Interactive, Health Literacy Promoting Text Messages and HPV Vaccine Completion In Minority Adolescents

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Study Purpose and Rationale

Vaccination is one of the most effective public health interventions[1], yet fundamental problems exist in translating highly effective vaccines into vaccination coverage levels sufficient to achieve population immunity or to realize their prevention potential. Phenomenal successes in eradication of older vaccine-preventable disease such as diphtheria, smallpox and polio have been unachievable for many other vaccinations such as influenza, human papillomavirus, and measles. Additionally, significant disparities in vaccination coverage exist for low-income and other disadvantaged populations.[2,3] While other factors play a role, limited vaccine health literacy such as decreased knowledge about disease risk or misperceptions about vaccination is associated with pediatric and adult under-vaccination[4-12]. Emerging communication technologies, such as text messaging, linked to electronic health records (EHR) data offer low-cost, scalable opportunities to improve health literacy and to promote healthy behaviors, such as vaccination. Our work is at the forefront of this emerging field.[13,14]

Nearly all U.S. adults (87%) have a cell phone, with higher rates (93%) among 30–49-year-olds.[15] Additionally, most cell phone owners use text messaging.[15] Text messaging platforms such as ours can deliver thousands of messages simultaneously, allowing significant and rapid penetration of large target populations. Parents value health-related text messages, including those for vaccination,[16-19] and we have reported successful trials of text message vaccinationreminders.[13,14,20] These trials took place in low-income populations for whom vaccination disparities exist, but for whom traditional mail and phone vaccination reminders have had limited effects.[21-24] While our first text messages were non-enhanced reminders that solely notified parents that their child was due for vaccination, our next generation of messages included health literacy promoting information.[14,20] These messages primarily used an untailored approach that did not maximize their effect. The trans-theoretical model of behavior change supports tailoring interventions to an individual's stage of decision-making.[25] While there is evidence for the effectiveness of this model in changing vaccination behavior,[26-28] it has not been tested in a clinical trial. We propose to assess the next generation of text messages enhanced with interactive, vaccine health literacy-promoting information tailored individual families' stages of vaccination decision-making. Human papillomavirus (HPV)

is the most prevalent sexually transmitted infection in the U.S., and can lead to genital warts, and cervical, anal and penile cancer.[29-36] Despite the availability of a highly effective vaccine,[37-40] completion rates of the 3-dose vaccine series remain low, with only one third of female adolescents and 1% of male adolescents protected.[3,41-45] Minorities have higher HPV prevalence and greater cervical and penile cancer incidence,[29,46] but lower vaccine completion rates.[3,42,47] Using a preliminary non-randomized design, we demonstrated the effectiveness of non-enhanced text message HPV vaccine reminders on increased receipt of the next dose due.[20] While substantial vaccination differences were seen, overall completion rates remained low. Limited health literacy about the HPV-vaccine can affect series completion,[48,49] and there is an indication for the potential use of the trans-theoretical model for changing HPV vaccination behavior.[26,27] As HPV vaccine recommendations have not translated into high vaccination coverage levels, these new generation of tailored, text messages have potential for stronger disease prevention, but have not been assessed. In this study, 960 parents of female and male 9-17 year-olds receiving their first HPV vaccine dose will be randomized to: (1) enhanced text messages with interactive, vaccine health literacy-promoting information tailored to vaccine decision making-stage vs. (2) non-enhanced text messages that only notify when the next dose is due. The primary outcome is completion of the 3-dose HPV vaccine series within 12 months of initiation.

Aim: To compare the effectiveness, in a randomized controlled trial, of the addition of interactive, tailored vaccine-health-literacy-promoting information to text-message vaccine reminders in improving HPV vaccine series completion for minority adolescents.

We hypothesize that completion will be higher in those whose families receive enhanced text message reminders vs. non-enhanced text message reminders. Linking a new technology with a novel use of a well-tested behavioral theory builds on our previous work, and has the potential to provide important evidence for the next generation of text message reminders both for vaccination and potentially for other health problems. It also has high potential for dissemination.

