ABSTRACT

Addressing Cervical Cancer Prevention in McLennan County, TX

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Persistent infection with human papillomavirus (HPV) is known to cause up to 99.7% of all cervical cancers. Two highly effective cervical cancer prevention methods exist – vaccination against HPV and cervical screening. Studies have documented the motivating effects of clinical intervention on preventative care compliance. Through the use of Bayesian time-series forecasting and a thorough healthcare needs assessment, this study identifies McLennan County, Texas as a candidate for population-level cervical cancer care intervention. Currently, only 54.9% of Texas residents have completed the series of HPV vaccinations, and predictive modeling anticipates stagnation in the rate of vaccination within McLennan County, a county with a high percentage of people who experience barriers to healthcare. Annual health promotions clinics that combine the services of HPV vaccination and cervical cancer screening can be implemented to address this problem. Cervical cancer is an easily preventable disease, thus effective clinical strategies for its prophylaxis should be introduced to medically underserved populations of McLennan County.

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ADDRESSING CERVICAL CANCER PREVENTION IN MCLENNAN COUNTY, TX

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By

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CHAPTER ONE

Cervical Cancer as a Preventable Disease

Currently, cervical cancer is estimated to be the fourth most common cancer in individuals with a cervix worldwide and the leading cause of cancer death in this group in some of the world's poorest countries (1). Two very effective prevention strategies for cervical cancer deaths exist – vaccination against the human papillomavirus (HPV) and cervical cancer screening. Comprehensive screening includes primary testing to detect HPV in the cervix followed by examination to detect precancerous lesions within/on the cervix. McLennan County in central Texas falls below national averages for both levels of HPV vaccination and cervical cancer screening. Additionally, cervical cancer incidence in McLennan County is slightly higher than national averages (7.7 per 100,000 as compared to 7.5 per 100,000). Furthermore, the state of Texas has the largest population of uninsured persons in the country. Lack of insurance often prevents access to HPV vaccination and cervical cancer screening, allowing for the persistence of the preventable disease that is cervical cancer. For these reasons, I hypothesize that targeted efforts that are smartly designed, can reduce the incidence of cervical cancer in McLennan County. To address this thesis, this document serves to a) establish the preventability of cervical cancer, b) identify target populations for intervention within Texas and McLennan County, c) determine optimal clinical design for intervention, and d) statistically forecast the positive effect of clinical intervention on HPV vaccination in McLennan County.

HPV and Its Role in Cervical Cancer Development

Infection with HPV is the leading cause of cervical cancers, with 99.7% of cervical cancers linked to persistent HPV infections (2). HPV is a sexually transmitted infection (STI), meaning infections with HPV are passed from one person to another through sexual contact, including penetrative vaginal, anal, or oral sex. Researchers estimate that, without intervention, 80% of men and women will become infected with HPV before the age of 50, rendering it the most commonly transmitted STI in the United States. Many HPV infections are unnoticed, leading to a large number of people unknowingly harboring and possibly transmitting the virus (3). Early HPV infections can be detected through cytology and HPV testing, alone or in combination.

Although most people infected with HPV will clear the infection without intervention or effect, a small fraction of infections become persistent. Failure to clear an HPV infection leads to disease progression and the development of a range of symptoms including, but not limited to, genital warts, head and neck lesions, as well as certain cancers when infected with oncogenic viral types (4). These cancers include cancer of the cervix, oropharynx, anus, penis, vagina, or vulva (5).

HPV is a DNA virus with more than 100 different subtypes (6). Viral types vary in both the type of tissues targeted by infection (tissue tropism) as well as the symptoms accompanying infection. All basal epithelial cells of skin or the inner lining of tissues are susceptible to infection by HPV. However, mucosal epithelium of the mouth, throat, respiratory tract, or anogenital (vaginal, vulvar, penile, or anal) region are the most common sites of HPV infection (7). The infection becomes localized to these areas by penetrative vaginal, anal, or oral sex (8). Approximately 30-40 of the HPV viral types

infect the genital tract, conferring a gradation of symptoms ranging from genital warts to cancerous lesions. Within these 30-40 viral types, there are several identified oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, and 58); persistent infections with these viral types are associated with the development of cervical, vulvar, vaginal, and anal cancers (9). In addition to oncogenic viruses, several non-oncogenic HPV types also infect the genital tract (6, 11, 40, 42, 43, 44, and 54) are associated with the development of benign genital warts (10). Most commonly, HPV vaccines are formulated to target highly oncogenic viral types (i.e., 16 and 18) (11).

