Title: Increasing HPV Vaccination Rates through Virtual Immersive Communication Training on Recommending Immunizations: An Efficacy Study of VICTORI

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Increasing HPV Vaccination Rates through Virtual Immersive Communication Training on Recommending Immunizations: An Efficacy Study of VICTORI

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Background:

Despite strong evidence the human papillomavirus (HPV) vaccine is effective in preventing certain anogenital cancers, only 65% of adolescent females and 56% of males in the U.S. have initiated the series, and only 43% of girls and 31% of boys have completed it.[1] These rates fall short of Healthy People 2020's objective of 80% coverage for adolescents 13-15 years of age.[2] Research has demonstrated that the leading predictor of parents' decisions to vaccinate their child against HPV is a strong clinician recommendation.[3-8] However, evidence suggests that many parents of age-eligible adolescents are not receiving HPV vaccine recommendations[9] or are receiving weak recommendations from clinicians.[10-12] Previous interventions aimed at increasing HPV vaccination rates have had variable effects in part due to reach and adoption of the interventions within the practices.[13-19] Also, the diffusion of successful interventions have been limited by lack of scalable designs.[20] Thus, we will solve this limitation by standardizing the training component and moving towards developing a scalable model that translates into consistently improved HPV vaccine rates.

Simulation-based medical education (SBME) has become an essential component of clinical training, demonstrating superior effectiveness in teaching a wide range of medical skills compared to conventional training methods.[21-23] Immersive virtual reality (VR), one type of SBME, is a three-dimensional, computer-generated environment where users interact with graphical characters called avatars. Within VR, a facilitator can design scenarios based on specific behavioral objectives and create environments and avatars based on training needs. The technology facilitates deliberate practice, a personal and goal-oriented approach to skill development derived from Ericsson's Theory on Expertise.[24] In our preliminary study conducted in 2015, we developed an intervention for resident physicians to address influenza vaccine hesitancy, comprised of a self-directed application (app) based curriculum about HPV vaccination followed by immersive VR simulations.[25] Completion of the VR simulations, compared to receipt of standard training, led to a significantly lower rate of influenza vaccine refusal.[26] Based on these promising preliminary results, we developed VR simulations focused on HPV vaccine counseling.

Purpose:

Our approach will be to implement **Virtual Immersive Communication Training on Recommending Immunizations (VICTORI)**, an intervention that includes a self-directed app-based curriculum and VR simulations, designed to increase the strength and consistency of HPV vaccine recommendations among clinicians. VICTORI will be implemented using a framework informed by behavioral (Social Cognitive Theory, Health Belief Model, and Theory of Planned Behavior) and educational theory (Ericsson's Theory on Expertise). The primary outcome will be an increase in HPV vaccine rates among adolescent patients. We will also assess theory-based mechanisms by which the intervention changes vaccination rates, including clinicians' knowledge, attitudes, perceptions, self-efficacy, and strength of recommendations.

Our *long-term goal* is to increase HPV vaccination rates in adolescents, which will decrease rates of HPV-associated cancers and pre-cancers. Our short-term *objective* is to evaluate the efficacy of VICTORI, a novel VR intervention, designed to enhance the strength of clinicians' HPV vaccine recommendations and improve HPV vaccine rates among 9 to 17-year-old patients. Our *central hypothesis* is that VICTORI, which includes VR simulations, will be positively associated with an increase in vaccine rates, and this association will be mediated by improvements in clinician attitudes, self-efficacy, and strength of vaccine recommendation. The *rationale* for the proposed

research is that an evaluation self-directed app based curriculum about HPV vaccination and VR simulations will inform effective and scalable strategies to train clinicians to provide strong vaccine recommendations, resulting in increased HPV vaccine rates and ultimately lower rates of HPV-associated cancers. To accomplish our objective, we will achieve the following specific aims:

1. ***Evaluate VICTORI for acceptability and feasibility.*** The working hypotheses, based on our preliminary data and previous experience with a vaccination-focused intervention that included VR simulations,[26] are that: 1) clinicians (physicians) and staff (nurses and medical assistants) will find VICTORI (self-directed app based curriculum and VR simulations) acceptable (i.e., they will find it realistic, immersive, and easy to use) and will appreciate the user-centered components and presentation of information and 2) VICTORI will be feasible in terms of time required for participation and ease of incorporation of training into the outpatient setting. Results from this aim will be used to modify the intervention to optimize acceptability and feasibility.

2. ***Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine rates.*** The working hypotheses are: 1) adolescent HPV vaccination rates will increase significantly following implementation of VICTORI compared to pre-intervention rates and 2) this increase will be mediated by clinicians' more positive attitudes, higher self-efficacy, and stronger vaccine recommendations.

3. ***Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly.*** We will obtain information about barriers to vaccine series completion from a retrospective chart review of patients who initiated but did not complete the HPV vaccine series during our study.

Location

Aim 1: Evaluate VICTORI for acceptability and feasibility will take place within the Division of Adolescent Medicine in a conference room at CCHMC. Participants will include clinicians and staff from the Teen Health Center (THC). The THC at CCHMC serves as a medical home for 6,442 patients with just over 7,000 visits each year. The THC manages and treats medical, social, emotional, sexual, educational, and nutritional concerns impacting adolescent youths. HPV vaccination is an important preventative care action at the THC. The clinicians at the THC frequently discuss HPV vaccination with patients and families and are thus suitable candidates to provide meaningful feedback regarding the acceptability and feasibility of the proposed intervention.

