavirus; CHICA, Child Health Improvement through Computer Automation system; EHR, electronic health record

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Table of Contents Summary

This study examines the effect of a digital educational intervention linked to prior vaccine history on HPV vaccination decisions in urban pediatric settings.

What's Known on This Subject

Human Papillomavirus (HPV) remains the most common sexually transmitted infection. Despite availability of effective vaccines, HPV vaccination rates are suboptimal. Prior research on improving HPV vaccination rates has focused primarily on decision aids that target providers.

What This Study Adds

Patient-centered education strategies delivered in a clinic setting via information technology platforms can positively impact the adoption of preventive health behaviors. Yet integration of IT platforms into routine care is challenging. More research on strategies that can be scaled is warranted.

Contributors' Statement Page

Profs Dixon and Zimet conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, and reviewed and revised the manuscript.

Profs Xiao and Tu contributed to the study design, carried out all analyses, and contributed to drafting the manuscript.

Dr Downs conceptualized and designed the study, reviewed and revised the data collection instruments, coordinated the intervention in the clinical settings, coordinated data collection, and reviewed and revised the manuscript.

Prof Lindsay contributed to the study design, reviewed and revised the data collection instruments, and critically reviewed the manuscript for important intellectual content.

Ms Church coordinated the activities of the study team, including regulatory compliance, data collection, and she drafted parts of the initial manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background: Human Papillomavirus (HPV) infection can lead to serious health issues and remains the most common sexually transmitted infection. Despite availability of effective vaccines, HPV vaccination rates are suboptimal.
Methods: In a cluster randomized trial, an intervention targeting parents of adolescents (11-17 years) eligible for a dose of HPV vaccine was tested in pediatric clinics part of an urban health system. Parents watched a digital video outlining the risks and benefits of vaccine using a tablet in the exam room. The primary outcome was change in HPV vaccine status two weeks after the clinic visit. An intention to treat analysis for the primary outcome utilized generalized estimating equations to accommodate the potential cluster effect of clinics.
Results: A total of 1596 eligible adolescents were observed during the 7-month trial. One-third of adolescents visited an intervention clinic. Adolescents who attended an intervention clinic were more likely to be younger (11-12 years) than those who attended a control clinic (72.4% versus 49.8%; $p<0.001$). No differences in race or gender were observed. The proportion of adolescents with an observed change in vaccine status was higher for those attending an intervention clinic (64.8%) versus control clinic (50.1%; OR=1.82; 95% CI=1.47-2.25; $p<0.001$). Adolescents whose parents watched the video had a three times greater odds of receiving a dose of the HPV vaccine (78.0%; OR=3.07; 95% CI=1.47-6.42; $p=0.003$).
Conclusions: Educational interventions delivered within a clinical setting hold promise to improve vaccination behaviors.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the U.S., with approximately 79 million infected and 14 million new cases each year.[1] Infection with HPV is a causal factor for serious health issues including cervical, vaginal, and vulvar cancers in women, anal and oropharyngeal cancers as well as genital warts and recurrent respiratory papillomatosis in males and females, and penile cancer in men;[2] making HPV a significant threat to public health.

Moreover, many HPV infections are preventable via vaccination. The Advisory Committee on Immunization Practices (ACIP) recommends that HPV vaccine be routinely administered to early adolescents (i.e., 11–12-year-olds) in the United States.[3] Healthy People 2020 goals for vaccine coverage include 80.0% of individuals completing the HPV vaccine series by age 13-15.[4] Despite availability of the 9-valent HPV vaccine (9vHPV) that can prevent up to 90.0% of cervical cancers and genital warts,[5] HPV vaccination rates in the U.S. remain well below the Healthy People 2020 goals.[6] In 2016, only 65.1% of adolescent girls and 56.0% of adolescent boys ages 13 through 17 years received one or more doses of vaccine.[7] The percentages are even lower for series completion (49.5% of girls and 37.5% of boys). With respect to Indiana, 2016 data show the state to be ranked 46th in first dose administration among females and tied for last for males.[7]

Prior research on interventions to improve HPV vaccination rates focused on three levels: community, provider, and consumer (parent/adolescent). At the community level, there is moderate-level evidence across studies in multiple countries for policies that can nearly double HPV vaccination rates among adolescents, such as requiring vaccination for school-age children.[8] While effective, public health strategies are often challenging to implement.

