SEARCH: Short Message Service (SMS) Electronic Adolescent Reminders for Completion of HPV Vaccination - Uganda: Pilot

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SEARCH: SMS Electronic Adolescent Reminders for Completion of HPV vaccination in Uganda

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OPERATIONAL DEFINITIONS

Adolescence: The period of physical and psychological development from the onset of puberty to adulthood.

Adolescent: A person of age 10 – 19 years.

Vaccine: is a suspension of live (attenuated/weakened) or inactivated microorganisms (e.g. bacteria, viruses) or fractions of microorganism administered to induce immunity and prevent an infectious disease or its complications.

Vaccine completion: defined as having received two doses of the HPV vaccine series with an interval of 6 months between the first and second doses.

LIST OF ABBREVIATIONS

HPV- Human papillomavirus

KCCA - Kampala Capital City Authority

UNEPI – Uganda National Expanded Programme on Immunization

USA – United States of America

ABSTRACT

Background- Cervical cancer is the leading female cancer in Uganda. HPV is the principal cause of cervical cancer, making vaccination the single most important primary preventive measure. However, in Kampala, Uganda only 29% of girls receive both needed doses. Reasons for under-vaccination include school absenteeism on special vaccination days, failing to remember to come to a health facility for a needed dose, and lack of knowledge regarding HPV and the vaccines. While research regarding the use of text message has not yet been demonstrated in a preteen/adolescent population in sub-Saharan African or other low- and middle-income countries (LMICs), phone reminders may improve adherence to vaccination completion rates. According to the World Bank, 89.9% of urban households in Uganda have a cell phone. While text messages can be used in populations with low literacy, families can opt to receive automated phone call reminders instead.

Objectives- This protocol is for text and voice phone message intervention development for a subsequent pilot randomized control trial to improve adherence to HPV vaccination schedules in Kampala City. The specific objectives are as follows:

1) To identify HPV vaccine text message reminder content (and parallel automated voice phone reminders) desired by the caregivers and their adolescent girls in Kampala.
2) To develop and pre-test HPV vaccine reminders with caregivers and their adolescent girls in Kampala.
3) To pilot assess the impact and feasibility of vaccine reminders on HPV vaccination

Methods- This study will utilize a qualitative approach as part of an exploratory sequential design with the primary intent of the exploratory design is to develop a digital tool which will then be tested. We will conduct formative research using key informant interviews with families of preteen/adolescent girls (throughout will be called adolescent) (n=30 dyads/triads), clinicians and immunization nurses of involved study sites (n=10), administrative staff and school leadership of involved study sites (n=12), and leadership within the KCCA and Ministry of Health (n=4) to assess attitudes towards HPV vaccination and text message reminders. Using the results from the interviews we will create prototypes of messages that will be shared with families (n=30 dyads) to identify issues with clarity, tone, and persuasiveness. Next, we will conduct a pilot trial to

randomize caregivers of adolescents at one KCCA site and the adolescent clinic, stratified by site, language and HPV vaccine dose needed (initiation vs. completion). Feasibility milestones will include reach, effect size determination and implementation measures. If the pilot is succesful, we will conduct a future full-scale RCT assessing the impact of the HPV vaccine text message reminders. The main outcome will be timeliness of vaccination. We will also collect process/feasibility measures.

Utility of the Study - The messages will be used for a pilot randomized control trial to examine their impact on HPV vaccination initiation and completion.

Anticipated Study Outcomes- This study will allow us to understand the types of educational information parents and providers believe is needed in HPV vaccination reminders in an LMIC. We will be able to use this information in a future large-scale intervention that will utilize text message reminders to prompt caregivers to return their adolescents for their next HPV dose.

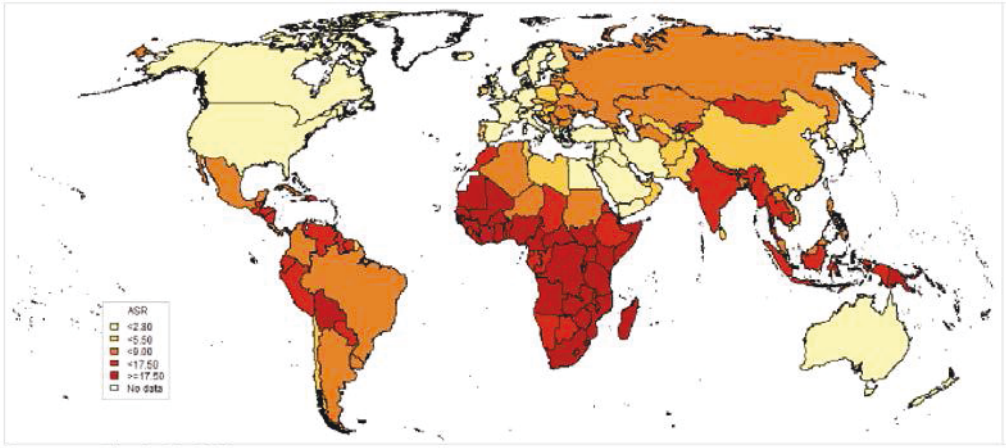
CHAPTER ONE

1.0 INTRODUCTION

1.1 Background:

Cervical Cancer rates in Uganda are high. Sub-Saharan Africa overall has the highest cervical cancer mortality rates in the world (Fig 1).[1] Cervical cancer is the leading cancer among women in Uganda. There are 6,413 new cases diagnosed and 4,301 deaths annually, and that number is rising, nearly doubling since 2017.[1] Up to 72% of women are diagnosed with late-stage disease,[2] and 80% die within 5 years of diagnosis.[3] The age-standardized cervical cancer incidence rate in Uganda of 54.8/100,000 women per year is ***over 4-times*** that of the rest of the world. The age-standardized mortality rate of 40.5/100,000 women is nearly ***6-times***.[1] HPV is the principal cause of cervical cancer and 57.0% of invasive cervical cancers are attributed to HPV strains 16 or 18. HPV point prevalence in normal cervical cytology in Uganda ranges from 15.2%-73.2%.[1]

Fig 1: Age-standardized mortality rates of cervical cancer in the World[1]



Data accessed on 05 Oct 2018.
ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference;
Rates per 100,000 women per year.
Data sources: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [05 October 2018].

HPV Vaccination is the single most important primary preventive measure for HPV.[4-7] Initial clinical trials of HPV vaccination among 20,000 young women in 33 countries showed near 100% efficacy in risk reduction in type-specific cervical, vulvar, and vaginal cancers, cervical dysplasia and genital warts.[8-12] A systematic review of HPV vaccine programs across 69 countries over ten years found approximate maximal reductions of 90% for HPV 6/11/16/18 strain infection, 90% for genital warts, 45% for low-grade and 85% for high grade cytological

cervical abnormalities.[13] HPV also plays an important role in anal, vulvar, penile and oropharyngeal cancer.[1]

1.2 Problem statement:

An important public health goal is enhancing HPV disease prevention through HPV vaccination. Despite high efficacy and an excellent safety profile HPV vaccine completion remains low compared to other routinely recommended vaccines worldwide. Uganda rolled out the HPV vaccination into the national extended programme on immunization (UNEPI) in November 2015. However, of the adolescents who receive the first dose of HPV vaccine many do not receive the second dose they need to complete the series for adequate protection. Furthermore, of those who do receive the second dose, many do not receive it in a timely fashion within the recommended 12 months, resulting in more days at risk. In two previous national surveys, 72% and 83% of girls assessed initiated vaccination, but only 39% and 27% of them, respectively, completed the series.

