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Official Title of the Study:

Social Determinants of HPV Vaccine Completion Among Adolescents

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STUDY PROTOCOL

PRIMARY STUDY OBJECTIVES

Aim 1: Determine the effects of social determinants of health for adolescent HPV vaccine completion (age, sex, race/ethnicity, insurance type, area deprivation index for residence, and distance to clinic) within a 14-month period using EHR data from retrospective chart reviews.

SECONDARY STUDY OBJECTIVES

Aim 2: Explore barriers and facilitators to vaccine completion by describing parent and adolescent experiences with the HPV vaccine, including individual, relationship, and community level determinants influencing vaccine completion, and integrating interview data with social determinants explored in Aim 1.

PURPOSE OF THE STUDY AND HYPOTHESES TO BE TESTED

The purpose of this study is to identify individual-, relationship-, and community-level determinants of HPV vaccine completion among adolescents ages 11 to 14 who received one dose of the vaccine, and barriers and facilitators to completion as described by parents and adolescents. The following hypothesis will be tested for Aim 1:

H1: Younger adolescents, boys, racial/ethnic minorities, adolescents without health insurance and those living in areas with high deprivation and far distances from the clinic will be less likely to complete the HPV vaccine series.

BACKGROUND & SIGNIFICANCE

The human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the U.S. and causes nearly 90% of cervical and anal cancers and 70% of vaginal, vulvar, penile and oral cancers (Centers for Disease Control and Prevention (CDC), 2016; Gillison, Chaturvedi, & Lowy, 2008; Reiter et al., 2013). The HPV vaccine, Gardasil 9, is recommended for administration to adolescents before engaging in sexual activity to prevent exposure against nine commonly transmitted strands. Despite the efficacy of the vaccine in preventing HPV and associated cancers, HPV vaccine rates remain low, with initiation rates (i.e. receive 1 dose) at 65% among adolescent girls and 56% among adolescent boys. Completion rates (i.e. receive 2 or 3 doses depending on certain age groups) are significantly lower at 49.5% and 37.5% among adolescent girls and boys respectively (CDC, 2017; Walker et al., 2016).

Recently, the Advisory Committee on Immunization Practices (ACIP) lowered the number of required doses for adolescents (ages 11 to 14 years) to 2 doses based on evidence demonstrating sustained immunogenicity after the second dose (Meites, Kempe, & Markowitz, 2016). However, since these changes occurred in late 2016 (Walker et al., 2016), current completion rates do not reflect vaccine completion solely for this age group (Meites et al., 2016). Further, the vaccine remains on a 6 to 12-month administration schedule, requiring adolescents to return to clinics to receive subsequent doses (Meites et al., 2016). Given the gap between vaccine initiation and completion rates it is believed that disparities in HPV vaccination might be exacerbated due to social determinants. To date, most of the literature on HPV vaccination in adolescence has largely focused on individual-level determinants influencing parents to refuse vaccination and initiate the vaccine series, including parents' beliefs, attitudes, awareness (Tsui

et al., 2013; Askelson et al., 2010; Hertweck et al., 2013) and knowledge about the HPV vaccine (Dempsey et al., 2012; Thomas et al., 2012; Reiter, Katz, & Paskett, 2013), insurance coverage (Tsui et al., 2013; Ylitalo, Lee, & Mehta, 2013; Reiter et al., 2009), and family socioeconomic status (Polonijo et al., 2016; Gerend, Zapata, & Reyes, 2013; Perkins et al., 2013). Contrary to research on social factors influencing health (World Health Organization (WHO), 2018; Marmot, 2017; Braveman & Gottlieb, 2014), adolescents with public health insurance, who were Black or Hispanic descent, and lived in low-income communities are more likely to receive the first dose of the HPV vaccine series. While these findings hold promise for addressing disparities related to vaccine initiation, they may not reflect potential determinants influencing vaccine completion. For example, although Black and Hispanic adolescents are just as likely to initiate the vaccine at the same rate as non-Hispanic White adolescents, they are less likely to complete the vaccine series (Reiter et al., 2013; Ylitalo et al., 2013; Spleen et al., 2012; Bartlett & Peterson, 2011). Thus, further exploration is warranted to identify which social determinants influence vaccine completion.