Aim 2: Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine initiation and completion rates will take place within the Division of General and Community Pediatrics in a conference room at CCHMC. The PPCC is a busy, academic clinic in Hamilton County, Ohio with about 33,000 visits annually, serving 19,000 patients that are predominantly underserved with approximately 90% insured through Medicaid. Seventy-five percent of the patient population is African American and 5% is Latino. PPCC serves a population that is at high risk for HPV infection and its sequela, and therefore, we anticipate the findings to be generalizable to other urban primary care clinics that serve predominantly minority populations. The

Hopple Street Neighborhood Health Center (HSNHC) will serve as a control during Aim 2. The HSNHC serves a similar population to the PPCC with 6000 unique patients and 13,000 patient visits per a year. VICTORI, our educational intervention, will be conducted in such a way as to not disturb or interrupt typical clinical flow.

Aim 3: Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly. The procedures for this aim will take place within the Division of General and Community Pediatrics at CCHMC. The PPCC is a busy, academic clinic in Hamilton County, Ohio with about 33,000 visits annually, serving 19,000 patients that are predominantly underserved with approximately 90% insured through Medicaid. Seventy-five percent of the patient population is African American and 5% is Latino. PPCC serves a population that is at high risk for HPV infection and its sequela, and therefore, we anticipate the findings to be generalizable to other urban primary care clinics that serve predominantly minority populations. Hopple Street Neighborhood Health Center (HSNHC) which served as a control during Aim 2, serves a similar population to the PPCC with 6000 unique patients and 13,000 patient visits per a year.

Duration

This study will take a total of 24 months. Aim 1 will take place over the first 6 months. Aim 2 will take place over the entire 24-month period. A timeline has been included below.

VICTORI Timeline

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Recruitment and enrollment												
Aim 1 feasibility and acceptability testing												
Aim 1 analyses												
Aim 2 baseline data collection												
Aim 2 VICTORI implementation												
Aim 2 post VICTORI data collection												
Aim 2 environmental control data collection												
Aim 2 analyses												
Aim 3 retrospective chart review data collection												
Aim 3 analysis												

Protection of Subjects

Aim 1: Evaluate VICTORI for acceptability and feasibility

Physicians (target number = 11, maximum =18) and staff members (target number = 15, maximum = 30) at CCHMC THC will be recruited for this study to evaluate the acceptability and feasibility of VICTORI. Participants will receive $50 for their efforts. Staff will also be provided lunch. The

research materials to be obtained from physician participants are interview data collected through semi-structured interviews. The interviewer will record field notes during the interviews, including the amount of time it takes a participant to complete the VR simulations and any additional adjustments needed for the technology. Additionally, the interview content will include overall impressions of the VR simulations, perceived purpose of the VR simulations, suggestions for changes to the simulations, if the participant would recommend the intervention to a colleague, and if the participant experienced motion sickness. Interviews will last approximately 30 minutes and will be audio and video recorded. The research materials to be obtained from staff participants are data collected through focus group interviews of 5-8 individuals. A study member (JR, BR, MB, SM) other than the focus group facilitator will record field notes during the interviews, including any additional adjustments needed for the technology. Questions for the focus group will focus on overall content, length of training, engagement in group learning activities, and suggestions for changes to the intervention. Focus groups will last approximately 45 minutes and will be audio-recorded. All semi-structured interviews and focus group interviews will be transcribed by HIPPA compliant transcription company. Transcribed interview and focus group data will be de-identified and data files will be kept in a password-protected file on a password-protected computer. Data collection will continue until a saturation of themes is met per qualitative research guidelines. At the completion of the VR simulations, physician participants will complete the MEC-Spatial Presence Questionnaire (MEC-SPQ), a validated tool to assess the realistic and immersive nature of virtual environments,[27] as well as provide participant characteristics. This survey will take an additional 5 minutes to complete. Staff participants will also complete a survey assessing participant characteristics. These data will be entered into Research Electronic Data Capture (REDCap)[28] upon study completed with hardcopies of surveys being destroyed. Only study personnel will have access to the data.

Aim 2: Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine initiation and completion rates

Physicians (n = 70) and staff (n = 40) at CCHMC PPCC will be recruited for this study to evaluate the effectiveness of VICTORI on HPV vaccine initiation and completion rates. Physicians from PPCC will receive $50 for their efforts. Staff will receive a $10 gift card for their efforts. Additionally, physicians (target number = 35) from HSNHC will be recruited to serve as the control. HSNHC participants will receive the self-directed app based curriculum component of VICTORI though will not undergo the VR simulations. Participants from HSNHC will receive $25 for their efforts.

The primary outcome is the increase in the proportion of patients receiving HPV vaccination seen by resident and attending physicians following participation in VICTORI. These data will be obtained from the EPIC electronic medical record on a monthly timeline from PPCC 6 months prior to implementing VICTORI (baseline), the months during intervention implementation, and 6 months after the intervention (post) for physicians, as well as 6 months after the intervention (post) for staff. These data will be compared with monthly HPV vaccination data from HSNHC from the start of the study until 22 months to serve as a control. Data will be blinded and entered into a REDCap database. The research materials to be obtained from participants are data collected through audio/video recordings during VICTORI and items from validated survey instruments to evaluate secondary outcomes. These secondary outcomes include physicians' behavioral capability, self-efficacy, perceived benefits, barriers, and risk, as well as attitudes, subjective norms, and strength of recommendations. We will also collect data on staffs' behavioral capability, perceived

benefits, barriers, and risk, as well as attitudes, subjective norms and ability to provide consistent positive messaging about the HPV vaccine. We will also collect data on participant characteristics. Survey data will be collected pre-intervention, immediate post-intervention, and 3 months post-intervention for physicians and pre-intervention and immediate post-intervention for staff. Data files will be kept in REDCap. Only study personnel will have access to the data.

Aim 3: Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly.