Approach Overview: propose to build upon our prior research to determine, using a RCT, whether the provision of individualized vaccine health literacy-promoting

information combined with reminders improves HPV vaccine series completion. We will randomize 960 primarily minority adolescents aged 9-17 years who have received their first HPV vaccine in equal numbers to: (1) enhanced text messages with interactive, vaccine health literacy-promoting information tailored to vaccine decision making-stage plus vs. (2) non-enhanced text messages solely notifying when the next dose is due. The primary outcome will be completion of the entire 3-dose series within 12 months from the randomized adolescent's first HPV vaccine dose. Although we recognize we could include a partial vaccination outcome represented by receiving 2 doses, we define success as series completion since vaccine efficacy data are based on thisdefinition.[37,39,50] If subsequently it is determined that two doses are protective, we will be able to analyze the intervention's impact on 2 doses.

Preliminary Studies

1) HPV vaccine coverage: At the study sites, 87.8% of adolescent females and 52.2% of adolescent males 13-21 years-old received1 HPV vaccine dose; this exceeds other established rates in 13-17 year old females: 53.0% nationally, 46.6% New York (NY) State, and 56.8% NY City and in 13-17 year old males 8.0% nationally, 6.4% New York (NY)State, and 10.1% NY City.[51] However, at the study sites, among 13-17 year old adolescents who received their first HPV vaccine dose between June 2010 and May 2011, only 56.8% of females and 45.6% of males received all 3 doses. This is lower than reported at the national (69.6%), and at the NY state (76.9%) and NY City (72.7%) levels during the same period.[51] Higher initiation, but poorer completion rates is reflective of the national pattern for minority femaleadolescents.[51] Among 11-17 years-olds, only 40.0% of females and 30.7% of males received 3 doses within 12 months.

2) Use of text messaging, including for HPV and other adolescent vaccines reminders: In addition to the HPV text message reminder study, we also assessed the impact of text message reminders on receipt of meningococcal (MCV4) and/or tetanus, diphtheria, acellular pertussis (Tdap) vaccines.[14] In a randomized intervention with urban adolescents without a MCV4 and/or Tdap vaccine and age-, gender- matched

controls (n=361), adolescents whose parents were texted were more likely to be vaccinated at weeks 4 (15.4% vs. 4.2%; p<0.001).

3) Experience conducting randomized controlled trials of text message vaccine reminders: We recently published the first large-scale RCT of text message vaccination reminders.[13] We randomized 9,213 children and adolescents (6 months to 18 years) receiving care at 4 community-based clinics. This study is relevant to the present application for several reasons: (1) it was conducted in the same 4 clinical sites we propose to use; and (2) we implemented this influenza vaccine text messaging/health literacy intervention successfully in English and Spanish. Specifically, we found that children whose parents were assigned to the text messaging intervention were more likely to receive an influenza vaccine both by a fall review date, 27.1% of the intervention vs. 22.8% of the usual care group (difference, 4.3% [95% CI, 2.3,6.3]; RRR, 1.19 [95% CI, 1.10,1.28]; P < .001), and by March 31 (intervention: 43.6% vs. 39.9% usual care (difference, 3.7% [95% CI, 1.5,5.9]; [RRR], 1.09 [95% CI, 1.04,1.15]; P = .001).

4) Experience conducting health literacy related interventions: In an NIH-funded study, we assessed an educational intervention to improve health literacy regarding upper respiratory infections in low-income, Latino families. Compared with controls, school age children of intervention parents were more likely to receive the 2009 H1N1vaccine (56.5% vs. 26.1%; p<0.05) and their parents were more likely to receive a seasonal influenza vaccine (OR 2.7,95% CI 1.3,5.7) (unpublished data).

5) Use of interactive vaccine health literacy-associated text messaging: We assessed the impact of text messages on receipt of influenza vaccine for 5,462 children/adolescents still unvaccinated by early winter. In this difficult to vaccinate population, those whose parents received interactive vaccine health literacy-promoting text messages were more likely to be vaccinated (38.5%) than both usual care (34.8%, p<0.05) and those receiving non-interactive text messages (35.3%, p<0.05) (unpublished data). In another study of 453 children in need of a second

dose of influenza vaccine this (2012-13) season, (76.7%) of those whose parents received health literacy-promoting text messages including an interactive message were more likely to receive a second dose than those receiving non-enhanced reminders (67.8%) or solely a written reminder (58.7%;p<<0.01).

