Examples of Funded Grants in Healthcare Delivery Research

Overview
The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About
We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application).

Accessibility
Individuals using assistive technology (e.g., screen reader, Braille reader) who experience difficulty accessing any information should send an email to the Healthcare Delivery Research Program (NCIHDRP@mail.nih.gov).

424 R&R and PHS-398 Specific
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SF 424 R&R Face Page

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Title: Statewide Assessment of HPV Vaccination Among Childhood Cancer Survivors

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Organization: UNIVERSITY OF UTAH

Department: Pediatrics

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Organization: University of Utah

Role Category: PD/PI

Project Summary

Survivors of childhood and young adult cancer have a substantial risk of developing a second cancer, including Human Papillomavirus (HPV)-related cancers. Female childhood cancer survivors have 40% relative excess and male survivors have 150% relative excess of HPV-associated malignancies compared to the general population. Since 2009, the Children's Oncology Group guidelines have recommended HPV vaccination to reduce the risk for HPV-related cancers for all eligible childhood cancer survivors. The limited research to date demonstrates low uptake and completion of the 3-dose HPV vaccination series among survivors of childhood cancer. However, these studies have been focused on self-report assessments at single institutions among female survivors. Evaluating HPV vaccination among survivors in Utah is of great public health importance as Utah's 3-dose HPV vaccine series completion is among the lowest in the nation for both female teens (49th state) and male teens (43rd state). As many survivors of childhood cancer do not expeditiously transition back to primary care at the end of their cancer treatment, it is likely that their rates of HPV vaccination completion are even lower than the general population. We propose the first statewide assessment of HPV vaccination among both female and male childhood cancer survivors and an age and sex-matched general population comparison group from a largely rural state with low rates of HPV vaccination over a nine year time period (2006-2015). Building on two statewide resources 1) the Utah Population Database, which is linked to clinical data from Intermountain Healthcare, including Primary Children's Hospital, where the majority of pediatric cancers in Utah are treated, and the 2) Utah Statewide Immunization Information System, we will conduct the first statewide evaluation of the rate of HPV vaccination among a sample of 1,863 childhood cancer survivors. Using UPDB allows us to generate an age and sex-matched general population comparison group without cancer to compare to the survivors. Our outcomes of interest are HPV vaccination initiation, receipt of 2 doses, 3-dose completion, and missed opportunities (defined as a healthcare visit when a patient received at least one immunization, but not a HPV vaccine dose). In the first aim, we will compare HPV vaccination among survivors of childhood cancer with the general population. In the second aim, we will identify high-risk groups of survivors of childhood cancer, such as survivors who are Hispanic, publically-insured, rural, and living in a health professional shortage area, who may be more likely to forego the HPV vaccine. At the end of the study, we will have identified whether both male and female childhood cancer survivors are less likely to get the HPV vaccine compared to adolescents and young adults without cancer. Also, we will establish at statewide level whether certain childhood cancer survivors (e.g., Hispanic) are more likely to miss getting the HPV vaccine, which is essential information to developing cancer prevention strategies for this growing population.

Project Narrative

Survivors of childhood cancer have a substantial risk of developing second cancers, including Human Papillomavirus (HPV)-related cancers; however, despite being recommended by the Children's Oncology Group, their rate of HPV vaccination may be very low. By utilizing a unique epidemiologic database linked with Utah immunization data, this study represents the first assessment of HPV vaccination among childhood cancer survivors that, includes male survivors, compared to an age and sex-matched general population comparison group from a largely rural state. Findings will be used to design interventions to promote HPV vaccination uptake among childhood cancer survivors in Utah and other states.

A. SPECIFIC AIMS

Survivors of childhood cancer have a substantial risk of developing second cancers,[1,2] including Human Papillomavirus (HPV)-related cancers. Nationally, the relative excess of HPV-associated malignancies was 40% among female survivors of childhood cancer and 150% among male survivors compared to the general population.[3] While the Children's Oncology Group (COG) guidelines recommend the HPV vaccine to reduce the risk for HPV-related cancers for all eligible childhood cancer survivors, the limited research to date demonstrates low uptake and completion of the 3-dose HPV vaccination series among these survivors.[4,5] In a cross-sectional analysis of female survivors at a single healthcare institution, only 34.6% had initiated and 20.9% had completed the 3-dose HPV vaccination series, which was significantly lower than those without cancer.[6] Factors associated with greater vaccine uptake among survivors include physician recommendation and greater cancer treatment intensity. When examined by demographic characteristics, non-white survivors and survivors of lower income are less likely to initiate or complete the HPV vaccine series.[7]