We will conduct a retrospective chart review to explore social determinant of health barriers to vaccine series completion from a retrospective chart review of patients who initiated but did not complete the HPV vaccine series during our study. We will identify patients within the cohort at PPCC and Hopple who initiated but did not complete the HPV vaccine series within a 14 month period following a visit with physicians that participated in the Aim 2 portion of the study. For patients under the age of 15 years, the second dose of the HPV vaccine series is to be administered six months following the first dose. We have operationalized HPV vaccine series completion to occur within 14 months as this provides an adequate and pragmatic timeframe for vaccine series completion at a follow-up visit or annual well child visit.

The primary outcome is the proportion of patients within a cohort at PPCC and Hopple who initiated but did not complete the HPV vaccine series within a 14 month period following a visit with physicians that participated in the Aim 2 portion of the study. These data will be obtained from the EPIC electronic medical record of patients who initiated the HPV vaccine series but have yet to complete it. Data will be entered into a REDCap database. The research materials to be obtained from participants are data collected through review of retrospective chart review of the GPC Social Risk Family Questionnaire, demographic data (DOB, age, sex, race, ethnicity, health insurance), visit information, and HPV vaccine dates (see appendix VICTORI Chart Review).

Potential Benefits

Providers who participate in the VICTORI curriculum will obtain additional knowledge on how to appropriately counsel parents that express vaccine hesitancy. The goal is to improve physician-patient communication which results in improved clinical outcomes (less vaccination refusal) for this high-risk population.

Potential Risks

Aim 1: Evaluate VICTORI for acceptability and feasibility

We estimated the risks of participating in this study to be minimal since participation is limited to VICTORI, interviews, focus groups and a survey focused on spatial presence within the VR simulations. Some participants might be uncomfortable participating in the VR simulations in the presence of a researcher, while being recorded. However, we expect this to be minimal as it is a low-stakes environment. There is a small risk of breach of confidentiality through focus group and transcription of interview data, but we expect the risk to be minimized due to the efforts and protocol described.

Aim 2: Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine initiation and completion rates

We estimate the risks of participating in this study to be minimal since participation is limited to the VICTORI intervention and survey. Some participants might be uncomfortable participating in the intervention in the presence of a researcher, while being recorded. However, we expect this to be minimal as it is a low-stakes environment. There is a small risk of breach of confidentiality through collection of survey data and transcription of the interview data, but we expect the risk to be minimized due to the efforts and protocol described.

Aim 3: Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly.
There is a small risk of breach of confidentiality through collection of data, but we expect the risk to be minimized due to the efforts and protocol described.

Risk/Benefit Analysis
Given the minimal risks and the potential benefits, the investigators believe that the benefits outweigh the risks. The main risk posed by this study is the potential for loss of confidentiality. All electronic data files will be kept on a secure, password-protected server with access determined by the Co-PIs and the analytic team. Hardcopies of all information will be kept in locked filing cabinets. Only the Co-PIs and study staff will have access to this information.

All participants will be monitored for safety during the study. We do not anticipate any adverse events as a result of participating in the intervention as this is not a medical intervention. We will review all VICTORI experiences among enrolled participants to ensure that the intervention does not contribute to an adverse event directly linked to the intervention experience. We will use a case report form that will record specifics surrounding an experienced adverse event, including type, severity, and relationship to the study, actions that were taken, and current status of the participant. Study staff will notify the Co-PIs or a qualified designee immediately of any serious adverse events or any adverse events that are suspected to be related to the study.

Research Methodology
The aims for this study will be accomplished through mixed qualitative and quantitative research methods. **Aim 1** will utilize mixed-methods research to obtain information from clinicians and staff about the acceptability and feasibility of VICTORI. Based on these data, adjustments and revisions will be made to VICTORI to optimize acceptability and feasibility. **Aim 2** will be a single-site intervention assessing the efficacy of VICTORI (self-directed app-based curriculum and VR simulations) on HPV vaccine rates (primary outcome). We will assess the theory-based constructs that have been used in the design of VICTORI to determine whether they impact clinician recommendations and are mediators of the effect of VICTORI on vaccination rates. These constructs will include behavioral capability and self-efficacy from SCT, perceived benefits, barriers, and risk from HBM, and attitudes and subjective norms from TPB. The rationale for selecting these constructs is they have been identified as the most powerful predictors of clinician recommendations for and parental acceptability of HPV vaccines.[7,29-49] **Aim 3** will be a single-site retrospective chart review exploring social determinants of health that are associated with HPV vaccine series completion.

Aim 1: **Evaluate VICTORI for acceptability and feasibility.**

Setting and Population: Before implementing the VR simulation, all clinicians will receive a self-directed app based curriculum. Clinicians will receive education to increase their knowledge of HPV and the vaccine, perceived benefits, positive HPV vaccine attitudes, and subjective norms as well as decrease their perceived barriers to recommending the vaccine. The participants will engage in the VR simulations independently. The simulations will be audio and video recorded. The VR simulations, already developed through funding from APA, consist of four simulated scenarios in which participants will counsel caregiver avatars hesitant to accept the HPV vaccine for their child. During each simulated encounter, the participant will counsel the HPV vaccine-hesitant caregiver through verbal dialogue. For the participant to succeed (vaccination accepted), the participant has to demonstrate the following best-practice communication skills related to HPV vaccine counseling: (1) using presumptive "announcements" or short statements assuming parents are in agreement to vaccinate their child, (2) consistent positive messaging, (3) providing a strong recommendation, and (4) accurately addressing caregiver concerns without medical jargon.[13,50-53] The parent avatar's verbal and nonverbal responses to the participant's counseling will be driven by a single facilitator (either Dr. Real or Dr. Rosen; Figure 1). Each scenario will use a flow sheet to standardize the experience. Simulations flowsheets were developed using an iterative process and collaborative effort between pediatricians and technologists. Table 1 provides details regarding the four VR scenarios that include the most salient and important sources of hesitation.[54-58] The four-scenario intervention will take approximately 20 minutes to complete and will be scheduled at a time convenient for the participants. After each scenario, the facilitator will provide the participant with specific feedback regarding his or her use of best-practice communication skills based on a modified version of a previously developed rubric.[26]

Figure 1: (A) Education is administered using a head-mounted display that shows 3D graphics. (B) After each simulation, a learner receives feedback.