6) Factors that affect HPV vaccine completion: We conducted a preliminary study addressing the need to identify key health literacy-related themes associated with HPV vaccine series completion. In the same population where this proposed RCT study would take place, we audio-recorded and transcribed 40 in-depth structured interviews of parent-adolescent dyads with adolescents who had received their first HPV vaccine 12 months previously; including adolescents who did and did not complete the HPV vaccine series within 12 months. Transcripts were analyzed utilizing thematic analysis.52 Most interviews (65.0%) were in Spanish. Adolescents were primarily Latino (88%), publicly insured (95%) and female (65.0%). One-third (36%) of parents had less than a high school education, and20% only graduated from high school. All parents (100%) reported initiating vaccination to protect their child, largely from cancer or less commonly from sexually transmitted infections (HPV). Nearly all (93%) viewed their health care provider as an important source of HPV vaccine information. Families were asked questions to elicit factors affecting their attitude toward completing the HPV vaccine series. The majority of responses (95%) fell into three themes: (1) once the decision was made to start, the series should be completed and all needed doses received; (2) protection of their child; (3) presumption of a good experience with subsequent doses if the first one went well. Half of parents mentioned side effect or vaccine safety concerns. These concerns were similar for the parents of female vs. male adolescents (46% vs. 50%) and Spanish vs. English-speaking parents (50% vs. 43%). In nearly all families, parents were seen as responsible for vaccination decisions and the logistics of ensuring the adolescent received the needed doses. Although most parents and adolescents knew the HPV vaccine was a multidose series, the majority 90% did not know the correct intervals between doses. Of note, all who knew the correct timing for both doses completed the series within 12 months. Over 90% of parents and adolescents

thought that they received their HPV vaccine doses “on-time”, but when records were checked, only (45%) received second and third doses on-time. All but one parent was interested in receiving HPV vaccine text message reminders, and none had concerns, confirming our previous study findings.[16] Overall, parents wanted messages to include both positive and negative information. In addition to information regarding the number and timing of doses, all participant comments regarding desired content for messages, except one, could be divided into 3 themes: (1) what the vaccine protects against and why it is important; (2) what can happen if someone is not fully vaccinated, and (3) vaccine side effects and safety. These themes were the same across all gender and language sub-groups. These results provide important information that will be useful for this proposed intervention. First, parents were seen as the ones responsible for vaccination decisions and logistics, which supports our plan to text the parents of the adolescent. Second, health care providers were viewed as a very common source of information; to underscore this connection we will tag the messages as coming from the clinic where the family was recruited, as in our previous studies. Third, in terms of parent suggested message content: (a) protection of their child was a key reason why families continued or planned to continue to vaccinate, and also a content area for which they wanted to receive messages about; (b) many families felt that once they decided to start the series, they should finish it, which relates to their suggested text message content regarding the consequences of not being fully vaccinated; (c) side effects and safety still remain a concern even after initiation and should be included in the text messages. This view relates to the reported parental attitude that they presume subsequent doses will be side-effect free if the first dose experience was good. The following themes did not differ based on the gender of the vaccine recipient or parent language: (1) reason for initiating vaccine, (2) attitude towards continuing the series, (3) identifying the parent as responsible for vaccination decisions, and (4) desired vaccine health literacy message content. We interpret these findings as a basis for not tailoring the message content for Arm 3 by gender or language. Parents will be able to self-tailor the content of the messages by requesting more information about

certain topics, which will be sent to them automatically. Differences in requested information can be assessed in the analytic phase.

Research Aims & Abstracts

Research Aim and Hypothesis: To compare the effectiveness, in a randomized controlled trial, of the addition of interactive, tailored vaccine-health-literacy-promoting information to text-message vaccine reminders in improving HPV vaccine series completion for minority adolescents. We hypothesize that completion will be higher in those whose families receive enhanced text message reminders vs. non-enhanced text message reminders.