Vaccination to Prevent HPV Infection

Prophylactic vaccines against oncogenic HPV subtypes are available in many countries for the prevention of HPV-related disease (12)(13). Based on vaccine efficacy, the WHO recommends a threefold approach to the implementation of the vaccine for maximum efficacy in the results of intervention (14). Firstly, countries should make cervical cancer and other HPV-related diseases a priority in public health policy. While no specific parameters for prioritization are outlined, the goal is to provide not only vaccination but also readily available screening and treatment for pre-existing or breakthrough infections. Secondly, vaccinations should be implemented as a comprehensive strategy for prevention of cervical cancer and other HPV-related disease without detriment to the efforts made to cervical cancer screening. Lastly, the WHO and American Cancer Society (ACS) recommend the HPV vaccine for girls and boys 9-14 years of age, with vaccination schedules varying for age of first vaccination and immune status (15).

Many HPV infections (40%) are acquired within the first two years of sexual experience, and risk of infection increases with additional sexual partners (16)(17). A majority (70%) of 20-year-olds with a cervical HPV infection and with no other relevant medical history cleared the infection within one year, and by two years post-infection, 91% cleared the infection (18). However, the rate of viral clearance does not reach 90% for the highly oncogenic HPV types or if infection occurs in immunosuppressed populations, people who smoke, or groups taking oral contraceptives (19)(20)(21). Each of these factors decreases the ability to clear HPV infection. For example, only 72% of individuals with a cervical HPV infection clear HPV 16 type in 2 years, a 19% deviation from the 91% mean clearance rate (22).

Vaccination against HPV can be up to 98% effective in preventing persistent infection with HPV (23). Vaccination produces an immune response that is far stronger than clearance of natural infection. So, even if an individual has contracted and cleared HPV previously, it is still recommended to follow through with vaccination (24). Vaccination in individuals aged 9-26 produces a strong immune response to HPV (25). Because of the nature of the vaccine as a method of primary prevention, it is important to become vaccinated before possible exposure or infection with HPV. If there is an already persistent HPV infection, the vaccine is not recommended and does not affect the progression of disease (26). For this reason, girls aged 9-14 are most frequently the target of vaccination efforts; if vaccinated at this younger age, only a 2-dose schedule of vaccination with six months between doses is required as opposed (27). Girls older than 15 (with uppermost age of vaccination being 26) and immunocompromised individuals must adhere to a 3-dose schedule to achieve maximum efficacy (28). Some adults aged

27 to 45 may receive vaccinations after speaking with their physician regarding personal sexual history and risk for new HPV infection. In a three-dose regimen, the second dose is given 1 to 2 months after the first, and the third dose is received six months after the second. While there is no maximum timeframe between doses, the World Health Organization states that there should be no interval greater than 12 to 15 months between one dose and another (29).

Development and Dissemination of the HPV Vaccine

In developing a vaccine for HPV, expression of HPV L_1 structural proteins, found in the viral capsid of specific strains of HPV, were used to generate virus-like particles (VLP's)(30). VLPs contain no active virus but elicit the same form of immune response as an infection produces, with a greater intensity than a natural infection provides (31). This immune response, in turn, releases high levels of serum-antibodies against all of the vaccine-specific HPV types. Although HPV infections are often cleared through an immune response mounted by the body, natural infections produce only transient local immunity at the level of basal keratinocytes. Because the viral capsid and associated proteins do not reach beyond the basement membrane and do not incite systemic humoral immunity, they fail to prevent reinfection with the same viral strain or infection with a different HPV strain (32). Prophylactic L_1-based VLP HPV vaccines induce much stronger immunogenicity with a long lasting and effective humoral immunity, thus offering prolonged and effective protection from HPV (26). Currently, there are three mainstream vaccine types on the market, all conveying immunity against different combinations of viral strains (33).