Since 2006, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has recommended that all eligible females ages 11 and 12 years routinely receive the 3-dose HPV vaccination series to prevent cervical and other HPV-related cancers.[8] In 2011, it was approved and recommended for males.[9] More than 11 years after vaccine approval, only 41.9% of U.S. females and 28.1% of males ages 13- 17 years have completed the series, well below the Healthy People 2020 goal of 80%. Utah's 3-dose series completion is among the lowest in the nation for female teens (49th state). Utah is also among the lowest states for HPV vaccination initiation (41st state) and 3-dose series completion for males (43rd state).[10] HPV vaccination provides an important opportunity to reduce morbidity and subsequent HPV-related cancers for childhood cancer survivors, but little is known about their HPV vaccine uptake to inform prevention strategies.[11]

HPV vaccines and other adolescent vaccines including Tdap (Tetanus, Diphtheria, Pertussis), meningococcal, and yearly influenza, are typically provided at a primary care provider (PCP) office or at state health agencies. While most childhood cancer survivors eventually transition to a PCP for the majority of their healthcare,[12] many will only see their oncologist for several years after completing therapy. This is likely a barrier to HPV vaccination as oncology providers may not consider the need for vaccines during cancer follow-up care. As a result, it is likely that childhood cancer survivors are less likely to initiate or complete the HPV vaccine series. Research to date on survivors has been from single institution studies of self-report data and has been limited to female survivors, which means more diverse studies that include male survivors are needed to understand whether HPV vaccination disparities exist. In addition, survivors may be more likely to experience HPV vaccine missed opportunities - that is, a healthcare visit when they received at least one adolescent immunization such as the yearly influenza vaccine, but no HPV vaccine dose. We found that 65% of Utah girls have a HPV vaccine missed opportunity.[13] We expect survivors to experience similar, if not greater, missed opportunities.

We propose the first statewide assessment of HPV vaccination among childhood cancer survivors using a unique and powerful epidemiologic resource, the Utah Population Database (UPDB), linked with the Utah Statewide Immunization Information System (USIIS). The UPDB includes clinical data from Primary Children's Hospital (PCH), which treats the vast majority of pediatric cancers in Utah.[14] These resources allow us to identify a statewide sample of 1,863 survivors of childhood cancer, and generate a 3:1 age- and sex- matched comparison group of unaffected adolescents and young adults to compare to the survivors. We hypothesize that survivors who are Hispanic, publically insured, rural residents, or who live in designated health professional shortage areas (HPSA) with few PCPs, may be at higher risk for low HPV vaccination rates, demonstrating similar disparities to the general population with these characteristics.[9,15-18] We aim to:

Research Aim 1: Determine statewide characteristics of HPV vaccination among survivors of childhood cancer and compare them to the general population. *Hypothesis: HPV vaccination will be lower among survivors than the general population.*

Research Aim 2: Identify predictors associated with lower levels of HPV vaccination among survivors of childhood cancer. *Hypothesis: HPV vaccination will be lower among survivors who are Hispanic, publically-insured, or live in rural or HPSA areas, compared to survivors without these characteristics.*

This study will be the first to report on HPV vaccination behaviors among male childhood cancer survivors and will improve on earlier clinic-based studies by including a statewide sample. At the end of the study, we will have identified whether childhood cancer survivors are less likely to get the HPV vaccine compared to adolescents and young adults without cancer. Moreover, we will determine whether certain groups of childhood cancer survivors (e.g., Hispanic, rural) face higher risks for not receiving the HPV vaccine, which is essential information to developing cancer prevention strategies for this growing population.

B. SIGNIFICANCE

Human papillomavirus (HPV) is a sexually transmitted infection that causes cervical, anal, penile, vaginal, and oropharyngeal cancers, and genital warts.[19] In the U.S., more than 20,000 women and 12,000 men are diagnosed with HPV-associated cancers annually.[20] In 2006, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended that girls ages 11 and 12 years receive a routine 3-dose human papillomavirus vaccine to protect against cervical and other HPV- associated cancers and genital warts.[8] Since 2011, the vaccine has been approved and recommended for boys.[9] In December 2016, the CDC revised their guidelines to recommend that 11- to 12-year-olds receive two doses of HPV vaccine at least six months apart, but that adolescents ages 15 and older continue the three dose series.[21] The vaccine is recommended for girls and boys aged 11-12 years because they exhibit a stronger immune response to the vaccine and are less likely to have initiated sexual activity at this age.[22] Since the HPV vaccine is also effective in older adolescents, ACIP recommended it as a catch-up vaccination for young women ages 13-26 years and young men ages 13-21 years.[22,23] More than 11 years after vaccine approval, only 41.9% of eligible U.S. females and 28.1% of males ages 13-17 years have completed the series.[24]

