Title: A tailored school-based intervention to INcrease VaccinE uptake among adoleScenTs (INVEST) in the rural South

Short Title: INVEST

Sponsor: Centers for Disease Control and Prevention (CDC)

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1 Research Abstract

The benefits of adolescent vaccines are well known for preventing meningococcal infection and human papillomavirus (HPV)-related pre-cancerous lesions. Yet, many adolescents in the United States (US) remain under-vaccinated, with vaccination rates among rural adolescents significantly lower than among their urban peers. Of all recommended adolescent vaccines, the urban-rural disparity is exceptionally stark for coverage of HPV vaccine, particularly in Southern states like North and South Carolina, which currently fall below the Healthy People 2020 goal of ≥80% coverage. Barriers to vaccine uptake among rural youth identified in the literature include a paucity of pediatric primary care providers in rural areas, financial barriers to vaccinations, and negative parental attitudes towards vaccines. Our multidisciplinary team of investigators from Duke University and the University of South Carolina, in partnership with the state health departments from North and South Carolina, proposes to examine barriers to HPV vaccination reported by parents of adolescents in the rural South, healthcare providers, and key stakeholders and then use these findings to inform a school-based intervention. The tailored intervention will address vaccination barriers reported by parents of adolescents in rural communities across the Southern US. The intervention will be adapted for dissemination via public schools, with the core intervention component consisting of educational modules on adolescent vaccines, delivered by school nurses to parents of middle school aged adolescents, followed by reminders to promote vaccine uptake. A quantitative survey in 13 Southern states and qualitative data from stakeholders and parents in rural and urban counties in North and South Carolina will identify differences in barriers to vaccination between rural and urban parents and inform the adaptation of the intervention. The intervention will be evaluated in a feasible study. The central hypothesis is that a school-based intervention will be feasible and acceptable to key school-based stakeholders in North and South Carolina.

The specific aim is to:

- Evaluate the intervention feasibility and preliminary efficacy for increasing vaccine uptake among adolescents in rural North and South Carolina.

If successful, this project will significantly improve our understanding of urban-rural vaccination disparities and yield a school based intervention to increase vaccination coverage, particularly of the HPV vaccine, among rural adolescents. The study will describe the acceptability, feasibility, and preliminary efficacy of a school-based intervention and inform future efforts to scale up the intervention to rural counties across the Southern US.

2 Research Summary

The study has one aim:

(1) Evaluate the efficacy of the intervention for increasing vaccine uptake among adolescents in rural North and South Carolina.

2.1 Objectives and Hypotheses to be tested:

The study purpose is to examine barriers to HPV vaccination reported by parents of adolescents in the rural South, healthcare providers, and key stakeholders and then use these findings to inform a school-based intervention. The central hypothesis is that a school-based intervention will be feasible and acceptable to key school-based stakeholders in North and South Carolina.

2.2 Background & Significance

The Centers for Disease Control and Prevention (CDC) recommends the administration of vaccines against tetanus, diphtheria, and pertussis (Tdap), human papillomavirus (HPV), and meningococcal (MenACWY) infections in early adolescence(*1*). Despite the availability of these vaccines in the United States (US), many youth remain under-vaccinated. Increasing adolescent vaccination coverage is an urgent public health priority with the potential to avert 14 million new HPV infections and nearly 1,000 cases of meningitis in the US annually(*2*). Achieving high coverage of HPV vaccination in early adolescence is particularly important in order to achieve protection prior to the onset of sexual activity and initial HPV exposure (*3*). Yet currently, only 60% of adolescents between the ages of 13-17 in the US have received at least one dose of the HPV vaccine, and HPV coverage (i.e., receipt of >1 HPV vaccine dose) remains 22- 28% lower than coverage for other recommended adolescent vaccines (i.e., Tdap, MenACWY)(*4, 5*). These low rates of HPV vaccine coverage are alarming, given the estimated 30,000 new cases of anogenital cancer and 4,000 deaths from cervical cancer estimated this year alone that are caused by infection with HPV(*6*). In addition to the low coverage of adolescent vaccinations in the US, there is significant geographic variation, with Southern states like North and South Carolina falling significantly below national averages and failing to meet the Healthy People 2020 goal of ≥80% adolescent vaccination coverage(*4, 7*). Furthermore, recent data provide evidence for urban-rural disparities in vaccination coverage, with rural adolescents living in these states demonstrating lower rates of vaccine uptake(*4*). This study is significant because decades of research have established that residents of the rural South face significant health disparities (e.g., cardiovascular disease, cancer, diabetes, obesity) and are less likely to have access to health promoting resources(*8*). Current data from the CDC indicate that rural youth in the South are less likely to receive routine vaccinations, including against HPV. Drivers of this disparity are likely numerous and intersecting, potentially including socio-cultural factors (e. g., socio-religious norms, stigmatized sexuality), structural factors (e.g., racism, poverty, disparities in education and healthcare), and policy factors (e.g., restrictive Medicaid criteria, limited sexual education). Yet, few studies have systematically evaluated such barriers and sought to create tailored approaches to mitigate disparities. This proposal is innovative in its focus on rural youth in the South; findings will inform not only the proposed intervention but also future initiatives to enhance vaccination rates across the Southern US.