The first of the available vaccines is a bivalent vaccine commonly referred to as Ceravix or GSK(34). This vaccine is effective in prevention of infection with the two most oncogenic HPV types, HPV-16 and -18. The quadrivalent vaccine, known as Gardasil, confers the same protections as Ceravix with additional protection against the non-oncogenic HPV-6 and -11 types. HPV -6 And -11 are responsible for 90% of benign genital warts. Merck later developed a nonavalent vaccine, Gardasil 9, similar to Gardasil but containing L1 VLPs of 5 additional oncogenic types: HPV 31, 33, 45, 52, and 58. Gardasil 9 has the potential to provide type-specific protection against approximately 90% of cervical cancers worldwide (35)(36).

Despite its proven effectiveness, HPV vaccination uptake and utilization are still found to be lower than expected in the United States compared to other high-income countries. Most states in the US do not require HPV vaccination for school enrollment, leading to a significantly reduced uptake when compared to other vaccines which are mandated for school entry (37). In 2016, 60% of all 13–17-year-old adolescents in the United States had received at least 1 dose of the vaccine series (65% of females and 56% of males) and 37% had completed the HPV vaccination series. Healthy People 2020 in conjunction with the American Cancer Society established a goal of 80% 13–15-year-old individuals being fully vaccinated by 2026 (38). Texas is one of the states with the lowest HPV vaccination rates in the country with only 54.9% of boys and girls having received more than one dose of the vaccine (39). This is about 15 percentage points lower than other high-ranking states like Massachusetts and Colorado which have achieved 85.2% and 77.2% of 13–15-year-old children fully vaccinated, respectively (40). Limited vaccination and clinical availability hinder many from receiving the HPV vaccine in low-

resource countries as well as in certain low-income communities in high-resource countries (41) (42). These barriers of access to care include lack of insurance, inability to travel to clinical locations, distrust of medicine or medical providers, and inadequate education regarding cervical cancer and its prevention.

Intervention to Increase Rates of HPV Vaccination

Increasing rates of vaccine dissemination and uptake within low-resource areas of the United States requires a multi-level approach to care. To lower barriers of access, various intervention methods have been tested in several types of clinical settings, and the most effective of these methods differs depending on whether the endpoint examined was vaccine series initiation versus vaccine series completion. Interventions that increase HPV vaccine series initiation are most effective when included as a part of a short-term clinic, where program education and enrollment are prioritized before the start of the event. Efforts for enrollment and education include the offering of educational materials before and during appointments, as well as the availability of staff to answer patient questions leading up to the day of the appointment. Despite efficacy in clinical access, short-term clinics are often funded as a part of a grant. Due to the limited duration of these funding sources, efforts to achieve vaccination series completion 1-2 months later are often neglected after the first dose is received at a one-day clinic. To achieve the goal of vaccination series completion, providers must be trained to more strongly communicate consistent recommendations for adolescent patients to receive HPV vaccinations, and clinic centers must have the infrastructure to continue care for all patients who attend clinic events. (43)

In addition to barriers of access, a long and complex social history surrounding HPV vaccination impedes its uptake (44)(45). This vaccine is unique in comparison to most other vaccines for many reasons, a few of which have been identified through comprehensive surveys of vaccination attitudes. The most prominent of these anomalies is that the vaccine is targeted to adolescent girls with the intention to prevent infection with an STI, oftentimes with the start of vaccination preceding the sexual debut of the individual. Further, for many communities, this vaccine was seen as a way to encourage early onset of sexual activity. Repeated studies of age of sexual onset in correlation with HPV vaccination show that HPV vaccination status is not significantly associated with an increased likelihood of sexual debut, decreased age of sexual debut, nor an increased number of sexual partners (46). None-the-less, pervasive negative attitudes toward the HPV vaccine impede its uptake, and HPV vaccination rate is far outpaced by other school-mandated vaccines (47). HPV vaccination education programs have been shown to be effective in both rural and urban settings within the United States, with some intervention-based clinics reporting a 14.8% increase in vaccination uptake when compared to clinics not providing vaccine education and promotion (48).