Evidence at the provider level is mixed. A small set of clinical decision support (CDS) interventions to increase provider recommendation of the vaccine to parents or adolescent patients

have been developed and tested, because provider recommendation is consistently cited as a primary reason that parents vaccinate or indicate intent to vaccinate their adolescent children.[9-11] Of the prior studies (N=6) examining CDS interventions, half found no difference in HPV vaccination rates post-intervention.[12-16] While these studies suggest CDS prompts are associated with provider recommendation of the HPV vaccine, the evidence also suggests achieving the Healthy People 2020 goal will require more than just provider-based CDS prompts.

Evidence for interventions at the consumer level is positive but weak. A heterogeneous set of studies (N=12)[8,12] examined interventions that target parents and adolescents. These interventions typically involved postal or telephone-based reminders that the adolescent was due to start or complete the HPV series. Two of the studies examined video-based interventions targeting high school and college age female students.[17,18] Two review articles[8,12] concluded that most of these interventions improved HPV vaccination uptake. Yet the methods employed in these studies were generally weak with many lacking a control group. Furthermore, few studies targeted younger adolescents, and few took place within a typical outpatient clinic setting.

While prior research provides a foundation that suggests a combination of community, provider and consumer directed interventions will be required to achieve the Healthy People 2020 goals, there is limited evidence on the best strategies to reach younger adolescents of both genders in typical pediatric clinic settings. In particular, there is a dearth of evidence on whether and how digital technologies can support informed decision-making about preventative health behaviors.

Objectives of the study

Given poor HPV vaccination rates in Indiana as well as limited evidence on consumer-centered technology applications that can be deployed in a typical clinical setting, we designed a cluster randomized trial to test the effect of a digital HPV vaccine educational intervention to be delivered

during a clinic visit. Our study contributes evidence on whether and how information technologies can increase awareness and support parental decision-making about prevention behaviors such as vaccination. In this paper, we summarize the results of the trial.

Patients and Methods

Study design

The study employed a cluster randomized trial with 2-arm design to examine the efficacy of an education intervention on HPV vaccine series 1st dose (initiation), 2nd dose, and/or 3rd dose (completion) among 11-17 year old boys and girls from October 2015 to May 2016. Five urban health clinics were grouped into clusters based on patient volume, race, and gender. Clusters were randomized by coin flip. After randomization, the intervention cluster contained two clinics and the control cluster contained three clinics. The study was approved by the Indiana University Institutional Review Board. The IRB waived the requirement for written informed consent.

Setting

Eskenazi Health is one of the five largest safety net health systems in the United States. The health system contains a 315-bed hospital and nine community health centers located across the metropolitan area of Indianapolis, Indiana; the eleventh largest city in the United States. All five pediatric clinics within the health system served as the setting for this study.

Technical system

The Child Health Improvement through Computer Automation system (CHICA) is an operational CDS system used in the five pediatric clinics for over 12 years.[19] When a child signed into one of the pediatric clinics, the EHR system sent an HL7 ADT (registration) message to CHICA. In response, CHICA queried the patient's medical record. At the same time, the system sent an HL7

request to CHIRP (Children and Hoosier Immunization Registry Program), Indiana's immunization information system (IIS).[20,21] In response, CHICA received a download of the child's immunization history. The download included CHIRP's "forecast" of the immunizations for which the patient was due. The electronic transfer of immunization information between CHICA and CHIRP is a form of health information exchange (HIE).[22]

Theo™ is an interactive, consumer-directed mHealth software developed by Noble.MD (recently acquired by WellTrackOne; Hilton Head Island, SC) that functions on a tablet platform. Theo™ can screen for health risks at the point-of-care using validated screening surveys, identify specific patient risks, and deliver a standardized educational video in real time. Theo™ measures pre- and post-intervention patient knowledge, attitudes, readiness for change, and risk mitigation. Theo™ can create a HIPAA-compliant digital record that can be integrated into an EHR.