The scientific premise of this study is that survivors of childhood cancer are less likely to receive the HPV vaccine than the general population of adolescents and young adults. The limited number of studies to date that investigated HPV vaccination among survivors of childhood cancer show low uptake and completion of the 3-dose HPV series.[6,11,25] However, earlier studies of HPV vaccination among childhood cancer survivors have been limited to single site assessments of self-reported data of female survivors or mothers of female survivors. Also, no studies have investigated whether missed opportunities for HPV vaccination - that is, a healthcare visit when a patient received at least one adolescent immunization, but not a HPV vaccine dose - are more common among survivors compared to adolescents and young adults without cancer, which is important information for understanding gaps in their primary care. This lack of research to improve HPV vaccine uptake among survivors is of concern as the HPV vaccine is a key opportunity to reduce morbidity among this population.[7] Since 2009, the Children's Oncology Group guidelines have recommended HPV vaccination for all eligible childhood cancer survivors.[4,5] In April 2016, the American Society of Clinical Oncology recommended aggressive efforts to increase HPV vaccination among survivors and acknowledged the key role of oncologists in promoting the vaccine for their eligible cancer patients.[26]

The nearly 400,000 survivors of childhood cancer in the U.S. represent a growing population with unique HPV-related health risks.[7,27] The direct and indirect effects of cancer treatment may increase survivors' risk for HPV-related cancers.[7] Female and male survivors have, respectively, 40% and 150% higher relative excess cases of HPV-associated malignancies (e.g., cervical, anal, and oropharyngeal) than the general U.S. population, and these cancers occur, on average, 7 years earlier.[3] Certain cancer treatments, such as hematopoietic stem cell transplant, pelvic irradiation, and immunosuppressive medications can increase the risk of HPV infection and persistence. While most cancer patients are thought to return to normal immune functioning by 3 months after the end of chemotherapy,[28] some experience persistent immune limitations, which could increase the risk of cervical dysplasia and HPV-related cancers.[29] However, the long-term immunosuppressive effects of treatment may leave survivors less able to fight off HPV infection. As such, public health efforts to improve the uptake of the HPV vaccine for survivors of childhood cancer are needed. Before we can develop such studies, a broader understanding of HPV vaccination disparities is needed for this population.

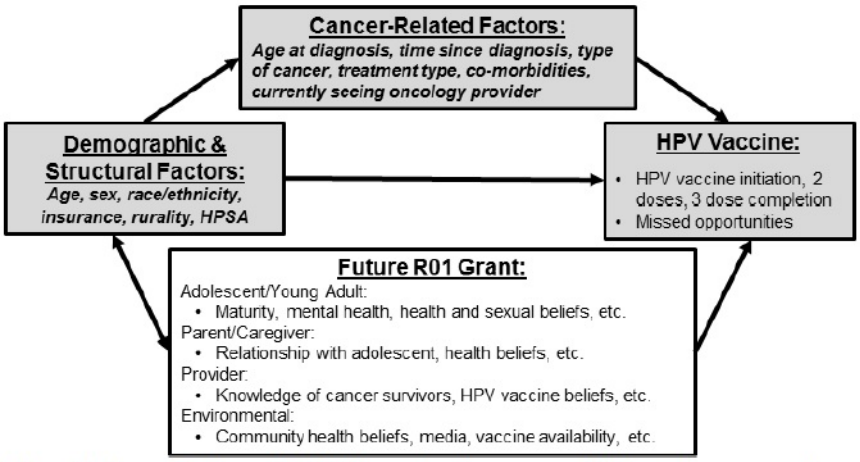

Figure 1: Conceptual model of HPV vaccination among childhood cancer survivors

We developed a **Conceptual Model of HPV Vaccination among Childhood Cancer Survivors (Figure 1).** This model

was adapted from Katz's Vaccine Perceptions, Accountability and Adherence Model.[30] The domains were identified based on the literature and on factors hypothesized to be related to vaccine uptake, and are described below:

Demographic and Structural Factors: Age may affect whether survivors receive the HPV vaccine. While the recommended age for children to receive the HPV vaccine is between 11 and 12,[8] a recent U.S. report of adolescents aged 13 to 17 from the National Immunization Survey-Teen (NIS-teen) shows that higher proportions of older female adolescents receive the HPV vaccine compared to younger adolescents.[24] Similar to general population, older survivors are more likely to have gotten the HPV vaccine.[11] This is concerning as adolescents with later age of initiation patterns have higher odds of not completing the three-dose vaccine.[31] Although survivors tend to begin sexual activity at a later age than adolescents without cancer, survivors may engage in high risk sexual activities more often due to hyperactivity and/or inattention, which are commonly reported side effects of cancer treatment.[29] Due to the effects of their treatment, survivors may perceive their fertility to be lower, which may affect their sexual behavior and potential likelihood of getting HPV.[29] In addition, female adolescents have a higher uptake and completion of the HPV vaccine compared to male adolescents.[24]

Geographic and other healthcare disparities may also exist. Male adolescents from urban and suburban regions in the U.S. have a higher likelihood of receiving the HPV vaccine compared to those from rural areas.[9] Health insurance coverage is positively associated with HPV vaccination initiation and successful completion of the 3-dose vaccine among young adult females.[32-34] Low income adolescents who are Hispanic are more likely to initiate the HPV vaccine, whereas low income Black adolescents have lower initiation rates of the HPV vaccine.[34-36] Collectively, these studies demonstrate persistent disparities in HPV vaccine coverage in the U.S. To date, none of the earlier studies of the HPV vaccine among survivors of childhood investigated potential high-risk groups, such as survivors who are Hispanic, publically-insured, rural, or with low primary care access. These survivors, however, tend to report receiving preventive healthcare less often than survivors without these characteristics,[37] potentially limiting their access to the HPV vaccine.

Cancer-Related Factors: Little is known about how cancer-related factors, such as time since diagnosis, cancer type, and treatment affect whether survivors receive the HPV vaccine. However, as time from diagnosis increases, survivors are less likely to receive any type of medical care,[38] potentially reducing their access to the HPV vaccine. Also, during the initial years after the end of their cancer treatment, most survivors continue to see their oncologist rather than a primary care provider (PCP) for follow-up care. As a result, survivors may face greater access issues to the HPV vaccine than the general population as they may not see a PCP where recommended preventive medicine vaccines are typically administered. Furthermore, an earlier report of pediatric cancer late effects clinic attendees found that that survivors were less likely to be recommended the HPV vaccine by their provider than compared to adolescents without a cancer history.[11] Providers may not understand that survivors are eligible for the HPV vaccine[7] nor their risks for HPV-related second malignancies,[3] and thus may not promote the vaccine.

Study Impact: Findings from this study will guide the development of a future intervention. As shown in our conceptual model **(Figure 1)**, following the successful completion of the current project, we will develop a larger study to identify barriers and facilitators for HPV vaccine uptake from the survivor, parent/caregiver, and provider perspectives. In our next phase, we will build on our survivorship care plan (SCP) tool that includes recommendations for future healthcare including vaccines.[39] SCPs help patients coordinate care between their oncologist and PCP. We will develop and test a multi-level primary care intervention that utilizes SCPs and electronic health record reminders for providers, parents, and patients. We will test this model in diverse geographic and socio-economic populations in Utah for future dissemination to other states.

C. INNOVATION

Our proposal is innovative in two distinct areas:

1. We will be the first team to identify barriers to HPV vaccination for medically underserved cancer survivors by conducting this analysis in a rural state with a large number of Hispanic, uninsured, and publically-insured children. Utah has several unique characteristics that will allow our team to generate

important and generalizable information on disparities in HPV vaccination among cancer survivors.

- Over 15% of our cohort resides in a rural community and 35% in a HPSA,[40] allowing contextual factors affecting vaccination among childhood cancer survivors to be investigated for the first time.
- In Utah, almost 10% of children are uninsured and 19% are publically insured.[41]
- Salt Lake City, Utah's largest urban area, is 22% Hispanic, and the entire state is 14% Hispanic; 16% of our childhood cancer cohort are Hispanic.
- These unique population characteristics mean we can conduct important subgroup analyses to understand whether disparities exist in HPV vaccination to inform our future intervention efforts.