DESIGN AND PROCEDURES

Design: This study will use a parallel mixed method design that combines retrospective chart reviews and individual qualitative interviews to examine the effects of social determinants of health (SDH) for HPV vaccine completion among adolescents and explore parents and adolescents' experience with the HPV vaccine including perceived barriers and facilitators to completing vaccine series. Chart reviews will be used to identify individual and community-level characteristics of adolescents (age 11 to 14 years) and determine vaccine completion by whether the second recommended dose was received within a 14-month period. A descriptive qualitative design will be used for Aim 2 to describe barriers and facilitators to vaccine completion among parents and adolescents who did or did not complete the vaccine series.

Procedures: Aim 1. A request for waiver of informed consent will be submitted to the IRB to access previously collected data on adolescents' charts retrospectively. The PI will collaborate with a research data manager to abstract eligible electronic health records through the Maestro Care database. Data pulled from the Maestro Care database will be imported and stored in a secure folder in PACE, a highly protected network space where users can analyze and work with identifiable protected health information. Data on adolescents' HPV vaccine completion will be recorded on data collection forms using the number of vaccine doses received, the date in which the vaccine doses were administered, and clinic location in which the vaccine doses were received. The North Carolina Immunization Registry (NCIR) will be used to verify HPV vaccine completion in the event that the adolescent receives any of the vaccine doses outside of the Duke University Health System (DUHS) network. The NCIR is a secure, web-based database where healthcare providers report immunizations administered to patients within North Carolina. I have gained view-only access to the NCIR through the selected pediatric clinic and will only use the database to record the number of HPV vaccine doses, the dates in which the doses were administered, and clinic location in which the doses were received for eligible adolescent charts for Aim 1. A cohort of adolescents will be created by examining charts of all adolescents ages 11 to 14 who received 1 dose of the HPV vaccine from January 2017 to December 2017. This cohort will be followed from January 2018 to February 2019 to assess vaccine completion within a 14-month period documented in the adolescents' electronic medical chart. Data from chart reviews will be partially de-identified; zip codes, addresses from participants and the person listed as the emergency contact, and the dates of HPV vaccine administration will be the only identifiable data recorded from the chart reviews. Zip codes will be recorded to determine

the area deprivation index of the adolescent's place of residence. Addresses will be recorded to calculate the number of miles for the distance from clinic variable. Lastly, the date of HPV vaccine administration will be used to determine the number of months between receipt of the first and second dose within a 14-month period. However, once area deprivation index values have been determined, the distance from clinic miles calculated using geographic information systems (GIS) software, and the date of vaccine administration have been converted to months (e.g. 1st dose = 1 month; 2nd dose = 8 months from first dose) participants' zip codes, addresses, and date of vaccine administration will be deleted from the dataset. Each eligible adolescents' chart will be provided with a subject ID number. To minimize the risk of loss of confidentiality, all data will be stored and secured in the PACE network. Additional data (i.e. analyses results) will be stored in an electronic, password-protected share drive at Duke University School of Nursing and will be backed up daily. Only the study team will have access to both the share drive and PACE network.