The technical system integrating CHICA and Theo™ is summarized in **Figure 1**. Once CHICA determined an adolescent registered into the clinic to be eligible for the intervention by analyzing their combined medical record (1) and immunization registry (2) data, a medical assistant (MA) in the clinic was notified (3) and provided the patient's study identifier (a randomly generated study ID). The MA then provided the parent of the adolescent with a tablet and entered the study identifier into the THEO™ software (4). One of two programs then launched (5), depending on the adolescent's current HPV vaccination status.

The first program, created for adolescents who had not yet received the first dose of the HPV vaccine, assessed whether the family had already decided in favor of the HPV vaccine or if the family wanted more information. If the system determined the family was in favor of receiving a vaccine at the visit, the program provided a simple reinforcement message. If the family indicated a desire for more information about the HPV vaccine, the program provided information specific

to the cancer prevention benefits and safety profile of the vaccine. The second program, for adolescents who had already received the first or second vaccine in the series, emphasized the need to make the first vaccine count by receiving the full series. Both programs were available in English and Spanish.

<Insert Figure 1 approximately here>

The program scripts were created by several authors (GZ, SD, BED, BL) with expertise in adolescent health, HPV vaccination, epidemiology and health communication. Although not assessed in this paper, the scripts and questions used by participants was guided by the Theory of Planned Behavior, which has been used in prior HPV vaccine uptake research.[23,24] Once finalized, the scripts were recorded in English and Spanish then integrated into the THEO^{TM} platform. The scripts are available for review and use by others following permission from the authors.

Participants

Participants were parents or guardians of unvaccinated and partially vaccinated adolescents aged 11-17 as of the date of visit during the study period. All parents or guardians of adolescents attending intervention clinics were potentially eligible. Parents were excluded if their children had received the full HPV vaccination series. Parents further needed to read and comprehend either English or Spanish.

Data management and analysis

Spurious records were removed prior to analysis (25 out of 1621 were deleted). These records were either missing key values, such as a determination of whether or not the adolescent received a dose of the HPV vaccine, or calculated values were out of range (e.g., adolescent went from having the

first dose of HPV vaccine prior to the visit to having not started the vaccine series two weeks after the encounter).

Demographic and insurance data were summarized by treatment group to examine the overall characteristics of the cohort. Continuous variables were summarized using means and standard deviations. Comparisons were made between the two treatment groups using t tests. Categorical variables were summarized using proportions and differences between proportions and significance testing was carried out with the Chi-square test.

The primary outcome of interest was HPV vaccine uptake, defined as a change in vaccination status as a result of a clinic visit. Vaccination status could be one of four potential states: 1) 'patient lacks documentation on starting the series'; 2) 'patient had documented first dose'; 3) 'patient had documented second dose'; or 4) 'patient had documented third or final dose'. Documentation was determined by CHICA which integrated records from both the adolescent's EHR and CHIRP, the state immunization registry. The outcome variable was modeled as a binary change between two time periods where a value of '1' represented a change in status (or state). A two-week window was observed following a clinic visit to allow for any vaccines delivered in the clinic during an encounter to be recorded in the EHR or CHIRP.

To analyze the effect of the intervention on vaccine uptake, we employed an intention to treat (ITT) analysis using generalized estimating equations (GEE) to accommodate the potential cluster effect of clinics, when a significant cluster effect was identified. Specifically, GEE accounts for the correlations in treatment outcomes from children seen at the same clinic. GEE is frequently used in generalized linear models for correlated data and produces robust standard error estimates.[25] We performed two ITT analyses to compare vaccine uptake in 1) the intervention versus control clinics as well as 2) the group of adolescents who received the tablet versus those

who did not receive the intervention. All significance testing was two-tailed and the significance level was set at 5%. All data analyses were completed with SAS version 9.3 (Cary, North Carolina).

Results

Cohort characteristics

A total of 1,596 adolescents visited one of the clinics during the seven month trial. One-third (N=537) visited an intervention clinic with the remainder visiting a control clinic. The characteristics of the cohort are summarized in **Table 1**. Overall, adolescents were predominantly non-white, 11-12 years of age, and had Medicaid insurance.