3 Design and Procedures

3.1

Evaluate the efficacy of the intervention for increasing vaccine uptake among adolescents and identify barriers and facilitators affecting the implementation of the school-based intervention in rural North and South Carolina.

Primary hypothesis: The proportion of age-eligible adolescents in intervention schools who receive at least one dose of the HPV vaccination will increase post-intervention implementation when compared with proportion prior to intervention implementation

Secondary hypothesis: Compared to the proportion of age-eligible adolescents who receive at least one dose of the HPV vaccine in control counties, we will see an increase in the proportion of age-eligible adolescents who receive at least one dose of the HPV vaccine in intervention counties after intervention implementation.

Procedures:

(a) Caregiver Survey: Caregivers (parents and legal guardians) of 6th, 7th, and 8th graders from schools in the intervention counties will be invited to opt-in to surveys where we will collect quantitative data to explain intervention implementation, reach, and effects. All caregivers of 6th-8th graders in the intervention schools will be eligible to participate in the survey, and response rates up to 1000/county (n=2000 total) are possible. The survey will be conducted pre-implementation of the intervention and collect caregiver and adolescent demographics, HPV vaccine knowledge, attitudes towards vaccination, access to healthcare, intervention exposure and caregiver-reported adolescent vaccine uptake. Surveys will be self-administered remotely, or by the study team in person or over the phone. All surveys will be completed electronically although paper-versions may be used if access to electronic systems are limited at the time of the survey. Any data from paper-surveys will be entered by study staff using the electronic survey system.

(b) Caregiver Interview: Up to 25 caregivers from each intervention county (n=50 total) will be invited to participate in group or individual interviews to discuss intervention effects and implementation as well as barriers to HPV vaccination. Each interview is anticipated to last approximately 60 min (for individual interviews) to 90 min (for group interviews). Interviews will be conducted by trained research study staff, in English, and in-person or over the phone or using tele-conferencing platforms such as zoom. Interviews will be audio recorded using encrypted recorders or in-software recording features (e.g., in zoom) to facilitate transcription and analysis.

(c) Stakeholder Interview: In each intervention county, up to 15 school nurses, local health providers, and stakeholders (n=30 total) will be invited to participate in group or individual interviews to discuss intervention implementation and implementation factors (in intervention schools only; e.g., barriers and facilitators, intervention acceptability etc.), as well as residual barriers to HPV vaccination. Stakeholders included in these interviews may be from the selected county's schools/school districts, local health departments or other local organizations engaged in health promotion, regional or state school and health entities, or other individuals or entities relevant to the intervention). Each interview in this activity is anticipated to last approximately 60 min (for individual interviews) to 90 min (for group interviews). Interviews will be conducted by trained research study staff, in English, and in-person or over the phone or using tele-conferencing platforms such as zoom. Interviews will be audio recorded using encrypted recorders or in-software recording features (e.g., in zoom) to facilitate transcription and analysis.

(d) Nurse survey: In each intervention county, up to 40 school nurses will be invited to opt-in to a post-intervention survey. The survey will collect quantitative data including measures of vaccine advocacy, communication difficulties with vaccine hesitant caregivers, training needs, and nurse demographics. School nurses in the intervention school districts may be eligible to participate in the survey. The survey will be self-administered electronically although paper-versions may be used if access to electronic systems are limited at the time of the survey. Data from paper surveys will be entered by study staff using the electronic survey system.

(e) Post-training evaluation surveys: Professional development or training sessions may consist of courses provided by Duke, other organizations or created by the study team members. If the course is created by study staff members, these materials will be submitted to the IRB in a future amendment. This course could contain material regarding misinformation, motivational interviewing, vaccine registry information and other information determined to be useful by study team members. School nurses, local healthcare providers, and other individuals who take part in any professional development and/or training sessions as part of the intervention will be asked to provide feedback on the training using structured evaluation forms. Evaluation questions will include prompts to elicit feedback on the knowledge gained, residual information gaps, training format and duration, and suggestions for improvements. Closed (e.g., rating scales) and open ended questions on these topics will be included in the survey and tailored to the content covered in the training. As much as possible, data will be collected via electronic surveys, and time will be provided at the end of the training session for completion of the evaluation surveys. Study staff may follow up and complete surveys on the phone or in-person with individuals who are unable to access the surveys for any reason. The surveys will be available in English and take approximately 5 min to complete.