While the staff participants will complete the same intervention, the staff will receive the intervention through a different method. Staff members will receive the intervention in a small group setting. The rationale for this method, which has been shown to be effective in delivering key educational

Table 1: Virtual Reality Simulations

Setting: Cincinnati Children's Hospital Medical Center Pediatric Primary Care Clinic

Scenario 1	Scenario 2	Scenario 3	Scenario 4
Narrative: 11 yo female patient presents for well-child care **Characters**: parent and female adolescent avatars **Source of Hesitation**: none	**Narrative**: 11 yo male patient presents for well-child care **Characters**: parent and male adolescent avatars **Source of Hesitation**: concerns regarding safety and side effects	**Narrative**: 11 yo female patient presents for well-child care **Characters**: parent and female adolescent avatars **Source of Hesitation**: concerns regarding necessity, young age, and promoting sex	**Narrative**: 11 yo male patient presents for well-child care **Characters**: parent and male adolescent avatars **Source of Hesitation**: concern regarding that vaccine is not required by school and male patients don' t need it.

Key Skills: Presumptive announcement, consistent positive messaging, strong recommendation, emphasizes timing of second dose, and addressing specific concerns without medical jargon

components,[59,60] is to inform the staff (nurses, medical assistants, and other patient facing staff members—who are often the first health professional to meet with patients)[61,62] about the communication training physicians are receiving and ensure staff members are providing consistent, positive vaccination messages that align with the VICTORI objectives. After watching a 5-minute video on evidence-based practices in recommending the HPV vaccine, participants will observe Dr. Real or another co-investigator clinician (a clinician) participate in the VR simulation while Dr. Rosen or another co-investigator facilitates the experience. Staff will be able to observe the VR scene and interactions through a projector set-up. A debrief of the VR observation will occur to reinforce background knowledge, attitudes, perceptions and consistent positive messaging.

Measures and Data Analysis: To evaluate the acceptability and feasibility of VICTORI, we will use a mixed methods approach. Physicians will complete the MEC-SPQ, a validated tool to assess the realistic and immersive nature of virtual environments (see Appendix A)[27] after implementing VICTORI. The MEC-SPQ is simply meant to inform the extent of immersion experienced by users. It will be used to identify deficiencies in the virtual environment or programming that require modification prior to study implementation. Next, individual cognitive interviews for clinicians lasting approximately 30 minutes in a private location will be conducted. Interviews will be directed by either Dr. Real or Dr. Rosen. The interview items were developed from seminal literature in usability testing (Table 2).[63-66] For staff member participants, Dr. Real or Dr. Rosen will conduct a focus group to obtain feedback regarding acceptability and feasibility following demonstration of VICTORI. Questions only for staff are noted by superscript letter ([a]) in Table 2. The interviews with providers will be audio and video recorded and transcribed by a HIPPA compliant transcription company and

Table 2: Post Interview Questions

Participating in the Intervention
1. What are your overall impressions of the VICTORI curriculum?[a]
2. Name three words or characteristics that describe the VICTORI curriculum. a) **RN/MAs:** Name one word or characteristic that describes the VICTORI curriculum.[a] b) Explain why you picked these words or characteristics.[a]
3. What are the three things you like least about the VICTORI curriculum?
4. Would you participate in a virtual reality intervention like this (VICTORI) in the future?[a] a) Please share more?[a]
5. Would you recommend the VICTORI curriculum to a colleague? Why/why not/please share more? [a]
6. What information would you like to see added to the VICTORI curriculum? [a] a) Any changes to the current scenarios? b) Any frequently encountered scenarios missing?[a]
7. What information from the *HPV Vaccine: Same Way, Same Day*™ app was helpful to you before participating in the virtual reality training component of VICTORI? a) If not, what components were missing?
8. Did you think the duration of the VR experience was appropriate?[a] a) Too long? What should be removed?[a] b) Too short? What should be added?[a]
9. Did you think the feedback during the VR experience was appropriate?[a] a) What should be removed?[a] b) What should be added?[a]
10. What concerns did you have while participating in the experience?[a]
The VR Device
11. How easy or difficult was the VR device to use? Tell me more.
12. How did participating in the VR simulations make you feel? a) Did you feel immersed? b) Did it feel realistic? c) Did you experience any side effects? (PROBES: distracted, anxious, at ease, motion sickness, etc.)
13. How did you feel about the environment in which the training took place? What could we have done to make the environment more conducive to learning?

[a] indicates specific questions for staff

the research team. The focus group will be audiotaped and transcribed by a HIPPA compliant transcription company. The interviewer will record field notes during the clinician and staff participation in the intervention, including the amount of time it takes to complete each component of the intervention as well as any possible adjustments needed for the 5-minute video on evidence-based practices in recommending the HPV vaccine and VR simulations. The research team will review interview transcripts using the framework analysis approach, a multistep method for analyzing qualitative data, to assess the interview data and create a conceptual framework.[38,67] NVivo (QSR International, Doncaster, Australia) will be utilized to support data coding and analysis. Data collection will continue until a saturation of themes is met per qualitative research guidelines. A content analysis of the transcribed interviews will be conducted, and themes will be examined for evidence of needed revisions.