2. Our study sample and analyses represent a new strategy in understanding cancer prevention behaviors among childhood cancer survivors. The **Utah Population Database (UPDB)** links multiple statewide data resources, including residency information from driver licenses, voter registration, vital records (i.e., birth certificates, death certificates, marriage records), and medical records. In the U.S., there are no other similar statewide databases. By using the UPDB, we propose a new approach to investigating HPV vaccine behaviors by combining the UPDB with a statewide immunizations registry and medical records data.

- To date, only self-report assessments of HPV vaccination in childhood cancer survivors have been conducted among female patients or mothers of patients attending oncology clinics, which were located in urban areas; thus, participants may not represent the general population of cancer survivors.[42] Our study overcomes this limitation by including a statewide sample that is linked to immunization records.
- In addition, as HPV vaccine recommendations continue to change, we can investigate for the first time predictors of 1, 2, and 3 doses of the HPV vaccine among childhood cancer survivors. Thus, our study will help to advance the state of science on survivors by being responsive to changes in guidelines.

D. SCIENTIFIC APPROACH

D1. PRELIMINARY STUDIES

This project brings together health services, clinical, and epidemiologic expertise at the Huntsman Cancer Institute, University of Utah, and Primary Children's Hospital to address the gap in research on HPV vaccination among survivors of childhood cancer. Dr. Kirchhoff, Co-PI, is a health services researcher who has extensive experience using the UPDB to investigate healthcare utilization among childhood cancer survivors.[43-45] Dr. Kirchhoff created, validated, and published reports on the Intermountain childhood cancer cohort being used in the current study.[46,47] She is the principal investigator of the survivorship care plan intervention at Primary Children's Hospital,[39] which will serve as the foundation for the next steps of this HPV vaccination initiative. Dr. Kepka, Co-PI, is an expert in health disparities, HPV vaccination, and USIIS. Using USIIS, she demonstrated that 65% of girls in Utah had at least one missed opportunity for the HPV vaccine and that rural residence was associated with more missed opportunities.[13] As the Founder and Director of the Intermountain West HPV Vaccination Coalition, Dr. Kepka's connections will provide guidance to the dissemination of our findings to inform our future R01 efforts. Dr. Kirchhoff and Dr. Kepka lead several projects together on cancer disparities in Utah[48] and have offices together at the Huntsman Cancer Institute, facilitating a successful collaboration. Clinical expertise will be provided by Mark Fluchel, MD, pediatric oncologist, Huntsman Cancer Institute investigator, and expert in cancer outcomes and geographic disparities who has worked with Dr. Kirchhoff on several childhood cancer studies[45,46,49,50] **(see letter of support).** Nancy McConnell from the Utah Department of Health provided our team with the USIIS data and will assist with interpretation of our analyses. Ms. McConnell and Dr. Kepka have a history of collaboration **(see letter of support)**.

D2. DATA SOURCES

Utah Population Database (UPDB) is a powerful statewide population registry that contains records for over eight million individuals and is the only database of its kind in the United States. The database includes demographic information (e.g. sex, ethnicity), health, economic, and cancer data, by linking various sources, including medical records from the two largest health care systems in the state (Intermountain Healthcare and University of Utah Health Care), the Utah Cancer Registry, state driver licenses, and birth, marriage, and death certificate data. Because of its size and the varied sources of its information, most families living in Utah are represented in the UPDB.

Utah Statewide Immunization Information System (USIIS) database at the Utah Department of Health maintains a secure and confidential system that collects and consolidates immunization records for Utah residents of all ages. USIIS includes a web-based application that is designed to track immunization records

and provide clinical decision support for patient care for clinicians. USIIS complies with state law and CDC functional standards to protect patient privacy and is populated with birth records of Utah born children as well as immunization records from 100% of public health care providers and more than 78% of private providers. For this analysis, we will utilize USIIS patient immunization and demographic data starting in 2006, when the HPV vaccine was first approved.

Intermountain Healthcare (IH) and University of Utah Health Care (UUHC): Between 85%-90% of Utahns receive their healthcare in the IH and UUHC systems. Both IH and UUHC maintain Enterprise Data Warehouses (EDW) that record diagnoses and clinical histories for all patients. The UPDB has data crosswalks with both IH and UUHC EDWs. IH is the largest healthcare system in Utah. It is not-for-profit and includes over 185 clinics and 22 hospitals. In addition to tertiary-level teaching and research facilities, Intermountain also has several small hospitals and clinics that are the only source of care in some rural Utah communities. Primary Children's Hospital (PCH) is part of IH and the only children's hospital in Utah,[14] ensuring that our cohort represents the majority of childhood cancers. UUHC is a separate health system of 59 clinics and four hospitals. The Huntsman Cancer Institute, the only National Cancer Institute Designated Comprehensive Cancer Center in Utah, is part of UUHC. Approximately 60% of IH records and 78% of UUHC records link to at least one UPDB record,[51] allowing us to identify survivors and comparison group individuals who receive healthcare in either or both systems. IH and UUHC records will be used to supplement the vaccine data from USIIS.