Target enrollment: 15,000

Scientific Abstract: Vaccination is one of the most effective public health interventions, yet fundamental problems exist in translating highly effective vaccines into high vaccination coverage. Emerging communication technologies, such as text messaging offer low-cost, scalable opportunities to improve health literacy and promote healthy behaviors, such as vaccination. While we reported the success of text message vaccine reminders, effects were limited by their untailored approach. The trans-theoretical model of behavior change supports tailoring interventions to an individual's stage of decision-making. Human papillomavirus (HPV) is the most prevalent sexually transmitted virus in the U.S. and can lead to genital warts, and cervical, anal and penile cancer. The three-dose vaccine is 90-100% efficacious. Minorities are at greatest risk for such cancers but have low HPV vaccine completion rates. Limited health literacy regarding the vaccine can affect series completion. We will compare the effects of enhancing text message vaccination reminders with interactive, vaccine health literacy-promoting information tailored to vaccine decision making-stage on HPV vaccine series completion. The effects of these messages represent a new paradigm in interactive health communications.

Study Design

Study Sites

This study will be conducted in four community health clinics affiliated that are part of the NewYork-Presbyterian Hospital (NYP) Ambulatory Care Network (ACN) and Columbia University. These clinics are in Health Professional Shortage Areas (HPSA) and care for many families living in the Washington Heights/Inwood section of northernManhattan.53 These practices provide >55,000 visits annually; 87% for publicly insured patients, and the vast majority of families are Latino. The Vaccines for Children (VFC) Program provides the majority of vaccines given at the practices for free. Although the patient population and providers are similar across sites, baseline variability between sites will be accounted for in the randomization. All vaccinations given at the study sites are documented in the NYP Immunization Registry, EzVac, of which Dr. Stockwell is Medical Director. The EzVac database contains over 2.2 million vaccinations administered to >275,000patients. EzVac extracts information about vaccinations directly from the provider order entry module of the electronic health record (EHR) making data accurate for HPV vaccines administered at the clinical sites. EzVac as part of its regular practice synchronizes data with the New York Citywide Immunization Registry (CIR) which is a population-based registry. NY City Public Health Law requires documentation for all vaccinations administered to those18 year- olds be submitted to CIR,54 which captures more than 85% of vaccines administered in NY City, and 93% of vaccines from the Vaccines for Children Program (VFC).[55,56] Almost all (91.4%) adolescents at the four study sites are VFC-eligible, i.e. publicly insured or uninsured. Therefore, the few vaccines administered outside of the practice network to patients from the study sites are also captured in EzVac through this synchronization for patient care. Dr. Stockwell's team has built a secure text messaging platform linked to EzVac. This platform allows custom text messages to be created, and sent out according to a schedule. Before a set of scheduled message is sent, the system can re-query the EzVac database to identify if patients have received the appropriate vaccination and exclude them from receiving additional reminders. The text messaging platform is designed to be interactive; patients can text a reply to stop or resume

reminders, toggle the language of messages, and ask for assistance. It is also already programmed to send and respond to interactive text messages.