Gender and race were similar between intervention and control clinics. Adolescents attending the two intervention clinics were slightly younger, on average, than those who attended the control clinics (mean age 12.2 years versus 12.9 years, $p < 0.001$). The study arms also differed by insurance type with adolescents attending the intervention clinics more likely to have commercial or Medicaid insurance and less likely to be self-pay or other form of insurance than those attending the control clinics ($p < 0.001$).

<Insert Table 1 Approximately Here>

Intervention effect

Vaccine status during visits as well as two weeks following visits is summarized in **Figure 2**. Similar patterns are observed across intervention and control clinics. The proportion of adolescents with no dose of the HPV vaccine two weeks after a clinic visit (36.2%) is lower than at the time of the visit (56.8%). In parallel there is a rise in the proportion of adolescents with a documented first, second, or third dose of the vaccine two weeks after a clinic visit. The exception to this pattern

is in the intervention clinics, where the proportion of adolescents with a documented first dose actually fell slightly two weeks post-visit (29.1% to 27.9%).

<Insert Figure 2 approximately here>

Results of the ITT analysis examining the effect of the intervention are summarized in **Table 2**. Of those presenting to a control clinic, 531 (50.1%) received a dose of the HPV vaccine within two weeks of a visit. Of those presenting to an intervention clinic, 348 (64.8%) received a dose of the HPV vaccine within two weeks of the visit. Comparing HPV vaccination uptake (e.g., a change in HPV dose status) between intervention and control clinics, adolescents presenting to an intervention clinic had nearly double the odds of receiving a dose of the HPV vaccine (OR, 1.82, 95% CI, 1.47-2.25, $p<0.001$).

A total of 141 (25% of those presenting to an intervention clinic) adolescents received a tablet from a medical assistant during their visit. Nearly four-fifths (78.0%) of these adolescents received a dose of the HPV vaccine. Slightly more than half (52.8%) of adolescents who did not receive a tablet received a dose of the vaccine. Comparing HPV vaccination uptake between these groups, adolescents who received a tablet had three times greater odds of receiving a dose of the HPV vaccine (OR, 3.07, 95% CI, 1.47-6.42, $p=0.003$). For this analysis, the cluster effect was significant ($p=0.005$), therefore the GEE accounted for the clustering by clinic.

<Insert Table 2 Approximately Here>

Discussion

In a cluster randomized trial across five pediatric clinics within an urban health system, we examined the effect of a digital educational intervention aimed at increasing HPV vaccination uptake among adolescents. At intervention sites, a video on the risks and benefits of the HPV

vaccine or reinforcement message was presented on a mobile tablet to parents or guardians of eligible adolescents in an exam room while they waited for clinicians during a routine, non-acute care visit.

The efficacy of the tablet-based educational intervention was significant, tripling the odds of HPV vaccine uptake among adolescents who received the tablets. Viewing tailored messages on the tablets with respect to vaccine initiation or series completion likely 'activated' families to either request the vaccine or discuss the vaccine with providers during the visit. It is further likely that, when families asked about the vaccine following use of the tablets, providers delivered positive reinforcement messages that also contributed to vaccine uptake, a 'feature' of interventions like the one used in this study. These results suggest that patient-centered education strategies delivered in a clinic setting via information technology platforms can positively impact the adoption of preventive health behaviors.

This study adds to our understanding of consumer-oriented interventions that seek to improve HPV prevention behaviors. Prior studies[8,12] employed a heterogeneous set of communication media to reach adolescents or their parents, with most studies employing automated phone call reminders. Just two studies[17,18] utilized interactive computer-based approaches. In DiClemente et al.,[18] adolescent females 14-18 years in age viewed a 12-minute interactive media presentation. Researchers observed a significant difference only in completion of the second dose of the HPV vaccine; there was no change in initiation rate and there was a non-significant increase in completion of the third dose. In Hopfer et al.,[17] female college students 18-26 years in age watched videos of vaccine decision narratives delivered by peers, medical experts, or a combination of peers and experts. Women who watched the videos delivered by a combination of peers and experts were almost twice as likely as controls to vaccinate within two months of watching the video.[17]

Compared with prior studies, our study included younger adolescents (11-17 years of age) and observed significant increases in series initiation as well as second and third doses of the vaccine. The younger population in the intervention clinics may explain, in part, impact on series initiation as compared to DiClemente et al.[18]