Expected Outcomes: These findings will provide insight from the users' perspective regarding the strengths and weaknesses of the intervention. These data are required for the design of effective, scalable, user-centered interventions for clinicians to increase strong HPV vaccine recommendations to hesitant parents. These data will be used to guide revisions to the intervention before implementation (Aim 2). We will specifically adjust the intervention based on the responses to post interview questions with potential modifications including: adjusting the content of simulations, adjusting the order of simulations, adjusting the timing of simulations, adjusting the environment in which VICTORI will be administered, and/or adjusting the VR headset specifications (i.e. sizing). Staff will specifically provide feedback regarding small group learning. We plan to trial the modified version of the simulation with study team members (FR, BR, JK, MK, DD) prior to study implementation to ensure feedback from acceptability study has been successfully addressed.

Potential Problems and Alternative Strategies: Low response rate may occur; to mitigate this possibility, we will work with the study team to recruit chief residents at CCHMC. Chief residents are a feasible alternative population as the majority previously worked at the PPCC as residents, and there is no risk of contamination. Furthermore, if the Food and Drug Administration releases new recommendations for existing vaccination, we will revise VICTORI along with the survey instrument to reflect these changes.

Aim 2: Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine rates. Aim 2 will utilize quantitative research methods to determine if rates of HPV vaccine uptake among 9 to 17-year-old boys and girls increase following the implementation of VICTORI for physicians and staff compared to pre-intervention rates. In addition, a survey instrument will be used to measure theory-based behavioral constructs hypothesized to mediate the intervention effect.

Setting and Population: We will recruit and implement the intervention in the CCHMC PPCC. There is no concern of contamination from the preliminary flu study as it was completed in 2015 since staff members were *not* included and all participants graduated by spring 2017. The PPCC is a busy, academic clinic in Hamilton County, Ohio with about 33,000 visits annually, serving 19,000 patients that are predominantly underserved with approximately 90% insured through Medicaid. Seventy-five percent of the patient population is African American and 5% is Latino. PPCC serves a population that is at high risk for HPV infection and its sequela, and therefore, we

anticipate the findings to be generalizable to other urban primary care clinics that serve predominantly minority populations. The PPCC is staffed by approximately 20 attending physicians (total: 8.0 Full-time equivalent), 80 pediatric residents, 25 nurses, 21 medical assistants, 5 nurse care managers, 3 social work care managers, 3 social workers, 1 community engagement specialist, 14 community health workers, 2 customer service representatives, and 6 psychologists. Additionally, we will recruit resident and attending physicians from the HSNHC who will not receive the VR intervention but will serve as controls, only receiving the self-directed app-based curriculum. HSNHC serves a predominantly underserved population as well with 90% publicly insured. Seventy-three percent of the patient population is African American, and 5% is Latino. HSNHC is staffed by approximately 7 attending physicians (total: 2.5 Full-time equivalent) and 28 pediatric residents. HPV initiation rates in Ohio are 57% for girls and 55% for boys; completion rates are 42% for girls and 41% for boys.[1] The completion rate in Hamilton County is 16% for boys and girls combined.[68] The vaccination initiation rates in the PPCC (FY17) for 11 to 12-year-old girls was 48% (257 vaccinations initiated out of 537 visits) and for 11 to 12-year-old boys was 52% (289 vaccinations initiated out of 557 visits). The HPV vaccination initiation rate in the PPCC (FY17) for 11 to 17-year-old boys and girls was 43% (619 vaccinations initiated out of 1450 visits). The rationale for including adolescents 9 to 17 years old is this will allow us to perform a stratified analysis to determine if the intervention is more effective during the target range (11-12 years), the catch-up range (13-17 years), or early vaccination range (9-10 years). In addition, the National Immunization Survey (NIS) for Teens assesses vaccination rates in children age 13-17 years. By including all children age 9-17 years within our study population, it will allow comparison with the NIS-Teen outcome measures. The PPCC cares for very few patients 18 years and older, and we therefore did not extend our population beyond 17 years. HSNHC, environmental control, had a 51% HPV initiation rate (FY17) for 11 to 17-year-old boys and girls (183 vaccinations out of 357 visits). The HSNHC serves a comparable site to the PPCC and is similarly staffed by physicians from CCHMC though distinct from those physicians practicing at PPCC.

Design and Measures: Once acceptability of VICTORI has been assessed through Aim 1 and modifications have been finalized, Dr. Real and Dr. Rosen will undergo fidelity training to ensure uniform usage of the simulation flow sheets and performance rubrics. Minimum passing score (i.e., performance on simulation that results in vaccine acceptance) will be established using the borderline group standard setting method.[69-71] The borderline group method is a well-established process for evaluating examinees that uses a checklist to assess proficiency when directly observing a performance test. VICTORI will be implemented using the same methods as described in Aim 1 for physicians and staff. VICTORI VR simulation implementation may take place over ZOOM based on the COVID-19 pandemic and institutional guidelines limiting in-person research visits. VICTORI VR simulation implementation sessions will be audio and video recorded. VICTORI's effect will be assessed using a repeated measures pre-post study design with follow-up period. We will collect monthly baseline data on HPV vaccine initiation and completion rates in PPCC for six months prior to implementing VICTORI. In phase I, VICTORI will be administered to resident and attending physicians. We will then collect HPV initiation and completion rates monthly during the time of intervention implementation and for the following six-months. To assess vaccination rates in clinic compared to HPV vaccination, we will also collect influenza, Tetanus, Diphtheria, and Pertussis (Tdap), and meningococcal conjugate (MCV4) vaccine for the six months prior and post VICTORI implementation in PPCC.

