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Predicting HPV Vaccination Coverage Rates Using Indicators of Health Department Clinic Access: A Case Study with South Carolina and Georgia

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Table of Contents

1.0 INTRODUCTION

1.1 Abstract

Since its introduction in 2006, the human papilloma virus (HPV) vaccine has made substantial developments. The use of the vaccine was expanded to include males. The completion dose series was decreased from three to two shots, if started before the age of 15. The cost of the vaccine is fully covered by private insurance and public programs for various ages ranging from 9 to 26 years old[1]. With these improvements the HPV vaccine has the capability to safely and significantly prevent and reduce many cancers that cause the deaths of women and men across the United [1,2]. Therefore, the underuse of the HPV vaccine is a serious but correctable threat to progress against cancer[3,4]. During 2012-2016, an estimated average of 34,800 HPV-attributable cancers were diagnosed each year. Among these estimated cancers, 92% were attributable to the HPV types that are included in the 9-valent HPV vaccine and could have been prevented if HPV vaccine recommendations were followed[5]. However, HPV vaccination rates across the U.S. remain low[6].

Using public health data sources, choropleth maps, new variables of Health Department (HD) clinic access and prediction modeling, this research advanced the field of health services research by informing the third goal of the President's Cancer Panel 2012-2013 report: maximize access to HPV vaccination[3]. The short-term impact of this research quantified and located HPV vaccination for adolescents, in addition to highlighting prognostic indicators of access and identifying barriers to HPV vaccination uptake among HD clinics at the county level in Georgia. The long-term impact of this research provided greater insight for targeting efforts to optimize HPV vaccine uptake at the county level in

South Carolina and in other states with low HPV vaccination coverage. This research demonstrated the important use of small area estimation by public health professionals in states with low HPV vaccination coverage and limited or no immunization registry data for small geographic areas. This research provided valuable data toward the access of vaccination services and the dissemination and implementation of HPV vaccination interventions at the county level. Ultimately the findings from this study may be used to predict correlations to the incidence of HPV-associated cancers, which may help reduce public health costs, morbidity and mortality related to HPV infections in the United States.

1.2 Specific Aims

The underusage of the human papilloma virus (HPV) vaccine is a serious but correctable threat to the prevention of cancer[4]. More than 90% of cervical and anal cancers, approximately 70% of vaginal and vulvar cancers, 60% of penile cancers, and about 70% of oropharyngeal cancers are a result of a HPV infection[7]. As of 2019, 54.2% of U.S. adolescents are fully vaccinated with the HPV vaccine, and 71.5% of them have received at least one dose of the HPV vaccine average[6]. National efforts to increase HPV vaccination to 80% are being made[8] and include resources often administered and utilized at the county level through the state health department (HD). However, the lack of county level HPV vaccination coverage data in many states is a major obstacle to effectively monitor health department resource utilization. Efficiently allocating health department resources is necessary to improve HPV vaccination coverage and ultimately protect adolescent residents from HPV-attributable cancers[9,10].

The overarching goal of this research is to generate a predictive model of county level HPV vaccination coverage rates in SC and Georgia (GA) to address access barriers to HPV vaccine uptake. Because the tetanus, diphtheria and pertussis (Tdap) vaccine is a school mandated vaccine for all adolescents in both states and an indicator of access to vaccination services, we evaluated adolescents who received the HPV vaccine among those who have received the Tdap vaccine. Using factors associated with HPV vaccination we will evaluate additional indicators of access to health department (HD) clinics: the number of public and private clinics, the number of HD clinics with Vaccine For Children (VFC) provider registration, and availability of public transportation. We used the number of administered HPV and Tdap vaccine doses previously collected from each state's immunization registry for the years 2016-2018. Given that SC and GA are in the same Region 4 of the Department of Health and Human Services (HHS) and their population demographics are similar, it is expected that vaccination rates in SC's counties would be comparable to GA's counties. However, GA's adolescent HPV vaccination coverage trend of greater than or equal to one dose exceeds or is close to the national average. When population subgroups share characteristics, the systematic underuse of vaccination services may indicate a problem with the equity of access[11]. Eliciting a secondary data analysis of the vaccination data from both states, we evaluated our primary hypothesis that HPV coverage rates are associated with the equity of access to health department clinics. To test this hypothesis the following specific aims were completed:

1.2.1 Aim 1

Specific Aim 1: Characterize all counties in GA based on administered doses of the HPV vaccine, the Tdap vaccine and HD clinic access. Graphical maps were created for each state using Bayesian spatial analysis of HPV and Tdap vaccine doses, public transportation routes and VFC provider registration by public and private health clinics. Hypothesis 1.1: In GA, administered doses of the HPV vaccine and the Tdap vaccine will be associated with indicators of HD clinic access.

1.2.2 Aim 2

Specific Aim 2: Develop and validate a predictive model to describe the association between county level HPV vaccination coverage and HD clinic access in GA among Tdap vaccinated adolescents. Controlling for known factors associated with HPV vaccination, we used 2016 and 2017 data from GA to predict 2018 HPV vaccination coverage rates. Hypothesis 2.1: Significant factors of HPV vaccination coverage will be predicted at the county level in GA among Tdap vaccinated adolescents.

1.2.3 Aim 3

Specific Aim 3: Apply the predictive model of HPV vaccination coverage developed from GA data to SC. Using the final model selected in Aim 2, the best set of beta estimates were applied to all counties in SC via linear regression to predict HPV vaccination coverage. Hypothesis 3.1: Differences in SC's HPV vaccination coverage between observed and predicted rates will be identified.

2.0 BACKGROUND

2.1 Overview

This dissertation research builds upon and extends my mentor's current research of a statewide HPV vaccination awareness campaign in South Carolina to increase HPV vaccination rates. Using the adolescent population (ages 13-17) of South Carolina, two primary research questions are examined: 1) who is getting vaccinated and 2) what can be done to improve HPV vaccination. These research questions prompted the consideration of a better tool for HPV vaccination surveillance.

2.2 Introduction

In 2016, South Carolina had the lowest rate of HPV vaccine completion among adolescent girls in the United States (30.8%) and second-to-last for up-to-date (UTD) vaccination among adolescent boys (27.4%). In 2017, 38% of males and 47.4% of females were up-to-date[12]. As a result, South Carolina had the third largest increase in HPV vaccinations in the United States from 2016 to 2017. Currently, South Carolina is close to the national average of 54.2%[6] but the Healthy People 2030 goal is to reach 80%[8]. Problems with access to care as they relate to HPV vaccination in South Carolina consist of barriers at different levels within the patient, provider, health system and political environment. Patient barriers include: lack of provider recommendation, lack of knowledge about the vaccine and HPV related diseases, concerns about vaccinating an adolescent against a sexually transmitted infection, the disbelief that the vaccine is essential, particularly with males, and concerns about the vaccine's safety and cost. Provider barriers include: a lack of understanding about HPV-related diseases, specifically for males, safety concerns about the vaccine, concerns about reimbursement

for vaccines, personal attitudes, being uncomfortable with talking to parents and children about a topic related to sexual behavior, concerns about parental resistance, preferring to vaccinate older rather than younger adolescents, lack of vaccine reminder and recall systems, and limited time to provide education about the vaccine. Health system and political barriers include: the lack of electronic health record reminders[13], a lack of vaccine insurance coverage among some populations and a lack of legislation for mandatory vaccination [14].

However, South Carolina is just a small piece of the big picture, as national and state levels HPV vaccination coverage rates still vary by geography and race. Reported disparities by geographic location broadly reference metropolitan vs non-metropolitan areas. HPV vaccination rates are particularly low in rural areas even though the uptake of other adolescent vaccines is comparatively higher. In urban areas over 50% of the adolescents are up to date on their HPV vaccination compared to 42% of adolescents in rural areas[15]. Racial disparities have been reported among Black, Hispanic and Asian adolescents being more likely to initiate the HPV vaccine series compared to White adolescents, but less likely to complete the vaccine series[16]. Previous studies have also identified factors at the local level associated with HPV vaccination coverage are the uptake of other adolescent vaccines, gender, race/ethnicity, socioeconomic status, religiosity, political ideology, education policies and insurance status[17–19]. Religiosity and political ideology have been used as proxy measures for macro-level acceptability and attitude towards the HPV vaccine[19]. Differences in HPV vaccination uptake also exist between certain geographically distinct populations and among adolescents who have received the school mandated tetanus, diphtheria and pertussis (Tdap) vaccine. While

mandates have been effective with other vaccines, states with HPV vaccine mandates have similar rates of HPV vaccination compared to those without mandates, thus indicating that differences are not fully understood [18,20]. While there is a need to further explore these disparities, within state variability of HPV vaccination is either unknown or rarely reported[21] and in some states county level HPV vaccination coverage rates are currently not available.

In terms of barriers, a distinct contributing factor to incomplete HPV vaccination among adolescents is parental hesitancy. Parental hesitancy contributes to missed opportunities[22], physician hesitancy [3], and the physicians' perception of parental reservations [23]. In 2014 a qualitative study was published that investigated the rationale of parents/guardians and providers for delaying or administering the HPV vaccination to girls. Among providers who reported that over 80% of their patients receive HPV vaccination, the higher uptake was driven by always recommending co-administration of HPV, tetanus, and meningococcal vaccines and emphasizing cancer prevention[22]. Many of the missed opportunities for HPV vaccination were due to parents and providers agreeing to delay vaccination until the risk for sexual activity was predicted[22]. Other studies have reported that health care providers also perceived parental attitudes and hesitancy related to vaccinating an adolescent against a sexually transmitted infection as a barrier. Lack of provider recommendation, in turn, is one of the most influential reasons why parents do not get their adolescents vaccinated against HPV. Additional key contributors of parental hesitancy are needing more information about the HPV vaccine, the belief that their child is too young for the vaccination, safety of the vaccine, cost of the vaccine, and finding a clinic that offers the HPV vaccine [23].

To address parental hesitancy effective HPV vaccine messaging in an important strategy to increase HPV vaccine uptake. In South Carolina, the most trusted messengers include healthcare organizations, and providers, patient and parent peers, and local public figures[24–26]. Messages that appeal to parents' moral responsibility to protect children against cancer are recommended due to moral values such as purity and liberty being associated with vaccine hesitancy. Additionally, messages that highlight HPV's connection to sexual activity negatively influenced vaccine-hesitant parents, specifically in South Carolina due to a large population that identifies as Christian. Therefore, disseminating messages from the CDC that highlight cancer prevention, knowledge about HPV transmission, risks and prevention are recommended. Examples of messages are "The HPV vaccine is safe, effective and provides long-lasting protection", "HPV Vaccine is Cancer Prevention" and "One vaccine plus two doses equals protection against six types of cancer". Overall, HPV-specific messages that align with constructs from behavior models such as the Health Belief Model and Social Cognitive Theory to communicate the high risk for HPV infection, the severity of cancers associated with HPV, a cue to action for parents to protect children from known risk and the normalization of HPV vaccination as standard practice are effective [26]. Recommended strategies for disseminating these messages are using personal stories from cancer survivors and parents who have vaccinated their children. Additionally the use of trusted experts to discuss scientific data emphasizing the safety and efficacy of the HPV vaccine across multiple media platforms will engage a wider audience and effectively communicate the benefits of the vaccine to parents[26].

2.3 Molecular Biology of HPV that Drives Carcinogenesis

Papillomaviruses are a distinct taxonomic family, the Papillomavirida. The bovine papillomavirus type 1 (BPV-1) and human papillomavirus type 1a (HPV-a1) genomes were the first papillomavirus genomes to be completely sequenced. Interestingly, the BPV-1 has been utilized as a prototype for studies of the molecular biology of papillomaviruses. Papillomaviruses replicate and assemble entirely in the nucleus of a cells. The expected replication cycle has an early and a late phase. The early phase includes viral entry, and the initial viral genome replication, stimulation of cell division and inhibition of apoptosis in the infected cell. The late phase includes viral genome amplification, virion formation and its release into the surrounding environment from the surface of the epithelium. Specifically during the early phase the virus infects the keratinocytes (basal cells) in the basal epithelial layers [27,28]. Once infected, basal epithelial cells divide, the viral genome copies are replicated and separated equally into daughter cells. An infected daughter cell will make multiple copies and move up through the various epithelial layers. During this process there is a pattern of viral gene expression in response to epithelial differentiation that is specifically connected to different epithelial layers [27].

The viral genome responds by expressing viral regulatory proteins: E1, E2, E4, E5, E6 and E7 from the early region of the viral genome and two structural viral capsid proteins: L1 and L2 from the late region of the genome[28]. E1 and E2 support viral DNA replication and the regulation of transcription so that the infected basal cells can be maintained for a long period. E4 is linked with reassembling differentiated basal cells for the release of progeny viral particles and regulation of the cell cycle. E5, E6 and E7 are

viral oncogenes and their expression initiates cell immortalization and transformation by coordinating a host cell environment suitable for viral DNA replication which promotes host cellular DNA synthesis and prevents apoptosis. E5 is involved in keratinocyte signaling and immune evasion. E6 and E7 inactivate interferon (IFN) regulatory factor (IRF) so that the viruses can remain as persistent, asymptomatic infections in differentiating epithelial cells where cell division would normally be repressed. L1 and L2 are expressed in cells replicating viral DNA in the upper epithelial cells. Taxonomic status of papillomavirus types, subtypes, and variants is based on the sequence of their L1 genes which differ from each other by at least between 2 – 10% [27–29].

Papillomavirus infections typically result in benign lesion however, the human papillomavirus (HPV) infection sometimes develops cancerous lesions. HPV is a small non-enveloped deoxyribonucleic acid (DNA) virus that infects skin or mucosal cells. The circular, double-stranded viral genome of about 8 kilobases in length. As a member of Papillomavirida, the HPV genome encodes for 6 early proteins responsible for virus replication and 2 late proteins that are the viral structural proteins. The cancerous lesions emerge once HPV infects a cell and produces oncoproteins E6 and E7 that are particularly instrumental in the conversion of normal cells to cancerous ones. These inappropriately dividing cells in the upper epithelial layers would normally be disposed via apoptosis but E6 promotes tumor cell growth by breaking down the tumor suppressor protein p53 and inactivating pro-apoptotic proteins such as Bak or Bax. E6 degrades p53 thorough the ubiquitin pathway by targeting it for proteasome mediated degradation which allows HPV infected cells to survive and support replication [27,30]. Normally, the tumor suppressor protein p53 prevents the transition of cells from the checkpoint G1

phase to the replication S phase, thus allowing for the repair of damaged DNA or the initiation of apoptosis.

For that reason it has been suggested that high risk HPV types do not have a functional G1 checkpoint and that the E6 protein has been shown to influence the telomerase enzyme to elongate chromosomal telomeres which is necessary for cell immortalization [31]. As a result, the ability to target p53 for degradation contributes to the impact of oncogenic activity. With high risk HPV type E6 proteins, the interaction of an E6-associated protein (E6-AP) is necessary for the complex formation of E6 with p53. Furthermore, the E6-AP can initiate the ubiquitination of cellular components without E6, so the function of E6-AP is not just to mediate the binding of E6 to p53, but it provides the functional link to the ubiquitin system as an E3 ubiquitin ligase. However, this complex formation is not definitively seen with low risk HPV type E6 proteins [32]. The weak interaction between low risk HPV type E6 proteins may explain their inability to target p53 for degradation, resulting in a lack of oncogenic activity. However, it is also possible that additional proteins are required to facilitate the interaction of E6-AP with low risk HPV type E6 proteins and/or that the E6-AP complexes are not detectable under current conditions of coprecipitation experiments [33]. The E6 protein further cooperates with the E7 protein to convert normal cells to cancerous one. E7 binds to the retinoblastoma protein (pRb) in the pocket domain. The pocket domain sequences are necessary for its tumor suppressor function which negatively regulates the cell cycle in the G1/S and G2/M transitions.

In a normal cell, pRb and E2F- family transcription factors regulate cell replication together by keeping the cell ‘off’ in the resting phase, G0, before the cell goes

into mitosis and divides. Therefore when E7 blocks the interaction between pRb and E2F-family transcription factors, it activates the E2F factors to stimulate replication and cell division [27,30]. Specifically, when bound to pRB, E7 promotes C-terminal cleavage of pRB by the calcium activated cysteine protease calpain which is required for the proteasomal degradation of pRb. Additionally, E7 may initiate cancerous cell transformation by binding the AP1 transcription factors to prevent the differentiation of keratinocytes and by interfering with other cell cycle regulators such as cyclin A and cyclin-dependent kinase2 [29,31]. However, E7 proteins from low risk HPV types inactivate cellular pRB tumor suppressor proteins less efficiently than high risk HPV types [28] and the genetic variation of E7 within an HPV type in specific regions of the viral genome has been suggested to impact carcinogenicity. Specifically, in a recent study with cervical cancer it was shown that the conservation of the 98 amino acids of E7 is critical for HPV 16 carcinogenesis. Even compared to E6, E7 has significantly fewer, rare non-silent genetic variants in cancers and E7 was shown to be less constrained in benign infections. These results were consistent in different geographic locations and racial groups and thus suggests that E7 genetic variation notably decreases the risk of invasive cancer [34].

HPV is the most common sexually transmitted infection in the United States but only approximately 10% to 15% of infected persons have persistent infections, of which a small portion has the potential to progress to invasive cancer [35]. This suggests that host defense mechanisms are successful at clearing the initial HPV infection for the majority of HPV infected persons. Host defense mechanisms against HPV are physical barriers, innate immunity and adaptive immunity. Physical barriers of basal keratinocytes, the host cells of HPV, are the skin and mucous membranes secrete a thick protective fluid and

antimicrobial peptides. HPV moves across the skin and mucous membrane via tissue damage and once inside many of its particles are degraded via host autophagy. The nuclear envelope also blocks HPV DNA from entering the nucleus. Innate immunity uses pathogen sensors to recognize HPV DNA once HPV enters a host cell. The high expression of nucleic acid-sensing toll-like receptors (TLR) is significantly correlated to women clearing the initial HPV infection. The HPV infected microenvironment also attracts dendritic cells, Langerhans cells, natural killer cells and natural killer T cells, thus suggesting that the early inflammatory response may be critical for initiating a strong defense against HPV infection. Adaptive immunity is seemingly less instrumental because the HPV lifecycle is only intraepithelial, and virions are only produced from the fully differentiated upper layer of skin. In the outer layers of epithelium, viral DNA is in capsids and progeny virions are released to re-initiate infection. Therefore, there are no virus induced cell eruptions or released viruses in the blood. However, host T cell responses are required to eliminate HPV infected cells. To escape being detected by the immune system HPV alters host gene expression, dysregulates protein functions, hides surface expression of MHC-I molecules to evade immune defenses and establish persistence. As a result, the continued presence of the viral genome over a period of several years in actively dividing epithelial cells results in a persistent infection [27,29,35].