The impact of consumer-oriented educational interventions on public health could be significant if broadly used across the health system. Vaccination rates against HPV remain low in Indiana and many other states for early adolescents.[7] Vaccine series completion rates also remain well below the Healthy People 2020 goals, especially for adolescent males. An educational intervention accessible to adolescents as well as their parents or guardians could support more informed decision-making about the risks of HPV infection and benefits of vaccination. Moreover, an educational intervention might enable additive effects when combined with community- and provider-oriented interventions, which prior research suggests can also improve vaccination rates.[8-11]

A key component of the intervention was the interoperable HIE network that enabled the CHICA system to gather and integrate data from the health system's commercial EHR as well as the state IIS, known as CHIRP in Indiana. Automated query and integration of vaccine history information to the point of care provided a strong infrastructure[26,27] upon which the intervention could be tested. While HIE networks exist elsewhere, the technical architecture and approach used in this study would likely need to be adapted to succeed in states with less comprehensive HIE networks or IIS.

While the results from this trial are encouraging, implementing the trial involved several challenges. A major challenge was distribution of the tablets to eligible patients. Only a quarter of eligible patients received a tablet upon clinic check-in. This presented a logistical barrier. Before providing a tablet to a patient, the MA had to be alerted by CHICA to the patient's eligibility and

manually enter the patient's trial study identifier into the tablet. These steps proved quite challenging for a busy pediatric clinic environment. If tablets were routinely distributed to all patients of a certain age, or every patient regardless of age, and patients could use the tablets to view a variety of content, then administration of the devices might be easier on clinic staff.

Another challenge was variable wait times, since some providers came into the room just before or during the video interaction. Similarly, some clinics take patients right away to the exam room, while other clinics routinely have waiting periods in a lobby. These present challenges as to when it would be an appropriate time to ask patients to interact with a tablet to view an educational intervention. One possibility for future research would be to examine pre-visit delivery of videos and interactive media using the Internet or mobile phone to view an educational intervention 24-48 hours prior to the visit. A recent review by Badawy and Kuhns,[28] which examined mobile phone applications designed to support positive adolescent preventative health choices, concluded that less than half of the studies (N=19) observed a significant improvement in prevention decisions. Additional studies on mobile interventions would contribute to the growing evidence base on consumer-focused informatics applications.[29]

Limitations

This study has three limitations of note. First, the clustering of clinics occurred within a single, urban health system cautioning broad generalizations across all care settings. Additional testing across a variety of settings and multiple health systems would be necessary to demonstrate sustained effects prior to adoption into routine care. Second, the mere presence of the tablets in the clinic might have influenced provider behavior for all patients in that clinic (e.g., un-blinding) rather than just those patients who received the tablets. Finally, the outcome was modeled as a dichotomous variable with respect to a change in vaccine status. Because analysis was not

performed separately for vaccine initiation versus series completion, the intervention may have had more effect on one of these groups of patients since the educational software showed different videos to each group of patients. Future research should explore whether educational interventions are more effective for initiation or completion.

Conclusions

In a cluster randomized trial of an educational intervention to improve HPV vaccination rates delivered via a digital tablet in an exam room, efficacy was high. While results are promising, the intervention occurred at two clinics in a single urban health system. An expanded, multisite trial of the intervention, perhaps in combination with an intervention targeting providers, would be necessary to demonstrate both how the intervention could scale across the health system and how the intervention might work in combination with other evidence-based methods for improving HPV vaccination rates.

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Legends for Figures

Figure 1 – Information architecture and workflow used to trigger a clinical encounter involving the tablet educational intervention. As patients sign into the clinic, vaccination records are gathered electronically from the EHR and IIS. The CHICA CDSS determines eligibility and notifies the MA if the patient should receive a tablet and provides a subject identifier. The subject ID is entered into the tablet, which is given to the parent of the adolescent as the MA escorts them back to the exam room. EHR = Electronic health record; IIS = Immunization information system; CDSS = Clinical decision support system; CHICA = Child Health Improvement through Computer Automation; MA = Medical assistant

Figure 2 Proportion of control and intervention clinic populations with no dose, one dose, two doses, and three doses of the HPV vaccine at the time of clinic visit and again two weeks after visit during the six month trial of a tablet-based educational intervention.