Next, we will implement VICTORI with staff including nurses and medical assistants in groups of up to 15-20 participants (phase II; secondary outcome). These sessions may take place through a technology-based platform to allow for social distancing dependent on the COVID-19 pandemic and institutional guidelines limiting group meetings and in-person research visits. Staff will watch a 5-minute video on evidence-based practices in recommending the HPV vaccine and observe a facilitator and clinician participating in the VICTORI VR simulations, and then engage in a 5-minute debriefing. Staff will complete a brief pre and immediate post survey assessing their perceived benefits and barriers, subjective norms, and positive messaging about the HPV vaccine on paper or via REDCap. We will collect an additional six months of monthly HPV vaccination initiation and completion data, along with influenza, Tdap, and MCV4. We will collect the same vaccination data from the HSNHC over the same study period to serve as a control. The primary outcome will be the **increase** in the proportion of patients receiving HPV vaccination seen by resident and attending physicians following participation in VICTORI. Additional secondary outcomes, including physicians' behavioral capability, self-efficacy, perceived benefits, perceived barriers, perceived risk, attitudes, subjective norms, and strength of recommendations, as well as staffs' perceived benefits and barriers, subjective norms, and positive messaging will be assessed via validated survey instruments created by Dr. Kahn and colleagues (see Appendix B and C).[41,49,72-76] Physicians' strength of recommendation will be self-reported, which is a common method of measuring this construct.[30] In addition, this method (self-reported strength of recommendation) is supported as it is positively associated with vaccination rates documented through medical records.[77] Physician and staff demographics will also be collected to assess for moderation or confounding. Confidentiality of the results will be maintained. All surveys will have unique IDs with one REDCap form, separate from the surveys including their email and ID. Surveys will also be administered through the REDCap Database. Participants will receive a total of 3 emails encouraging survey completion prior to and following completion of VICTORI. Participants will receive a newsletter periodically via email to enhance retention and provide study updates (appendix). Powerpoint slides will be presented in clinic to as a retention tool as well (appendix).

Data Analysis: Repeated measures generalized linear mixed-effects regression (GLMER) will be used to test whether vaccine initiation and completion rates of 9 to 17-year-old boys and girls increase in response to VICTORI. Models will include a logit link function to model the binary patient-level response of vaccine initiation (yes/no) and a random subject-specific intercept to account for patient encounters nested within physicians. *Our primary outcome*, determining the increase in the proportion of patients receiving HPV vaccination seen by resident and attending physicians in response to the intervention will be tested using the GLMER model including fixed-effect terms for study month (i.e., time) and period (pre-intervention vs. post-intervention). A likelihood ratio test (LRT) for period will provide a formal test of whether vaccine initiations increase in response to the intervention. Differences in the trajectory (i.e., change in slopes) of vaccine initiations between pre- and post-intervention periods will be tested by the inclusion of an interaction term for time and group. The inclusion of a random slope for time will be determined based on assessment of model fit. Polynomial terms or restricted cubic splines will be considered to model non-linear associations in vaccine initiation (i.e., capture the possible early intervention effect and subsequent decline). Additional terms as described for resident and attending physicians in phase I will be added to capture changes in the level and slope of vaccine initiation in response to training staff in phase II. Primary analyses will be conducted for

physicians (resident and attending combined) enrolled in both the pre- and post-intervention periods. *Secondary analyses* will examine the intervention effect on completion rates, for resident and attending physicians separately, and for all physicians and staff combined. GLMER models as described above will also be used to assess whether background rates of vaccine initiation and completion change over the study period in the absence of the intervention at the control site (HSNHC). Additional secondary analyses will focus on identifying potential mediators of the intervention effect on PPCC providers; whether the effect of the intervention is mediated by changes in the strength of vaccine recommendations and relevant theory-based constructs. Stratified analyses and formal testing of interactions will also be used to assess whether the effect of the intervention differs (i.e. effect modification) according to baseline provider characteristics such as age, sex, and attending vs. resident status, as well as patient characteristics (female vs. male patient, age of patient). As discussed, providers at HSNHC will be receiving the self-directed app-based curriculum component of VICTORI though will not participate in VR simulations and thus will not engage in deliberate practice of curricular skills. HSNHC providers survey responses will be compared to PPCC providers to assess for relevant changes in theory-based constructs including physicians' behavioral capability, self-efficacy, perceived benefits, barriers, and risk, as well as attitudes, subjective norms, and strength of recommendations that might occur following participation in the app-based curriculum only. Survey data will be collected before the app-based curriculum, immediately post-curriculum, and three months after the curriculum. This comparison will be conducted using a two-independent sample t-test.
VR sessions will be reviewed as part of secondary analyses to qualitatively explore providers' language around addressing particular sources of hesitancy for HPV vaccination. Language will be assessed through thematic analysis and summative content analysis. For example, we will assess provider's responses to parental concerns regarding HPV vaccination prompting early sexual activity initiation. We will explore if race of the animated parent avatar influences providers' word choice. We will explore if baseline provider characteristics such as age, sex, and attending vs. resident status, year of residency impact language.

Transcripts from the VR simulations will be coded by a study team member to assess primary learning objectives. An artificial intelligence (AI) software from IBM, Watson, will be used to train the software through machine learning to process and code data to begin exploring the feasibility of adapting the VR simulation training to use AI instead of requiring a human facilitator. Watson is a password protected software (add URL). IBM Watson has been used in Medical Education research[79]. The coded portions of the transcripts will be used as examples for Watson to create "intents." Intents are a collection of inputs, in our project they are the primary learning objectives, that Watson is taught to recognize. In this way, Watson recognizes that a participant intended to use a particular skill. A study team member will use the de-identified transcripts to train Watson, to recognize and code portions of transcripts from the VR simulations. Next, we will test Watson's coding against members of the research team's coded transcripts to test the inter-rater reliability between AI and study team members. The goal is to train Watson to accurately identify primary learning objectives as a first step in assessing the feasibility for an automated version of the VICTORI intervention.