2.4 Etiology of HPV Vaccine Development

While 90% of HPV infections do not show symptoms and clear naturally within two years, persistent infections can cause cancer and genital warts. There are more than 100 types of HPV. More than 40 HPV types can infect the genital areas of men and women, including the skin of the penis, vulva, and anus, as well as the linings of the

vagina, cervix, and rectum. These types can also infect the lining of the mouth and throat. Of these, 13 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66) can cause cervical cancer, and one of these types can cause cancers of the vulva, vagina, penis, anus, and certain head and neck cancers; specifically, the oropharynx, which includes the back of the throat, base of the tongue and tonsils [36]. As a result, more than 90% of cervical and anal cancers, approximately 70% of vaginal, vulvar and oropharyngeal cancers, and 60% of penile cancers are the result of a HPV infection [7]. In particular, HPV types 16 and 18 are associated with about 70% of cervical cancers, with type 16 having the strongest evidence for overall carcinogenicity and types 6 and 11 are associated with 90% of genital warts [37].

Gardasil 9, the only HPV vaccine available for use in the United States, prevents infection from these four types (16,18,6,11) and five additional cancer-causing types (31,33,45,52 and 58). Therefore, of the total identified 13 HPV types there are five remaining HPV types (35,39,51,56,59 and 66) associated with cervical cancer that need vaccine development [38]. There are numerous other individual reports of human papillomavirus types in cancers of the esophagus, prostate, bladder, breast, lung and other organ sites. With the exception of nail bed cancers, none of these reports show a consistent association of the virus with the respective site. Therefore, although high risk HPV types may sometimes cause cancers in atypical locations, the inconsistency of these reports does not provide strong support for researching these additional locations[39].

Many of the ongoing searches for novel HPV types use established consensus primers in polymerase chain reactions. This somewhat allows for the detection of partially homologous sequences because in theory HPV types not discovered by these

primers or those very distantly related to a known type of this virus group, would likely escape detection [39]. The direct detection of HPV genomes and their transcripts could be improved through hybrid testing procedures. However, new technical approaches that might increase the sensitivity of detecting new HPV types need to consider the clinical significance because not all HPV infections are persistent and lead to a clinically relevant disease. The development of a new technical approach that determines if the presence of multiple infections is a useful marker for persistent infection and the onset or progression of disease would assist with clinical significance.

Current approaches to increase the clinical sensitivity are testing only for clinically relevant high risk HPV types, adding a viral load measure and testing for high risk HPV E6 and E7 transcripts [38]. In spite of current technical limitations, a defining characteristic of cancer associated with persistent infection by the high risk HPV types is that viral genomes are commonly found integrated into the cancer cell genome, however, minute viral variations may show risk differences that could distinguish molecular mechanisms. It is already well established that while all the high-risk HPV types are genetically related, they greatly differ in prevalence, evolutionary fitness and in risk of causing precancer and cancer. HPV genetic variation represents slow evolutionary drift and the HPV types are made up of phylogenetic variant lineage as well as sublineage evolutionary clades that differ from each other by approximately 1% to 9% [28,34]. These minute viral variations may contribute to the increased number of identified HPV strains and the corresponding number of carcinogenic strains.

Understanding the unique carcinogenicity of high-risk HPV types, such as identifying patterns to explain the amino acid changes in HPV proteins, would be useful

for vaccine development. The use of antibodies to inhibit protein function is a viable option for treatment because viruses express proteins that are different from those expressed by the cell and they are directly involved in causing disease. However, the disease associated proteins resemble their normal cellular counterparts at most of the sites, making the discovery of molecules that can specifically target disease associated forms difficult. Specifically, one reason for the difficulty in targeting HPV infection is because most papillomavirus proteins bind to cellular proteins instead of using their own enzymatic activity to enact their effects. Alternatively, since E6 and E7 are co-expressed in cancers from a bicistronic mRNA, RNA interference could be a promising approach for vaccine development as well [29,40]. Being immune to one HPV type may not prevent the infection of another HPV type. Therefore, the ultimate prevention goal would be to have a prophylactic vaccine that includes all carcinogenic HPV strains according to potential genetic variation of HPV types and targets HPV proteins E6 and E7.

2.5 The Efficacy and Delivery of HPV Vaccination

Pressing questions related to HPV vaccination efficacy and delivery are who should get the vaccine, is it safe, and is it effective. According to CDC the best age for boys and girls to get the Gardasil vaccine is 11 to 12 years of age since children are not yet sexually active at this age. Data suggests that 6% of US high school students had sexual encounter before age 13. Also, research has suggested that girls who get vaccinations at age 12-16 have significantly more antibody titers present in their blood compared to older women favoring that the vaccinations be administered at an early age. As more antibody research is done with boys, the central idea is to get people protected against the virus before they encounter the virus for the first time. The vaccine can also

be given as early as 9 years of age and is now approved by the U.S. Food and Drug Administration (FDA) for men and women up to 45 years of age. Children who start the series between 9 and 14 years of age should get two shots of the HPV vaccine six months apart. Adolescents who start the series after their 15th birthday will require three doses of the HPV vaccine, with the second dose 2 months after the first, and the third dose 6 months after the first. This same three dose schedule is recommended for adults and for immunocompromised individuals [41,42].

Twelve years of monitoring and research have shown that the HPV vaccine is safe and effective in large clinical trials and extensive post-licensure data further supports the vaccine's safety and efficacy. All of the HPV vaccines use virus like particles which mimic the viral capsid but do not contain genetic material and are produced in biologic systems, which have well established safety records. In the large licensing trials, baseline HPV infection status was measured through serologic testing and DNA detection in cervical specimens. Efficacy in the overall trial populations was consistently lower than among those without baseline HPV infection. This revealed that many trial participants were already sexually active and previously infected with vaccine HPV types; thus emphasizing the importance of receiving vaccination before the onset of sexual activity to maximize effectiveness [43]. Since cancer registries do not routinely collect data on whether HPV is in the cancer tissue, case-control studies are emphasized as opposed to prospective cohort studies due to a larger number of invasive cancers that have been evaluated [38]. Clinical trial research continues to monitor and evaluate HPV vaccination efficacy.

Currently, there is no scientific evidence to associate the HPV vaccine with any specific adverse event[43–47]. However, like any vaccine or medicine, HPV vaccines can cause side effects. The most common side effects are pain, redness, or swelling in the arm where the shot was given; dizziness, fainting, nausea, and headache [48]. It was reported that recipients of the 9-valent vaccine were slightly more likely to experience these side effects than recipients of the quadrivalent vaccine (90.7% vs 84.9%) possibly due to higher amounts of virus like particles and adjuvants in the 9-valent vaccine [10]. In an analysis of seven trials in which over 15,000 individuals received at least one dose of the 9-valent vaccine, serious adverse events occurred in less than 0.1%[43]. Some surveys of parents of adolescent girls identified a concern the HPV vaccine to have a behavior impact on sexual promiscuity. However, studies have not confirmed an association between vaccination and increased sexual behavior [43]. Additionally, multiple large studies have provided evidence that the HPV vaccine is as safe as any other vaccination and that those who receive this vaccine are not at a higher risk of any negative events when compared to receiving any other vaccine immediately or in the long-term future[49]. Therefore the cancer prevention benefits of HPV vaccination far outweigh the potential risk of side effects [48].

Research shows that HPV vaccine protection is long-lasting. Current studies have followed vaccinated individuals for 12 years and show that there is no evidence of weakened protection over time. HPV vaccination research includes over 10 years of data and continues to be monitored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA)[48]. HPV vaccination has shown high quality duration of protection for this 10 year time period even though the precise level of

antibody needed for protection against infection is unknown [43]. As a result, over 120 million doses of the HPV vaccine have been administered in the United States.

A potential clinical trial to further address HPV vaccine delivery would be one that finds a biomarker related to immune response and host susceptibility to HPV. Focusing on cervical cancer would provide an adequate source population because nearly all cases of cervical cancer types are resultant of an HPV infection and the primary prevention strategy against cervical cancer is HPV vaccination. Hispanic women have the highest incidence rate of cervical cancer, however, the highest death rate from cervical cancer is among African American women. In comparison to White women, African American women are more likely to be diagnosed with cervical cancer. Of the known HPV strains that are strongly associated with cervical cancer, it is unclear if these various strains are significant to mortality. Research studies have indicated that biologic, socioeconomic, cultural, environmental and other factors may affect cervical cancer incidence and mortality [50]. Therefore, the investigation of disparities in immunologic host susceptibility factors due to ethnicity are of interest. The independent variable of interest would be the clearance of high-risk HPV infection types by African American women and the dependent variable of interest would be the mortality of African American women with cervical cancer**.** The relationship between the clearance of high-risk HPV type infections by African American women and the mortality of African American women with cervical cancer, is potentially due to how the immune system responds to viral infections. Quach et al investigated the differences in the transcriptional responses of Africans and Europeans to immune stimulation. They found distinct differences among antiviral and inflammation-related genes that significantly differed in responsiveness between Africans

and Europeans. Specifically, the master regulator, TLR1, controls the inflammatory response in Europeans and contributes significantly to differences in the strength of the inflammatory response between Africans and Europeans [51]. This evidence provides good support for genetic variants of immune responses. However, there does not seem to be any exploration as to the TLR pathways that are activated and regulated in Africans for their inflammatory responses. Also, the variants affecting immune responses in African genomes are not discussed. Therefore, this evidence appears to be lacking sufficient information on African genetic differences and regulatory variants to adequately determine differences in host immune responsiveness between Africans and Europeans.

Banister et al (2015) investigated the persistence of high-risk HPV genotypes between African American and European Women of College Age. They found that of the 2,121 clinic visits for the study, on 40% of them European American women were HPV positive and on 51% of them African American women were HPV positive. For European American women, 37.1% of the visits produced high risk HPV types and 8.7% produced low risk HPV types. For African American women, 47.4% of the visits produced high risk HPV types and 14.4% produced low risk HPV types. Using multivariable analysis of the association between ethnicity and high-risk HPV infection, African American ethnicity and lifetime number of sex partners was significant; thus, indicating that clearance of high-risk HPV could be different between African American and European American women. The required time for 50% of high-risk HPV infections to clear was almost double the days for African American women compared to European American women. African American women also had 1.61 times the odds of not clearing a high-risk HPV infection compared to European American women. African American

women had more abnormal Pap test results (ASCUS, LSIL, and HSIL) compared to European American women and were significantly associated with an abnormal Pap test result when the lifetime number of sex partners, HPV vaccine receipt and smoking were controlled for. However, high risk HPV type was significantly associated with an abnormal Pap test result when ethnicity, the lifetime number of sex partners, HPV vaccine receipt, and smoking were controlled for. This suggests that the high-risk HPV status is the reason for differences in abnormal Pap test results between African American and European American women. Therefore, the increased risk of an abnormal Pap test result and the increased probability of being high risk HPV positive is potentially due to persistent infection of high risk HPV rather than differences in exposure to HPV [52]. This evidence provides good support for increased cervical cancer incidence in African American women. However, there does not seem to be any exploration into the connection of the high-risk HPV type and increased mortality rates of African American women with cervical cancer.

Clifford, Franceschi, Diaz, Muñoz and Villa (2006) investigated the distribution of HPV type in women with and without cervical neoplastic diseases. After comparing a pooled analysis and a meta-analysis, the most common HPV types in invasive cervical cancer were HPV-16,-18,-33,-45,-31,-58,-52,-35,-59,-56,-51,-39,-68, and -73. The most common HPV types in high grade lesions (HSIL) were HPV-16, -31, -58, -18, -33, -52, -35, -51, -56, -45, -39, -66 and -6. The most common HPV types in low grade lesions (LSIL) were HPV-16, -31, -51, -53, -56, -52, -18, -66 and -58. The most common HPV types in women with atypical squamous cells of undetermined significance (ASCUS) were not reportable because no meta-analysis on HPV type specific prevalence existed at

that time. The most common HPV types in women without cytological abnormalities were HPV-16, -42, -58, -31, -18, -56, -81, -35, -33, -45 and -52. The shifts in HPV type distribution across cervical lesions of increasing severity show that HPV types 16, 18 and 45 are significantly more common in squamous cell carcinoma (SCC) than HSIL, HPV types 16 and 18 are more common in SCC than LSIL but other HPV types are more frequent in HSIL and LSIL than SCC. These differences indicate that HPV type can differ in the risk of developing cervical cancer from HSIL [53]. This evidence provides good support for the distribution of HPV type related to LSIL, HSIL and cervical cancer. Their findings allow for inference of HPV types that may be connected to cervical cancer mortality. However, there does not seem to be any exploration into HPV type distribution by ethnicity. Even though geographical variations were taken into consideration, North America was not represented in the pooled analysis from the International Agency for Research on Cancer (IARC) but was stated to be similar to Europe in terms of proportion to HPV-16 infection. This clarification is important because a woman of African descent living in North America is different from a woman of African descent living in Europe.

Therefore, based on the literature, early inflammatory responses may be critical for initiating a strong defense against HPV infection, however, there are genetic variants of immune responses. It has been shown that for African American women, the increased risk of an abnormal Pap test result and the increased probability of being high risk HPV positive is potentially due to persistent infection of high-risk HPV. Meanwhile, the cause for increased mortality among African American women with cervical cancer is unknown. For this reason, the identification of HPV type in African American women with cervical cancer is needed when investigating their death because HPV type can

differ in the development of cervical cancer even from HSIL. My hypothesis is that if the high-risk HPV types of African American women with cervical cancer were identified and cleared or prevented due to the improved efficacy of HPV vaccination, then their mortality rates would decrease. This is of particular interest because cervical cancer mortality rates are especially high in African American women in the rural South, but not for African American women in the West.

For African American women in the South, some shared characteristics are that the poverty levels are above the national average, educational level is low, geographic isolation, lack of transportation, greater exposure to environmental and occupational hazards, poor housing, distrust of the government and mainstream medicine and a tenacity to sustain themselves in harsh living conditions[50]. Retrospective reviews of women diagnosed with cervical cancer indicate that 50% to 70% of them did not have a Pap test within five years prior to diagnosis or they never had been screened [50]. Many women living in areas with high rates of cervical cancer mortality rely on publicly funded programs for their health care; therefore addressing cervical cancer mortality could serve as an indicator of an inefficient health care system concerning issues of medical care access, cultural issues, health communication and health education that disproportionately affect poor and underserved women. Areas with high cervical cancer mortality also experience high mortality rates for breast cancer, colon cancer, heart disease, stroke, infant mortality and other conditions that improve with regular screening or early intervention [50]. Because cervical cancer mortality is an avoidable cause of death, the overall health status of these geographic regions with high cervical cancer mortality

includes additional parameters of critical importance for improving the efficacy and delivery of HPV vaccination.

2.6 Using Geospatial Data to Improve HPV Vaccine Delivery

HPV vaccination data measurements associated with geographic locations are becoming more available from immunization registries. However, the fundamental nature of spatial data imposes some analytic challenges that should be considered with HPV vaccine delivery. When using spatial methods in epidemiologic research there are positive and negative aspects of spatial data that contribute to the accuracy of estimation. Measuring distance from one location to resources is frequently used to estimate environmental exposure. For example, the distance from a residence to a health department clinic or pharmacy to receive the HPV vaccine could be used to estimate environmental vaccination access. However, straight-line distance can be a poor proxy for estimating access if there are no direct roads or other means of traveling to a particular location[54].

When considering the relationship of spatial features geographical information systems (GIS) it is important to use topology. GIS topology is broadly defined as the spatial relationships between adjacent or neighboring features. Adjacency is a type of spatial relationship where two or more polygons share a side or a boundary. For example, Georgetown, Berkeley, Dorchester and Colleton counties are all adjacent to Charleston county. Neighborhood is a defined shape or area in which only the cells that have their cell centers within the neighborhood are considered part of the neighborhood. There should be no overlapping features. For example, a rectangle neighborhood can be created by specifying the height and width in map units such as degrees, meters or feet. So, in

measuring the neighborhood of Mt Pleasant, only include the land area of 116.8 km^2 would be included. Adjacency and neighborhoods are effective for modeling spatial relationships and the analyses of contiguity and connectivity. However, these data are inherently static and do not allow for real world representation of spatial changes over time. As a result, boundary problems such as edge effects must be considered. Edge effects are evidenced when the boundaries of a study area affect a given spatial measurement and lead to inaccurate estimates. This happens when the study area is defined by a border that does not prevent travel, therefore the geographic distribution of variables within an area may in fact extend beyond the border. Not accounting for edge effects introduces biases and under-reporting. For example, Berkley county may show a low count of administered HPV vaccination doses that they have administered, but this does not mean that fewer adolescents are receiving the HPV vaccine because in fact, many adolescents could be traveling to Charleston county to receive their vaccine[55].