Table 1. Characteristics of Adolescents Visiting Control and Intervention Clinics in the Eskenazi Health System in Indianapolis, Indiana, Between October 12, 2015, and April 12, 2016

Characteristic	**Overall, *N* = 1596**	**Control, *N* = 1059**	**Intervention, *N* = 537**	***P***
Sex, *n* (%)				0.474
Female	723 (45.3)	473 (44.7)	250 (46.6)	
Male	873 (54.7)	586 (55.3)	287 (53.4)	
Race, *n* (%)				0.128
White	141 (8.8)	100 (9.4)	41 (7.6)	
African American	870 (54.5)	559 (52.8)	311 (57.9)	
Other or unknown	585 (36.7)	400 (37.8)	185 (34.5)	
Insurance, *n* (%)				<.001
Medicaid	1241 (77.8)	796 (75.2)	445 (82.9)	
Commercial	101 (6.3)	64 (6.0)	37 (6.9)	
Self-pay	53 (3.3)	43 (4.1)	10 (1.9)	
Other or unknown	201 (12.6)	156 (14.7)	45 (8.4)	
Age, y, *n* (%)				<.001
11–12	916 (57.4)	527 (49.8)	389 (72.4)	
13–14	409 (25.6)	320 (30.2)	89 (16.6)	
15–17	271 (17.0)	212 (20.0)	59 (11.0)	

Table 2. Association Between Digital Educational Intervention and HPV Vaccination Uptake in the Eskenazi Health System in Indianapolis, Indiana, Between October 12, 2015, and April 12, 2016

Group	**No. Subjects, *N***	**Count of Change in Vaccine State (%)**	**OR**	**95% CI**	***P***
Intervention versus control clinics					
Adolescents who presented to an intervention clinic	537	348 (64.8)	1.82	1.47–2.25	<.001
Adolescents who presented to a control clinic	1059	531 (50.1)	N/A	N/A	Reference
Tablet versus no tablet					
Subjects who received a tablet during clinic visit at an intervention clinic	141	110 (78.0)	3.07	1.47–6.42	0.003
Subjects who did not receive a tablet during clinic visit at a control or intervention clinic	1455	768 (52.8)	N/A	N/A	Reference

Figure 1.