Procedures: Aim 2. Purposive sampling will be used to recruit key informants from the Duke Primary Care Pediatrics at Roxboro Road to complete individual interviews on barriers and facilitators to HPV vaccine completion. A request for waiver of informed consent will be submitted to the IRB to use adolescents' charts and the NCIR database to prescreen for potential eligible subjects and gather contact information through chart reviews prior to obtaining consent from parents and assent from adolescents. The NCIR will be used for screening purposes to determine vaccine completion by identifying whether adolescents received any HPV vaccine doses at other clinics outside of the DUHS network, or if the adolescent is a new patient to the clinic and does not have their immunization records established with their chart. Names, date of birth, and/or EHR chart numbers of eligible participants will be used to search for adolescents in the database; however, will not be recorded. Key informants will include male or female adolescents who completed the vaccine series or began the series but did not finish it, as well as their parents (n=32). To ensure informational representation, 16 parents and adolescents who completed the vaccine series (Completers) and 16 parents and adolescents who did not complete the vaccine series (Non-completers) within 14 months will be recruited. Both English and Spanish-speaking participants will be recruited. For Spanish-speaking participants, an approved Duke University Health System, Spanish interpreter provided by the selected pediatric clinic will be used to assist with translating the study eligibility criteria, information about the study, and contact information from the participants. Face to face, semi-structured, individual interviews will occur at one-time point in a private location at the preference of participants (i.e. reserved room at Duke University campus or local library, home, etc.) and will be conducted in either English or Spanish. For Spanish-speaking participants, a bilingual data collector will be assigned for the interview. The bilingual data collector is a native Spanish speaker and proficient in the Spanish language. All interviews will last approximately 45 minutes to 60 minutes and will be recorded using a recorder device to be transcribed verbatim. Interview data will be transcribed verbatim from an electronic recording device by a hired, bilingual transcriptionist through a Duke University School of Nursing (DUSON) approved vendor. I will double-check the accuracy of the transcribed text. Audio recordings will be uploaded in a secure folder on an electronic share drive at DUSON which only key study personnel will have access to. These files will be sent to the transcriptionist using Duke Box, a secure method of sharing data that is approved by the Duke IRB. During transcription, participants' names and other identifiable information (i.e. provider's name, clinic name/location, etc.) will be removed from the text. Audio recordings will be destroyed after qualitative data analysis has been completed. Field notes will capture parents' and adolescents' emotions and

behaviors as responses are provided during the interviews. De-identified demographic data (e.g., age, race/ethnicity, and sex) collected after interviews will be recorded on paper surveys then entered into a password-encrypted Excel spreadsheet for descriptive statistics. Informed consents, child assents, transcribed text, field notes, and demographic surveys will be stored in a locked file cabinet until the study is completed. All participants will be provided with pseudonyms to protect their identity.

Translation Plan: The informed consents, child assents, brief demographic survey, recruitment materials (e.g. mail or emails from the healthcare provider, study brochure) and interview guides will be provided to participants in both English and Spanish, at the preference of the participant. The PI and I will translate all documents previously mentioned above and conduct English to Spanish translations or Spanish to English back-translations of the documents. After translation, both the PI and a bilingual PhD student will compare the original English version and the back-translated version to denote discrepancies and make revisions as necessary. The PI is of Cuban-American descent and is proficient in Spanish and conducted most of her research with primarily Spanish speaking participants. She has been translating documents for research purposes since 2001. The bilingual PhD student has achieved a level of proficiency in Spanish as indicated by advanced Spanish education (e.g., obtaining a minor or major in Spanish in college) and has experience conducting research with Spanish-speaking participants and assisting with back translation.

MEASURES

Data collected will include (1) adolescent and parent demographic characteristics, (2) vaccine completion, and (3) parent and adolescent individual interviews.

Demographic Characteristics (Aim 1). The adolescent's age, sex, race/ethnicity, insurance type, area deprivation index for residence, and distance from clinic will be obtained from EHR data and recorded on data collection forms. Adolescent's insurance type will be determined by the parent's insurance provider listed in the chart. Area deprivation index for residence, determined by the parent household where the adolescent lives, will be measured using zip codes and linked by subject ID number with the area deprivation index public database to determine the index value for their place of residence. This index value is assigned to neighborhoods using 9-digit zip codes and identifies the percentage of the population that experiences socioeconomic deprivation within a neighborhood in a given geographic area based on the following variables: Education, median family income, employment, income disparity, housing units, federal poverty level, single-parent households, and household characteristics. Higher index values indicate higher levels of deprivation among a geographic area which has been associated with poorer health outcomes (University of Wisconsin Health Innovation Program, 2017). Distance from clinic will be calculated using the adolescent's address listed as the primary residence in their chart and measured as the number of miles from their place of residence to the pediatric clinic. The number of miles will be calculated using geographic information systems (GIS) software. All data will be used to describe the relationship between social determinants and vaccine completion. Parent or legal guardian characteristics including their age, sex, race/ethnicity, and relationship to the adolescent will also be collected to further describe the sample.