1.3 Justification:

Text messages could be used to address many of the problems identified with poor HPV vaccine uptake. The study assessing HPV demonstration projects in LMICs found main vaccination barriers to include: 1) school absences on vaccination days and 2) lack of knowledge or awareness about cervical cancer, HPV vaccine and HPV vaccination programs. All these, and more, are targetable with HPV vaccine text message reminders.

Although there is evidence from developed countries that text messaging is an effective intervention to promote vaccine completion rates, there is a knowledge gap about its use in resource-limited settings. Since the rates of mobile phone possession is high in this population, it is important to test the effectiveness of vaccine reminder text messages.

1.4 Research Questions

What message content would key stakeholders prefer for HPV vaccination reminders?

Are text message vaccine reminders for HPV vaccination feasible?

Do text message vaccine reminders demonstrate potential impact on timely HPV vaccination initiation and completion?

1.5 General Objective

To explore attitudes of key stakeholders (adolescents, caregivers, health workers and school authorities) towards HPV vaccination and text message reminders in Kampala, and to use those messages in a pilot randomized control trial to asesss the feasibility of text message reminders on HPV vaccination

1.5.1 Specific Objectives

1) To identify HPV vaccine text message reminder content (and parallel automated phone reminders) desired by the caregivers and their adolescent girls in Kampala.

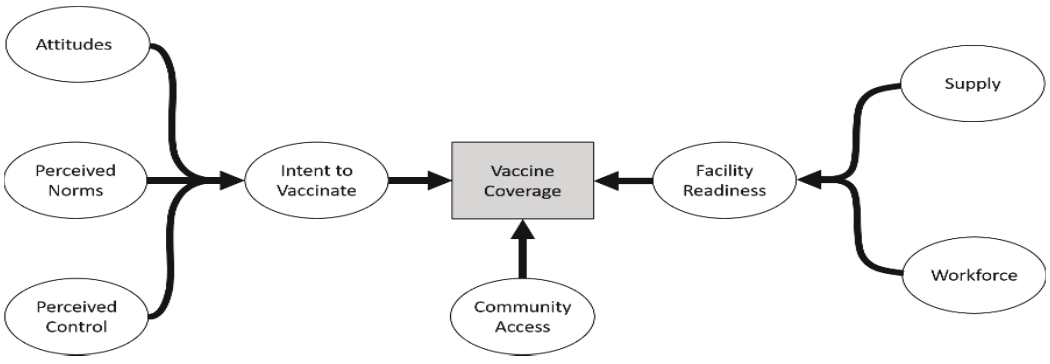
2) To develop and pre-test HPV vaccine reminders with caregivers and their adolescent girls in Kampala.

3) To pilot assess the impact and feasibility of vaccine reminders on HPV vaccination

1.6 Conceptual Framework

To understand the determinants influencing HPV vaccination we will ground our analysis in the general domains of the critical interpretive synthesis framework put forth by Phillips et al in their comprehensive systematic review of vaccination studies in LMICs (Figure 2). This will be used to analyze interviews with caregivers, adolescents, clinical staff, headmasters and school staff, and government workers to inform message content and understand the barriers and facilitators to HPV vaccination in Kampala.

Fig 2: Conceptual framework for vaccine coverage in LMIC. Phillips DE, et al Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis. *BMC Health Serv Res.* 2017;17(1):681.



CHAPTER TWO

2.0 **Literature Review**

Completion rates of HPV vaccination in Uganda are low. The national HPV vaccination program in Uganda began in November 2015,[14] and targets girls who are 10 years old.[15] In Kampala, the *school-based* program is to be delivered during every health facility and outreach immunization session, but intensified during Child Days Plus- month-long outreach sessions held two times a year in April and October, or whichever months they will be held during the course of the study. The *community-based* program occurs throughout the year at health facilities- overseen by city authorities or health institutions.

Not all adolescents who receive the first dose of HPV vaccine receive the second dose they need to complete the series. Furthermore, of those who do receive the second dose, many do not receive it within the recommended 12 months, resulting in more days at risk. In two previous national surveys, 72% and 83% of girls assessed initiated vaccination, but only 39% and 27% of them, respectively, completed the series.[16] While coverage rates have gone up in some areas of Uganda, in Kampala City currently only 29% of girls in the target age range have received two doses of the vaccine.[17] Similarly, at an adolescent clinic (*study site)* in Kampala, of the girls aged less than 14 years old who initiated vaccination between November 2015 and July 2017, only 30.2% completed the series within 6 months and 36.5% within 12 months—and only 69.8% completed the series at all.[18] At three local health centres and affiliated schools (*study sites*), average completion rates are even lower, ranging from 10.5% to 40.5% of those who initiated.[17] The current rate of completion HPV2 is 12%.[19]

A number of barriers to HPV vaccination in Uganda exist. The recent full country evaluation of HPV vaccination in Uganda highlighted the need for caregiver engagement to improve HPV vaccination rates, as well as the need to increase awareness of the importance of HPV vaccination.[20,21] A number of caregiver factors can impact timely HPV vaccine completion. Investigators found that the most common reason the vaccine was missed was school absenteeism- making reminders to attend school that day of paramount importance.[22] For health facility-based vaccination, families may not know when it is time to bring their adolescent back for the second dose. This is likely worsened by some girls being away at boarding school when the next dose is due; when they return from school break, the family may not remember to return

for vaccination. A recent Gavi full country evaluation noted inadequate follow-up system for second dose of HPV to be a key factor as to why coverage rates for HPV2 are low.[21]

In addition to these logistical barriers, parents may have knowledge gaps regarding the link between HPV and cervical cancer as well as misperceptions regarding the vaccine. In one study that included stakeholder interviews, investigators found that a key driver of vaccination was fears about vaccine safety.[2] Another showed that the perceived benefits of vaccination- particularly cancer protection as well as perceived safety of HPV vaccination- increased girls' and caregivers' acceptability of HPV vaccination.[23] Similarly, in a study that took place at an adolescent clinic (*a site for this study*), knowledge about cervical cancer, HPV, and HPV vaccination were associated with increased vaccine coverage. Other investigators have also found that families chose vaccination because it protects against cervical cancer, prevents infection, and because vaccines overall are good for health.[22] In one evaluation, caregivers who received information about the vaccine in advance of the vaccination day at school were more likely to have their child vaccinated.[20]

Failure to come in for vaccination is common. Reminders are an evidence-based approach to overcome this barrier to vaccine receipt. One of the important factors affecting vaccination is failure to remember to come in for doses.[24,25] The U.S. Task Force on Community Preventive Services found strong evidence that general vaccination reminders that notified families when vaccines were due improved vaccination rates.[25] In Uganda, the only current reminder available is a paper appointment card, which can easily be misplaced or destroyed. Moreover, there is no electronic database for the immunization program.