Since the development and licensing of the vaccine, there have been more than 200 million doses of the vaccine distributed (49). Reports of ESAVI's (events supposedly attributable to vaccination or immunization) in the U.S. are gathered through the Vaccine Adverse Event Reporting System (VAERS). VAERS is a surveillance program that is sponsored by both the CDC and FDA. As of 2011, over 40 million doses of the quadrivalent HPV vaccine had been administered, with only 504 reports of adverse effects (50). Of these adverse effects, 92% were determined to be non-

serious. Documented minor adverse reactions include local pain or soreness at the injection site and low to moderate fever. Adverse anaphylactic reactions are rare (2.6 per 100 000 doses), and the vaccination process is discontinued in affected individuals (51). Although the overall safety of the HPV vaccine has been supported by abundant evidence, there do remain valid contraindications to vaccination which must be taken into account when making a decision on whether or not to pursue vaccination. These include pregnancy, febrile illness, or allergy to the vaccine or its ingredients (52). The risk-benefit profile for HPV vaccination remains highly favorable (53), further supporting claims that continued lack of vaccination served only to decrease opportunities for early cancer prevention.

Impact of Persistent HPV Infection on Cervical Development

A major target of HPV infection is the cervix (54). The cervix can be divided into three areas: supravaginal, intermediate, and intravaginal (55). Histology of the cervix can also be divided into three categories: the columnar epithelium and stratified squamous epithelium, separated by a border, called the squamocolumnar junction (SCJ). Stratified squamous epithelium covers the ectocervix, the portion of the uterine cervix extending into the vagina, and a single layer of columnar cells (simple columnar) cover the cervical canal. The ratio at which these two cell types appear in the cervix changes throughout reproductive years, with the changes beginning after the onset of puberty (56).

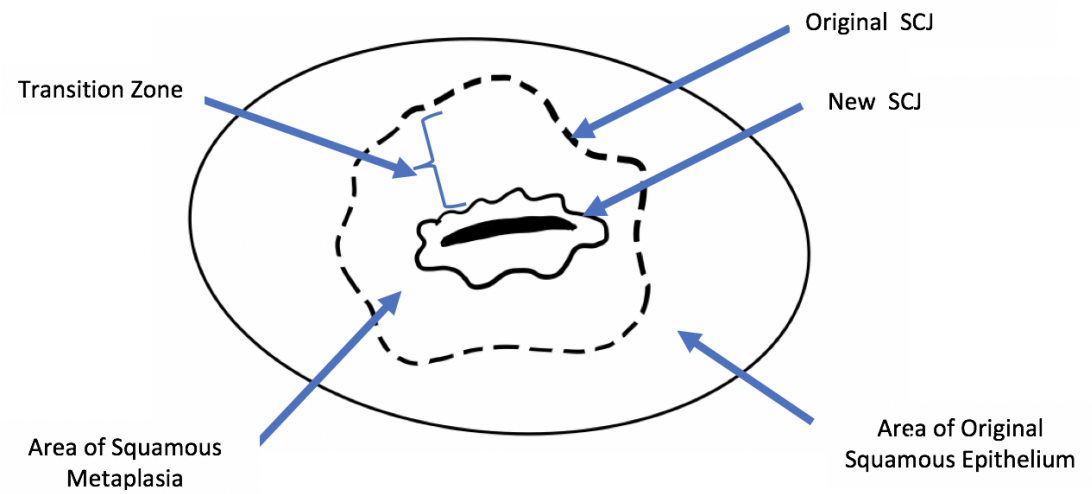

Figure 1: Diagram of Post-Pubescent Cervical Epithelial Changes

The acidic post-pubescent environment of the vagina slowly elicits conversion of columnar cells to squamous epithelial cells in a process called squamous metaplasia (SM). Metaplasia is a term which denotes the change of cells from one cell type to another. Cervical SM through female puberty produces a second SCJ, which can be continuously visualized throughout an individual's lifetime. The area between the first and second SCJ is termed the transition zone (TZ). The TZ is the area of the cervix that must be carefully inspected for precancerous lesions during an annual exam. The TZ contains immature epithelia due to the cellular changes of squamous metaplasia, making it more susceptible to HPV infection (57).