Arm 1: Message Design

During grant month 1-2, using the information gathered from the preliminary studies regarding health literacy-related information affecting completion of the HPV vaccine, our previous texting studies, and the relevant literature, we will design the two sets of text messages (enhanced vaccine health literacy-promoting and non-enhanced text messages). We will follow procedures established in the development and testing of text messages, outlined below, used in our recent trial assessing the impact of influenza vaccine text message reminders.[13] We will first design the message in English paying attention to reading level, as assessed by the Flesch–Kincaid readability test.57 Our previous text messages have been on a third grade reading level, which is in accordance with the American Medical Association health literacy-related guidelines that written materials be at no more than a 6th grade reading level.[58] We strongly considered the need to tailor the vaccine health literacy-promoting messages in Arm 3 differently for Spanish- and English-speaking Latino families as well as parents of male and female adolescents. Yet, as previously described, our HPV vaccine interview study showed no differences by gender or language in elicited themes or desired content. Likewise, in our previous studies, we used equivalent English and Spanish content, and found no interaction between intervention effects and language of message; there was also no interaction with gender. Finally, using the same content, although translated or gender-specific, allows comparisons to be made across the study population. Thus, the messages will be similar for English and Spanish-speaking parents, ensuring proper linguistic and cultural equivalency, as well as for males and females, adjusting the wording for gender and gender-specific HPV associated disease (e.g. cervical vs. penile cancer). Importantly, parents will be able to self-tailor the content of the interactive messages by texting back indicators about which items they want more information; the text messaging platform then automatically responds with that information. We will be able to note if this self-tailoring differed for parents of male vs. female adolescents and English vs. Spanish-speaking parents. We will follow best practices based on guidelines

to translating health services research measures,[59] to translate messages to ensure that we have linguistically and culturally equivalent messages in Spanish and English. We will then pre-test the messages at the study sites with families. The research assistant will approach families after the adolescent has received an HPV vaccination, in coordination with the nursing staff. After obtaining informed consent, the research assistant will text parents in real-time, while meeting with the parent, the proposed messages and ask the parent to say back in their own words what the message means to them. This adaptation of the "teach-back" method, commonly used health literacy tool,[58] verifies that the message conveys the desired information. S/he will then ask families if there was anything confusing about the message and suggestions for change. This process will be iterative until no new changes are made to the messages. Preliminarily, we will complete this process with 20 families. If we do not reach saturation with 20 families, i.e. changes to the messages are continuing to be made, we will continue to recruit using the same sampling plan.

Study Population

Eligibility Criteria:

- Parent of adolescent age 9-17 years
- Adolescent receives their first HPV vaccine dose at study site within last 2 weeks
- Has a cell phone number that can receive a text message
- Parent speaks English or Spanish

Exclusion Criteria

- Intends to move away from the NYC area in the study

Enrollment: Families of adolescents will be enrolled one of two ways. First, they can be given an information sheet by their provider or the nurse describing the study. This will be attached to an enrollment card on which interested families can write their cell phone number. In providing their number they are agreeing to be in the study. This card will be placed in a box in the clinic. Those who do not want to enroll can indicate that as well. Those who are not given an information sheet or do not have a card in the box, due to provider time, will be called and verbal consent obtained from those who are interested.

We will identify in EzVac those who received their first HPV vaccine in approximately the last week for whom we do not have a card. On inclusion, either via return of the enrollment card or over the phone, a confirmation text message will be sent to the participant family and delivery status assessed to ensure that the family has a working cellphone with text message. An undelivered message will be attempted to be delivered twice moreover the next week. If there are three undeliverable messages then the family will not be considered to have met eligibility criteria and will not be considered enrolled in the trial; they will be notified of this. We will enroll only one child per family. If more than one is eligible, we will select the one with the next most proximal birthday, e.g. a child whose birthday is in 7 days will be selected over a sibling whose is in 75 days. In the case of twins, whoever was designated at birth as twin A will be enrolled. If another adolescent becomes eligible during the trial, the family cannot re-enroll.

Randomization: Randomization will occur with a 1:1 allocation ratio stratified by (1) clinical site; (2) adolescent's gender; (3) parental language; and adolescent's age group (9-14; 15-17). These factors will be excerpted from the medical record after enrollment. Randomization will be done centrally by the programmer using an algorithm based on site, gender, language, and age. The statistician and analyst will be kept blinded to group assignment.