Spatial autocorrelation measures the correlation of a variable with itself through space and refers to the relationship/pattern that variables of proximal entities will share more similar values than distant entities. It is expected that the level of spatial autocorrelation diminishes as a function of distance between two regions, unless there is some reason for similarity due to some other associated factor[56]. However, this assumes initial independence of data, which may not be appropriate. For example, the spatial autocorrelation between HPV vaccination rates in urban counties is assumed to be the same in the state of South Carolina. This would mean that the relationship between HPV vaccination rates was purely a function of distance between the counties and not relative to their location. Since a map is the representation of various locations, it can be defined

as a collection of spatially defined objects. The modifiable area unit problem (MAUP) is the inconsistency in how the map scale can yield different results when aggregated in different ways. Therefore, the changes the scale makes on the analysis needs to be quantified, otherwise variable measures could be underestimated. If results are significantly different, then the scale may need to be modified so that the results are more consistent. Scale refers to the ground area of the map and can be described as large or small. For example, a county level map of South Carolina is large scale representation compared to a state level map of South Carolina, which is small scale representation. When administered HPV vaccination doses are aggregated on a small scale (state level), areas with decreased HPV vaccination access are underestimated[56].

2.7 Insufficient Data

Studies have shown that Immunization Information Systems also referred to as immunization registries, are effective in improving vaccination related activities to increase vaccination rates and reduce risk for vaccine preventable diseases[4,57]. However, in the literature there is a gap between national state level vaccination data and local level adolescent vaccination data often tracked by state immunization registries[19,21,58–61]. Hence, within state variability has not been commonly studied. Additionally, there is very little information about how vaccination is affecting the prevalence of HPV-associated cancers in rural areas. These areas may be medically underserved, have high rates of cervical cancer, and low rates of HPV vaccination[20]. The National Immunization Survey (NIS) provides data on HPV vaccination rates by state but there is less detailed information on the prevalence of HPV-associated cancers within states or how changing vaccination rates affects the prevalence of HPV-associated cancers directly in each

region. With the limitation of state level data, the reasons for geographic vaccination disparities are currently not well understood and this may be due to the lack of state immunization registry data at the local level. As a result, these local areas may continue to be a source of geographical disparities in HPV-associated cancer incidence as well [20]. Therefore, more data are needed to evaluate impact of HPV vaccination in smaller geographic areas. With improved tools for HPV vaccination surveillance, the impact of county level vaccination programs and policies on population level vaccination and the prevalence of HPV-associated cancers can be evaluated better.

3.0 SIGNIFICANCE & INNOVATION

3.1 Clinical and Public Health Significance

The occurrence of HPV associated cancers varies by cancer type, sex and race/ethnic group and is estimated to have a combined cost of $8 billion per year in the United States[4]. Approximately 44,000 new cases of HPV-associated cancers occur in the United States each year affecting women and men. HPV associated cancers most commonly occur in the cervix among women and in the oropharynx (back of the throat, including the base of the tongue and tonsils) among men[62]. Among these cancer types, it is estimated that 35,900 cancers (79%) were actually caused by HPV during 2011-2015 and that 31,200 of these cancers could have been prevented by the 9-valent HPV vaccine[62]. However, as of 2019 no state in the United States has reached the Healthy People 2020 HPV vaccination goal of 80% coverage and HPV vaccination coverage varies substantially by state[15,63].

The between state variation of HPV vaccination may be due to insufficient HPV surveillance. Unlike other reportable sexually transmitted infections in every state, HPV is not a nationally notifiable condition because HPV infections are too common. However, the delivery of HPV vaccinations is monitored. Frequently health-care claims data from adolescents and adults with employer-provided private health insurance in the United States are used to examine the population effectiveness of HPV vaccinations on HPV infections[64]. Additionally, in some states, all health care providers are required to report the administration of all vaccines to state immunization registries, however, the tracking and reporting of vaccine delivery is inconsistent among state health departments. A consistent source of data is the National Immunization Survey–Teen (NIS-Teen),

which is an annual survey that estimates vaccination coverage among adolescents aged 13–17 years in the 50 states, the District of Columbia (DC), selected local areas, and territories. However, NIS-Teen data do not report HPV vaccination below the state level whereas state immunization registries are able to. Therefore, using state immunization registries is a critical step in overcoming the challenge of HPV vaccination surveillance beyond the state level. This research quantified HPV vaccination coverage at the county level using administered doses of the HPV vaccine collected by GA and SC state immunization registries.

The clinical significance of monitoring HPV vaccination is that immunization coverage rates are a key indicator of overall community health[65]. The extent to which health departments deliver immunization services is associated with multiple components of quality public health services such as vaccine supply, surveillance, advocacy and communication and logistics. As a result, HPV vaccination coverage rates at the county level are impacted by the equity of access to health care services provided by health department clinics. Therefore, examining indicators of HD clinic access offers more insight into why HPV vaccination coverage rates differ by locality even though HDs implement many of the same immunization services. For example, HDs must conduct more quality assessment visits to providers enrolled in the VFC program. Nationally, under the VFC program, the Center for Disease Control (CDC) purchases vaccines at a discount and distributes them to grantees, such as state HDs and certain local and territorial public health agencies. These grantees distribute the vaccines at no charge to private physicians' offices and public health clinics that are registered as VFC providers. Because the federal government pays for the vaccine, providers are not paid for the cost

of the vaccine product. Instead, they are paid an administration fee for the costs that the provider incurs in administering the vaccine. For children enrolled in Medicaid, the Medicaid program pays the vaccine administration fee. For uninsured and underinsured children enrolled in VFC, the parents are billed for the administration fee and the administration fee varies by state[66].

3.2 Innovation

GA and SC are both in public health region IV and therefore share the same regional office for programs and policies through the U.S. Department of Health and Human Services (HHS) (Figure 1). Despite the difference in the number of counties, GA and SC share similar population demographic characteristics[67–69] (Figures 2, 3, Table 1). The estimated vaccination coverage rates in the public health region IV have shown GA's Tdap and HPV vaccination rates to consistently be near or exceed the national average from 2016 to 2018. Conversely, during this same time period, SC was consistently below the national average with the lowest HPV vaccination coverage estimate in the United States in 2016 according to the National Immunization Survey – Teen data[70]. Systematic underuse of services that impact health by populations that share similar demographic characteristics may indicate a problem with equity of access[11]. Hence, access may be a significant driver of the different vaccination rates between GA and SC. To explore these differences at the county level GA has comprehensive adolescent HPV vaccination data available at the zip code level that can be aggregated to the county level using Zip Code Tabulation Areas but SC does not. Therefore, GA's availability of county level HPV vaccination data and similar population demographics to SC, supports GA as a suitable model state for increasing SC's HPV vaccination coverage rates.

This research innovatively 1) predicted county level HPV vaccination coverage using public health surveillance data previously collected by two different state immunization registries, census tracts and the department of transportation, instead of the exclusive use of national self-report surveys. With these data we 2) geographically characterized HPV vaccination coverage data at the county level using adolescents who have received the school mandated Tdap vaccine as the sample population. This sample population controlled for many sources of confounding such as parents who oppose vaccines, children with medical conditions preventing them from receiving vaccines, and those without any access to vaccines. This research 3) assessed indicators of health care access using health care utilization properties related to the health care settings [11]: the number of public and private clinics and the number of health department clinics with VFC provider registration. This research 4) assessed indicators of health care access using a health care utilization property related to health equity[71]: public transit transportation. Using an adapted model of access to personal health care services from the Institute of Medicine (Figure 4) as our conceptual framework, this research innovatively 5) examined the effect of key factors associated with HPV vaccination to highlight counties with HD clinic access problems resulting in the poor health outcome of low HPV vaccination coverage. The mediators in this conceptual framework of provider recommendation, uptake and delivery of HPV vaccine and parental hesitancy were not adjusted for in analyses in order to examine the total effect and any effect of HPV vaccine delivery in HD clinics on HPV vaccination coverage.

3.3 Table

Table 1. Population Demographic Characteristics		
	Georgia	**South Carolina**
Counties	159	46
HPV vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)*		
2016 (60.4 %)	67.30%	44.20%
2017 (65.5 %)	64.30%	59.60%
2018 (68.1 %)	68.10%	63.70%
Tdap vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)		
2016 (88.0 %)	92.80%	77.50%
2017 (88.7 %)	93.30%	89.40%
2018 (88.9 %)	94.20%	88.90%
Race Ethnicity[+]		
Black/African American	31.30%	26.80%
White	52.80%	63.80%
Asian	4.20%	1.70%
Hispanic	9.60%	5.70%
American Indian/Alaskan Native	0.50%	0.50%
Native Hawaiian/Other Pacific Islander	0.10%	0.10%
Below 18 years of age[+]	24.10%	22.00%
Education[+]		
Highschool graduation	81%	84%
Some College	63%	62%
Median Household Income[+]	$56,100	$50,700
Uninsured children[+]	7%	4%
Children in poverty[+]	22%	22%
Living in rural area[+]	24.90%	33.70%

Data Sources:
* (Walker et al., 2019)
+ ("County Health Rankings & Roadmaps," 2019)

3.4 Figures

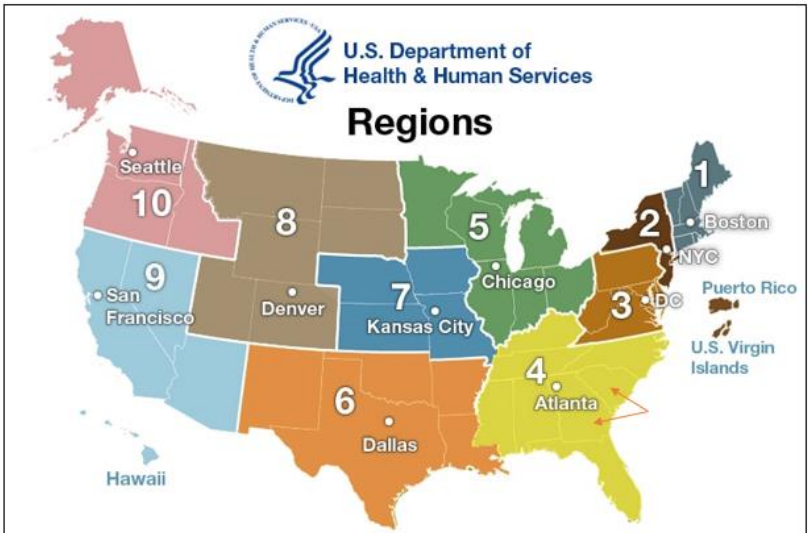

Figure 1. Regions of U.S. Department of Health & Human Services

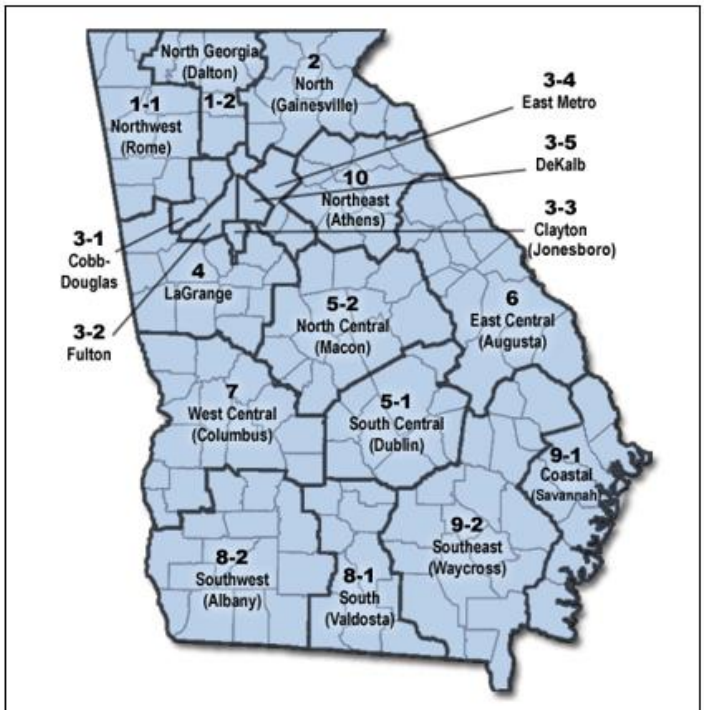

Figure 2. Public Health Districts and Counties of Georgia

Figure 3. Public Health Districts and Counties of South Carolina

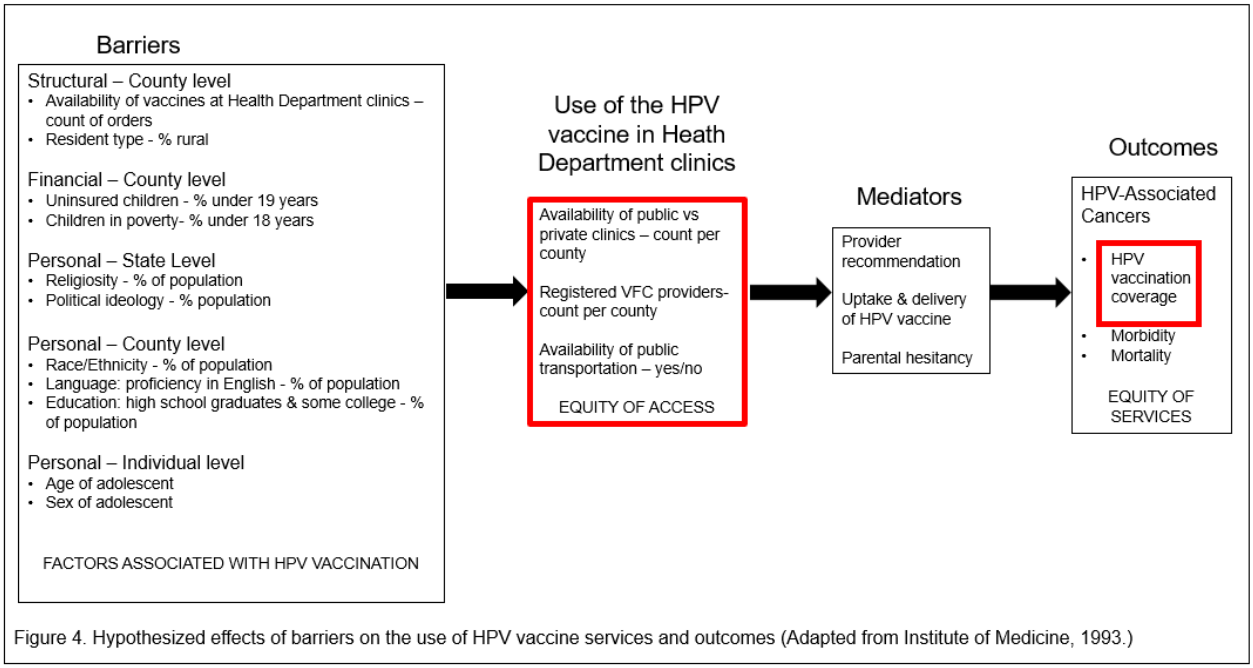

Figure 4. Hypothesized effects of barriers on the use of HPV vaccine services and outcomes (Adapted from Institute of Medicine, 1993.)

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5.0 ORIGINAL MANUSCRIPT 1: Spatial patterns of HPV and Tdap vaccine dose administration and the association of health department clinic access in Georgia counties

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5.1 Abstract

Objective: To characterize counties in GA by quantifying administered doses of the HPV and Tdap vaccines collected by the state health department immunization registry and indicators of HD clinic access.

Methods: Using a cross sectional study design, secondary data were collected from 2010 US Census, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the Georgia Department of Transportation for the years 2016 to 2018 for all 159 counties of GA. The study population was all male and female adolescents aged 13-17. The number of administered doses of the HPV vaccine and the number of administered doses of the Tdap vaccine were modeled in relation to number of private and public HD clinics, number of HD clinics registered in the VFC program and the availability of public transportation using Poisson regression, negative binomial regression and Bayesian spatial analysis.

Results: Choropleth maps showed similar clustering patterns between administered doses of the HPV vaccine and Tdap vaccine and increased counts of administered vaccine doses in counties with both public and private clinics. Administered doses of HPV vaccine were found to exhibit spatial dependence across counties. Accounting for spatial dependence, the availability of public transit has a significant positive effect on administered doses of HPV vaccine. Administered doses of the Tdap vaccine were also found to exhibit spatial dependence across counties. Accounting for spatial dependence, the number of private health department clinics has a significant positive effect on administered doses of the Tdap vaccine.

Conclusions: This study calls attention to the need for maps at the county level to show vaccination variability and clustering patterns to provide additional insights on the access to health care. Using Bayesian spatial models to account for the effect of spatial variability on HPV vaccine and Tdap vaccine dose administration between counties changed the significant effects of HD clinic access on HPV vaccine and Tdap vaccine dose administration to non-significant. This suggests that spatial statistical models are needed to accurately identify and estimate factors associated with administering doses of the HPV and Tdap vaccines. Future work is needed to further examine the utilization of HPV vaccination services among urban groupings.

Keywords: Choropleth maps, HPV vaccine, Tdap vaccine, Bayesian spatial models

5.2 Introduction

In its 2012-2013 report, the President's Cancer Panel concluded that underuse of human papilloma virus (HPV) vaccines was a serious but correctable threat to progress against cancer[1,2]. Approximately 91% of cervical and anal cancers, 75% of vaginal, 69% of vulvar, 70% oropharyngeal cancers, and 63% of penile cancers are the result of an HPV infection[3,4]. During 2012-2016, an estimated average of 34,800 HPV-attributable cancers were diagnosed each year. Among these estimated cancers, 92% were attributable to the HPV types that are included in the 9-valent HPV vaccine and could have been prevented if HPV vaccine recommendations were followed[5]. The 9-valent vaccine, Gardasil 9, was studied in clinical trials with more than 15,000 females and males and found to be safe and effective[6]. Currently, the HPV vaccination coverage rate is increasing at national and state levels. As of 2019, about half of U.S. adolescents aged 13-17 are fully vaccinated (54.2%) and 71.5 % of them have received at least one dose of the HPV vaccine[7]. At the state level, South Carolina has impressively improved from a rate of 44.2% in 2016 for adolescents receiving at least one dose of the HPV vaccine, which was substantially below the national average of 60.4% (44.2%) to matching the national average (71%) in 2019[7]. However the overall national goal is to increase HPV vaccination coverage levels for adolescents to 80%[8].