Vaccine Completion (Aim 1). Data on the number of HPV vaccine doses that the adolescent received within a 14-month period will be obtained from EHR data. In addition, the date of

vaccine administration and clinic location in which the vaccine doses were received will also be collected. The NCIR database will be used to determine vaccine doses received from clinics outside of the DUHS network for each subject. In the event that any of the HPV vaccine doses were received outside of the DUHS network, the clinic location in which the dose was received will be recorded. Vaccine completion will be operationalized as the receipt of 2 doses, as defined in the new vaccine administration guidelines for adolescents ages 11 to 14 years (Meites et al., 2016). Data on time to second dose and whether each dose was received during a well- or illness-visit will also be collected.

Interviews (Aim 2). Semi-structured, individual interviews will be conducted with parents and adolescents from the selected pediatric clinic. Parents and adolescents will participate in separate, concurrent interviews to maintain confidentiality and capture specific individual experiences with the HPV vaccine and barriers and facilitators to vaccination completion. Interviews will be conducted at one-time point with two members of the research team and last approximately 45 to 60 minutes. An interview guide for parents and adolescents will be used during interviews. Following interviews, demographic information will be collected from parents and adolescents to obtain descriptive data from participants.

SELECTION OF SUBJECTS

Subjects will be identified in person at the Primary Care Pediatrics at Roxboro Road. I have gained permission from the selected clinic to conduct chart reviews and use the NCIR database to prescreen for eligible participants prior to their scheduled clinic visit. Eligibility will include: Adolescents ages 11 to 14 years who have received 1 dose of the HPV vaccine series between January 2017 and December 2017; parents as defined as the adolescent's biological mother or father, step-parents, or legal guardian; and, parents or legal guardians who self-identified as the primary caregiver of the adolescent child and most likely to make medical decisions for the adolescent. Only one parent or legal guardian and one adolescent per household will be included in the individual interviews. Exclusion criteria includes: Parents and adolescents with cognitive impairment, adolescents emancipated from their parents or legal guardian, and pregnant adolescent girls will be excluded from this study. Pregnant girls will be excluded from the study because the vaccine is not recommended for use in this population (CDC, 2016). Further, adolescents who did not receive any doses of the series are excluded since the focus of this study is to understanding barriers and facilitators to HPV vaccine completion.

SUBJECT RECRUITMENT AND COMPENSATION

Recruitment will occur in-person at Duke University Primary Care Pediatrics at Roxboro Road, by phone, email or mail. Sixteen adolescents and 16 parents will be recruited from the clinic (n=32 participants). This clinic was carefully chosen for their diverse patient population of adolescents (26.4% White, 40.9% Black, 20.5% Hispanic, 2.8% Asian, and 16.7% Other). I will track race/ethnicity and gender of potential subjects to ensure participant selection is representative across all demographic groups. A request for waiver of informed consent will be submitted to the IRB to access previously collected data on adolescents' charts and the NCIR database retrospectively for Aim 1. For Aim 2, a request for waiver of informed consent will be submitted to the IRB to use adolescents' charts and the NCIR database to identify potential eligible subjects through chart reviews and to make initial contact with eligible subjects for study participation by the healthcare provider prior to obtaining consent from parents and assent from adolescents. I have gained permission to conduct chart reviews and access to use the NCIR

database to prescreen for eligible participants prior to their scheduled clinic visit. Prior to the start of the clinic day, I will provide a list of eligible participants to each healthcare provider. Clinic healthcare providers have agreed (letters of support) to provide a brief introduction of the study during clinic visits, by phone, email, and through letters sent via mail. Initial contact with eligible parents and adolescents will occur after the study has been introduced and participants have expressed their interest in the study to the healthcare provider. A brochure will be given to healthcare providers and eligible participants to provide them with additional information about the study.