Study Sample and Enrollment

Based on EzVac data, there were 817 adolescents (females and males) 11-17 years old who received their first HPV vaccine at the four study sites between October 2012 and September 2013. Nearly all of those families (n=805) spoke English or Spanish. A few (n=51) were from the same family. Therefore, we expect 1885 adolescents to be eligible over the 30-month recruitment period. Across various studies conducted at the study sites, we found that between 83%and 89% of parents had text messaging. In one study, we assessed those with and without text messages and found no significant differences between those who had texting and those who did not in terms of adolescent's gender, parents' primary language, education level, or parent age. Using the low-end of this range, i.e. 83%, we expect 1,564 families to meet age, language and cell phone/texting inclusion criteria. To meet our sample size of 956 total (478 per arm), we would need to

recruit 61.1% of eligible families. In our most recent text message vaccine related study in which we completed active recruitment, 92% of eligible patients enrolled. We therefore believe our enrollment goal is realistic. At the study sites, 35% of 11–17-year-olds who initiate HPV vaccination and receive usual care receive 3 doses within 12 months. In our previous study, we had an effect size of 16% between those receiving conventional text messages and usual care. Therefore, based on this data, we expect a completion rate of 51% in the conventional group (Arm 2). With the proposed sample size in each arm and allocation, we will be powered to detect a minimum of 9% difference between arms with 80% power, allowing for a type I error of 5% for the primary outcome. In our second dose influenza vaccine study (section D3.1), our effect size was 9% between each arm; we expect the effect size in this trial to be higher since the messages will be personalized.

Intervention and Usual Care: The study will include approximately 30 months of recruitment. The intervention period for each individual is the 12-month period starting from administration of their first dose, as is standard in studies assessing HPV series vaccine completion as well as the efficacy trials.[37,39,50,60-62]

Arm 1: Randomized to receive additional enhanced text messages with vaccine health literacy-promoting information: An interactive query sent before the next dose is due will assess whether a parent is in the pre-contemplation stage and unaware their adolescent needs another HPV dose or when the dose is due, or if they are in the contemplation stage knowing that their adolescent needs further doses, but still undecided maybe due to questions regarding the vaccine efficacy, side effects and safety, or if they are in the preparation phase and planning to vaccinate but still in need of information on where to go or when. These will be based on previously published HPV vaccine decisional measures that used the trans-theoretical model.[26] Messages will then be tailored to their stage. In addition, we will include interactive text messages in the series that will allow participants to select to receive more information according to their specific needs, allowing self-tailoring of the text messaging. Finally, the current health literacy recommendations include “universal precautions” with all patients receive health literacy-promoting information regardless of perceived risk for limited health

literacy.[63] Therefore, all participants in this arm will receive some text messages related to the most common HPV vaccine related health literacy needs. The text messages have been attached to the protocol.

Arm 2: Randomized to receive non-enhanced text message reminders: Will receive non-enhanced text reminders notifying them when the next dose is due. They will receive messages in parallel timing to Arm 1. These will not include vaccine health literacy-promoting information and will be similar to those used in our previous adolescentstudies.[20,14] These are also attached to the protocol. Based on our preliminary studies, all text messages will be personalized and designed to be from the patient's medical home. In our previous studies, parents indicated that they wanted their child's name on the message as well as that it was being sent on behalf of the clinic.[16,19] The recipient will be the parent based on our previous work. We will text the cell phone number listed in the registration system, indicative of the parent who is to be contacted regarding medical care. Messages will be sent in English or Spanish based on the language preference of the participant. Throughout the study, participants will have the option to stop receiving text messages by replying to a text message with the word "quit" or "stop" in English or the corresponding commands in Spanish. Participants can request help by texting "help". They can also call the study team. These instructions will be given in a text message. After the first message sent to categorize those in Arm 1 and the parallel-timed message for Arm 2, preliminarily, we will send the first series of automated weekly reminders, beginning around d35 after the second HPV vaccine dose due date and will end two weeks after the vaccine is first over-due. Two booster doses will then be sent 28 and 42 days later, if the child has not been vaccinated. We will repeat the intervention beginning approximately d35 after second dose as a reminder for the third dose. The messages will be the same but refer to the third dose. The hospital's immunization registry will be queried before the third dose to ascertain if the patient received the second dose on time. If not, the message schedule for the third HPV vaccine dose will be readjusted for the new due date, based on CDC recommendations for minimal and desired intervals. All the study sites allow walk-ins for second and third doses of HPV vaccine, so no appointment is needed.