(f) Fidelity Checklists: School nurses in the intervention schools will be asked to complete brief fidelity checklists to document intervention implementation at regular intervals during the study period. Due to the nature of the checklists, only those nurses who are directly involved in intervention implementation will be included in this activity. The checklists may be completed by the nurses on paper or using a link to an electronic survey. Study staff may administer the checklist over the phone and enter data into the electronic survey. In general, the administration of the checklist will occur after each intervention activity (e.g., after each newsletter is due for dissemination). Regular implementation meetings will be held by the study team to offer technical support to school nurses.

(g) Vaccination Outcome Assessment: School districts will provide vaccination data as de-identified data sets. District staff such as school nurses or data managers will review vaccination documentation using the state immunization registry data, school data management systems and/or in official records submitted by the students. The data will be provided to the study team by the schools nurses from the individual middle schools located in the intervention counties.

4 Selection of Subjects

(a) Caregiver Survey

Inclusion:

- Parents or caregivers of a 6th, 7th, or 8th grader in County 1, SC or County 2, NC Public Schools
- 18 years of age or older
- Ability to speak/read English by self-report

Exclusion:

- Individuals not able to consent for themselves

(b) Parents and caregivers participating in a focus group or interview post-intervention

Inclusion:

- 18 years of age or older
- Speak and read English by self-report
- Parent or caregiver of a 6th, 7th, or 8th grader in County 1, SC, or County 2, NC, public schools
- Willing to have their interview audio recorded
- Have either seen health education materials from their school nurse or interacted with their child's school nurse

(c) Local Stakeholder Interview

Inclusion:

- Individuals who are part of the local public school systems in one of two school districts: County 1, SC, or County 2, NC, (e.g. school nurses, administrators, PTA/PTO members, school board members, staff affiliated with school based health centers)
- Individuals who are involved with the state department of education and/or state department of public health
- Individuals from organization involved in health promotion in schools
- Other relevant stakeholders identified by study team
- Fluent in English
- 18 years of age or older

Exclusion:

- Individuals not able to consent for themselves

(d) Nurse Survey

Inclusion:

- 18 years of age or older
- School nurses in one of two school districts: County 1, SC, or County 2, NC, public schools

(e) Post-training evaluation surveys

Inclusion:

- School nurses, local providers or other local stakeholders who participate in training provided.

(f) Fidelity Checklist

Inclusion:

- School nurses who are tasked with vaccine and health promotion in public middle schools in intervention counties

(g) Vaccination Outcome Assessment

Inclusion:

- Any public middle public middle schools in County 2, NC and County 1, SC

5 Subject Recruitment

Caregiver Survey: Eligible caregivers will be able to opt in to the surveys by using QR codes or links that will be listed on the bottom of the health newsletters (letters will be submitted in future amendment). The link to the survey will also be sent out through emails and social media blasts. To ensure that we reach caregivers without technology access, we will also use flyers and mailings to reach eligible caregivers. Information about the study may also be distributed or communicated in person at venues such as football games, orientation sessions, PTA meetings or related activities where eligible caregivers or their adolescents may be present.

Caregiver Interview/Focus Group: We will employ a combination of school-, community-, social media- and web-based strategies to seek participants. Eligible participants include caregivers who have a middle schooler in County 2, NC or County 1, SC. Participants will be recruited through one or more of the following methods: letters, emails, newsletters and social media. A url and/or QR Code to an interest/enrollment survey will be provided as well as a phone number for those who are interested in the study but do not have access to the internet or prefer to communicate by phone.

Local Stakeholder Interview/Nurse surveys: Nurses, health providers, and stakeholders will be recruited based on existing networks of the study team, via email, phone, or mailings. In addition to this purposive strategy, we will use snowball sampling, based on recommendations of current or prospective participants, to reach other relevant participants.

Post-Training Evaluation Survey, Fidelity Checklist, Vaccine Outcome Assessment: School nurses will be providing the vaccination outcome data and feedback regarding the intervention in the form of the post-training evaluation survey, fidelity checklist and focus groups.

6 Risk/Benefit Assessment

Risks from participation in this study are minimal and commensurate with normal life. Participants will be briefed in the informed consent form regarding the nature of the questions they will be asked, and they can choose not to participate. If any emotional distress is experienced while answering the questions during the interview, participants can choose to withdraw from the study. The only anticipated risk is that of loss of confidentiality. Measures to minimize the risk of loss of confidentiality are described in the section on privacy, data storage and confidentiality. The knowledge gained from the research will help us better understand the reason for urban-rural disparities in adolescent vaccine uptake in the Southern US, as well as inform the tailoring of an intervention which aims to provide information to parents in support of their decision to vaccinate their adolescent children.