In-person recruitment. After the study has been introduced by the healthcare provider, participants will be approached for recruitment in the patient's room and taken to a private area in the clinic to further discuss information about the study including the purpose and aims, describe participant expectations in the study, address any questions or concerns, gather their contact information, and schedule a date, time, and location to conduct the interviews at the participant's discretion and preference. The brochure and a copy of the informed consent and child assent will be provided during initial contact with participants to take home and allow them time to decide their participation in the study.

Telephone recruitment. I will identify eligible participants at prescreen through chart reviews and provide a list of patients to the clinic healthcare provider. At this point, the clinic healthcare provider will call the participant to briefly introduce the study using a telephone script. Eligible participant's phone numbers will be obtained from the EHR. If the participant expresses interest in the study, I will then further screen for eligibility, provide more information about the study—including participant expectations, address any questions or concerns, gather their contact information, and schedule a date, time, and location to conduct the interviews at the participant's discretion and preference. Contact information of the PI or study coordinator will also be provided to participants. A copy of the informed consent, child assent and study brochure will be provided to participants during their scheduled interviews.

Mail recruitment. As described above, I will identify eligible participants at prescreen through chart reviews and provide a list of patients to the clinic healthcare provider to verify that the provider has previously seen the selected patient. A letter will be sent to all eligible participants on behalf of the healthcare provider using the listed address within the EHR. The letter will contain a brief introduction of the study from the healthcare provider, the eligibility criteria, participant expectations in the study, and contact information of the PI or study coordinator (e.g. phone number and email address) to follow-up with study participation. The study brochure will also be enclosed with the letter to provide the participant with further information about the study. Per DUHS IRB policy, a two-week period from the date of the postmarked mail will be allotted to allow participants time to contact me for study participation. After the two-week period and there is no response from the eligible participant, I will contact them with study participation. Once contact has been made with participants, I will further screen for eligibility, address their questions and concerns, and schedule a date to conduct the interview at the participant's preference.

Email recruitment. After eligible participants are identified at prescreen through chart reviews, I will provide the list of patients to the clinic healthcare provider. An email script will be provided to healthcare providers to send out to all eligible participants. The script will include a brief introduction of the study, the eligibility criteria, participant expectations in the study, and contact information of the PI or study coordinator for participants to follow-up with study participation.

Eligible participant's emails will be obtained from the EHR and provided to the healthcare provider. As previously mentioned, after initial contact with the eligible participant has been made, I will further screen for eligibility, address their questions and concerns, and schedule an interview date and time at the participant's preference. A copy of the informed consent, child assent and study brochure will be provided to participants during their scheduled interviews.

For all recruitment methods**,** informed consent from parents and assent from adolescents will be obtained at the beginning of the scheduled interviews. To compensate parents and adolescents' time to participate in interviews, $45 in cash will be provided ($30 for parents; $15 for adolescents).

RISK/BENEFIT ASSESSMENT

This study poses minimal risk to participants. Nevertheless, there may be a small risk related to a breach of confidentiality and psychological distress related to topics discussed during the interviews. Further, children will be recruited in this study requiring special precautions to minimize potential additional risks for vulnerable populations. There will be no direct benefit to the adolescents and parents participating in this study. However, findings from this study may inform programs and interventions to reduce multi-level determinants influencing HPV vaccine completion among adolescents.