If the site does not have vaccine, we will send a message to participants due for second or third dose letting them know not to come in yet and that we will inform them when the sites have vaccine available again.

Measures

Outcome Measure: The primary outcome measure is completion of the 3-dose HPV vaccine series within 12 months from date of first dose. A secondary outcome is timeliness of vaccination, defined as time elapsed in days between dose 1 and 2, and dose 1 and 3.

Process Measures: Individual level information from the log files of the text-messaging platform will be collected to demonstrate that the correct messages were sent to each recipient for Arms 1 and 2. We will also determine the percentage of (1) text messages that sent back as undeliverable; and (2) participants opting out of the reminders during the study. We will also determine which specific vaccine health literacy-related information families request via text message, providing, in a prospective fashion, an indication of the most common parent identified HPV vaccine health literacy needs arising at the time that parents are making decisions regarding return for subsequent doses. This prospective information does not currently exist.

Follow-Up: Minimizing attrition and missing outcome data are crucial for valid results. We expect there will be little attrition with respect to outcome data. The hospital immunization registry, EzVac, automatically collects vaccine administrations from the EHR used at the 4 study sites as well as from the New York Citywide Immunization Registry (CIR) as part of the usual patient care, thereby allowing capture of vaccines administered to clinic patients both at study sites and at practices other than study sites in NY City.[55,56] Thus, we will have outcome data for subjects who receive HPV vaccination at facilities other than a study site. A second important issue is documentation of the intervention. In our previous HPV study, no one dropped out of the study after enrollment;[20] in our influenza text message RCT, only 4.5% of the 9,213 families declined further messages.[13] In addition, we expect only a small number of cell phone numbers will change over the course of the intervention. In our previous adolescent study, the number of cell phone numbers that changed was <2%.[14]

Data Management: Vaccination data will be retrieved from EzVac. All data will be accessed using a password-protected computer in a locked office and stored on a secure server managed by Columbia University IT, and backed up on a daily basis. All data files will be cleaned and edited prior to analysis, under Dr. Stockwell's supervision. Data analysis will be performed using SAS (Cary, NC). The programmer will monitor log files of text messages sent, replies received, and “undeliverable” messages and provide summaries to Dr. Stockwell on a daily basis.

Statistical Procedures

Data Analysis: We will first assess the randomization process by comparing baseline variables among the three groups. Hypothesis: Completion and timeliness will be higher in adolescents in families who receive enhanced text message reminders plus usual care vs. non-enhanced text message reminders plus usual care.

Series Completion: HPV vaccine completion rates in EzVac will be compared for all adolescents of participant parents at the end of a 12-month observation period starting at receipt of their first HPV vaccine dose. As in our previous RCT of influenza vaccine reminders,[13] all primary analyses will be done on an intention-to-treat basis, such that all randomized participants will be included in the analysis whether or not they at some point declined further messages or messages were returned as undeliverable. A secondary analysis will compare completion rates for adolescents of participants who received the entire set of reminders. Study arms will not be combined. Completion rates in the two randomized groups will be compared in the separate combinations delineated above using 2-sided 2 tests at a significance level of $P<0.05$ for each comparison. The number of subjects in each cell is expected to be high enough that the Fisher exact test will not be needed. Asymptotic confidence limits on the differences and relative rate ratios will be calculated.

Sub-group Analyses: We will perform subgroup analyses in different covariate-defined subgroups, for each outcome, to assess the possibility of intervention effects being different in these subgroups. This will be tested by including pre-specified covariates (adolescent: age, gender, year of entry, clinic site, dichotomized visit count; parent: language, previous participation in text message vaccination reminder study),[42,43,60,61,64-