D3. SAMPLE AND ELIGIBILITY

Our childhood cancer cohort was identified via IH records and has already been linked to UPDB records to verify residence and vital status.[47] The comparison group of Utah residents has also been identified from the UPDB. The UPDB includes the date that each person in the database was last known to be residing in Utah. This allows us to follow the comparison group individuals from their index case's date of entry until their date of death or emigration from Utah.

Table 1: HPV Vaccine Eligible Survivors

	Females[2] N=1,290	Males[3] N=573
Current Age[1]	**%**	**%**
11-18	31	39
19-28	47	61
29-35	23	0
Diagnosis		
Hematologic	27	34
CNS	26	26
Other Solid Tumor	47	41

[1]As of December 31, 2016
[2]Ages 11-26 between 2006-2015
[3]Ages 11-21 between 2011-2015

Cancer Survivors: Eligible survivors: 1) aged 21 years or younger at diagnosis; 2) females aged 11 to 26 years from 2006 to 2015 and males aged 11 to 21 years between 2011 and 2015, based on recommended ages for receiving HPV vaccination and the years of HPV vaccine approval; 3) diagnosis meets International Classification for Childhood Cancer criteria; and 4) residing in Utah at diagnosis. Survivors will be eligible for analysis starting 3 months off therapy or 12 months from stem cell transplant.[28] We have 1,863 survivors that meet these criteria **(Table 1)**.

General Population: Utah residents were selected from UPDB birth certificate records and excluded anyone from the general population with a history of cancer. We have matched each survivor to three Utah residents by birth year and sex, who were alive and a Utah resident at least up until their matched survivor was diagnosed with cancer. Our sample size is 5,589 residents for the comparison group.

D4. DATA LINKAGE

Patient name, date of birth, sex, and other identifiers (parent names, addresses) are available to link USIIS to the survivors and comparison sample. UPDB uses a record linking software program called QualityStage that uses probability weighting to identify matches and is described elsewhere.[52] Of the 1,863 eligible survivors, all of them link to at least one IH or UUHC record. Also, in preliminary linkages using age and date of birth, 55% match with a least one USIIS record and we expect this improve once other identifiers, such as addresses, are incorporated.

Table 2: Definitions of HPV vaccination outcomes

Outcome	Females	Males
Initiation	At least one dose between the ages of 11-26.	At least one dose between the ages of 11-21.
2 doses	Received 2 doses within 12 months, among participants under the age of 15.	Received 2 doses within 12 months, among participants under the age of 15.
3-dose completion	Received 3 doses within 12 months, with first dose between the ages of 11-26.	Received 3 doses within 12 months, with first dose between the ages of 11-21.
Missed opportunities	Received another adolescent vaccine (e.g., Tdap) between the ages of 11-26, but no HPV vaccine ever.	Received another adolescent vaccine (e..g., Tdap) between the ages of 13-21, but no HPV vaccine ever.

D5. MEASURES

Our outcomes are HPV vaccine initiation, receipt of 2 doses, 3-dose completion, and missed opportunities (Table 2). USIIS records contain identification data on patients, vaccine types, date of vaccine,

and providers for each unique patient visit. Similar information is available in the IH and UUHC data, which will be used to supplement USIIS records for all participants. Age at vaccine administration will be considered as shown. Also, we can identify participants who had a missed opportunity for the HPV vaccine. Each year all adolescents and adults are expected to receive the influenza vaccine along with other occasional vaccines such as a tetanus booster. We will identify individuals who received an age-appropriate adolescent vaccine (e.g., influenza, Tdap, or meningococal), but never received an HPV vaccine at any point during their age of eligibility.[13] We will identify missed opportunities through follow-up using three categories: 1) participants who received a standard adolescent vaccination, but did not receive any doses of the HPV vaccine (had missed opportunities), 2) participants who received a standard adolescent vaccination and any dose of the HPV vaccine, and 3) participants who received no vaccines during the length of follow-up. These categories will be paired to create dichotomous outcomes as described below in Section D6.