Efforts to increase HPV vaccination are supported by resources often administered and utilized at the county level through state Health Departments (HD) such as childhood and adolescent vaccinations administered by school nurses and at public or private health clinics, community education and outreach, vaccine program enrollment,

and immunization registry reporting. Health care utilization can be determined by whether the provided health care can be accessed[9]. Access to health resources and quality healthcare services is an important determinant of health [10] and certain barriers such as physician shortage, lack of transportation, and insurance coverage can make gaining access difficult. Therefore, the underutilization of the HPV vaccine may be due to inequitable access. Equitable access to health care requires that everyone is able to receive an adequate level of care and resources without excessive burdens[11].

Maximizing access to HPV vaccination service was quantified as 80% vaccination coverage by Healthy People 2020[12]. As of 2019 no state in the United States reached the Healthy People 2020 HPV vaccination target of 80% coverage and HPV vaccination coverage varies substantially by state[7,12,13]. The between state variation of HPV vaccination may be due to the absence of standardized monitoring of HPV infections. Unlike other reportable sexually transmitted infections in every state, HPV infections and most HPV-associated conditions are not nationally notifiable[14]. Since HPV infections are too common to be reportable, making HPV-associated conditions reportable would increase the extent of public health surveillance which is useful for measuring the need and effect of HPV vaccination interventions and for targeting resources. Instead, health-care claims data from adolescents and adults with employer-provided private health insurance in the United States are used to examine the population effectiveness of HPV vaccinations on HPV infections[15]. The HPV vaccine is also not a required immunization for school attendance like the Tetanus, diphtheria, and pertussis (Tdap) vaccine. Therefore, strategically allocating HD resources is necessary to improve HPV vaccination coverage[16] and address the President's Cancer Panel's third goal of

maximizing access to HPV vaccination services[1]. An essential tool for allocating HD resources is the state immunization registry. GA's state HD immunization registry has a surveillance system that is able to monitor at the county level how many of their clinics are public, private, registered with the Vaccine For Children (VFC) program and the administered doses of the HPV and Tdap vaccine per clinic. This has contributed to Georgia's vaccination coverage trend of adolescents receiving at least one dose of the HPV vaccine staying close to the national average since 2016[13] (Table 1). However, some states to do not have county level HPV vaccination coverage data available and this is a major obstacle to effectively monitor HD resource utilization to increase HPV vaccination.

Therefore, the objective of this study was to characterize counties in GA by quantifying administered doses of the HPV and Tdap vaccines collected by the state HD immunization registry and indicators of HD clinic access. The rationale is based on the ability to evaluate the county level geospatial distribution of administered HPV vaccine doses compared to administered Tdap vaccine doses with indicators of HD clinic access to better understand county level access to adolescent HPV vaccination. The hypothesis is that in GA, administered doses of the HPV vaccine and the Tdap vaccine are associated with indicators of HD clinic access.

5.3 Methods

Data

Using a cross sectional study design, secondary data were collected from 2010 US Census, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the Georgia Department of Transportation for

the years 2016 to 2018 for all 159 counties of GA. The study population was all male and female adolescents aged 13-17 in GA. Differences in HD clinic access in relation to administered doses of HPV and Tdap were assessed. Indicators of HD clinic access were defined as the number of available public and private clinics, the number of HD clinics with Vaccine For Children (VFC) provider registration, and the availability of public transportation in the county. Administered doses were defined as greater than or equal to one vaccine dose given to adolescents aged 13 -17 from public and private clinics sites regardless of their VFC program participation and reported to the state immunization registry. The number of administered HPV and Tdap vaccine doses, the number of public and private HD clinics, and the number of clinics registered in the VFC program were collected by zip code and aggregated to the county level using Zip Code Tabulation Areas (ZCTAs). The availability of public transportation was defined by the presence of public transit routes inclusive of the metro Atlanta region, only rural, only urban, both rural and urban, and city only transit identified in each county by the Georgia Department of Transportation. Choropleth maps[17] of administered HPV and Tdap vaccine doses and indicators of access to HD clinics at the county level were created SAS statistical software version 9.4 [18].

Statistical Modeling & Analyses

Two dependent variables were individually modeled as outcomes: the number of administered doses of the HPV vaccine and the number of administered doses of the Tdap vaccine. These dependent variables were modeled in relation to the explanatory variables defined as indicators of HD clinic access: number of private and public HD clinics, number of HD clinics registered in the VFC program and the availability of

public transportation. For both outcomes three statistical methods were used: Poisson regression, negative binomial regression and Bayesian spatial analysis. While exploring the data with Poisson regression, overdispersion was detected so negative binomial regression was used for modeling[19]. Fixed effects only were evaluated first, and a backward stepwise selection method for selection of explanatory variables via the Akaike Information Criterion (AIC). To account for the non-spatial random effect of county, random intercept negative binomial models were evaluated using backward stepwise selection via AIC. Initially, the model was fit maintaining all the explanatory variables. The final model retained all variables that were statistically significant at $p<0.05$. Likelihood ratio tests were used to compare models, with the best model fit determined by AIC.

Systematic spatial variation also known as spatial autocorrelation in the counts of administered doses of the HPV vaccine and the Tdap vaccine were assessed using Moran's I[20]. Positive values of Moran's I indicate that nearby counties tend to exhibit similar counts of administered HPV and Tdap vaccine doses, while negative values indicate dissimilar counts. In the data used for this study the existence of a significant spatial autocorrelation points to the necessity of using Conditional autoregressive (CAR) models to represent this spatial autocorrelation[21]. CAR models smooth noisy estimates by pooling information from neighboring regions. A proportion of this spatial autocorrelation may be modeled by known covariate risk factors in a regression model, but it is common for spatial structure to remain in the residuals after accounting for these covariate effects. This residual spatial autocorrelation can be influenced by unmeasured confounding, neighborhood effects, and grouping effects. The most common remedy is to

augment the linear predictor with a set of spatially autocorrelated random effects, as part of a Bayesian hierarchical model. These random effects are typically represented with a conditional autoregressive prior, which generates spatial autocorrelation through the adjacency structure of the areal units[21].

For the spatial analysis two Bayesian models were compared: Besag-York-Mollié (BYM)[22] and Leroux[23] with Poisson family distributions. The BYM model uses a parameter for structured spatial random effects and a parameter for unstructured spatial random effects to account for over-dispersion not modelled by the Poisson variates. When the observed variance is not fully explained by the spatial structure of the data, the independent error term will account for the rest[24]. However, the BYM model only assumes a spatially structured component, so the spatial and non-spatial random effects cannot be identified independently from each other. This results in the non-spatial random error or pure overdispersion being modelled as spatial correlation[25]. The Leroux model is a variation of the BYM and CAR models in which there is only one spatial random effect parameter for each area that includes characteristics of both structured and unstructured spatial random effects[26]. For this illustration, the random effect terms can be interpreted as the county effect on HPV vaccine and Tdap vaccine dose administration.

To find the best fitting Bayesian model the Deviance Information Criterion (DIC) was used. Each spatial model was run to convergence based on multiple chain diagnostics using the Brooks-Gelman-Rubin statistics[27]. In the converged sample DIC was monitored. Convergence usually took place within 1,000 iterations and inference was based on a chain length of 1,000 after convergence. Regression analyses and estimation

of the model parameters carried out with MCMC simulation techniques were implemented in R V.3.6.3 software packages[28].

5.4 Results

Data Maps

Choropleth maps are thematic maps in which areas are colored or patterned to indicate differences of quantity in those areas[17]. In this study they show the geospatial distribution of the aggregated counts of administered does of the HPV vaccine and Tdap vaccine, counts of HD private clinics, counts of HD public clinics, and access to public transportation for each county (Figures 1-5). The clustering patterns of administered doses of the HPV vaccine and the Tdap vaccine are both similar with increased counts in the Atlanta (ATL) region. There is not a defined clustering pattern with the quantity of administered vaccine doses in counties with access to public transportation. However, there is a pattern of increased counts of administered vaccine doses in counties with both public and private clinics.

HPV Outcome

The fixed effects negative binomial model was fit maintaining all of the explanatory variables. None of the indicators of HD access variables were statistically significant at p-values less than 0.05. The non-spatial random intercept negative binomial model, to account for correlations within county, was fit initially with all of the explanatory variables. The variable of HD clinics registered in the VFC program was highly correlated with private HD clinics ($r = -0.961$) and therefore dropped from the model. The remaining explanatory variables of private HD clinics, public HD clinics and the availability of public transportation were all statistically significantly associated with

counts of administered HPV doses (Table 2). These estimates can be interpreted as 1) a one unit increase in the number of private HD clinics increases the expected counts of administered doses of HPV vaccine by 1.08 times for adolescents in the same county and holding all other variables in the model constant; 2) a one unit increase in the number of public HD clinics increases the expected counts of administered doses of HPV vaccine by 1.17 times for adolescents in the same county and holding all other variables in the model constant; and 3) having access to public transportation increases the expected counts of administered doses of HPV vaccine by 1.63 times for adolescents in the same county compared to not having access and holding all other variables in the model constant.

Using Moran's I, the hypothesis that the administered doses of the HPV vaccine are randomly distributed across counties following a completely random process was rejected at the 0.05 level of significance. Thus, suggesting that the spatial distribution of administered HPV vaccine doses are more spatially clustered than would be expected if the underlying spatial distribution was random. Figure 6 shows a scatter plot of the average sum of total administered doses of HPV vaccine for each county and Moran's I coefficient (I=0.393) as the slope of the line. The positive (upward) slope suggests that as the sum of administered HPV vaccine doses of a county increases, so does the sum of its neighboring counties.

Using the statistically significant explanatory variables in the negative binomial random effect model, comparison of the different Bayesian models showed the Leroux model was the best model (DIC = 1783.6). From the Leroux model posterior estimates for the parameters and measures of interest were obtained, including medians and 95% credible intervals. Estimates for the best-fitting Leroux CAR model are shown in Table 3.

Since the Leroux model showed evidence of convergence via the Potential Scale Reduction Factor (PSRF) of 1.2 with Gelman and Rubin's Convergence Diagnostic, it can be inferred that the availability of public transit has a significant positive effect on administered doses of HPV vaccine and that there is no significant effect of private HD clinics, and Public HD clinics on increasing administered doses of HPV vaccine.

Tdap Outcome

With the fixed effects negative binomial model, it was initially fit maintaining all of the explanatory variables. In that analysis, only the number of private HD clinics was statistically significant with a p-value less than 0.05. However, to account for correlations within county, a non-spatial random effect negative binomial model was fit using all explanatory variables. The number of HD clinics registered in the VFC program was highly correlated with the number of private HD clinics ($r = -0.976$) and therefore dropped from the model. Of the remaining explanatory variables, the number of private HD clinics and access to public transit remained statistically significant (Table 2). These estimates can be interpreted as a one unit increase in the number of private HD clinics increases the expected counts of administered doses of Tdap vaccine by 1.09 times for adolescents in the same county and holding all other variables in the model constant. Similarly, having access to public transportation increases the expected counts of administered doses of Tdap vaccine by 1.38 times for adolescents in the same county and holding all other variables in the model constant. The best negative binomial regression model was the fixed effect model (AIC = 2630.12) (Table 2). However, a likelihood ratio test comparing the final fixed effects and the final random intercept model showed that

the random intercept model is statistically more beneficial with the access to public transit variable and the county effect included (p-value = 0.004).

Using Moran's I, the hypothesis that the administered doses of the Tdap vaccine are randomly distributed across counties following a completely random process was rejected at the 0.05 level of significance. Thus suggesting that the spatial distribution of administered Tdap vaccine doses are more spatially clustered than would be expected if the underlying spatial distribution was random. Figure 7 shows a scatter plot of the average sum of total administered doses of Tdap vaccine for each county and Moran's I coefficient (I =0.4107) as the slope of the line. The positive (upward) slope suggests that as the sum of administered Tdap vaccine doses of a county increases, so does the sum of its neighboring counties.

Using the statistically significant explanatory variables in the negative binomial random intercept model, comparison of the different Bayesian models showed the Leroux model to be the best model (DIC = 1710.35). From the Leroux model posterior estimates for the parameters and measures of interest were obtained, including medians and 95% credible intervals (Table 5). Since the Leroux model showed evidence of convergence via the Potential Scale Reduction Factor (PSRF) of 1.3 with Gelman and Rubin's Convergence Diagnostic, it can be inferred that there is significant positive effect of the number of private HD clinics on increasing administered doses of Tdap vaccine, and the accessibility of public transit has no significant effect on administered doses of Tdap vaccine.

5.5 Discussion

Interpretation

In this study the counties of GA were characterized based on the quantity of administered doses of the HPV vaccine, the Tdap vaccine and indicators of HD clinic access using choropleth maps. Mapping county level counts provides greater understanding of the trends and variability in patterns not possible by examination of direct national and state level estimates. This was shown with no clustering pattern of administered doses across counties with public transit services. These results are novel in showing HPV and Tdap vaccination variability at the county level. Also, at the county level there were clustering patterns of higher counts of administered vaccine doses in the ATL region. These results were expected and support a common vaccination trend often seen at the state level due to the large urban demographic. Additionally, mapping county level vaccine counts can help highlight areas where HPV and Tdap vaccination coverage may be higher or lower than the national average and provide additional insights on the access to health care. This was shown with the clustering pattern of increased counts of administered doses in counties with both public and private clinics. This pattern is expected since health care services can be provided through public and private providers serviced by the HD. Public health care is usually provided by the government through national healthcare systems. Private health care can be provided through for profit hospitals and self-employed practitioners, and "not for profit" non-government providers, including faith-based organizations.[29] However, our results also show that there was a clustering pattern of less administered doses of HPV and Tdap vaccines in counties where there were fewer private health clinics. These results suggest further examination

into the number of HPV and Tdap vaccines ordered from public and private health clinics serviced by the HD to clarify the reduced number of administered vaccine doses.

The patterns seen in our maps were supported by our statistical analyses. Both administered doses of the HPV vaccine and the Tdap vaccine were significantly associated with indicators of HD clinic access. However, to account for extra uncertainty and inherent spatial autocorrelation, Bayesian spatial models were used because administered doses of the HPV vaccine and the Tdap vaccine were found to exhibit strong spatial dependence. Using these models to account for the effect of spatial variability on HPV vaccine and Tdap vaccine dose administration between counties changed the significant effects of HD clinic access on HPV vaccine and Tdap vaccine dose administration to non-significant. This suggests that spatial statistical models are needed to accurately identify and estimate factors associated with administering doses of the HPV and Tdap vaccines in GA.

In relation to public health efforts, HPV vaccination coverage is lower than Tdap vaccination coverage at the national and state level. This study showed that the inclusion of the spatial random effect at the county level explains additional differences in HPV and Tdap vaccine dose administration. Specifically, these results indicate that spatial variability between counties and public transit access affect HPV vaccine dose administration. Whereas, spatial variability between counties and the number of HD private clinics affect Tdap vaccine dose administration. Therefore, public health practitioners should be attentive to the differences and similarities of resources and demographics between counties. These results are similar to previous studies that found that HPV vaccination rates vary geographically[30]. Other studies have also demonstrated

that HPV vaccination has a strong spatial dependence when identifying and estimating factors associated with HPV vaccine uptake[16] and that spatial accessibility to vaccination providers increases overall vaccination[31]. Our results differed from a previous study that found overall geographic access measures of travel distance and public transportation to clinics were not significantly associated with vaccine initiation[32]. However, this difference may be due to the limitation of the study sample to an urban area.

Limitations

There are limitations to acknowledge in this study. First, not all clinic sites are represented because not all providers administer vaccinations, but these data do represent all clinics who offer vaccination. Administered vaccine doses are only from clinic sites that report to the state's immunization registry. As such, there may be vaccination doses administered that are not accounted for and would result in an underestimation of HPV and Tdap vaccination delivery and coverage. Second, with administered dosing data is that it is not possible to differentiate whether a dose was given to initiate or complete an HPV vaccination series due to the fact that the immunization registry is not linked with vital records. However, there are also several strengths to this study. This study is one of the first studies to look at the aggregated counts of HPV vaccine and Tdap vaccine dose administration at the county level as a proxy measure of HPV vaccination coverage. These county level maps can used by practitioners and public health officials as baseline visuals for further investigation of where clinics are not administering doses of the HPV and Tdap vaccines. These results highlight where additional resources from HDs in GA may be needed to improve the administration of HPV vaccination. Additionally, these

results can be generalized to other states that have similar decentralized governance structures like GA because of how vaccination health resources are administered.

Conclusion

Overall, reaching 80% HPV vaccination coverage among U.S. adolescents is an attainable goal. However more information is needed beyond data at the national and state level. This study showed the importance of considering spatial variation at the county level when investigating HPV and Tdap vaccine dose administration. Mapping spatial patterns provides a visual context to data that is helpful for informing the development of public health interventions and guiding the provision of health services. Additionally, mapping data can be useful as an advocacy tool for documenting how poor public health infrastructure contributes to poor health outcomes to support improving healthcare administration and public health infrastructure.

The need for public health interventions focused on HPV vaccination was emphasized in early 2020 when the coronavirus disease 2019 (COVID-19) pandemic changed the way health care providers operate and provide routine and essential vaccination services. Like dose administration, vaccine orders are another proxy measure for vaccination coverage[33]. Examination of VFC provider ordering data showed that vaccine orders for HPV vaccine and Tdap vaccine decreased in mid-March when COVID-19 was declared a national emergency. Therefore, public health interventions to ensure that routine vaccination services for adolescents are maintained is essential to continue progress in protecting communities[7]. To do so, future work is need with small area studies. The collection of data at local levels such as ZIP code could help pinpoint areas with the greatest disparities in HPV vaccination and inform the development of

targeted interventions for these populations. Also, as seen with our results in the ATL region, large populated urban regions have high HPV and Tdap dose administration. So comparing the utilization of HPV vaccination services among urban groupings like metropolitan geographic areas, inner cities of large metropolitan areas, fringes of large cities also known as suburbs, and small metropolitan areas could help examine the sensitivity of spatial modeling strategies in estimating within county HPV vaccine dose administration and explore additional indicators of HD clinic access.