[68] and their interactions with the intervention in a multiple logistic regression analysis. The models will also adjust for the direct effects of these covariates on the outcomes, thus increasing power to detect intervention effects. Initial models will be created including all of these covariates. Clearly non-significant ($p>0.2$) covariate terms will be removed from the final models. If more than one covariate appears in a final model, two-way (and, if necessary, multi-way) interactions of those covariates among themselves and with the study arm will be tested and included if significant at $p>0.2$) covariate terms will be removed from the final models. If more than one covariate appears in a final model, two-way (and, if necessary, multi-way) interactions of those covariates among themselves and with the study arm will be tested and included if significant at $p<0.05$. In addition to the covariates listed above, we will include race and insurance to the extent possible. Multivariate modeling with these covariates may not be possible depending on the degree of variability observed. The visit count will be defined as the number of clinic visits per adolescent in the 12-month period post-receipt of the first vaccine dose. Visits to the emergency department, hospitalization or specialty visits will not be included. The visit count will be dichotomized (the cut point determined by the frequency distribution of visit counts). With regard to longitudinal measurement, the outcome is defined as success or failure in receipt of 3 HPV vaccine doses within 12 months (no repeat measure of outcome). We will include a covariate for year of entry into study. We will also adjust for vaccine shortages as needed.

Timeliness: We define timeliness of vaccination according to the ACIP recommended intervals.[69] We will construct Kaplan-Meier curves of time from first to second dose and separately first to third dose,70 using both intention to treat as well as analyses accounting for message deliverability. We will then compare the curves using a log rank test. We will perform secondary subgroup analyses using Cox proportional hazards modeling to examine subgroup effects and to adjust for the same covariates as described above. Interactivity of messages: With regard to analyses pertaining to the interactive nature of messages in Arm 1, we will calculate the proportion of families who sought information about each individual topic both for the overall arm as well as subdivided by gender and parental language and stage of HPV vaccine decision-making at baseline. We will use Pearson’s chi square to compare completion rates at 12

months in adolescents in Arm 1 whose families requested further information vs. those in Arm 1 who did not.

Missing data: We will document missing data and classify it by variable and study arm. We will then assess if there are relationships between missingness and covariates such as demographics, study arm, or year of study entry. In the analysis of the study hypotheses, all randomized subjects will be included (intention to treat analysis). Missing outcome data will be imputed as failure in all study arms. We anticipate very few subjects will be missing outcome data. In the subgroup analyses, covariate data may also be missing. We will impute these variables using multiple imputation following the methodology of Rubin.[71] We will achieve this using the 3-phase SAS/STAT procedure that first creates “m” multiply imputed complete data sets using the MI procedure, then analyzes the “m” complete datasets using a standard procedure, PROC LOGISTIC, and finally generates valid statistical inferences about the missing values by combining the results using the MIANALYZE procedure properly reflecting the uncertainty due to missing values. In summary, the primary analysis of the study hypotheses will be based on intention to treat analysis using all randomized subjects. Subjects with missing outcome data will be retained in the analysis; failure to complete the 3-dose series will be imputed for those missing these data. We consider this to be the most conservative approach to hypothesis testing. We used this approach in our influenza-vaccine text message reminder study.[13] Multiple imputation will be used for the missing covariate data in subgroup analyses.

In addition as of 10/21/16: Any parents of an adolescent who was <15 years when first vaccinated who is already enrolled and has not yet received their second dose, will get a text message letting them know that there is an important update, that their child now only needs two doses with the second one being 6 months after the first and that we will text them when that dose is due. We have included that text message under documents.

Parents of adolescents first vaccinated before 15 years of age who have not yet received a second dose will receive an updated series of messages to be consistent

with the now 2 dose recommendation in both phrasing and timing (second dose now due 6 months after the first instead of 2 months and is now the last dose.

Recruitment And Consent

Families of adolescents will be enrolled one of two ways. First, they can be given an information sheet by their provider or the nurse describing the study. This will be attached to an enrollment card on which interested families can write their cell phone number. In providing their number they are agreeing to be in the study. This card will be placed in a box in the clinic. Those who do not want to enroll can indicate that as well. Those who are not given an information sheet or do not have a card in the box, due to provider time, will be called and verbal consent obtained from those who are interested. We will identify in EzVac those who received their first HPV vaccine in approximately the last week for whom we do not have a card. On inclusion, either via return of the enrollment card or over the phone, a confirmation text message will be sent to the participant family and delivery status assessed to ensure that the family has a working cellphone with text message.

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