Text messaging offers low-cost, scalable opportunities to foster vaccination. Traditional reminder strategies (mail and phone call) have historically had more limited effects in adolescent and low-income populations.[26-30] Moreover, a Cochrane review found that text messaging, as a single-method reminder, had the largest effect size with high certainty of evidence (RR: 1.29, 95% CI: 1.15 – 1.44; six studies; 7,772 participants).[31]

Text message vaccine reminders have several characteristics making them an attractive technology for vaccine reminders in all populations.

a) Text messages are a good way to reach people. The number of mobile phone user is high, with an estimated 6.8 billion users world-wide.[32] According to the World Bank, 89.9% of urban households in Uganda have a cell phone.[33]

b) Text messages act as cues to action. They may draw attention more than written information and may be perceived as less intrusive than a phone call.[24] In addition, they remain on a person's phone as a persistent reminder. This makes them particularly useful for interventions with a clear, desired behavioral outcome.

c) Text messages are useful across populations with various levels of literacy since space limitations force a minimal number of short, simple words.

d) Text messages are delivered outside the office setting. This is important for reaching patients not accessing care regularly, a key group for targeting HPV vaccine reminders as well as for school-based programs. Text messages also allow more frequent contact with a health care team than can be achieved with in-person visits alone.

e) Text messaging is scalable and can be personalized. It allows interaction with thousands of patients simultaneously thereby enabling an impact not only on an individual patients' health, but also on the health of the public by increasing population-level vaccination coverage. Yet, text messaging can also allow personalization based on individual characteristics such as age and language.

f) Text message reminders are a flexible platform. They can be used either for simple prompts or for reminders that inform a patient or family when a vaccine is needed, and even for more complex interactions that include embedded educational information and interactive responses that can close knowledge gaps and dispel vaccine misperceptions.

Text messages could be used to address many of the problems identified with poor HPV vaccine uptake. The study assessing HPV demonstration projects in LMICs found main vaccination barriers to include: 1) school absences on vaccination days and 2) lack of knowledge or awareness about cervical cancer, HPV vaccine and HPV vaccination programs. All these, and more, are targetable with HPV vaccine text message reminders.[22]

- ◊ They can notify families that their child is in need of vaccination either for their first dose or that it is time to return for the second dose
- ◊ Timing of reminders can be tailored to the individual child based on when their dose is due as well as where and when they should go to receive that dose, including special days at school.

◊ Educational information can be embedded into text messages to provide answers to common questions or concerns families have about vaccination or include information that has been shown to impact the likelihood of caregivers to accept vaccination, like cancer protection.

We have established strong evidence supporting HPV vaccine text message reminders. Dr. Stockwell (MPI of the grant) published the first studies using text message vaccine reminders for adolescent and pediatric populations.[34-40] In addition, she has previously identified the effectiveness of HPV vaccine text message reminders in two studies. In the first, caregivers whose child received a first or second dose of the HPV vaccine received a series of text message reminders when the next dose was due. Adolescents whose caregivers were texted were more likely to receive their next dose on-time vs. non-enrollees (51.6% of enrollees vs. 35.0% of non-enrollees [$p = 0.001$] or 38.1% of historical controls [$p=0.003$]).[40] In a secondary analysis (unpublished), those receiving text messages also had higher series completion rates (45% vs. 29% $p<0.01$). These *conventional* reminders solely notified caregivers via text that the next dose was due; they did not include any other information such as vaccination-related educational health information. While these results strongly supported the potential effectiveness of text message reminders, still fewer than half of adolescents (45%) completed the series.

In her most recent study, Stockwell demonstrated 74.1% completion rates of HPV vaccine series within 12 months for adolescents of caregivers receiving text message reminders.[41] This rate was much higher than both historical controls (34.8%) and the comparison group of non-enrollees (45.2%, $p<0.0001$).

This proposed project is innovative in four important ways.

1) This will be the ***first use*** of text message vaccine reminders for *adolescent* vaccinations in not only Africa but for any LMIC. Text message vaccine reminders have been used for *pediatric* vaccination studies in Africa in Kenya and Nigeria[33,42-45] and three other non-African LMICs,[46-48] but not for *adolescent* vaccines including HPV. While on the surface it may seem that the use of mHealth interventions for adolescent vaccination does not differ from that of pediatric vaccination, that is not true. Adolescent vaccination patterns, knowledge and perceptions do differ from that of pediatric vaccination, and interventions in high and low-middle income countries also differ.[49] Therefore, text message

performance cannot be extrapolated from those targeted to caregivers of young children or to caregivers in high-income settings.

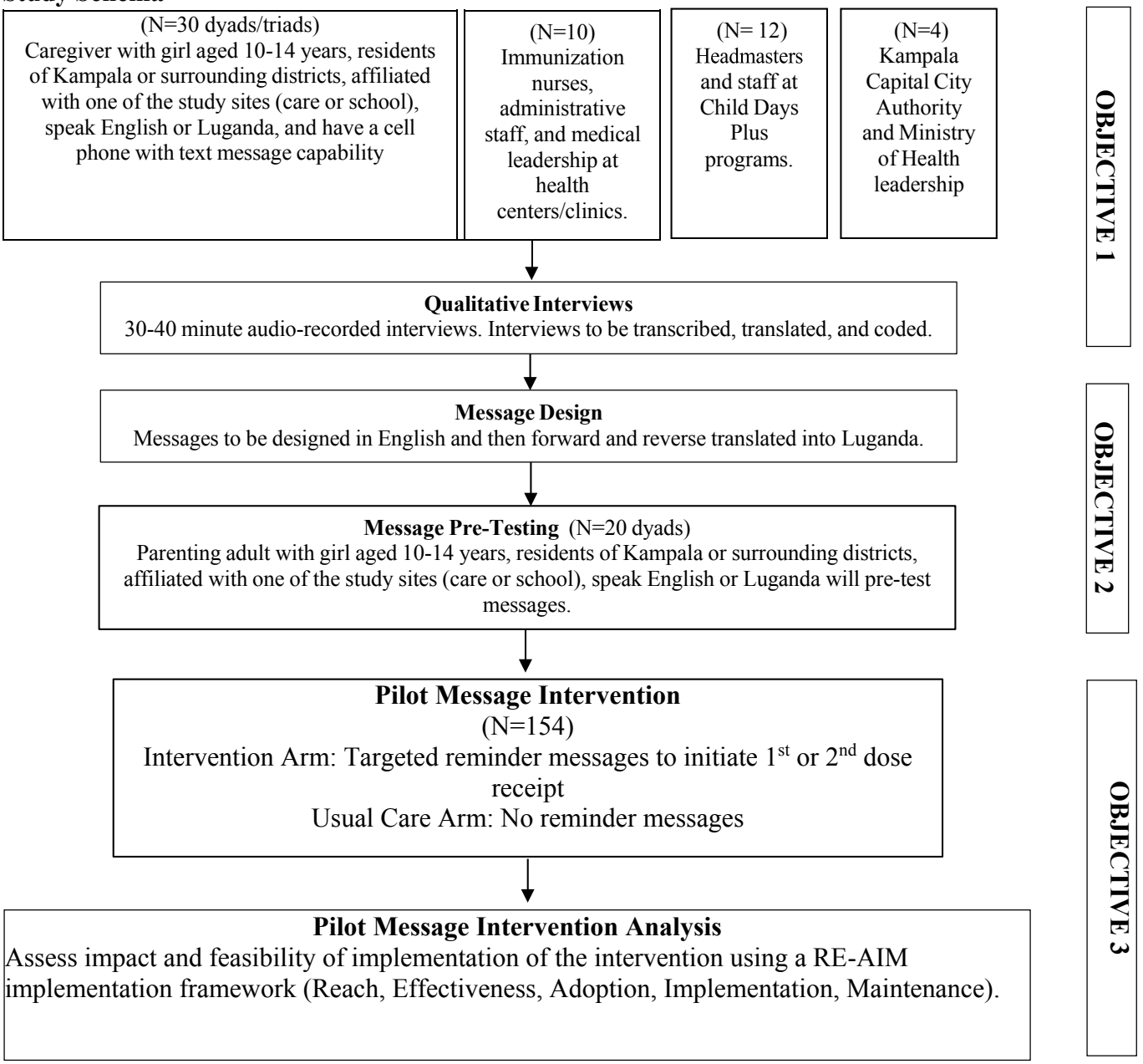
   a. In Uganda, similar to the rest of sub-Saharan Africa, vaccinations for young children are delivered as part of EPI (Expanded Programme on Immunization) in which primarily families bring their child in to a central location for vaccination. This differs from vaccination for adolescents, who are being vaccinated in a variety of places, including the school, health centres and immunization posts in the community. This means that a more tailored mHealth approach is needed to be able to provide reminders for these various groups.
   b. Caregiver views of pediatric vaccination are generally positive, while in contrast many concerns about HPV vaccination still exist making the embedded educational information in HPV reminders particularly important.
   c. Caregivers are very accustomed to thinking about vaccinations for their infants but vaccinations for adolescents are much newer to them and knowledge gaps remain.[50] In addition, care seeking patterns for infants may differ markedly than for adolescents, making this type of outreach potentially even more important.