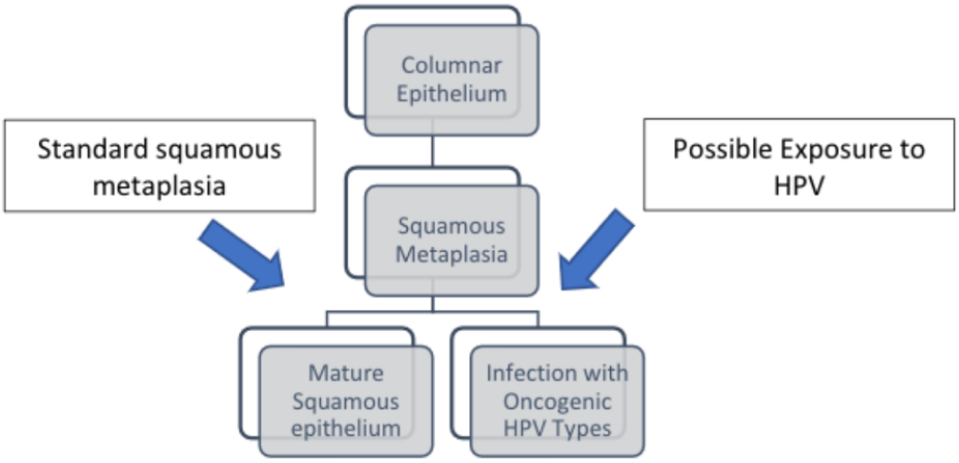

Figure 2: Introduction of HPV Infection to Developing Cervix

Progression from HPV Infection to Cervical Cancer

Carcinogenesis, or the formation of a carcinoma, involves uncontrolled cell growth following activation of oncogenes and suppression of tumor suppressor genes of the cervix (58). Cellular entry by the HPV is achieved through endocytosis of the viral particles, a process that is non-synchronous among cells and lasts over a period of several hours. Viral integration is seen as highly tissue-specific, infecting mucosal epithelia of the mouth, oropharynx, cervix, anus, vagina, and vulva. Virions approach the mitotically proliferative basal epithelial cells through micro-abrasions in stratified epithelium. Heparan sulfate proteoglycans (HSPGs) are cell-surface glycoproteins with one or more covalently bonded heparan sulfate groups. These cell-surface receptors initiate viral binding and endocytosis of the virion in the basal epithelium. Binding is enhanced in this region due to an upregulation of syndecan-1, a HSPG subtype seen in high levels in wound-prevalent edge-keratinocytes. Furthermore, wound-edge keratinocytes are found in a higher proportion in areas where genital epithelial contact occurs. The

virus integrates into the host cell after infection which is the first step in cancer formation. Mitotically active basal keratinocytes allow for viral proliferation and infection persistence.

Infection with HPV alone is not enough to trigger cancer formation. There are several other factors that are involved in cancer formation during the incubation period. Oncoproteins E6 and E7 in HPV alter the cellular functions of the host. The products of these two genes alter host-cell development to favor neoplastic development. E6 binds to and degrades the host-cell protein p53. An effect of this targeted degradation is to prevent apoptosis of the infected host epithelial cells. Telomerase is also activated, further augmenting oncogenic changes. The E7 protein has a similar effect on cellular activity by binding to retinoblastoma protein, inhibiting its function. This leads to disruption of the cell cycle. In addition, E6 and E7 proteins may cause chromosomal destabilization, and inhibit cyclin-dependent kinase inhibitors (59).

Hyperplasia is the first step in this process, where an altered cell divides in an uncontrolled manner. This is distinct from standard metaplasia seen in a healthy cervix. Hyperplasia then leads to an excess of relatively normal cells in a tissue. Dysplasia is the next stage of carcinoma development, with additional genetic changes being found in cells (60). At this point, there are noticeable changes to the appearance of the cells, which can be visualized through cytologic samples taken during a Pap test (61).