5.6 Figures

Figure 1. Spatial distribution of administered HPV vaccine doses
Georgia Counties 2016 - 2018

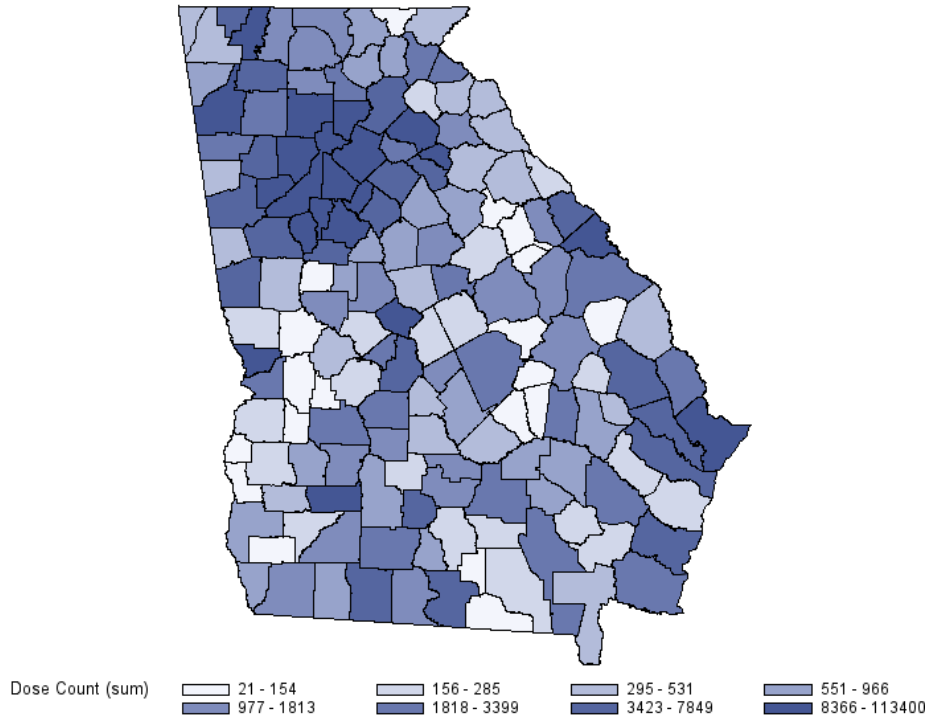


Figure 2. Spatial distribution of administered Tdap vaccine doses
Georgia Counties 2016 - 2018

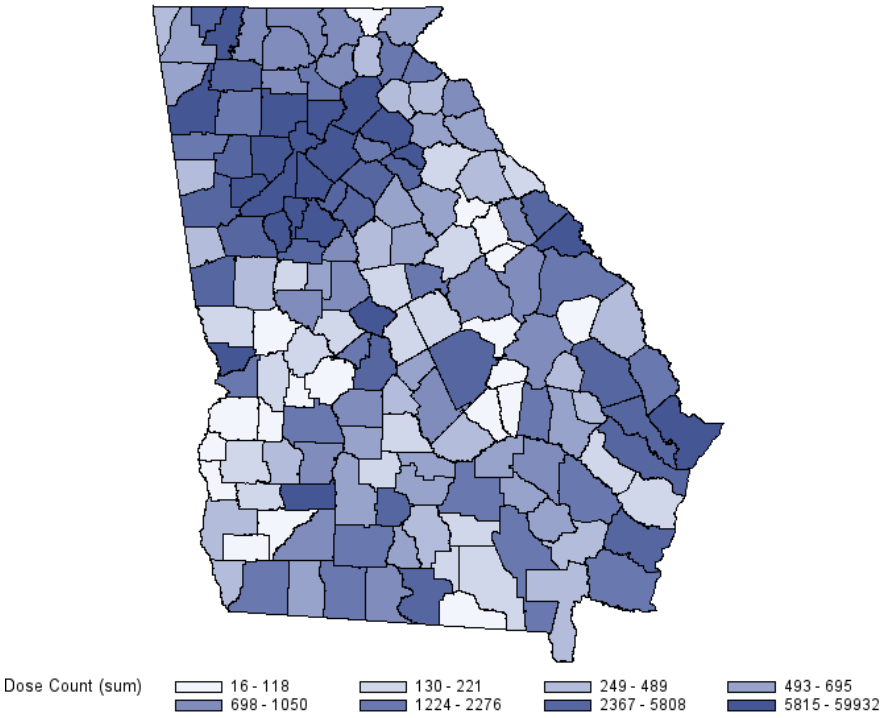


Figure 3. Spatial distribution of private Health Department clinics
Georgia Counties 2016 - 2018

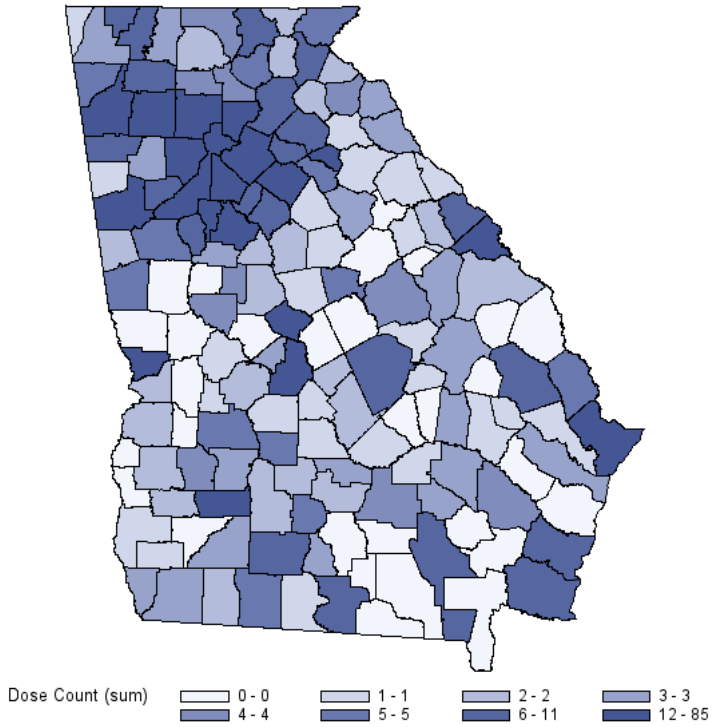


Figure 4. Spatial distribution of public Health Department clinics
Georgia Counties 2016 - 2018

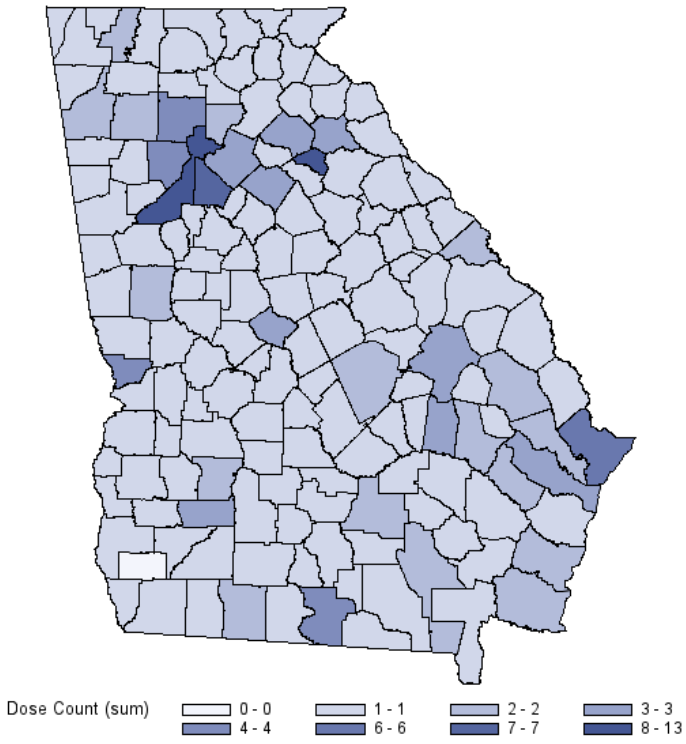


Figure 5. Spatial distribution of public transit access
Georgia Counties 2016 - 2018

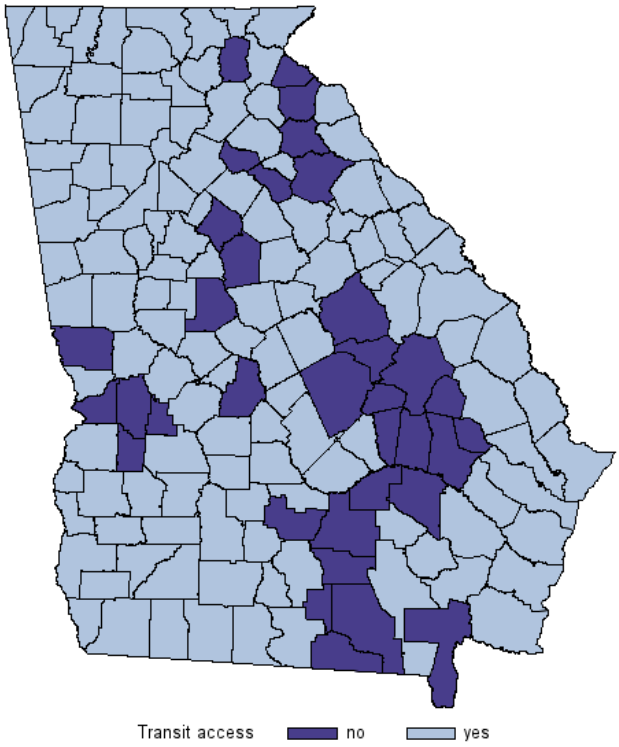


Figure 6. Relationship between administered HPV vaccine doses of neighboring counties

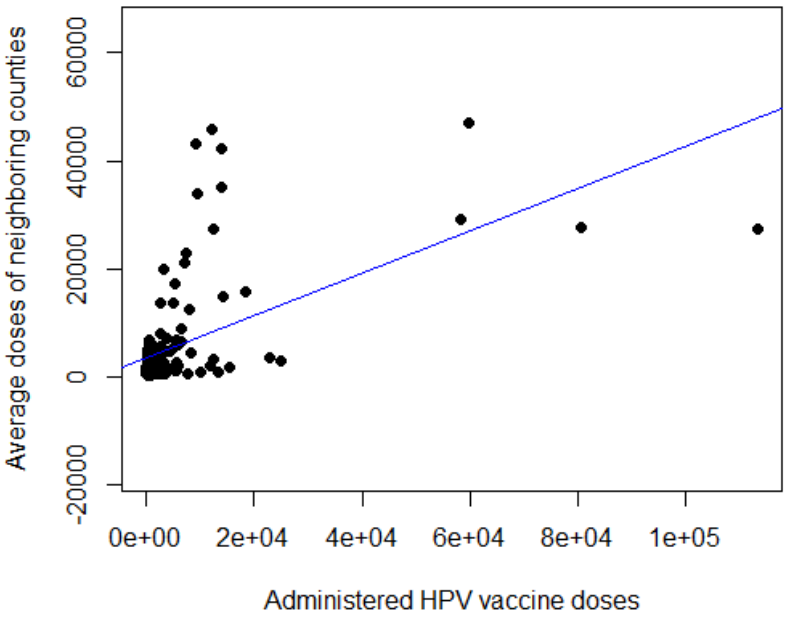
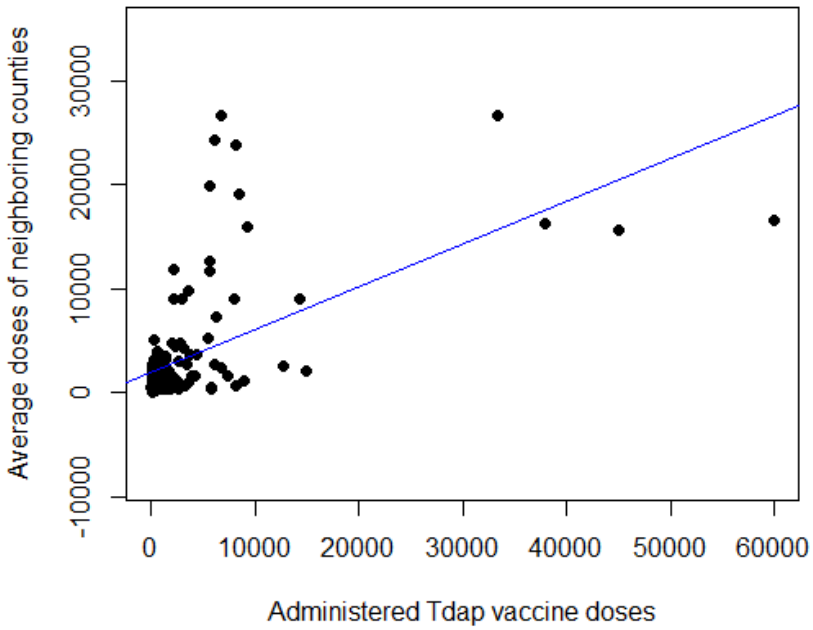


Figure 7. Relationship between administered Tdap vaccine doses of neighboring counties



5.7 Tables

Table 1. HPV & Tdap Vaccination Coverage Trends	
	Georgia
Counties (n)	159
HPV vaccination coverage trend: ≥1 dose, all adolescents aged 13-17 (United States overall)	
2016 (60.4%)	67.3%
2017 (65.5%)	64.3%
2018 (68.1%)	68.1%
2019 (71.5%)	65.9%
Tdap vaccination coverage trend: ≥1 dose, all adolescents aged 13-17 (United States overall)	
2016 (88.0%)	92.8%
2017 (88.7%)	93.3%
2018 (88.9%)	94.2%
2019 (90.2%)	92.5%
Data Sources: TeenVaxView | 2008-Present Adolescent HPV Vaccination Coverage Trend Report | CDC and Elam-Evans LD, Yankey D, Singleton JA, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020	

Table 2. Association of administered HPV vaccine doses and indicators of HD clinic access			
Random intercept model	**estimate**	**Exp(estimate)**	**P- value**
Intercept	5.915	370.77	< 2e-16
Private HD clinics	0.088	1.08	< 2e-16
Public HD clinics	0.153	1.17	3.51 e-08
Public transit access	0.486	1.63	< 2e-16

Table 3. Posterior results for the parameter estimates of the Leroux model:

administered doses of HPV vaccine ~ Private HD clinics + Public HD clinics + public transit

HPV vaccine parameters	median	2.5%	97.5%
Intercept	6.270	5.63	8.91
Private HD clinics	0.066	-0.11	0.15
Public HD clinics	-0.056	-1.00	0.20
Public transit access	0.423	0.12	0.80

Table 4. Association of administered Tdap vaccine doses and indicators of HD clinic access

Fixed effects model (AIC = 2630.12)	estimate	Exp(estimate)	P- value
Intercept	6.46	638.35	< 2e-16
Private HD clinics	0.14	1.15	< 2e-16
Random intercept model (AIC = 2645.3)	**estimate**	**Exp(estimate)**	**P- value**
Intercept	5.97	393.52	< 2e-16
Private HD clinics	0.08	1.09	< 2e-16
Public transit access	0.32	1.38	7.39e-09

Table 5. Posterior results for the parameter estimates of the Leroux model:

administered doses of Tdap vaccine ~ Private HD clinics + public transit

Tdap vaccine parameters	median	2.5%	97.5%
Intercept	6.036	5.34	6.50
Private HD clinics	0.087	0.033	0.16
Public transit access	00270	-0.27	0.71

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6.0 ORIGINAL MANUSCRIPT 2: A predictive model of HPV vaccination coverage among Tdap vaccinated adolescents in Georgia at the county level

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6.1 Abstract

Objective: To predict the association between HPV vaccination coverage and health department clinic access in GA at the county level among Tdap vaccinated adolescents.

Methods: Using a cross sectional study design, secondary data were analyzed from 2019 American Community Survey 5 year estimates, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the Georgia Department of Transportation for the years 2016 to 2018 for all 159 counties of Georgia. The study population was male and female adolescents aged 13-17 who received their Tdap and HPV vaccines in Georgia. Prediction models were developed using 2016-2017 data and predictions were validated using 2018 data. The number of administered HPV vaccine doses and the HPV vaccination coverage rates were modeled using indicators of heath department clinic access and age, sex, race/ethnicity, socioeconomic status, education, median household income, health insurance and resident type.

Results: The prediction model for counts of administered HPV vaccine doses showed statistical significance and a positive association with indicators of HD clinic access: public transit and the number of HD private clinics. The prediction model for HPV vaccination coverage rate accounted for Tdap vaccinated adolescents and was a better fit. The prediction model for HPV vaccination coverage rate showed statistical significance and a negative association with the variables of White race and rural residency.

Conclusion: Using data from adolescents who have received the Tdap vaccine as a sample population established access to vaccines and controls for multiple confounders such as vaccination ineligibility, vaccine exemption, and adolescents with parents opposed to vaccination. Therefore, within this population, rural counties and the White

racial category were identified as significant predictors of a decrease in HPV vaccine dose administration. Epidemiologists, program planners and health educators could use these data to target HPV vaccination efforts among non-Hispanic whites and in rural communities. Future work is needed with the use of geographically weighted regression models to improve predictions of HPV vaccination by accounting for spatial dependence in addition to overdispersion because this could incorporate the variability for other unmeasured factors.

Keywords: HPV vaccine, Tdap vaccine, prediction models, small area estimation

6.2 Introduction

The equity of access to health care services such as health screening services, public health nursing, the number of clinics, health education, immunization services and school health services at the county level significantly impacts Human Papillomavirus (HPV) vaccination coverage rates. A key indicator of overall community health is immunization coverage rates and vaccination coverage is the traditional metric used to assess vaccine usage; however, provider orders and doses administered represent two immediately available proxy measures[1]. State immunization resources and immunization service delivery through the Health Department (HD) are organized at the county level or local level[2]. Three indicators of access related to local Health Department clinics of particular interest are the number of public and private health clinics, Vaccine For Children (VFC) provider registration and the availability of public transportation. Public transportation is health equity metric related to community determinants of health. Some urban and rural communities are disproportionately affected by the access to a vehicle which then impacts their access to health care services[3].