Power considerations: Power considerations are provided for our primary aim and outcome of

determining whether VICTORI increases vaccine initiation. The PPCC is staffed by 80 residents and 20 attending physicians and reflects the maximum sample size for the intervention. To inform our power calculations for this proposal, we reviewed all PPCC patient visits for 11 to 17-year-old boys and girls from July 1, 2016 to June 30, 2017. HPV vaccination was initiated in 53% of visits for residents and 34% for attending physicians with greater between providervariation for residents. In addition, attending physicians saw more patients (n=9) in this age range on average per month than residents (n=2), and graphical analyses and formal regression modeling did not support material seasonal variation in initiation rates. Simulated outcomes based on these data were used to determine the minimum detectable odds ratio (OR) for vaccine initiation according to study period (i.e. pre- vs. post-intervention) as estimated from the proposed GLMER model. For resident and attending physicians combined, we assumed a total of 70 physicians having on average four patient encounters per month, a baseline probability of vaccine initiation of 43%, and a standard deviation for the subject-specific intercept of 0.55. Study power was determined to be 80% to detect an OR=1.5 based on 10k simulations. *This corresponds to a post-intervention vaccine initiation probability of 53%; or a 10% pre- to post-intervention difference.* Thus, conducting this intervention at CCHMC is expected to provide sufficient power to detect a clinically meaningful effect size for the response.

Potential Problems and Alternative Strategies: Insufficient recruitment may occur, but we do not anticipate this to be an issue as we have successfully conducted a VR intervention focused on flu vaccination with this population.[26] In addition, our team and expert consultants have provided extensive recommendations to recruit providers. There is the possibility of incomplete surveys; scale items with <25% missing data will be included in the analysis.[78] Multiple imputation and/or maximum likelihood estimation will be implemented should material missing values be realized for the survey responses and we will conduct a sensitivity analyses to determine the robustness of study findings to the assumptions of the imputation model.

Aim 3: Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly

Setting and Population: The PPCC is a busy, academic clinic in Hamilton County, Ohio with about 33,000 visits annually, serving 19,000 patients that are predominantly underserved with approximately 90% insured through Medicaid. Seventy-five percent of the patient population is African American and 5% is Latino. PPCC serves a population that is at high risk for HPV infection and its sequela, and therefore, we anticipate the findings to be generalizable to other urban primary care clinics that serve predominantly minority populations. Hopple Street Neighborhood Health Center (HSNHC) which served as a control during Aim 2, serves a similar population to the PPCC with 6000 unique patients and 13,000 patient visits per a year.

Design and Measures: We will first identify patients aged 9 to 17-year-old boys and girls who initiated the HPV vaccine series between 10/01/2020-06/01/2022 after seeing a provider who underwent VICTORI training. We will review social determinants of health screener of those who had not completed the HPV vaccine series by 14 months after initiation compared to those who did complete the HPV vaccine series. We will also collect demographic information (DOB, age, sex, race, ethnicity, health insurance; see appendix VICTORI Chart Review),

Based on these data, future revisions will be made to VICTORI to allow physicians to deliberately practice screening for and addressing barriers to vaccine series completion. Findings from this aim will provide

information to create a data-informed enhancement of VICTORI's simulated scenarios supporting series completion, which is critical to decreasing morbidity related to HPV-associated cancers.

Data Analysis and Sample Size Calculations:

- Review between n = 300 (minimum) – 720 (maximum) patient records
- These sample size calculations were derived from Peduzzi et al.{Peduzzi, 1996 #3012} guideline for the minimum number of cases to include for a logistic regression. The formula used for the calculation of the minimum number of participants was N = 10 * 18 variables / 60% (the estimated proportion of patients who completed the HPV vaccine series). The formula used for the calculation of the maximum number of participants was N = 10 * 18 variables / 25% (the estimated proportion of patients who completed the HPV vaccine within the recommended timeframe). As a note, we will also examine the proportion of patients who meet the guidelines for timely series completion (N = 400 minimum) using the following equation: N = 10 * 18 variables / 45% (the estimated proportion of people who completed the HPV vaccine within the recommended timeframe.
- Descriptive analyses as well as data variance and distribution to characterize variables.
- Logistic regression to determine factors independently associated with completing the HPV vaccine series including: clinic location (PPC v Hopple), type of visits at first dose, resident v attending physician, provider sex, age of patient at first dose, patient sex, patient race, insurance at first dose, and social risk screener questions.

Required dose for vaccine series completion (2 doses v 3 doses) will also be included in the descriptive analyses

Training of Study Personnel

All staff will undergo training in maintaining confidentiality and have completed the required Collaborative Institutional Training Initiative (CITI) courses and research ethics classes as required by CCHMC and Cincinnati Children's Research Foundation.

Recruitment and Consent Procedure

Aim 1: Evaluate VICTORI for acceptability and feasibility

Before recruiting any participants, approval from the CCHMC IRB will be obtained. Physicians working in the CCHMC THC will be sent invitations to participate in the study via email. The email will explain the purpose of the study, what participation entails, data to be collected, reimbursement, and contact information for study personnel. Participants will also be recruited in person. Staff working in the CCHMC THC will be recruited in person with an informational flyer explaining the purpose of the study, what participation entails, data to be collected, reimbursement, and contact information for study personnel. THC staff will be consented as a group prior to engaging in the study. Written consent, as appropriate, will be obtained from all participants for their participation in this phase of the study.