2) We will also be able to assess for the ***first time*** what types of educational information caregivers and providers believe is needed in HPV vaccination reminders in a LMIC. An August 2018 article highlighted that while *nearly a quarter of the world's population are adolescents*, on average *only 1.6% of all global health development assistance funding goes to adolescent health*.[51] Given the very high burden of cervical cancer coupled with late diagnosis, the opportunity for primary prevention offered by vaccination is profound. Uganda has a young population, 59.7% are <19 years old, making it a particularly important country to understand the potential impact of HPV vaccine reminders.[33] Lessons drawn from this project may also be useful to other LMICs.
3) This project is at the intersection of two important governmental ministries- the Ministry of Health and the Ministry of Education- these mHealth reminders would be a ***novel intervention*** spanning the two arenas of health and education.

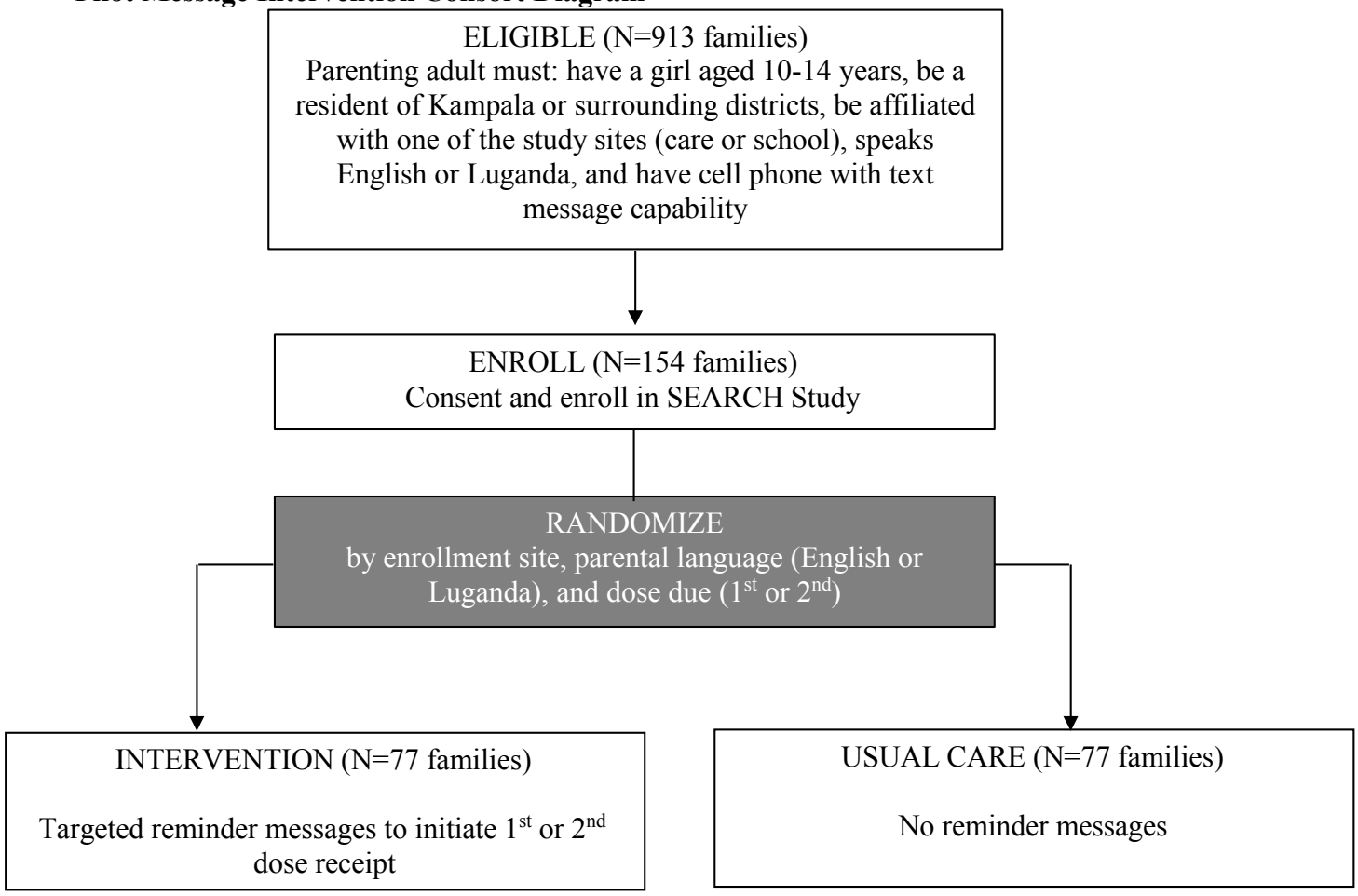
CHAPTER THREE

3.0 METHODOLOGY

Study Schema



Pilot Message Intervention Consort Diagram



3.1 Study Design

This is an exploratory sequential design study with the primary intent of the exploratory design to develop a digital tool which will then be tested in a pilot randomised control trial to assess the feasibility of text message reminders on vaccination. This study will be conducted in Kampala City involving adolescent girls, their caregivers, health workers, school authorities and government officials . Results from this phase (Objective 1: interviews) will be used to design the text and voice message reminders. We will use these results, along with the study teams' expertise in in text messaging, HPV vaccination, adolescent medicine, health literacy and community engagement (Objective 2: message design and pretest), for a pilot randomized control trial to assess the effectiveness of intervention messages on timely receipt of the second HPV dose (Objecive 3: pilot assess text message feasibility through RCT).