Another metric of access is the affordability of services. Under the Vaccine for Children (VFC) program, the Center for Disease Control (CDC) purchases vaccines at a discount and distributes them to grantees, such as state HDs and certain local and territorial public health agencies. These grantees distribute the vaccines at no charge to private physicians' offices and public health clinics that are registered as VFC providers. Because the federal government pays for the vaccine, providers are not paid for the cost of the vaccine product. Instead, they are paid an administration fee for the costs that the provider incurs in administering the vaccine. For children enrolled in Medicaid, the

Medicaid program pays the vaccine administration fee. For uninsured and underinsured children enrolled in VFC, the parents may be billed for the administration fee and the administration fee varies by state[4]. While this fee is rarely pursued in the event of non-payment, this practice could introduce a perceived barrier to vaccine access.

Georgia's (GA) state HD immunization registry has a surveillance system that is able to monitor at the county level how many of their clinics are public, private, registered with the Vaccine For Children (VFC) program and the administered doses of the HPV vaccine per clinic. Additionally, GA's vaccination coverage trend of adolescents receiving at least one dose of the HPV vaccine has stayed close to the national average since 2016[5]. However, persistent differences in HPV vaccination uptake have been observed among adolescents who receive the Tetanus, diphtheria, pertussis (Tdap) vaccine[5,6]. Even though the Tdap vaccine is school mandated, states with HPV vaccine mandates have similar rates of HPV vaccination as those without mandates, thus indicating that the underlining difference for vaccination uptake are not fully understood [7,8].

With equity of access to health services, there should be no differences in vaccination coverage by race, ethnic origin, income, geographical location or insurance status[9], yet HPV vaccine coverage rates vary by geographic location and other factors despite similar programing and activities provided by HDs[10]. Prior studies have identified factors at the local level associated with HPV vaccination coverage as the uptake of other adolescent vaccines, gender, race/ethnicity, socioeconomic status, religiosity, political ideology, education policies and insurance status[7,11,12]. However, the systematic underuse

of immunization services by populations that share characteristics, such as education or attitudes, indicates a problem with equity of access[9].

Since data have shown Tdap vaccination rates to surpass HPV vaccination rates, these adolescents are a prime target group for increasing HPV vaccinations. Therefore, the objective of this study was to predict the association between HPV vaccination dose coverage and HD clinic access in GA at the county level among Tdap vaccinated adolescents. The rational for this study was that using adolescents who have received the Tdap vaccine as a sample population establishes access to vaccines and controls for multiple confounders such as vaccination ineligibility, vaccine exemption, adolescents with parents opposed to vaccination and no access to vaccination services. Also, prior studies that have examined factors associated with low HPV vaccination did not include HD level variables. Therefore, this study contributes to the literature by incorporating new variables of HD clinic access as potential explanatory factors that significantly impact HPV vaccination dose administration at the county level. The hypothesis is that significant factors associated with HPV vaccine dose administration will be predicted among Tdap vaccinated adolescents at the county level in GA.

6.3 Methods

Data

Using a cross sectional study design, secondary data were analyzed from the 2019 American Community Survey 5 year estimates, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the Georgia Department of Transportation for the years 2016 to 2018 for all 159 counties of Georgia. Data from years 2016 – 2017 were used to develop the predictive models and

data from year 2018 were used to validate the predictive models. The study population was male and female adolescents aged 13-17 who received their Tdap and HPV vaccines in Georgia. The number of administered Tdap vaccine doses was used as a proxy measure for population who received the Tdap vaccine because adolescent Tdap is a single dose vaccine with a booster every ten years recommended for those who get it in the 13-18 age group. Predictor variables included indicators of access to HD clinics defined as the counts of public and private clinic sites, counts of clinic sites with Vaccine For Children (VFC) provider registration, and the availability of public transit routes. These variables were collected by zip code and aggregated to the county level using Zip Code Tabulation Areas (ZCTAs) for years 2016 - 2017 and then for 2018. Table 1 shows additional predictor variables selected as factors associated with HPV vaccination based on previous literature review were age (percent under 18 years) , sex (percent of total population), race/ethnicity (percent of population), socioeconomic status (percent below poverty level under 18), education (high school graduate or higher percentage), median household income, health insurance (percent uninsured and insured under age of 19 years) and resident type (urban and rural percentage). The education variable includes high school graduate equivalency, some college – no degree, associate's degree, bachelor's degree and graduate or professional degree.

Statistical Modeling & Analyses

Two predictive models were developed: one with a count outcome of the number of administered HPV vaccine doses and the other, a rate outcome of HPV vaccination dose coverage. The HPV vaccination dose coverage rate was calculated as the number of HPV vaccination doses administered among the number of adolescents who have

received the Tdap vaccine. The number of adolescents who received the Tdap vaccine in years 2016 and 2017 was modeled as an offset variable, (i.e. constant term) on the log scale to convert the number of administered HPV and Tdap vaccine doses to population-adjusted rates. The relationship between exposure variables and both outcomes were assessed using univariate analysis. While exploring the data with Poisson regression, overdispersion was detected so negative binomial regression was used to model[13] both outcomes. Distributional assumptions were tested and asserted. Final prediction models were selected based on the statistical significance of informative predictors using alpha 0.05 and the Akaike Information Criterion (AIC) statistic.

The beta coefficients of the final developed models were then applied to the external data from 2018. To evaluate prediction model performance the Root Mean Square Error (RMSE) and coverage probabilities with 95% prediction intervals for model calibration (i.e. agreement between observed outcomes and predictions)[14,15] were calculated. The comparative size of RMSE indicates model fit of how close the observed data points are to the model's predicted values. Hence a smaller RMSE value indicates that the prediction model is better at predicting the observed data. Coverage probabilities with a 95% prediction interval for administered doses of the HPV vaccine should include the true value of administered dose of the HPV vaccine approximately 95% of the time. Univariate and bivariate analyses were done in SAS statistical software version 9.4 [16]. Regression analyses and predictions were implemented in R V.3.6.3 software packages[17].

6.4 Results

Dose Count Outcome Prediction Model

The prediction model for the number of HPV vaccine administered doses was initially fit maintaining all of the predictor variables. Several of the predictor variables were statistically significantly associated with the number of HPV vaccine administered doses: rural residency, education, poverty, age, Asian, Hispanic, public transit and HD private clinics (Table 2). These estimates are interpreted individually holding all the other variables constant: 1) a one percent increase in rural residency decreases the number of HPV vaccine administered doses by 0.03%. 2) A change from no to yes in access to public transit increases the number of HPV vaccine administered doses by 1.32%. 3) An increase of one HD Private clinic increases administered doses of the HPV vaccine by 1.04%. The remaining estimates can be interpreted similarly. After applying the final developed count model to 2018 data, the coverage probability of model calibration was 86.8% and can be interpreted as the probability that the prediction interval contains the true values of HPV vaccine administered doses approximately 87% of the time.

Dose Coverage Rate Outcome Prediction Model

The HPV vaccination dose coverage rate prediction model was initially fit maintaining all of the predictor variables. Two of the predictor variables were statistically significantly associated with the number of administered doses of HPV vaccine among adolescents who received the Tdap vaccine: rural resident type and the White racial category (Table 3). These estimates are interpreted individually holding all the other variables constant: 1) a one percent increase in rural residency decreases the HPV vaccine dose coverage rate by 0.72%. 2) A one percent increase in White racial category

decreases the HPV vaccine dose coverage rate by 0.51%. After applying the final developed rate model to 2018 data, the coverage probability of model calibration was 98.1% and can be interpreted as the probability that the prediction interval contains the true values of HPV vaccine dose coverage rates approximately 98% of the time.

6.5 Discussion

Interpretation

In this study two prediction models were developed from 2016 and 2017 data, one using counts of administered HPV vaccine and the other using an HPV vaccination dose coverage rate. Both were validated using counts of administered HPV vaccine doses from year 2018. Both models used demographic data and indicators of HD clinic access as predictors at the county level. Both models at the county level predicted statistically significant factors of HPV vaccine dose administration. However, only the prediction model for counts of administer HPV vaccine doses showed statistical significance with indicators of HD clinic access: public transit and the number of HD private clinics. The prediction model for HPV vaccination dose coverage rates included Tdap vaccinated adolescents and was a better fit for the data because of lower AIC and RMSE values. Therefore, among adolescents who have received the Tdap vaccine, the dose coverage rate prediction model identified two prognostic factors of rural residency and the racial category of White as statistically significantly associated in a negative direction with administered doses of the HPV vaccine at the county level. Further examination of these demographic variables may explain the additional differences between HPV and Tdap vaccine uptake because in the prediction model for counts of administered HPV doses, the negative effect of rural residency was less (0.03% compared

to a 0.72% effect in the dose coverage rate prediction model) and the White racial category did not show statistical significance.

In relation to public health efforts, the National Immunization Survey-Teen (NIS-Teen) only provides state and national level rates with some large regional variation that can be examined. This study used prediction modeling and public health data sources, to estimate county level HPV vaccination rates. This novel approach enables people working at the community level to use these data to inform HPV vaccination promotion outreach efforts because this study showed that adolescents receiving the Tdap vaccine, the White racial category and rural residency affect the administration of HPV vaccine doses. These results are similar to previous studies that found decreased HPV vaccine initiation in rural communities[18,19] and among non-Hispanic white adolesents[20] and that the coadministration of the Tdap vaccine is helpful for HPV vaccine uptake[21]. These results were different from previous studies that found significant associations of county level estimates with Hispanic ethnicity, county poverty, household and percentage of uninsured[22,23]. However, these differences may be due to the limitation of the study population to girls.

Limitations

There are several limitations to acknowledge in this study. Counts of administered vaccine doses are only from clinic sites that report to the state's immunization registry. As such, there may be administered vaccination doses that are not accounted for and result in the underestimation of administered HPV and Tdap vaccine doses. Second, adolescents should have just received one dose of the Tdap vaccine within the study period, but it is possible that duplication vaccination may have occurred for a small

number of patients. Third, these prediction estimates are not geographically weighted to account for spatial variability. This absence may be evidenced by the rate prediction model's coverage probability of 98%, which is a little high and may indicate some inaccuracy of those predictions due to the confidence interval being wider than necessary[14] but this coverage probability also highlights valid and precise predictions. There are several strengths to this study. This study is one of the first to predict HPV vaccine dose coverage rates among adolescents who received the Tdap vaccine at the county level. These results found multiple statistically significant variables associated with HPV vaccine dose administration but emphasize rural residency and the White racial category as the variables to account for with HPV vaccination efforts. Additionally, this methodology can be used in different states that have vaccination registries with disaggregated population-level data to estimate small area HPV vaccination rates or these models can be generalized to other states with similar population demographics.

Conclusion

Overall, this study showed the effect of accounting for adolescents who have received the Tdap vaccine when investigating HPV vaccine dose administration. The rate prediction model used in this study has important implications for HDs since state immunizations resources and immunization service delivery are organized as the county or local level. Using adolescents who have received the Tdap vaccine as a sample population established access to vaccines and controlled for multiple confounders such as vaccination ineligibility, vaccine exemption, adolescents with parents opposed to vaccination and no access to vaccination services. Therefore, within this population, increases in rural communities and the White racial population percentages were

identified as significant predictors of a decrease in HPV vaccine dose administration. Epidemiologists within HDs, program planners and health educators could use these data to focus HPV vaccination intervention efforts among non-Hispanic whites and in rural communities. To further improve HPV vaccination interventions, future work is needed with the use of geographically weighted regression models to improve predictions of HPV vaccination dose administration by accounting for spatial dependence in addition to overdispersion because this could incorporate the variability for other unmeasured factors. Additional small area studies on additional vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) such as Meningococcal conjugate, Measles, mumps and Rubella (MMR) and hepatitis B (HepB) would help to evaluate the application of predictive and other modeling strategies estimating county level vaccine coverage for delivering HD immunization resources.

6.6 Tables

Table 1. Overall Population Demographic Characteristics	
	Georgia
Counties	159
HPV vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)*	
2016 (60.4 %)	67.3%
2017 (65.5 %)	64.3%
2018 (68.1 %)	68.1%
Tdap vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)	
2016 (88.0 %)	92.8%
2017 (88.7 %)	93.3%
2018 (88.9 %)	94.2%
Race Ethnicity§	
Black/African American	31.6%
White	58.6%
Asian	4.0%
Hispanic	9.5%
American Indian/Alaskan Native	0.4%
Native Hawaiian/Other Pacific Islander	0.1%
Below 18 years of age§	24.1%
Education attainment §	
Highschool graduate or higher	87.5%
Median Household Income§	$58,700
Under 19 uninsured §	7.2%
Under 19 insured §	92.8%
Under 18 below poverty level§	21.5%
Living in rural area¶	24.9%
Living in urban area¶	75.0%

Data Sources:
* (Walker et al., 2019)
§ (U.S. Census Bureau, 2015-2019 American Community Survey 5-Year Estimates)
¶ (U.S. Census Bureau, 2010 Census.)

Table 2. Results of count prediction model for administered doses of HPV vaccine

Variables	estimate	Exp(estimate)	P- value
Intercept	5.61	273.66	1.35 e-06
rural	-3.44	0.03	< 2 e -16
education	2.80	16.52	0.01
poverty	-2.25	0.10	6.70 e-06
age	3.91	50.04	0.02
Asian	-12.30	0.00	0.0006
Hispanic	3.20	24.49	0.001
Public transit (yes)	0.28	1.32	0.02
HD private clinics	0.04	1.04	2.60 e-11

HPV = human papillomavirus; HD = health department

Table 3. Results of coverage rate prediction model for administered doses of HPV vaccine among adolescents who received the Tdap vaccine

Variables	estimate	Exp(estimate)	P- value
Intercept	0.65	1.92	1.83 e-08
rural	-0.33	0.72	0.001
White	-0.68	0.51	5.33 e-05

HPV = human papillomavirus; Tdap = Tetanus, diphtheria and pertussis; HD = health department

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7.0 ORIGINAL MANUSCRIPT 3: Application of predictive HPV vaccine coverage models to South Carolina: county level strategies to improve HPV vaccine delivery

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7.1 Abstract

Objective: To use GA as a predictor model to provide greater insight of where to more efficiently allocate HPV vaccination resources at the county level within SC and inform the implementation and dissemination of HPV vaccination interventions that focus on the use and quality of state immunization resources.

Methods: Using a cross sectional study design, secondary data were collected from 2015 – 2019 estimates of the American Community Survey, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the Statewide Immunization Online Network of South Carolina Department of Health and Environmental Control (SC DHEC) for the years 2016 to 2018 for all counties of GA and SC. The study population was all male and female adolescents aged 12-18 in SC based on the age groups reported by DHEC's SIMON and available census data. The number of adolescents who received one dose of the Tdap vaccine was used as an offset variable to calculate HPV vaccination coverage rates. Using the beta estimates of white and rural from the final GA prediction model, three predictive models for SC were developed using negative binomial regression to compare three different time spans for the best model fit.

Results: The best fitting prediction model for SC was for the 2018 one-year time span even though the prediction model based on GA was developed using 2016-2017 data. This suggests that the HPV vaccination coverage prediction model is more helpful when looking at a single subsequent year. Negative residual estimates indicated over prediction and the counties of Charleston, Greenville and Richland had the largest differences between their observed and predicted HPV vaccination coverage rates.

Conclusion: These results suggests the need for implementation and dissemination of HPV vaccination interventions that focus on the use and quality of state immunization resources in Charleston, Greenville and Richland counties. The observed HPV administered dose coverage in these counties is not largely indicative of white and rural county residents and adolescents who have received the Tdap vaccine; otherwise the predicted administered dose coverage rates would be closer to the observed. These results highlight the need for prediction modeling studies at a local level to help with public health decision making, low HPV vaccination coverage and limited or no immunization registry data for small geographic areas.

Keywords: Prediction modeling, HPV vaccine, South Carolina, Georgia, immunization registry, public health

7.2 Introduction

National and regional efforts are being made to increase Human Papillomavirus (HPV) vaccination to 80% [1]. The between state variation of HPV vaccination may be due to limited HPV vaccination surveillance[2]. Since HPV infections and most HPV-associated conditions are not a nationally notifiable[2] health-care claims data from adolescents and adults with employer-provided private health insurance in the United States are used to examine the population effectiveness of HPV vaccinations on HPV infections[3]. Furthermore, within state variability of HPV vaccination is not commonly studied. This may be due to the lack of state immunization registry data available at the zip code and county level[4,5]. These limited data on HPV prevalence in small geographic areas contribute to a limited capacity to characterize vaccination at smaller geographic levels such as county and zip code[6]. With immunization resources often delivered and utilized at the county level[7], to assess HPV vaccine usage, a proxy measure for vaccination coverage is dose administration[8].

The states of Georgia (GA) and South Carolina (SC) are both in public health region IV and therefore share the same regional office for programs and policies through the U.S. Department of Health and Human Services (HHS) (Figure 2). Despite the difference in the number of counties, GA and SC share similar population demographic characteristics[9–11] (Table 1). During the years of 2016 to 2018, the estimated HPV vaccination coverage trends of GA's Tdap and HPV vaccination rates were consistently near or greater than the national average. Conversely, SC was consistently below the national average with the lowest HPV vaccination coverage estimate in the United States in 2016 according to the National Immunization Survey – Teen data[12]. Systematic

underuse of services that impact health by populations that share similar demographic characteristics may indicate a problem with equity of access[13]. Hence, access may be a significant driver of the different HPV vaccination rates between GA and SC. GA has comprehensive adolescent HPV vaccination data available through the Georgia Immunization Registry (GRITS) of the Georgia Department of Public Health at the zip code level that can be aggregated to the county level using Zip Code Tabulation Areas. SC does not have zip code level, but rather counts of administered HPV vaccine doses at the county level available through their Statewide Immunization Online Network. In order to explore these differences at the county level in SC, the availability of zip code level HPV vaccination data in GA, coupled with its similar population demographics to SC, supports GA as a suitable model state for developing a working plan to increase SC's county level HPV vaccination coverage rates.

Therefore, the objective of this research was to use GA as a predictor model to provide greater insight of where to more efficiently allocate HPV vaccination resources at the county level within SC and inform the implementation and dissemination of HPV vaccination interventions that focus on the use and quality of state immunization resources. The hypothesis is that differences in SC's vaccination coverage between observed and predicted rates will be identified.