Risks: To mitigate the potential risk for psychological distress related to discussion about cancer, sexual health, and the HPV vaccine, participants will be provided their rights to refuse answering questions during interviews that make them feel uncomfortable and withdraw from the study at any time as specified in the informed consent and child assent. Further, interviews will be scheduled at times convenient with participants' schedule (as specified by parents and adolescents) and at a private location of their preference (i.e. reserved room at Duke University campus or local library, home, etc.) to promote schedule flexibility and to make participants feel at ease during interviews. To minimize risks to children, assent will be obtained from each child which will describe their rights to participate in the study and refuse to answer questions that make them feel uncomfortable. The child's confidentiality will also be maintained through separate individual interviews away from their parents. The interviewer will promote open and honest communication with each participant to create a trusting environment. To protect confidentiality and prevent against a potential breach, each subjects' charts will be provided a participant ID number. Names and date of birth will not be recorded on data collection forms or used in qualitative interviews. All electronic data will be stored in a password protected share drive in which only study personnel will have access to. All hard copy forms (i.e. informed consent, child assent, and demographic surveys) will be stored in a locked file cabinet at DUSON. For aim 1, EHR data containing protected health information (i.e. addresses, zip codes, and date of vaccine administration) will be imported and stored in a secure folder in PACE and later removed from the dataset once area deprivation values and the number of miles from participants' place of residence to the selected pediatric clinic have been determined, and the date of vaccine administration has been converted to months. For aim 2, protected health information obtained for recruitment (e.g. names, addresses, phone numbers, and email addresses) will be recorded on a password-protected Excel document that will be stored in a secure folder within the study's shared drive and destroyed at the completion of data analysis. All collected information will be stored in a database on a standalone database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and access to the server is controlled via firewall rules. All collected data is

backed up daily, both on the local server and by the DHTS enterprise backup system. The PACE network and secure folder on the shared drive for this study will be housed within this server. Only members of the study team will have access to this folder and PACE network.

Benefits: This study presents a minimal risk to participants. While there are no anticipated benefits to participants from being in this study, the benefits to society by helping to reduce barriers to HPV vaccine completion among adolescents outweigh the risks to individuals.

COSTS TO THE SUBJECT

There are no direct costs to the participants of the study.

DATA ANALYSIS & STATISTICAL PLAN

Aim 1: Descriptive statistics will be used to detail the characteristics and key measures for the eligible adolescents and their parents. Logistic regression will be used to determine the role that social determinants play in predicting HPV vaccine completion within 14 months. Individual-level determinants will be adolescent's age, sex, race/ethnicity, and insurance type; community-level determinants will be area deprivation index for residence and distance from clinic. Power calculations indicated a required sample size of 600 charts for adolescents who received the first dose of the HPV vaccine to achieve 80% power when conducting the primary analysis using multivariable logistic regression and supplemental regression analysis using Cox proportional regression models. This sample size estimate was based on the following assumptions: (a) up to 10 predictor terms in the final model; (b) medium effects, indicated by adjusted odds or hazards ratios; (c) two-tailed tests with significance set at 0.05 per test; and (d) an overall missing rate of less than 5% for terms in the model after imputation when needed. However, all charts that meet the eligibility criteria will be analyzed and it is estimated that the sample size will exceed the required sample size of 600 charts.

Aim 2: Directed qualitative content analysis will be conducted to examine parents and adolescents' experience with the HPV vaccine and barriers and facilitators to completing the vaccine series across level of determinant (e.g. individual, relationship, and community). For data integration, quantitative and qualitative data will be analyzed separately initially. Then, results from each separate analysis will be presented in data displays with an integrative summary for each level of determinant to assess patterns between quantitative and qualitative data and provide further description of the role that social determinants play on HPV vaccine completion.

DATA AND SAFETY MONITORING

A Data and Safety Monitoring Boards (DSMBs) is not required for this study since this study does not involve a clinical trial or intervention (NOT-OD-00-038.html). Nevertheless, a plan has been developed to protect quality of data. This study will abide by the Quality Assurance policies of the Center for Nursing Research at DUSON. The QA's services are to verify compliance; ensure all study personnel are properly trained to perform assigned duties and maintain regulatory requirements; monitor study procedures; and minimize the risk for protocol deviations that can affect data collection and maintenance of participants' confidentiality. I will verify compliance to the study protocol regularly (i.e. screening, consenting, and data management) to ensure I am complying to all the regulations and standards for the responsible conduct of research.

PRIVACY, DATA STORAGE AND CONFIDENTIALITY

All collected information will be stored in a database on a standalone database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and access to the server is controlled via firewall rules. All collected data is backed up daily, both on the local server and by the DHTS enterprise backup system. The PACE network and secure folder on the shared drive for this study will be housed within this server. Only the PI and faculty advisor will have access to this folder and PACE network.