PPCC staff will be consented as a group prior to engaging in VICTORI. Written consent will be obtained from each participant in accordance to CCHMC policy 41-1.4.

The physicians will be consented using REDCap e-consent. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 22, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies

and operations. The CCHMC REDCap team has templates available for research use for eConsenting which includes Consent to be a Research Subject and Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study (HIPAA). The REDCap electronic consent format does not accommodate the current CCHMC formatting which includes headers with logos and stamps on each page and will therefore require some modifications. Participants will be sent a link to review and complete the e-consent on their own, however, study team contact information will be available for questions. CRC will verify e-consent completion, and sign that consent has been obtained within one business day of participant completion. Since the participants will complete the consent on their own, an informed consent process note will not be completed for physician participants.

Copies of consent forms for staff and physicians will not be submitted to Health Information Management, since these participants are not patients at CCHMC.

Aim 2: Conduct a single-site intervention assessing the efficacy of VICTORI in increasing HPV vaccine initiation and completion rates

Before recruiting any participants, approval from the CCHMC IRB will be obtained. Physicians and staff working in the CCHMC PPCC and attending physicians working in the HSNHC will be sent invitations to participate in the study via email three times over a four-week period. Participants will also be recruited in person. Physicians and staff will be recruited as they were in Aim 1.

Physicians at PPCC and HSNHC will be consented using e-consent. A waiver of documentation of informed consent is requested since no private identifiable health information will be collected and the purpose of the study is to evaluate the effectiveness of VICTORI to increase HPV vaccination rates in clinic. This also aligns with institutional guidelines for remote consenting due to social distancing dependent on the COVID-19 pandemic. A study information sheet will be provided using the REDCap e-consent module. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 22, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations. The CCHMC REDCap team has templates available for research use for eConsenting which includes Consent to be a Research Subject and Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study (HIPAA). The REDCap electronic consent format does not accommodate the current CCHMC formatting which includes headers with logos and stamps on each page and will therefore require some modifications. Participants will be sent a link to review and complete the e-consent on their own, however, study team contact information will be available for questions. Participants will only be sent the surveys once the participant has electronically agreed to participant in the study, by checking “Yes, I consent to participate in the study”..

PPCC staff will be consented as a group prior to engaging in VICTORI. A waiver of documentation of informed consent is also requested for PPCC staff as no private identifiable health information will be collected and the purpose of the study is to evaluate the effectiveness of VICTORI to increase HPV vaccination rates in clinic. A study information sheet will be provided and reviewed with participants prior to the session if completed in person. If session occurs remotely, a study information sheet will be implemented using the REDCap e-consent module following procedures described for the physician participants.

Copies of consent forms for staff and physicians will not be submitted to Health Information Management, since these participants are not patients at CCHMC.

Aim 3: Determine modifiable barriers related to HPV vaccine non-completion for future enhancement of VICTORI accordingly.
Before initiating any study procedures, approval from the CCHMC IRB will be obtained. A waiver of informed consent, parental permission, and assent are requested for Aim 3, as data will be limited to chart review in Epic. This portion of the study can be considered exempt from informed consent procedures as it does not involve procedures for which written consent is normally required and is limited to collection of data previously collected.

Additionally, a waiver of HIPAA Privacy rule is requested of research participants' and their parents and guardians' authorization for use of protected health information (PHI) for research purposes. This is requested for the collection of retrospective data as the use of the PHI involves no more than a minimal risk to the privacy of individuals, participants will be assigned a Study ID in the REDCap database instead of using their name, identifying information will not be used in analyses, identifying information will be destroyed at study closeout, and only study team members will have access to the information linking the Study ID to the participant. All information will be stored in a secure study electronic folder and in REDCap. The research could not be conducted without this waiver nor could it be conducted without access to and use of the PHI.

Compensation

Aim 1
Physicians and staff will receive $50 for their efforts. Staff will also be provided lunch.

Aim 2
Physicians from PPCC will receive $50 total for their efforts. PPCC physicians will receive $40 after completing the pre-survey, the self-directed app, the VICTORI session and the immediate-post survey, and $10 after the 3-month post survey. Staff will receive a $10 gift card. Physicians from HSNHC will receive $25 total for their efforts. HSNHC physicians will receive $15 after completing the pre-survey, the self-directed app, and immediate post-survey and $10 after the 3 month post survey.

The electronic W-9 and ClinCard receipt templates developed by the REDCap team will be used for physician participants since not all participants will be seen in-person. They will be used for PPCC staff as well if sessions are conducted remotely. These forms are separate from study data forms in REDCap. ClinCards for physicians and gift cards for staff will be delivered to the participants' mailboxes or work locations within one week of participation.

Aim 3
Not applicable

Future Use

This project will be the first to provide data on the effect of deliberate practice using VICTORI to increase HPV vaccine rates. These data will provide the foundation for an R01 application that will evaluate the intervention's effectiveness in a multisite trial. Data will also support the enhancement of VICTORI to address modifiable barriers associated with vaccine series completion. Furthermore, if effective, we plan to incorporate artificial intelligence into the VR design to allow automated functioning without human facilitation to promote future scalability. This work will positively impact public health by determining the effect of deliberate practice principles to train physicians to strongly recommend HPV vaccines, and thus, increasing HPV vaccination rates and decreasing HPV-associated cancers.

Publication

The authors plan to publish and disseminate the curriculum and its evaluation at the conclusion of the study in the appropriate medical education journals, on-line medical education share sites, and national meetings.

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