7.3 Methods

Data

Using a cross sectional study design, secondary data were collected from 2015 – 2019 estimates of the American Community Survey, the Georgia Department of Public Health, Georgia Registry of Immunization Transactions and Services (GRITS), and the

Statewide Immunization Online Network of South Carolina Department of Health and Environmental Control (SC DHEC) for the years 2016 to 2018 for all counties of GA and SC. The study population was all male and female adolescents aged 12-18 in SC based on the age groups reported by DHEC's SIMON and available census data. For the predicted HPV vaccination coverage rate, adolescents who have received one dose of the Tdap vaccine were the sample population to establish access to vaccines and control for multiple confounders such as vaccination ineligibility, vaccine exemption, adolescents with parents opposed to vaccination and no access to vaccination services. To calculate the observed HPV vaccination coverage rate, the counts of administered HPV vaccine doses were reported by SC DHEC for ages 13-18 and the total number of adolescents in South Carolina were from ages 12-17 because it was the closest prespecified age group available in the US Census data for years 2016, 2017 and 2018.

Statistical Modeling & Analyses

The GA prediction model applied to SC data was developed using 1) adolescents aged 13-17. 2) Variables related to indicators of health care access via health care utilization[13]: the number of public health department clinics, the number of health department private clinics and the number of HD clinics with VFC provider registration. 3) A variable related to health equity[14]: public transit transportation. 4) Predictor variables from factors associated with HPV vaccination based on a literature review[6,15,16]: age (percent under 18 years) , sex (percent of total population), race/ethnicity (percent of population), socioeconomic status (percent below poverty level under 18), education (high school graduate or higher percentage), median household income, health insurance (percent uninsured and insured under age of 19 years) and resident type (urban and rural

percentage). All variables were aggregated to county level using Zip Code Tabulation Areas (ZCTAs). The final GA prediction model with the best performance only included the predictor variables of white and rural.

Using the beta estimates from the final GA prediction model, three predictive models for SC were developed using negative binomial regression. All the models also included the number of adolescents who received the Tdap vaccine as an offset (i.e., constant term) on the log scale to convert the HPV vaccine administered dose counts to HPV vaccination coverage rates. Model 1 predicted HPV vaccination coverage for years 2016 and 2017 combined to estimate the same year time span of the data used to develop the GA prediction model. Model 2 predicted HPV vaccination coverage for year 2018 to estimate the year following the time span of the data used to develop the GA prediction model, and model 3 predicted HPV vaccination coverage for years 2016, 2017 and 2018 combined to estimate the years included and after the time span of the data used to develop the GA prediction model. To evaluate prediction model performance, residuals were assessed and the Root Mean Square Error (RMSE) was calculated. The residual is the difference between observed and predicted administered HPV vaccine rates. The closer the residuals are to zero, the better the model fits the data. Residual outliers were calculated using the Interquartile Range (IQR). The comparative size of RMSE indicates model fit of how close the observed data points are to the model's predicted values. Hence a smaller RMSE value indicates the better prediction model. Regression analyses and model predictions were implemented in R V.3.6.3 software packages[17]. Choropleth maps[18] of observed and predicted administered HPV vaccine rates were created with SAS statistical software version 9.4 [19].

7.4 Results

Data Maps

Choropleth maps show the observed administered HPV vaccine coverage compared to the predicted administered HPV vaccine coverage among Tdap vaccinated adolescents. For all three time periods, the clustering patterns of observed and predicted rates of HPV vaccine coverage across counties are somewhat similar. However, there is a clear pattern of increased predicted rates is some counties (Figure 1).

HPV vaccine dose coverage 2016-2017

The negative residual estimates of the prediction model for HPV vaccination dose coverage 2016 – 2017 can be interpreted as the average coverage rate of administered HPV vaccine was over predicted by 721 doses based on the mean, 25% of coverage rates were over predicted by 896 doses based on the first quartile and 75% of coverage rates were over predicted by 191 doses based on the third quartile (Table 2). Figure 2 shows the values of the residuals for each county for 2016 - 2017. Negative residual values indicate over prediction. The lighter shades indicate a range of larger differences between observed and predicted HPV vaccination coverage and the darker shades indicate a smaller range of differences. Of the lighter shaded counties (i.e. counties with larger differences), Figure 3 shows that the residuals of three counties were calculated to be outliers (i.e. abnormally different): 10 – Charleston, 23- Greenville and 40 – Richland. Therefore, these counties need further examination to understand why the predicted HPV vaccination coverage was much higher than the observed compared to the other counties for 2016-2017. The RMSE for this model was 2384.3.

HPV vaccine dose coverage 2018

The negative residual estimates of the prediction model for HPV vaccination dose coverage 2018 can be interpreted as the average coverage rate of administered HPV vaccine was over predicted by 339 doses based on the mean, 25% of coverage rates were over predicted by 447 doses based on the first quartile and 75% of coverage rates were over predicted by 77 doses based on the third quartile (Table 2). Figure 2 shows the values of the residuals for each county for 2018. Of the lighter shaded counties (i.e. counties with larger differences), Figure 3 shows that the residuals of three counties were calculated to be outliers: 10 – Charleston, 23- Greenville and 40 – Richland. Therefore, these counties need further examination to understand why the predicted HPV vaccination coverage was much higher than the observed compared to the other counties for 2018. The RMSE for this model was 553.8.

HPV vaccine dose coverage 2016-2018

The negative residual estimates of the prediction model for HPV vaccination dose coverage 2016 - 2018 can be interpreted as the average coverage rate of administered HPV vaccine was over predicted by 1,060 doses based on the mean, 25% of coverage rates were over predicted by 1,362 doses based on the first quartile and 75% of coverage rates were over predicted by 282 doses based on the third quartile (Table 2). Figure 2 shows the values of the residuals for each county from 2016 - 2018. Of the lighter shaded counties, Figure 3 shows that the residuals of three counties were calculated to be outliers: 10 – Charleston, 23- Greenville and 40 – Richland. As outliers, these counties need further examination to understand why the predicted HPV vaccination coverage was

much higher than the observed compared to the other counties for 2016 - 2018. The RMSE for this model was 1735.3.

7.5 Discussion

Interpretation

In this study vaccination coverage rates of administered HPV vaccine doses among Tdap vaccinated adolescents in South Carolina were predicted using a model developed from GA. GA's availability of zip code level HPV vaccination data coupled with its similar population demographics to SC, supports GA as a novel and suitable model state for developing a working plan to increase SC's county level HPV vaccination coverage rates. These prediction models are also unique because the Tdap vaccine is a one-shot series and the HPV vaccine is a two-shot series before the age of 15 and a three-shot series after the age of 15. These predictions highlight what HPV vaccination coverage rates could be if each adolescent that received a Tdap vaccine received at least one dose of the HPV vaccine. Therefore, these predictions are best compared to HPV vaccination initiation instead of series completion.

Three prediction models were designed to evaluate which time span best fit the data. The negative residuals values of the counties indicate over prediction. The differences of HPV vaccine coverage rates were illustrated with multiple choropleth maps and supported with quantitative analyses. Under the prediction model assumptions, results clearly show that the predicted HPV vaccine coverage rates among Tdap vaccinated adolescents were higher than observed rates among all SC adolescents. This over prediction is interesting because the prediction model accounts for the variables of white race and rural residency. Therefore, these results suggest that among South

Carolinians within the white racial category and rural counties, if the adolescents who received the Tdap vaccine also received the HPV vaccine, the number of HPV vaccine administered doses would be greater. Accordingly, this frame of reference is useful to public health professionals and clinicians because it supports the co-administration of the HPV vaccine with the Tdap vaccine.

The best fitting prediction model for SC was for year 2018. This is interesting because the prediction model based on GA was developed using 2016-2017 data. This suggests that the HPV vaccination coverage prediction model is more helpful when looking at a subsequent year. Within this model all of the counties fell below the national average of 68.1% for 2018[20]. However, the counties of Charleston, Greenville and Richland had the largest differences between their observed and predicted HPV vaccination coverage rates. These residual differences suggests the need for further investigation because 1) the prediction model was based on county level rural residency and the white racial category but all three of these counties are designated as urban by the U.S. Census Bureau, the U.S. Department of Agriculture, Economic Research Service and the U.S. Office of Management and Budget[21]. Therefore, these residuals suggest that the observed HPV administered dose coverage rates in these counties are not largely indicative of white and rural county residents, because the predicted administered dose coverage rates would be closer to the observed. 2) Predictions were made using a subset of the population, adolescents who received the Tdap vaccine. Therefore, these residuals also suggest that the observed HPV administered dose coverage rates in these counties are not largely indicative of white and rural county residents and adolescents who have received the Tdap vaccine. These results highlight that prediction modeling studies are

needed at a local level because many of the HPV vaccine modeling studies designed to help with public health decision making are at the national and state level.

This study showed that predicting and visualizing HPV vaccination coverage rates at the county level is helpful for identifying within state variability and indicating counties that need further examination. There are no studies to our knowledge that use prediction modeling for HPV vaccination coverage rates or vaccine dose administration at the county level[6,22]. Many other studies use predictive modeling to assess HPV knowledge and behavior [15,23–26]. However, the results of this study are similar to previous studies that found that visualizing vaccination data at the county level can help multiple stakeholders, such as local and state health departments, pharmacists, insurers, and nonprofit organizations determine where to focus financial and physical resources to improve HPV vaccination and identify gaps in vaccine delivery [27–29].

Limitations

There are several limitations to acknowledge in this study. First, currently it is not possible to differentiate if an administered dose was given to initiate or complete an HPV vaccination series due to immunization registry data not being linked with vital records. With the data not being able to distinguish between the doses, it better to use HPV initiation a comparator for the predicted HPV vaccine administered dose coverage rates in this study since adolescents who received one dose of the Tdap vaccine were used to create the predictions. Second, the assumption that previously collected data can predict the future is not always accurate. Using associations from historical data to predict the future also assumes there are certain lasting conditions, such as number of doses needed to complete the vaccine series and age range of use. These inaccurate assumptions of lasting conditions can lead to inaccurate estimates[30]. Another potential complication with

predictive modeling is the possibility of new variables that have not been considered or even defined are critical to the outcome such as the number of school based health centers/clinics within a county, which could serve as an additional source of HPV vaccine delivery especially in rural counties. Until these and other measures become available, the use of proxy measures will need to be taken with caution. However, there are also several strengths to this study. This study is one of the first studies to apply predictive modeling to HPV vaccination dose administration at the county level. Furthermore, this study innovatively used a vaccinated population for modeling estimates, which supports the importance of co-administering the HPV vaccine with other scheduled adolescent vaccines to improve HPV vaccination rates. Another strength is that this methodology is applicable to other states with similar population demographics, low HPV vaccination coverage and limited or no immunization registry data for small geographic areas.

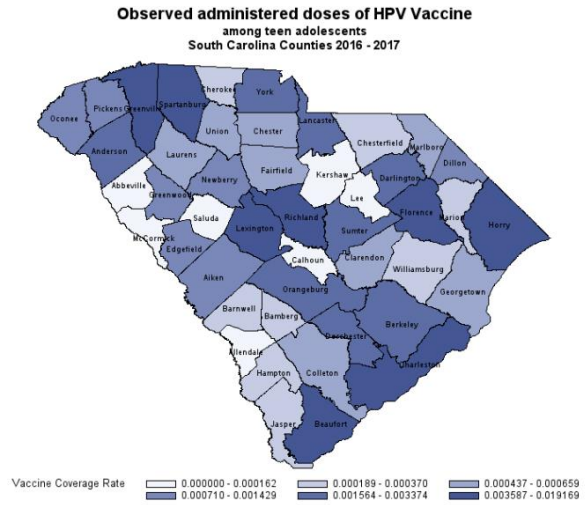
Conclusion

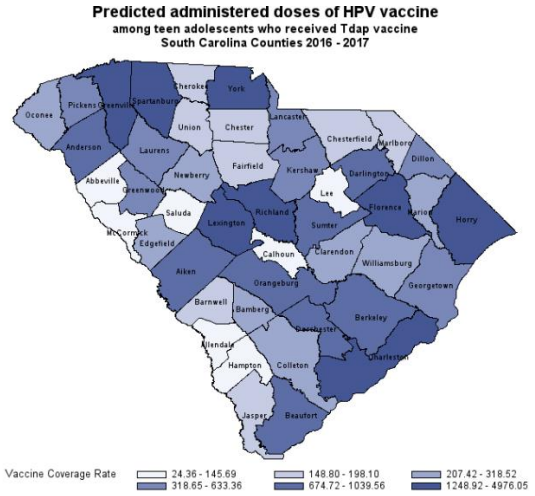
Overall, this study showed that immunization registries can be informative data sources for public health practitioners to identify priorities for HPV vaccinations interventions in targeted locations. Based on these results, a working plan to address the current limitations of SC's HPV vaccination coverage at the county level is to disaggregate statewide immunization resources and identify barriers to HPV vaccine access and delivery in Charleston county in the Lowcounty, Greenville county in the Upstate and Richland county in the Midlands region. Public health practitioners should first examine the similarities of county level characteristics such as race/ethnicity percentages, areas of rural residency and provider shortage areas because prior research has shown them to be associated with variation in HPV vaccination[6]. Once these county level area characteristics are identified, then practitioners can focus on regional

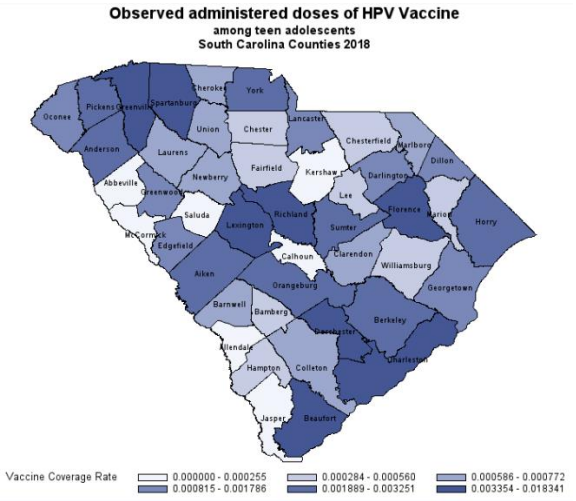
differences to develop systems level interventions that include HPV vaccine delivery and access to HPV vaccination services. To better inform HPV vaccine delivery, future work is needed with the use of health indices such as the social vulnerability index to help public health officials and practitioners plan, prepare and respond to public health needs. Additional predictive studies using other adolescent vaccines such as the meningococcal conjugate vaccine (MCV4) or other proxy measures for vaccination usage such as provider orders, would help to evaluate the application of predictive modeling strategies for better immunization resource allocation.

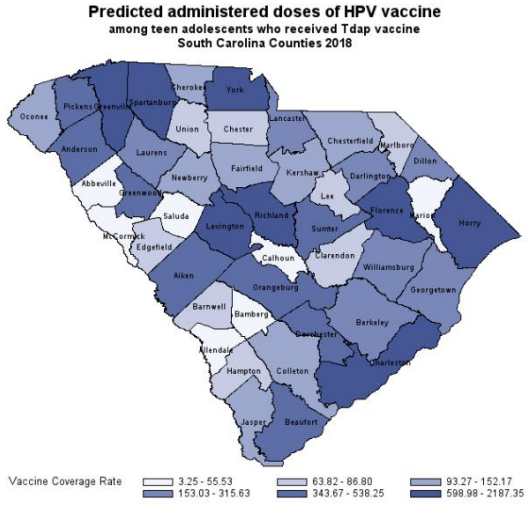
7.6 Figures

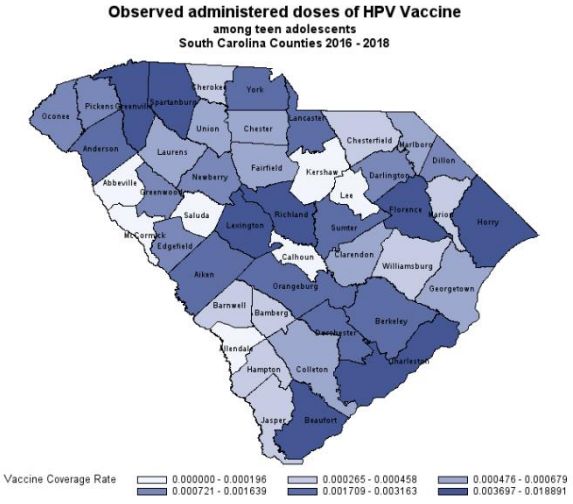
Figure 1. Maps of observed and predicted HPV vaccine coverage rates