3.2 Study Site

This study will take place at three health centres Kisenyi, Kawaala and Kiswa in Kampala, Uganda overseen by the Kampala Capital City Authority (KCCA) located in the suburbs of Kampala City. It will also take place in a sample of six KCCA schools selected from the schools in those areas (Appendix 26). It will also take place at the Makerere/Mulago/Columbia Adolescent Health Clinic (commonly referred to as the Friday Adolescent Clinic), at Mulago National Referral Hospital the teaching hospital for Makerere University College of Health Sciences. The study health facilities were selected purposively in consultation with KCCA to ensure inclusion of different city divisions as shown in Table 1.

Table 1: Distribution of study health facilities by Division

Health Facility	**Division**	**Catchment population[1]**
Kisenyi HC IV	Central	99,378
Kiswa HC III	Nakawa	64,509
Kawaala HC III	Lubaga	52,035
Mulago National Referral Hospital -Adolescent Clinic	Kawempe	

[1] KCCA (2019) Statistical Abstract https://www.kcca.go.ug/media/docs/Statistical-Abstract-2019.pdf

Each of the study health facilities provides HPV vaccination services to adolescent girls.

3.3 Objective 1: To identify HPV vaccine text message reminder content (and parallel-automated phone reminders) desired by caregivers and their adolescent girls in Kampala.

3.3.1 Population for Objective 1 Interviews

Target population: Families of adolescent girls, clinicians, immunization nurses, administrative staff, and school leadership (at the governmental level, key informants will include leadership within the KCCA and Ministry of Health).

Study population: Families of adolescent girls, clinicians, immunization nurses, administrative staff, and school leadership (at the governmental level, key informants will include leadership within the KCCA and Ministry of Health).

Accessible population: Families of adolescent girls, clinicians, immunization nurses, administrative staff, and school leadership (at the governmental level, key informants will include leadership within the KCCA and Ministry of Health).

3.3.2 Selection Criteria for Objective 1 Interviews

Inclusion criteria for interviews:

- School-affiliated participants must:
    - Be affiliated one of the identified KCCA schools (Appendix 26)
    - Be in leadership role at school (i.e. Senior Woman or Head Teacher title)
    - Be involved in HPV-vaccination efforts at school
- Government-Affiliated Participants must:
    - Be local or national government official involved in an immunization programs
- Caregiver participants:
    - Is the primary caregiver of adolescent girl aged 10-14 years who has not completed the HPV vaccination series
    - Resides in Kampala
    - Speaks English or Luganda
    - Have a phone in the household
    - Adolescent is willing to take part in interview

- Adolescent participants:
    - Is an adolescent girl aged 10-14 years
    - Have not completed the HPV vaccination series
    - Have a phone in the household
    - Caregiver is willing to take part in interview

Exclusion criteria:

- Those who are unable to consent/assent to the study
- Those unable to be interviewed at the affiliated study health centres

3.3.3 Study procedure for Objective 1 Interviews

Interviews will be conducted by trained research staff overseen by an experienced social scientist on our study staff. At the Kisenyi, Kawaala and Kiswa study sites, families of adolescent girls aged 10-14 who have not completed the HPV vaccine series will be given a consent form/information sheet by a member of our study team. Then, they will be asked if they have any questions and if they are willing to participate. After being read the consent/assent form, one willing adult participant who is the primary caregiver of the adolescent will be asked to sign the consent and the 10-14 year old adolescent girl will also be asked to give written assent. In the case of there being more than one eligible female adolescent between the ages of 10-14, we will give the opportunity to both adolescents to be interviewed. If two caregivers are present and willing to take part, we will select the primary caregiver who is usually responsible for the adolescent being vaccinated.

To increase reach, study staff will also call families of 10-14 year old adolescent girls who have not completed the HPV vaccine series and receive care at the study-affiliated healthcare centres about possible participation. If these families are interested, they will be asked to travel to their study-associated healthcare centre to be consented and participate in the study interview and their transport to and from the health centre will be reimbursed.

The interviews will be grounded in the general domains of the critical interpretive synthesis framework put forth by Phillips et al in their comprehensive systematic review of vaccination studies in LMICs. After obtaining informed consent, interviews will be conducted using a semi-structured interview guide by trained research assistants with experience in conducting

interviews with adolescent and their caregivers. The guide was developed based on the investigators' experience with HPV vaccination. Audio-recorded interviews will last 30-40 minutes. We will use open-ended questions with neutral probes to facilitate discussion and \encourage unbiased responses. In addition, rather than leading the interview based on a predetermined hypothesis, we will allow the concepts to emerge inductively.

We will seek to interview 30 caregiver and adolescent dyads/triads, but will use an iterative data collection and analysis approach and continue data collection until data saturation is reached (e.g. no new themes arise from the data). Eligible criteria are outlined as above. Adults and adolescents will be interviewed concurrently, but separately to facilitate comfort and encourage honest answers. Family interviews will concentrate on text message reminder content, focusing on the attitudes, perceived norms and perceived control that may affect intent to vaccinate in the Phillips et al model. We will also assess desired message timing and phrasing. Additionally, we will assess if families want for only the caregiver or the caregiver plus adolescent to receive the messages.

At the health centres/clinics, we will interview clinicians caring for 10-14 year olds, immunization nurses, administrative staff, and medical leadership (n=12). We will purposefully sample schools from the list of KCCA health centre-affiliated schools included in Appendix 26, focusing on two per division each of which represent a different student demographic composition. At the study-affiliated schools, we will interview up to two people per school including the headmasters and staff involved in Child Days Plus/HPV vaccination. Interviews will include content discussions regarding experiences with families' vaccine knowledge and attitudes as well as community access and facility readiness factors from the Phillips et al model in order to align reminder content and timing with current processes. Interviews will take place in person at the facilities in which the participant works, or another decided upon location.

In addition, local and national government officials, including KCCA and MOH leadership involved in immunization programs, will also be interviewed with focus on access and readiness from the Phillips et al model and an eye towards sustainability (n=4). Interviews will take place in the leadership offices after written informed consent is obtained. We will interview the KCCA Directors of Education and Social Services, and of Public Health and Environment as well as the

City Manager of Epidemiology and Surveillance. These individuals together oversee vaccination at the KCCA- affiliated schools, health centres, and immunization posts and in Kampala overall. At the MOH, we will interview the Program Manager of UNEPI.

During the process of data collection, COVID-19 risk management procedure (Appendix 24) will be followed to protect the health and safety of study participants and researchers.