We will evaluate other variables available from USIIS including whether the participant has an HPV vaccine exemption, which provider gave the exemption, data of the exemption, and the reason(s) why for the exemption. Data on contraindications due to medical reasons are also available and will be used to identify subjects who may not receive the HPV vaccine due to medical reasons. Common contraindications include pregnancy for women and hypersensitivity to yeast for Gardasil or latex for Cervarix, which are two of the HPV vaccines. As secondary outcomes, we will investigate whether survivors are more likely to have vaccine exemptions and contraindications than those without a cancer history.

Cancer and Treatment Variables: From IH records, we have information on survivors' demographics at diagnosis (e.g., age at diagnosis, insurance status), cancer diagnosis, tumor characteristics, and treatment factors (e.g., receipt of surgery, chemotherapy, or radiation). These data are currently undergoing validation by medical chart review by a pediatric oncologist to ensure accuracy. During this abstraction, we will also confirm date of end of therapy. We will investigate whether survivors receiving certain treatments, such as hematopoietic stem cell transplant, pelvic irradiation, and alkylators (e.g., cyclophosphamide), which can increase risk of infertility, lead to differences in HPV vaccination behaviors. Immunosuppressive medications such as steroids and cyclosporine will be considered. Our data include information on certain co-morbidities, cancer recurrence, and second cancers, which will allow us to evaluate whether these factor into our estimates. In addition, we have data on whether survivors in our sample receive follow-up care from an oncologist at Primary Children's Hospital or attend Huntsman Cancer Institute's Pediatric Cancer Late Effects Clinic, which we will investigate in our analyses as well.

Biologically Relevant Variables, including Sex: From the UPBD, we have data for the survivors and the comparison group on race/ethnicity, sex, and age. We will test for sex-specific differences and differences by race/ethnicity in the effects **(see planned enrollment report)**. We will investigate differences in the number of doses and missed opportunities by age at last follow-up: pre-teen (11-12 years when the vaccine is first indicted for both boys and girls), teen (13-18 years), or young adult (19-26 years for girls and 19-21 years for boys based on recommended ages of vaccine administration). In addition, we will conduct analyses to examine differences in 2 doses for participants who are under the age of 15, per CDC's new recommendations.[21]

Other Demographic Covariates: Rurality of residence at diagnosis and over the course of follow-up will be classified according to the 4-level Rural Urban Area Commuting (RUCA) code. RUCA codes are a geographic taxonomy that characterizes sub-county components of rural and urban areas.[53] We will link RUCA codes by zip code and aggregate categories into a 4-levels: (1) Urban, (2) Large Rural, (3) Small Rural, and (4) Isolated, which we will group into (Urban=1, Rural=2, 3, 4) although we will explore different groupings as feasible. Health professional shortage areas (HPSAs) are federally designated communities with critical shortages of primary care physicians (>3000 patients per physician) compared to national standards set by the Health Resources and Services Administration. Approximately 35% of children in Utah are estimated to live in a county designated as a HPSA for primary care access, which we will identify for our sample.[40]

D6. STATISTICAL METHODS

We have a matched cohort study with a general population comparison sample selected on birth year and sex. Matched cohort design allows for a scientifically rigorous approach, both increasing the study efficiency and reducing potential confounding. All regressions will be run separately for females and males due to the differences both in the recommended age for the HPV vaccine and because the vaccine was approved in

different years for females (starting in 2006) and males (starting in 2011).

Research Aim 1: Determine statewide characteristics of HPV vaccination among survivors of childhood cancer and compare them to the general population.

We hypothesize that HPV vaccination uptake will be lower among survivors than the general population. We will calculate summary statistics for survivors and the comparison group for vaccine initiation, 2 doses, 3-dose completion, and missed opportunities. We will use conditional Poisson regression offset by time due to the differing follow-up times for participants to generate relative risks and 95% confidence intervals with robust standard errors. In the regression models, HPV vaccination will first be modeled as separate dichotomous outcomes for initiation (≥1 dose vs. no dose), 2 doses (≥2 doses vs. 1 or no dose), and 3-dose completion (3 doses vs. 1-2 dose or no dose). Missed opportunities for the HPV vaccine will be investigated as two separate dichotomous outcomes: 1) receipt of an adolescent vaccine, but no HPV dose vs. receipt of an HPV dose, and 2) receipt of an adolescent vaccine, but no HPV dose vs. never received any vaccinations. All models will compare the relative risk for HPV vaccination between cancer survivors and the comparison group. Covariates include variables described in Section D5 above, including Hispanic ethnicity, age, and rural residence. Models will also adjust for calendar year due to differences in vaccine uptake over time.