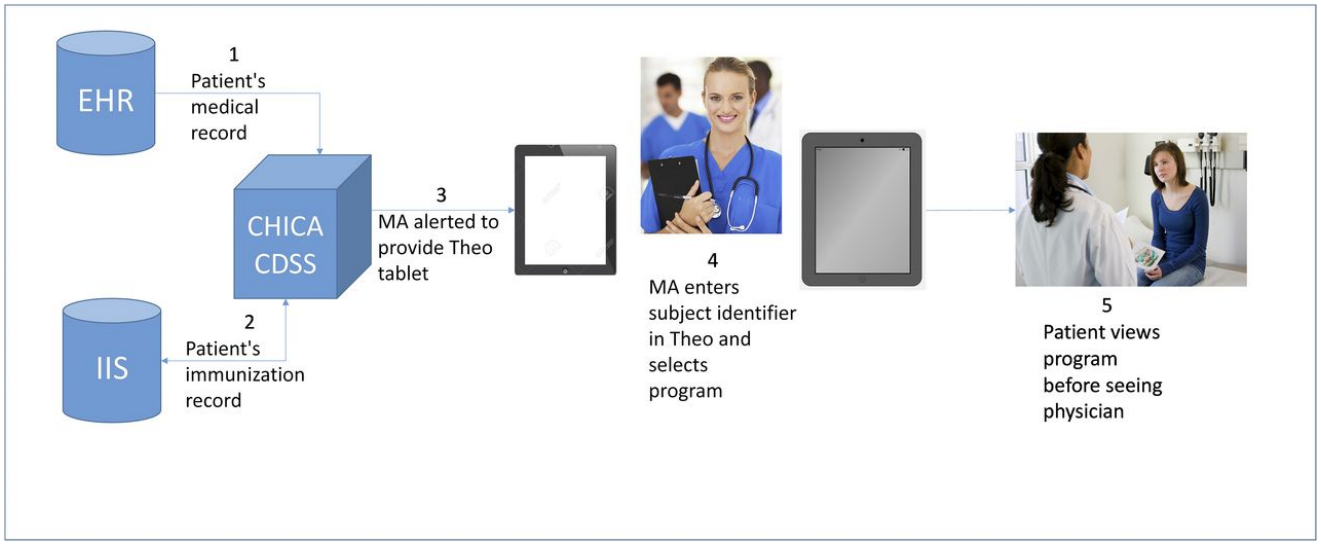
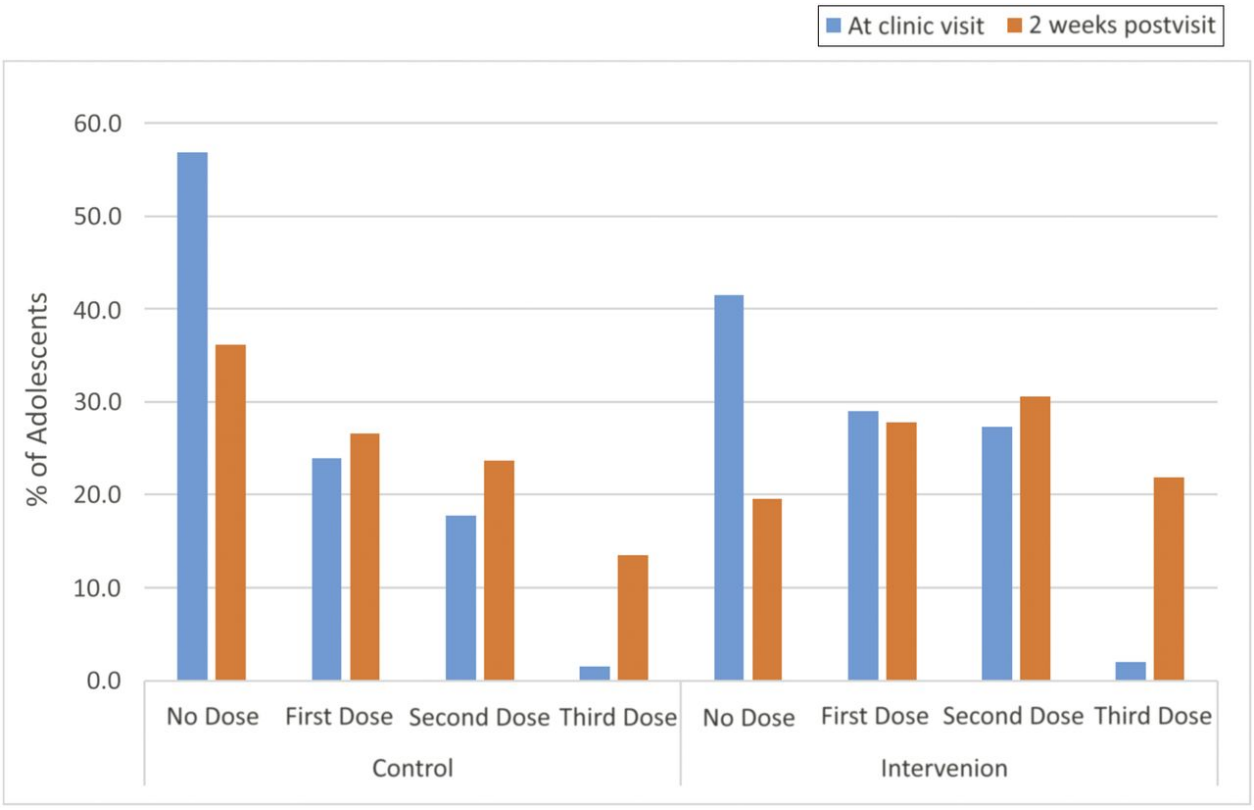

EHR
1
Patient's medical record
CHICA CDSS
2
Patient's immunization record
IIS
3
MA alerted to provide Theo tablet
4
MA enters subject identifier in Theo and selects program
5
Patient views program before seeing physician

Figure 2.


At clinic visit
2 weeks postvisit
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% of Adolescents
No Dose
First Dose
Second Dose
Third Dose
No Dose
First Dose
Second Dose
Third Dose
Control
Intervenion