3.3.4 Data management and analysis

Individual interviews will be transcribed verbatim from audiotapes and translated, as appropriate. Our qualitative lead and their team will review all transcriptions and conduct coding independently. Transcripts will be analyzed using immersion and crystallization process and thematic analysis, which are standard methods of qualitative analysis. Analyses will follow a systematic, iterative process in which transcripts will be independently read for familiarity with content. General thematic domains and codes will be identified, and then transcripts will be systematically and independently coded line-by-line by two team members. The coding scheme will remain flexible and open to accommodate expansion as the teams agree on new codes. Double coding of all data will occur to facilitate reliability. Coding inconsistencies will be reviewed and resolved during meetings with the research team. Thematic analyses will then be conducted on the data to identify emerging themes. Qualitative data coding and analysis will be facilitated by the use of NVivo software. Summaries of coded texts and comparative analyses will be discussed with the investigatory team who were not involved with the coding, as well as outside experts, to obtain validation. The themes identified through the qualitative analysis will be used to guide the construction of the text (and parallel phone) messages that will be pre-tested in Objective 2.

3.4 Objective

- **Objective 2a:** To develop HPV vaccine reminders with caregivers and their adolescent girls in Kampala.
- **Objective 2b:** To pretest HPV vaccine reminders with caregivers and their adolescent girls in Kampala.

3.4.1 Study procedure for Objective 2a message development

We will design the reminders using the information gathered under Objective 1 to identify the themes, content, timing and framing of the SMS reminders. We will also use content gathered during our previous studies described above, the relevant literature, and the team's expertise in text messaging, HPV vaccination, adolescent medicine, health literacy and community engagement. The same message content and timing will be used for those opting for voice reminders. The messaging will be behaviorally-informed with the framing based on findings from participants from Objective 1. Possible examples include "loss-frame" messages that focus on the negative consequences of an adolescent not being vaccinated, and/or "gain-frame" messages that focus on what can be achieved through vaccination. Messages may also include social comparisons that capitalize on social desirability bias in completing the HPV vaccine series, contigent on if this is found to be motivating to families based on the Objective 1 responses. Other messages may highlight doctor recommendations if Objective 1 respondents relay that this may motivate others.

The study team will design the messages. First, they will identify the key content, timing and framing for each message in the series as above. The project coordinator will then design the messages. The team will then iteratively revise the messages, keeping the text within the 160-character count and paying attention to reading level, as assessed by the Flesch–Kincaid readability test. The final draft messages will first be designed in English then will be forward translated from English into Luganda by an independent professional translator and then reverse translated by a second independent professional translator from Luganda into English. All the while, translators will ensure proper linguistic and cultural equivalence, following procedures adapted from guidelines for translating health services research measure. The two versions, the original English and the reverse-translated English, will then be compared by the study team.

3.4.2 Population for Objective 2b message pretest

Target population: Families at the adolescent clinics, KCCA health centres, immunization posts, and families of children registered at the affiliated schools.

Study population: Families at the adolescent clinics, KCCA health centres, immunization posts, and families of children registered at the affiliated schools.

Accessible population: Families at the adolescent clinics, KCCA health centres, immunization posts, and families of children registered at the affiliated schools.

3.4.3 Selection Criteria for Objective 2b message pretest

Inclusion Criteria

To receive take part in this pre-testing, one must:

- Caregiver participants:
    - Is the primary caregiver of adolescent girl aged 10-14 years who has not completed the HPV vaccination series
    - Resides in Kampala
    - Speaks English or Luganda
    - Have a phone in the household
- Adolescent participants:
    - Is an adolescent girl aged 10-14 years
    - Have not completed the HPV vaccination series
    - Have a phone in the household
    - Caregiver is willing to take part in the pretest

Exclusion criteria

- Those who are unable to consent to the study
- Those unable to be interviewed at the affiliated study health centres
- Participation in Objective 1 study activities

3.4.4 Study procedure for Objective 2b message pretesting

We will show/read the designed messages with caregivers and adolescent to identify issues with clarity and persuasiveness. Using methods previously utilized by members of the study team, the project coordinator will purposefully sample families meeting criteria a above from the waiting rooms at the adolescent clinic and KCCA health centres. Families will be consented/assented as outlined in objective 1. After obtaining informed consent, the project coordinator will share the proposed messages and ask the caregiver to relay back, in their own words, what the message means to them in order to assess clarity. S/he will then ask families about the level of persuasiveness as well as any problems or suggested changes. Messages will be updated in an

iterative process until no new message changes are made. Based on our previous work, we anticipate needing 20 dyads (with representation by language and site).

3.4.5 Data management and analysis

Final messages will be reverse translated from Luganda and team members will review to make sure that the content is the same between the messages in the two languages. We will also map the final messages back to the factors of the critical interpretive synthesis framework related to attitudes, perceived norms and perceived control, as well as access.

3.5 AIM 3: To pilot assess the impact and feasibility of vaccine reminders on HPV vaccination

3.5.1 Population

Target population: Families of adolescent girls who visited any of the following health centers: Kisenyi HC IV, Kiswa HC III, or Kawaala HC III.
Study population: Families of adolescent girls who visited any of the following health centers: Kisenyi HC IV, Kiswa HC III, or Kawaala HC III.
Accessible population: Families of adolescent girls who visited any of the following health centers: Kisenyi HC IV, Kiswa HC III, or Kawaala HC III.

3.5.2 Selection Criteria

To receive messages one must:

- Be an adult parent of an adolescent girl aged 10-14 years
- Reside in Kampala and/or the surrounding districts
- Be affiliated with the study sites (care or school)
- Speak English or Luganda
- Have a cell phone with text messaging capability
- Must have ability to consent.

Exclusion Criteria:

- Parenting adult speaks other language than English or Luganda only
- Parenting adult already enrolled in the study for another child
- Participation in Objective 1, 2a/2b study activities

3.5.3 Study procedure

We will recruit eligible participants from the sites outlined in Aim 1 and 2. This includes health centres overseen by the Kampala Capital City Authority (KCCA), as well as the associated schools and immunization posts in the community. In addition, we will also recruit at the

Makerere/Mulago/Columbia Adolescent Health Clinic at Mulago National Referral Hospital, the teaching hospital for Makerere University College of Health Sciences.

For those vaccinated through clinic sites: Families will be recruited multiple ways. First, families who are interested can enroll directly at the health centre at the times research staff are on-site, possibly at the time they are being evaluated for another health condition and are not receiving the vaccine that day. Second, if research staff are not on-site, providers and nursing staff at the study sites will ask families permission to provide the research staff with their contact information to reach out to them to explain the study and if interested to meet with them to enroll them into the study.

For those vaccinated through community immunization posts: Village health workers who already work in each village will be mobilized to approach households with 10-14 year olds who are in need of vaccination (have not yet been vaccinated or who have initiated but have not completed the series) to identify those who would be interested in the study. Research staff will contact those who are interested, as above. The use of village health workers has been previously successful for both immunization campaigns and other research studies.

For those vaccinated through the Child Days Plus: Girls will be given an information sheet and the study contact number to bring home to their parents. We would get permission from the schools to call families back as above.

We will enroll only one child per family; if more than one is eligible, one will be randomly selected. For the pilot feasibility trial, we will enroll families of girls who are in need of either the first or second dose, with an outcome of receipt of next needed dose. Due to the need to complete the pilot feasibility trial quickly, we will only enroll those in need of the second dose if their next dose is due strictly between 8-20 weeks from enrollment. We will seek written consent from caregivers. We will seek written assent from adolescents of consented caregivers given instead. At enrollment, parents will be verbally administered a demographic and HPV vaccination knowledge and attitude survey.