Research Aim 2: Identify predictors associated with lower levels of HPV vaccination among survivors of childhood cancer.

We hypothesize that HPV vaccination may be lower among survivors who are Hispanic, publically-insured, live in rural areas, or reside in a HPSA compared to survivors without these characteristics. The analyses here will be limited to survivors. Using Poisson regression offset by time due to the differing follow-up time, we will generate relative risks and 95% confidence intervals with robust standard errors. We will generate the relative risks for the vaccination outcomes (i.e., initiation, 2 doses, 3-dose completion, and missed opportunities as described above) among Hispanic vs. non-Hispanic, publically-insured vs. uninsured vs. private, rural vs. urban, and HPSA-residing vs. non-HPSA survivors. Differences by sex and cancer-related factors, such as time since diagnosis, will be investigated. We will also use generalized estimating equations models to investigate clustering of participants within HPSAs.

Sub-Analyses: All IH and UUHC providers report their vaccination data to USIIS. As a sensitivity analysis, we will run regression models limited to individuals who have had at least one primary care visit in either systems within the study years. This will allow us to ascertain if there are any potential differences in HPV vaccination due to USIIS reporting by providers for the survivors and the comparison group.

Power Calculations: In the interest of space, we present power calculations for the outcome of HPV vaccine 3-dose completion based on sample size shown in Table 1. By 2014 in Utah, 26.0% of eligible females and 12.4% of eligible males had received all 3 doses.[24] Based on power=0.80 and alpha=0.05, we have sufficient power to detect a Relative Risk=1.5 among both female and male survivors vs. male and female comparisons, if survivors' outcome rate of HPV vaccine 3-dose series completion is 10%-20% **(Table 3)**. These power calculations are conservative, as they do not take into account potential covariates.

Table 3: Power Calculations

	Female		
Outcome rates – high risk group	Survivors (N=1,290)* vs. Comparison (N=3,870)		
	RR=1.25	*RR=1.5*	*RR=1.75*
5%	0.37	0.89	>0.99
10%	0.68	>0.99	>0.99
20%	0.96	>0.99	>0.99
	Male		
Outcome rates – high risk group	Survivors (N=573)* vs. Comparison (N=1,719)		
	RR=1.25	*RR=1.5*	*RR=1.75*
5%	0.18	0.54	0.86
10%	0.35	0.87	0.99
20%	0.69	>0.99	>0.99

**High Risk Group*

Potential Limitations: Loss to follow-up could be an issue in our study, as it is in any longitudinal cohort assessment. We will not be able to identify doses that occur after a participant leaves Utah, but we will be able to identify all vaccinations that occur in Utah. As the UPDB provides residency information including when an individual is no longer living in Utah, we will be able to

identify these cases. We will examine those who are lost to follow-up and consider this potential bias in our interpretation of results. While the vast majority of providers in Utah report to USIIS, we may underestimate HPV vaccination rates. However, by using immunization registry data coupled with data from IH and UUHC, our study improves on earlier survey-based assessments with low response rates.

D7. CONCLUSION

Table 4: Study Timeline

	Pre grant	Year 1				Year 2			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
IRB approval									
Data Validation									
Aim 1 Analyses									
Aim 2 Analyses									
Manuscript preparation (n=2-4)									

We have a strong, collaborative research team with expertise in childhood cancer survivorship, HPV vaccination, primary care, and health disparities. We require two years to complete this project as in Year 1 we will finalize validation of treatment information as described in Section D4. Furthermore, administrative and clinical data require substantial data cleaning, which we will complete in Year 1 of the grant. In addition, we have expanded our analysis to investigate 2 doses of the HPV vaccine in light of the new recommendations for adolescents under the age of 15.[21] Based on our previous successful collaborations, we believe our team can conduct this project within the study timeline **(Table 4)**.

The **strengths of our study** are that: **(1)** We will utilize a statewide cohort of childhood cancer survivors linked to state immunization records, which addresses limitations of earlier studies based on self-report; **(2)** We will investigate HPV vaccine uptake among male and medically underserved survivors for the first time; **(3)** Using existing databases (UPDB, USIIS) is an efficient way to identify high-risk groups of survivors; **(4)** We have a multidisciplinary investigator team with the experience to expand this assessment and develop interventions to support survivors in future studies.

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