7 Data Analysis and Statistical Considerations

Caregiver Survey: Survey data will be analyzed in STATA (v.15 or higher StataCorp, College Station, TX) or SAS (SAS Institute, Cary, NC) using bivariate and multivariate regression methods. Characteristics between two arms will be summarized as the mean with standard deviation and/or median with range for continuous variables; and as counts and percentages for categorical variables. For bivariate tests, Chi-square test or Fisher's exact test will be used to compare the probability of categorical outcome between groups. Two-sided t test /ANOVA or Wilcoxon rank sum test will be used to compare the mean difference

in continuous risk factors between groups. For multivariate tests, clustering at the school level will account for error correlation within schools. The primary dependent variable will be coverage of at least 1 dose of HPV vaccine; correlates in bivariate and multivariate logistic regression models will include gender, age, race, ethnicity, and geographic location of the adolescent, household demographic and economic characteristics, and variables describing parental attitudes, access to primary care providers (e.g., health insurance coverage), and barriers to vaccinations.

Caregiver Focus Group/Interview: Using established qualitative research techniques, the interviews are aimed at understanding the attitudes, beliefs and practices related to HPV vaccination in adolescents from the viewpoint of the participants. Given that qualitative research aims to investigate factors that underlie behavior, and is concerned about richness rather than representativeness of data, it requires smaller, focused samples instead of large, random samples. For qualitative interviews and focus groups, evidence suggests that data saturation can occur within 12 interviews, with primary themes arising as early as six interviews(*9*).

Local Stakeholder Interview: We will import all transcripts into a qualitative analysis software package (e.g., NiVivo, Atlas.ti) to facilitate organization and analysis. We will use a 5 stage approach to conduct thematic analysis (familiarization; identifying a thematic framework; indexing; charting, and interpretation) (*10*). Experienced qualitative researchers on the study will conduct the analysis. Familiarization will involve the entire research team reviewing 2-3 transcripts to identify initial coding themes to become familiar with the data. The identified themes will be used as the initial coding framework to conduct line by line coding of a single transcript. The team will meet to discuss the transcript and modify the initial framework. Next, two experienced qualitative researchers will conduct line by line coding of remaining transcripts. Coding will include memos for each transcript to annotated coders questions, decision about the data, and reflections on analysis. Each coder will also create an overview memo to collect observations that cut across individual transcripts during the coding process. After coding is completed, the team will meet to discuss themes, sort codes, and restructure the initial framework as similarities and differences are identified. In the final stage, the team will identify major themes and associated quotes to summarize the results. Methods such as regular de-briefing and memo writing throughout the process will be used to enhance rigor and trustworthiness of study findings.

Nurse Survey: Descriptive statistics will be used and we may explore correlations using methodologies such as cross-tabulations and regression analyses.

Post-Training Evaluation Survey: Descriptive statistics will be used.

Fidelity Checklists: Descriptive statistics will be used.

Vaccine Outcome Assessment: Descriptive statistics and chi-square tests will be used.

8 Data and Safety Monitoring

The risks of participating in this study are minimal and commensurate with ordinary life. For this reason, a data and safety monitoring board will not be convened. The investigators will make all study related documents, including consent forms, readily available for inspection by the study's IRBs, and the Office

for Human Research Protection (OHRP). On-site study monitoring will be performed by the study and local PI or their designees, to verify compliance with human subjects and other research regulations and guidelines, assess adherence to the study protocol, and confirm the quality and accuracy of information collected and entered into the study database. The study will be conducted in full compliance with the protocol. With the exception of modifications required to eliminate immediate and unanticipated participant safety concerns, the protocol will not be amended without approval from the study PI, Dr. Walter.

9 Privacy and Confidentiality

Duke University will partner with Drs. Harrison and Ostermann at the University of South Carolina to implement study activities in South Carolina. Dr. Harrison will serve as the site PI and take the lead on study oversight and compliance in South Carolina, with support from Dr. Walter or his designees. Valerie Yelverton and Jingyi Yang will be hired by USC, under Dr. Harrison's supervision to conduct recruitment and data collection activities as needed. Dr. Nicole Hair will perform data analysis. All study staff based at USC will be documented in the protocol submitted to the USC IRB for ethical approval. USC will lead all data collection activities in South Carolina and collaborate with Duke on the activities related to protocol/instrument development, implementation, data analysis, and study dissemination. The cross-sectional survey will be conducted by Duke site only. Dr. Vasudevan, continues to remain affiliated with Duke as an adjunct associate professor of global health since Aug 1, 2022, will be a lead/co-author of will be a lead author or co-author of peer-reviewed journal publications. She may also represent the team and present findings at external meetings or conferences in consultation with the Pl, Dr. Walter. She will also support the development of the final scientific report and CT.gov reporting.

10 Bibliography

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