After enrollment, the Ugandan project coordinator will randomize families into intervention vs. usual care arms (1:1 ratio) stratified by enrollment site, parental language (English or Luganda), and dose due (1st or 2nd) using a randomization module. Research staff will not know the study assignment during enrollment. The outcome assessor and analyst will remain blinded to arm assignments.

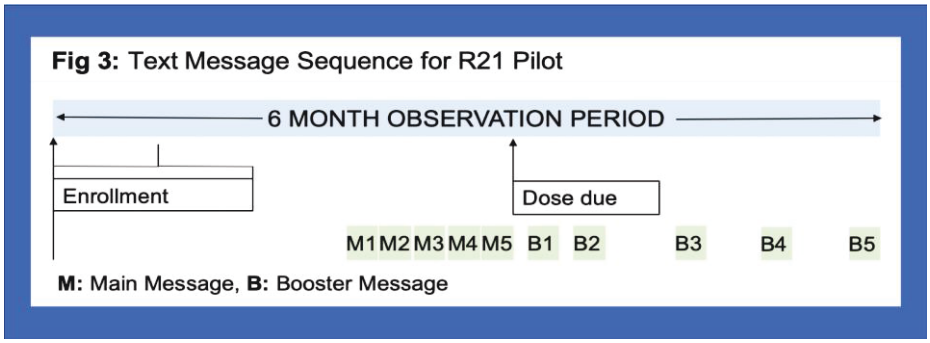
Families who report on the demographic survey their highest degree of schooling as P7 or below will be asked at enrollment if, in the case they are randomized to the intervention, they would prefer a voice reminder in lieu of texts; such reminders would include the same content, timing and interactivity as the texts. While in Kampala only 2.1% of women and 0.5% of men have no formal education, 17.6% of women and 17.1% of men completed only some primary school.31 Similarly, families whose daughter is returning to a boarding school and are enrolled at the Adolescent Clinic, health centres, or immunization post will be asked if, in the case they are randomized to the intervention, they want messages sent timed for the next school break. Alternatively, they can select the timing used for those not at boarding school. If the special timing is selected, we will account for the minimal interval between doses (for those in need of a second dose). Intervention-arm families enrolled through Child Days Plus will be sent their series prior to the next Child Days Plus event at their child's school or before any other special immunization day events, if the school holds one.

Intervention, Text Message Target, Content and Frequency:

For those families randomized to the intervention arm: Based on our previous studies as well as the full country HPV vaccine evaluation highlighting the parents involvement as vaccine decision makers, we plan for the messages to be targeted to the parent, unless in Aim 1 families suggest that girls should also receive the message. All text messages are automated and will be sent in English or Luganda based on parental preference.

The message sequence consists of 5 weekly, main message reminders beginning 5 weeks before the

HPV vaccine dose due date, followed by a series of 2 primary booster messages.(Figure 3). This is based on our previous studies that showed that the median number of messages needed to come in for a vaccine was 5. If enrollment happens more than 4 weeks before the main messages are due to start, engagement messages will be sent monthly until main messages start. The due date for the vaccine will depend on whether the first (initiation) or second (completion) dose is due and the enrollment site.



For those who need to initiate vaccination and are:

- *Recruited as part of the school-based program*, the due date will be defined as the next Child Days Plus
- *Recruited in health centre and not in boarding school*, the due date will be defined as 5 weeks after message initiation
- *Recruited in health centre and are in boarding schools,* the due date will be the next school break
- *Recruited in the community*, the due date will be defined as the next HPV vaccination day at the community immunization post that is at least 5 weeks after message initiation

For those who need to complete the vaccination series and are:

- *Recruited as part of the school-based program*, the due date will be defined as the next Child Days Plus
- *Recruited in health centre and not in boarding school*, the due date will be defined as 6 months after the date of the first dose (which is the recommended interval between doses)
- *Recruited in health centre and are in boarding schools,* the due date will be the next school break that is a least 5 months after the date of the first dose, which is the minimal allowed interval between doses
- *Recruited in the community*, the due date will be defined as the next HPV vaccination day at the community immunization post that is at least 5 months after the date of the first dose

Messages will focus on when/where to go for the next dose, and will include educational information identified in Aim 1. Messages will be different for those who need the first dose (initiation) and 2nd dose (completion). We will also include an interactive text message allowing participants to ask for and receive more information according to their specific needs, and receive an automated response with information on that subject. For those still unvaccinated, booster

messages will be sent bi-weekly for one month and then monthly until the end of the 6 month observation period for each individual during the pilot trial. Sites will be visited every 2-4 weeks to abstract data; we will stop messages for those already vaccinated. HPV registers for schools are generally kept with the affiliated KCCA health centre immunization nurses. For families of those unvaccinated who were first vaccinated at Child Days Plus will receive booster messages directing them to bring their daughter to the KCCA health centre affiliated with their school (who conducts their Child Days Plus outreach) as they will have missed the school vaccination day.

Usual Care arm: Families randomized to the ***usual care arm*** will not receive text message vaccine reminders.

3.5.4 Data management and analysis

Sample Size for Pilot For the feasibility pilot, we will plan to enroll 154 adolescents who are due for an HPV vaccine dose. With a minimal sample size of 77 in each arm, we will be powered to detect a hazards ratio of 1.67 with 80% power, allowing for a 5% type I error comparing time to next dose.

At the study sites, we expect there to be, on average, 1074 girls aged 10-14 in need of vaccination over a 4-month period. We expect 913 families to meet age, language and cell phone/texting inclusion criteria. To meet our minimal sample size of 154 (77/arm) for this pilot/feasibility study, we need to recruit 16.9% of eligible families, which is feasible. If recruitment is slower than expected, we will be able to use more KCCA sites.

Data Management

Vaccination data will be abstracted from the HPV vaccination registers in use clinically at the sites. Girls generally seek care from one site. All data will be entered into a REDCap database hosted at Columbia with secure access provided only to Columbia and Ugandan study staff. The Ugandan-based project coordinator will monitor text messages sent, replies, and "undeliverable" messages under the supervision of Drs. Bakeera-Kitaka and Stockwell. Linkages between parents' and girls' information, survey data and vaccine records will be maintained in separate password protected files. All final datasets will be coded.

D10. Analytic Plan

The primary analytic plan for the pilot will focus on feasibility of implementation of the

intervention using a RE-AIM implementation framework (Reach, Effectiveness, Adoption, Implementation, Maintenance). We will focus only on reach, effectiveness, and implementation (not adoption or maintenance which is not applicable for this pilot).

Reach: We will collect data on number of families

- approached
- eligible and ineligible (including reasons for ineligibility)
- eligible who enrolled
- number enrolled in text message vs. phone reminders

Effectiveness: While the focus of the pilot is on feasibility, we will also assess the effect size of the intervention. The outcome will be timeliness of vaccination (time to event). Time will be from start of main message series to receipt of the next needed dose. Data analysis will be performed using Stata. The primary analysis will be intention-to-treat (ITT), whether or not further messages were declined or undeliverable. A secondary per protocol analysis will only include those who received the entire set of reminders. Timeliness of vaccine receipt will be compared using Kaplan-Meier curves using a stratified log rank test. In addition, in order to gain effect sizes needed for a future large-scale intervention, comparisons will also be stratified assessing those due for the first dose (initiation) and second dose (completion).