There are two acceptable techniques for collecting the Pap Smear cervical cell sample: liquid-based and conventional. A physician will place a speculum into the woman's vagina and identify the cervix. The liquid-based method involves collecting

cells from the transformation zone of the cervix by using a brush and transferring the cells to a vial of liquid preservative. The conventional technique involves collecting cells from the transformation zone of the cervix by using a brush and spatula, transferring the cells to a slide, and fixing the slide with a preservative. Both of these methods require a pathologist to interpret cytologic changes. The cytologic changes of the cervix associated with precancer are called squamous intraepithelial lesions (SILs). SILs are graded or categorized based on the progression of the disease, with three categories of cervical intraepithelial neoplasia (CIN) designation. CIN 1 includes mild dysplasia. These lesions usually only invade less than a third of the depth of the epithelium. At this point in the progression of the pre-invasive disease, 60% of CIN1 positive patients are likely to clear the disease spontaneously. If the disease continues to progress without clearing, the next SIL grade (CIN2) typically develops 2-3 years after the onset of CIN1. CIN2 designation includes moderate dysplasia with two-thirds of the depth of the epithelium affected. CIN3 affects the entirety of the epithelium, with a 12% progression rate to cervical cancer (62) (63).

Cervical cancer differs from many other cancers because of the prolonged period of dysplasia before progression to malignancy. The transition from dysplasia to invasive carcinoma takes at around 10-12 years, leaving a large window for intervention (64).

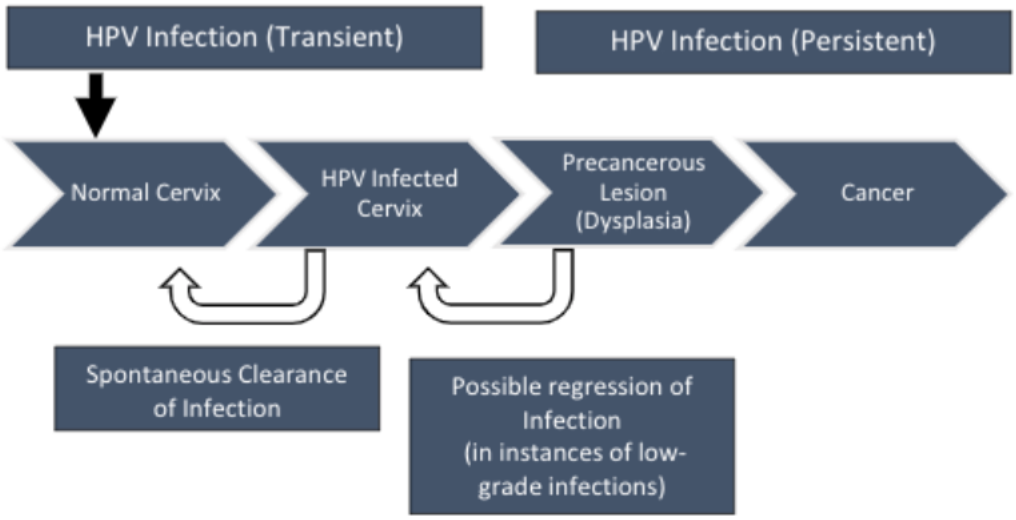

Figure 3: Post HPV Infection-Development of Cervical Cancer

Detection of Cervical Pre-Cancer

A lack of treatment seeking behaviors in women with persistent HPV infections can be attributed to both the asymptomatic progression of disease as well as inadequate knowledge of the role of HPV in cervical cancer development (65)(66). Screening measures, like the pap smear described above or HPV detection, are used as an intervention to identify asymptomatic target populations. It is important to note that the purpose of screening is not to diagnose a disease but to identify individuals with an increased risk of developing disease or experiencing disease progression. The purpose of screening is to detect HPV infection or pre-cancerous cells within the cervix; however, the presence of cancerous or pre-cancerous cells or a positive result for HPV infection does not stand as a diagnosis of cervical cancer. A screening test indicating positive HPV or CIN results requires additional testing through cervical biopsy to diagnose and grade

the level of cervical cancer or pre-cancer. The goal of additional testing is the detection of abnormal cells at early developmental stages when these cells are more responsive to clinical intervention.

Best screening practices in the United States and other high-income countries include screening via cytology (Pap) or combined HPV and Pap completed in conjunction with updated ACS guidelines. Lifelong screening for a disease must be economically justified to be considered a healthcare best practice. In the case of cervical cancer, regular screening meets all criteria for justification: a serious disease with an asymptomatic detectable stage for which treatment of the preclinical stage improves the long-term course of the disease. The WHO recommends screening between the ages of 30-49, but many resource-rich areas begin screening at age 21(67). Updated guidelines from the American Cancer Society recommend testing every 3-5 years for HPV negative individuals who test negative with cytology for any precancerous lesions. This is a significant adjustment from the yearly screening recommended previously (68).