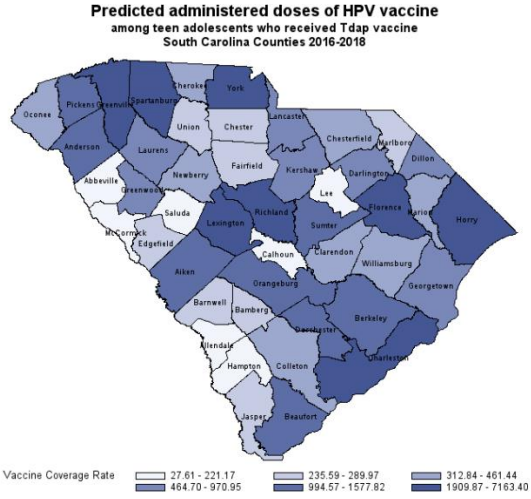
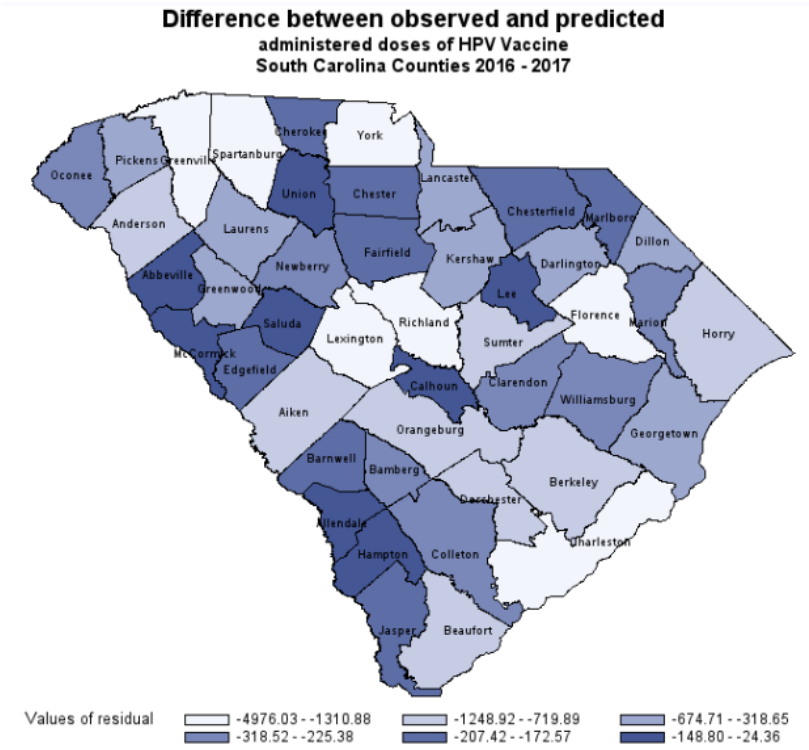
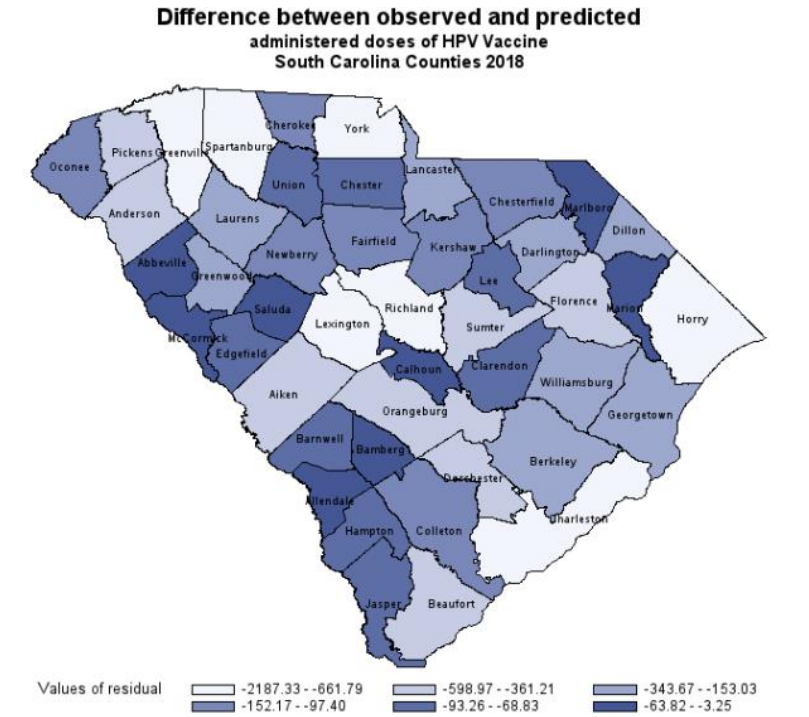


Figure 2. Maps of residual HPV vaccination coverage





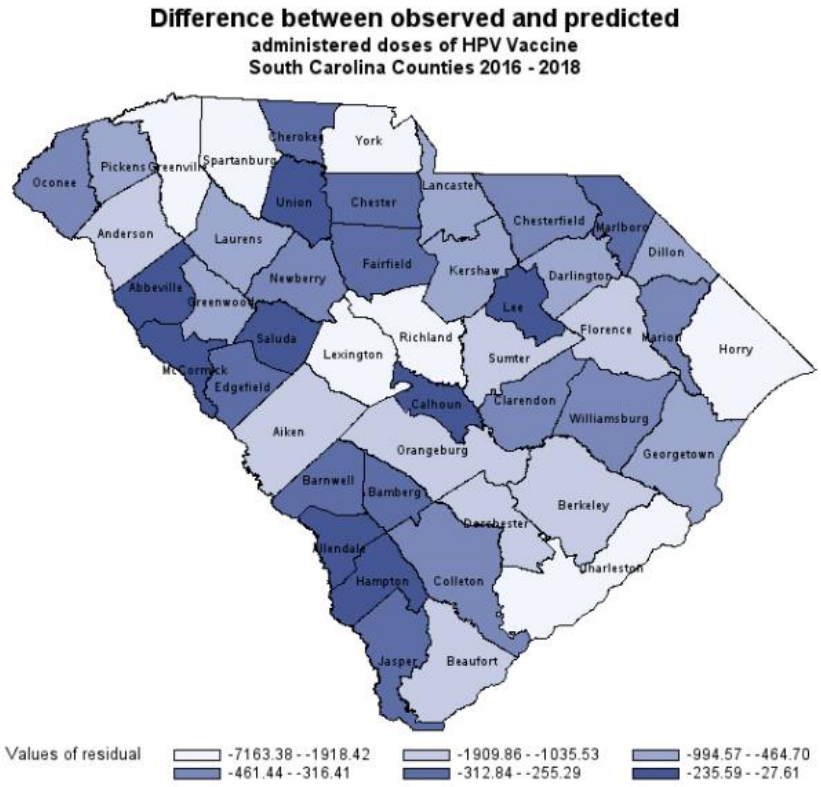
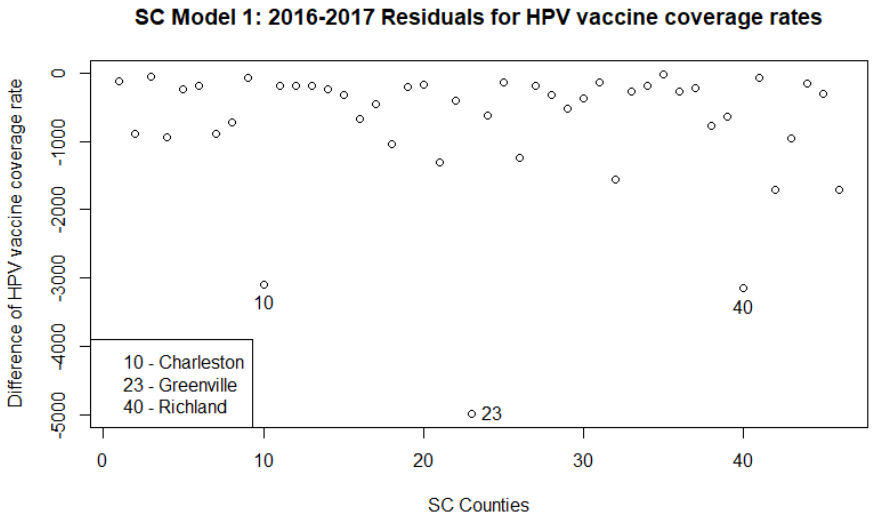
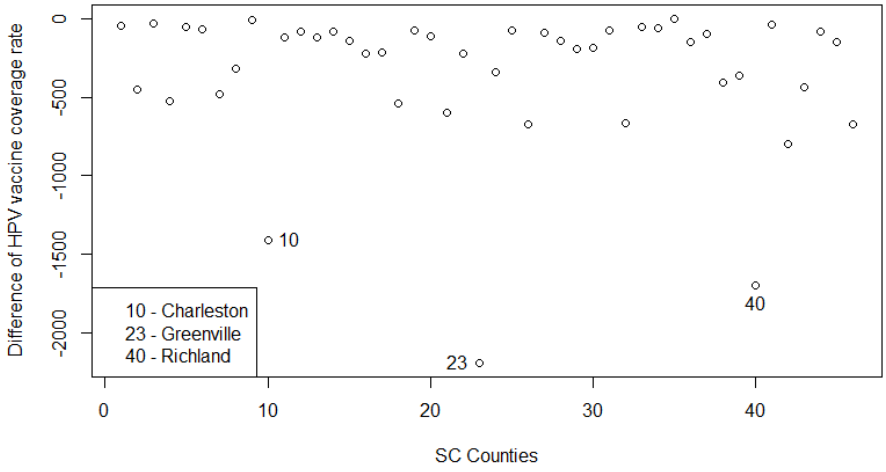


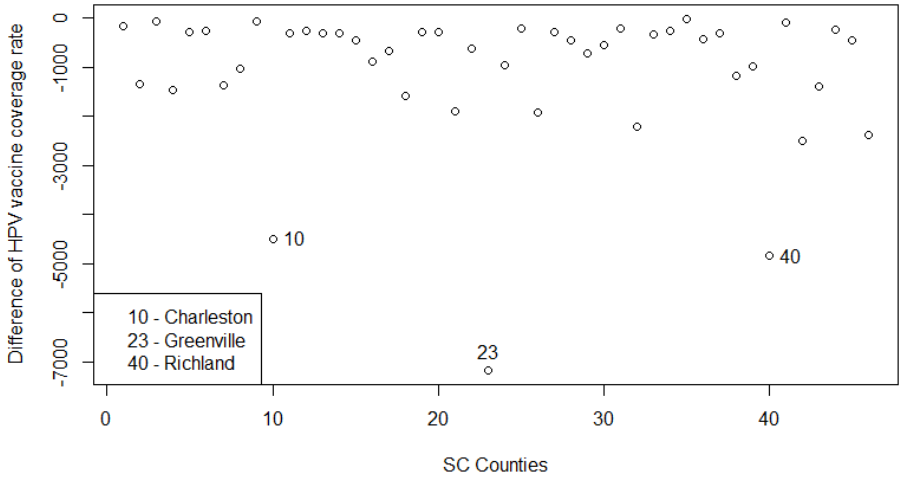
Figure 3. Residual plots for all models



SC Model 2: 2018 Residuals for HPV vaccine coverage rates



SC Model 3: 2016-2018 Residuals for HPV vaccine coverage rates



7.7 Tables

Table 1. Population Demographic Characteristics		
	Georgia	**South Carolina**
Counties	159	46
HPV vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)*		
2016 (60.4 %)	67.30%	44.20%
2017 (65.5 %)	64.30%	59.60%
2018 (68.1 %)	68.10%	63.70%
Tdap vaccination coverage trend: ≥ 1 dose, all adolescents aged 13-17* (United States overall)		
2016 (88.0 %)	92.80%	77.50%
2017 (88.7 %)	93.30%	89.40%
2018 (88.9 %)	94.20%	88.90%
Race Ethnicity[+]		
Black/African American	31.30%	26.80%
White	52.80%	63.80%
Asian	4.20%	1.70%
Hispanic	9.60%	5.70%
American Indian/Alaskan Native	0.50%	0.50%
Native Hawaiian/Other Pacific Islander	0.10%	0.10%
Below 18 years of age[+]	24.10%	22.00%
Education[+]		
Highschool graduation	81%	84%
Some College	63%	62%
Median Household Income[+]	$56,100	$50,700
Uninsured children[+]	7%	4%
Children in poverty[+]	22%	22%
Living in rural area[+]	24.90%	33.70%

Data Sources:
* (Walker et al., 2019)
+ ("County Health Rankings & Roadmaps," 2019)

Table 2. Results for the estimates of South Carolina Prediction Models				
	Residuals			
South Carolina Prediction Models	Mean	1st Quartile	3rd Quartile	RMSE
Model 1: HPV Vaccination coverage for 2016 - 2017	-721.1	-896.0	-190.9	1183.6
Model 2: HPV Vaccination coverage for 2018	-338.6	-447.1	-76.8	553.8
Model 3: HPV Vaccination coverage for 2016 - 2018	-1059.8	-1362.4	-282.4	1735.3

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8.0 DISCUSSION

HPV vaccinations are safe, effective, and long lasting[1]. However, they are being underutilized in the United States. A metric to assess vaccine usage is vaccination coverage, which can be measured using administered doses[2]. Factors associated with HPV vaccination coverage have been shown to include the uptake of other adolescent vaccines, gender, race/ethnicity, socioeconomic status, religiosity, political ideology, education policies and insurance status. As a result, national and state efforts are being made to increase HPV vaccination coverage to 80% by the year 2030[3]. However, health care utilization can also be determined by access to public health resources that are often managed by state the Health Department (HD): such as childhood and adolescent vaccinations administered by school nurses and at public or private health clinics, community education and outreach, vaccine program enrollment, and immunization registry reporting[4–6]. To effectively monitor public health resource utilization, data beyond the state level is needed but this is a limitation for some states. Therefore, the underutilization of the HPV vaccine may be due to limited surveillance. Thus, the main goal of this research was to generate a predictive model of county level HPV vaccination coverage rates in GA and SC to address access barriers to HPV vaccine uptake. The main hypothesis was that HPV vaccine coverage rates are associated with the equity of access to HD clinics.

Using a secondary data analysis of vaccination data from both states, this research was conducted in three specific Aims. The first Aim characterized all counties in GA by quantifying administered doses of the HPV and Tdap vaccines collected by the state health department immunization registries and indicators of HD clinic access. Indicators

of HD clinic access consisted of number of private and public HD clinics, number of HD clinics registered in the VFC program and the availability of public transportation. This Aim incorporated choropleth maps, regression modeling and Bayesian spatial analysis. The results of Aim 1 showed that administered doses of the Tdap vaccine and the HPV vaccine exhibited spatial patterns shown with maps and a spatial relationship across counties. Accounting for this spatial dependence, the number of private health department clinics had a significant positive effect on the administered Tdap vaccine doses and the availability of public transportation had a significant positive effect on administered HPV vaccine doses.

Building from the first Aim, the second Aim predicted the association between HPV vaccination coverage and HD clinic access in GA at the county level among Tdap vaccinated adolescents. This Aim incorporated known factors associated with HPV vaccination coverage in addition to hypothesized indicators of HD clinic access, and adolescents who received the Tdap vaccine as a sample population to establish access to vaccines and control for multiple confounders. The results of Aim 2 showed that the best prediction model for HPV vaccination coverage was not associated with indicators HD clinic access but had a statistically significant negative association with the White racial category and rural residency. Therefore, within this population, the White racial category and rural counties were identified as predictors of decreasing HPV vaccine dose administration.

Extending from the second Aim, the third Aim used GA as a predictor model to provide greater insight of where to more efficiently allocate HPV vaccination resources at the county level within SC and inform the implementation and dissemination of HPV

vaccination interventions that focus on the use and quality of state immunization resources. This Aim incorporated the betas from the best prediction model using GA's comprehensive HPV vaccination data and applied them to SC county data over three different time spans. The results of Aim 3 showed that the best fitting prediction model for SC was for the 2018 one-year time span. Negative residual estimates indicated over prediction and the counties of Charleston, Greenville and Richland had the largest differences between their observed and predicted HPV vaccination dose coverage. Therefore, the residuals of these three counties suggest the need for further investigation of what HPV vaccination resources are available, being used and needed.

Based on all three Aims, HPV vaccination coverage rates are not associated with this study's unique variables of HD clinic access as hypothesized. However, the indicators of HD clinic access did show statistical significance with counts of HPV vaccine administered doses; as well spatial dependence with the counts of HPV vaccine administered doses. This research showed HPV vaccination variability at the county level and presented reproducible methodologies that can be used by public health researchers and practitioners in states with low HPV vaccination coverage and limited or no immunization registry data for small geographic areas.

While research on HPV vaccination has been conducted for over 10 years, incorporating geographic factors and analyses is not commonly used[7–9]. Therefore, this research contributed to the current literature and showed the importance of considering spatial variation at the county level when examining HPV vaccine dose administration. Other state based studies also found that HPV vaccination rates vary geographically[10], HPV vaccination has a strong spatial dependence when identifying and estimating factors

associated with HPV vaccine uptake[11] and that spatial accessibility to vaccination providers increases overall vaccination[12]. Using aggregated zip code level data, this research showed that adolescents receiving the Tdap vaccine, the White racial category and rural residency affect the administration of HPV vaccine doses. Other zip code based studies found decreased HPV vaccine initiation in rural communities[13,14] and among non-Hispanic white adolesents[15] and that the coadministration of the Tdap vaccine is helpful for increasing HPV vaccine uptake[16]. Using predictive modeling, this research showed that predicting state immunization data at the county level was helpful for identifying within state variability and indicating counties that need further examination. This methodology was uniquely applied to HPV vaccination coverage because other prediction modeling studies assess HPV knowledge and behavior [17–21].

9.0 CONCLUSION

Local immunization coverage rates vary widely and the extent to which public health services are delivered depends on the level of surveillance performed by the Health Department. This research uniquely utilized the tools of mapping and prediction modeling to extend HPV vaccination coverage rates to the county level. Mapping spatial patterns provided a visual context to HPV vaccination data that is helpful for informing the development of public health interventions and guiding the provision of health services financially and physically. The underuse of the HPV vaccine is a serious but correctable threat to progress against cancer. Using the models or methodology from this research could inform specific recommendations for new strategies and the adaptation of current efforts to increase HPV vaccination coverage in SC and other states with low HPV vaccination rates. Furthermore, this research could then be used to predict correlations to the incidence of HPV-associated cancers. This would aid the field of health services research to understand and address health care inequities among populations with high rates of HPV cancers, which may help reduce public health costs, morbidity, and mortality.

10. FUTURE DIRECTIONS

To enhance the use of predictive modeling with HPV vaccination at the county level, new variables need to be considered and defined because they could be critical for improving estimations and reducing confounding. For example, the number of school-based health centers/clinics within a county could serve as an additional source of HPV vaccine delivery especially in rural counties. The reproducibility of prediction models also allows them to be used by various levels of public health practitioners to inform and guide their planning, dissemination and implementation of interventions. Additionally, health services research would benefit from the disaggregation of statewide resources and data from immunization registries at the county level or smaller. With more small area data, subtle barriers to HPV vaccine uptake not seen at the state or national level could be identified. Furthermore, with the availability of more small area data, the importance of using maps to visualize the data highlights the need for the collaboration of multiple stakeholders, such as local and state health departments, pharmacists, insurers, universities, epidemiologists, statisticians and nonprofit organizations.

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