Implementation: We will assess various process measures, including:

- Messages sent/delivered (if a text message is electronically returned as undeliverable, we will contact the family using alternative numbers that will be collected at enrollment)
- Number who opted out of further messages
- Number who responded to messages
- Topics families request more information about in reminders
- Factors associated with response and drop out
    - child characteristics (age, site, school status (in or out of school), grade, relationship with caregiver)
    - family characteristics (age, education, employment, income, marital status, distance to health facility, language)

We will also randomly select 30 intervention parents from whom we have received permission in the consent to re-contact. We will conduct a semi-structured interview that will focus on

intervention experiences and suggested changes, and follow the methods and analytic plan outlined under Aim 1. We will also have them complete two implementation measures: Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM). These were developed and psychometrically assessed by implementation scientists as consensus measures for *acceptability* and *appropriateness*. In addition, they will also complete an adapted Health Information Technology (IT) Usability Evaluation Scale (Health-ITUES).
We will then present findings to key non-parental stakeholders (as identified under Aim 1) and conduct semi-structured interviews to gather feedback. Conduction of the interviews and the analytic plan will follow the methods outlined in Aim 1.

3.6 Training of research assistants

Multiple research assistants with experience in collecting qualitative data in a health care setting will be recruited to work in pairs and trained for 2 days. The training will cover, study objectives and approach as well as an in-depth review of the consent and assent process and data collection tools. Research assistants will also take part in the pre-test of data collection tools at one of the health centres in Kampala City. Data from this phase will not be included in the final analysis. Research assistants will also be trained on the COVID-19 standard operating procedures and study risk management procedures.

3.7 Ethical considerations

Permission to carry out the study was already obtained Columbia University IRB in New York City under expedited review for meeting the following two criteria

a) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnoses).

b) Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodology.

We sought approval for the study through the IRB at Columbia University as part of our research team is located within that institution. We are seeking approval through SOMREC as the other researchers and research participants are located in Kampala, Uganda.

3.8 Dissemination

The findings of this study shall be availed to the Kampala Capital City Authority, the Columbia Department of Pediatrics and Child Health, and all other stakeholders.

Risks / Benefits to Subjects

This is a minimal risk study. Some caregivers might find there are interview questions they do not want to answer; they can skip any questions they like and can stop the interview at any time. Interviews can be converted to be conducted online to decrease risk of COVID-19 transmission if necessary. Patients do not receive any care as part of the study they or their parent/caergiver only receive a text message. They can choose to act or not act on the message. The vaccination is not directly part of the intervention. Some parents might find the alerts to be intrusive, but we will design them based on parental input. In addition, they can opt out at any time. There is also a minimal risk of loss of confidentiality. However, we will assure confidentiality as below.

Compensation

Staff, caregivers, and adolescents taking part in interviews will receive Ugandan Shillings (UgX) 30,000 which is equivalent to ~USD$8, officials taking part in interviews will receive UgX 75,000 which is equivalent to ~USD$18. Families who were contacted over the phone about the study and traveled to the study-affiliated health centre to be consented and participate in interviews will be given travel compensation of UgX 10,000 which is the equivalent of ~USD$3. Those enrolling in the pilot trial will receive Ugandan Shillings (UgX) 15,000 which is equivalent to ~USD$4. These compensation amounts were determined by our Ugandan investigators based on what is customary.

Informed Consent

We have outlined above procedures to obtain written informed consent and assent.

Confidentiality Assurances

Data will be audio recorded using a device such as an audio recorder or smartphone. All data collection will occur in Uganda. Only participant first or last names will be recorded (last names will be used when it would be culturally or otherwise inappropriate for an interviewer to address an interviewee by their first name). Data will be stored on an encrypted computers and/or servers and in locked research offices at Makerere University and/or Global Health Uganda (the subcontractor). Only Columbia and Ugandan research staff will have access to the recordings. The researchers will be responsible for ensuring that the confidentiality of the data is maintained at all times. Paper documents will be stored in a locked cabinet at Makerere University and/or Global Health Uganda. The study database will reside at Columbia on the RedCap server. The recordings will be used solely for research purposes to inform the content of the intervention and possible future publications. The recordings will be destroyed upon conclusion of the study.

Conflict of Interest

There are no conflicts of interests amongst any of the researchers

Collaborative Agreements

None

Intended Use of Results

The intended use of the results is to design a trial of text message vaccine reminders, which if successful could lead to a larger-scale text message reminder program on timely human papillomavirus (HPV) vaccination in Ugandan adolescents. In addition, we will potentially publish a manuscript related to this data. The data will be used for future grant applications**.**

Storage of and access to research data by other users

All the data including informed consent forms should be kept at by the PI for at least 5 years before destruction.

Data Sharing

We will register the clinical trial component of this project with U.S. Clinicaltrials.gov in accordance of all reporting requirements, with an expectation that the Clinicaltrials.gov registration will occur prior to enrollment of the first subject in the clinical trial. All results and findings will be disseminated through professional scientific conferences, peer-reviewed publications including the final text messages, and reporting on Clinicaltrials.gov.

Both institutions will have a de-identified copy of the final analytic trial dataset. In addition, we will permit access to the data on the basis of the experience and scientific qualifications of the investigator(s) and their agreement to not reproduce or share the data with others and to not attempt to determine the identities of patients or locations. Requests must be submitted in writing on the letterhead of the sponsoring institution at which the research will be conducted and include identifying information about the Principal Investigator and Co-investigators, including their curricula vitae or NIH biosketch. This data set will be free of identifiers that would permit linkages to individual research participants or specific practice sites. Research data will be made available only if appropriate IRB permission are obtained. Data Use Agreements will be executed as necessary. Data will be able to be exported to common statistical packages (SPSS, SAS, Stata, R) for analysis.

Data Safety

This is a minimal risk study. Some caregivers might find there are interview questions they do not want to answer; they can skip any questions they like and can stop the interview at any time. There is also a minimal risk of loss of confidentiality. However, we will assure confidentiality. The researchers will be responsible for ensuring that the confidentiality of the data is maintained at all times. Paper documents will be stored in a locked cabinet at Makerere University and/or Global Health Uganda. The study database will reside at Columbia on a RedCap server. The recordings will be used solely for research purposes to inform the content of the intervention and possible future publications. The recordings will be destroyed upon conclusion of the study.

Data will be stored on an encrypted computers and/or servers and in locked research offices at Makerere University and/or Global Health Uganda (the subcontractor).

Study timeline

Study Activity	**Time in Months**						
	1-4	**5**	**6**	**7-10**	**8-16**	**17-19**	**20-24**
Proposal preparation	X						

Hire and train study staff	X						
Data collection		X					
Transcription		X					
Develop messages reminders			X				
Pre-test reminder messages			X				
AIM 3: Pilot RCT Enrollment and Randomization				X			
Outcome observation					X		
Process evaluation, analysis, stakeholder presentations, R33 transition package preparation, manuscript preparation						X	
Data analysis and report writing			X	X	X		
Dissemination of results to stakeholders							X

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