Justification for recommending regular and repeated screening also requires a valid testing procedure. The parameters for test validity are twofold: both sensitivity to true positive cases and specificity to correctly identify negative samples must be high (69). Additional supporting measures are that of reproducibility, availability, ease of use, and safety of the screening procedure. The three widely accepted forms of cervical cancer screening are cytology-based testing, visualization with acetic acid (VIA), and HPV testing.

Visualization with acetic acid is a rudimentary visualization where acetic acid is applied to the cervix and abnormal areas are shown as white. The power in this test

involves the screen and treat ability to combine services. This is useful in low resource settings where the training and supplies for cytology-based testing is not available. Cytology-based testing (Pap) is widely used among high resource communities. This test is highly effective when there are resources for proper specimen capture as well as specialized interpreters of sample pathology. Because of the subjective nature of sample interpretation, there is a relatively low test-sensitivity (55.2%), but a very high specificity. Therefore, the effectiveness of this test is in the ability for repeated testing within the window of detection in high-resource settings (70).

Cervical Precancer Diagnostic Methods

As stated previously, screening methods such as Pap or HPV testing do not have clinical significance when diagnosing and grading cervical cancer and pre-cancer. Cervical precancer diagnostic methods include biopsy using colposcopy or endocervical curettage (ECC) (68). Colposcopy refers to the use of a colposcope to image and visualize the cervix. A colposcope is a piece of equipment that provides intense light and a magnified field for epithelial visualization. This is usually used on patients with positive screening results to verify the presence of precancer, cancer or other suspicious lesion. This visualization can help to guide the biopsy of the affected area, but it is not a tool for biopsy itself (69). A subsequent biopsy is performed and graded using the SIL categorization method mentioned previously. If the lesion is not visible with colposcopy, and it is suspected that cellular abnormality is located within the endocervical canal, an ECC is utilized (70). ECC is a procedure in which surface cells are scraped from the endocervical canal by a sharp Kevorkian curette (71). Then, collected samples are examined by both histology and pathology to designate gradation of the lesion. Each of

the aforementioned diagnostic methods require a high level of resources and specialty training.

Methods for Treatment of Cervical Pre-Cancer

For patients presenting with a pre-cancerous lesion, cryotherapy (ablative) or loop electrosurgical excision procedures (LEEP) (excisional) is the next step in treatment. Following pre-cancerous treatment, physicians require a 12-month follow-up to evaluate whether the intervention was effective. A negative result at this step allows patients to return to regular screening intervals (3-5 years). A positive result at this stage indicates the persistence of pre-cancer and retreatment is needed (72). High grade persistent lesions continue to be treated in the same manner as long as the lesions remain pre-cancerous. In the instance of diagnosed cervical cancer, surgery in the form of a hysterectomy is the primary recommendation. Individuals presenting with adenocarcinoma in-situ or metastasis, are recommended to undergo a combination treatment of radiation and chemotherapy (73).

The elimination of cervical cancer is achievable through the combination of both vaccination against HPV and cervical cancer screenings for individuals with a cervix not currently vaccinated. Up to 98% of all persistent HPV infections can be prevented through vaccination. Additionally, regular screening measures through Pap testing allow for the prevention of up to 91% of all cervical cancers. These two methods, operating in tandem, allow for the elimination of cervical cancer.

A combination of comprehensive HPV vaccination and cervical cancer treatment services made available through widely-accessible intervention strategies, has the ability to ensure no person dies from cervical cancer. Comprehensive care can be made available

through the development of clinical interventions combining the services of HPV vaccination and cervical cancer screenings.

CHAPTER TWO

Barriers to Healthcare, Cervical Cancer and HPV Vaccination in McLennan County, TX

Introduction to McLennan County

Having explored the role of HPV in the development of cervical cancer, the need for intervention to increase rates of HPV vaccination and cervical cancer screening in McLennan County is explored in this chapter. McLennan County, situated in central Texas, is the 20th most populated county in Texas. It includes the towns of Axtell, Bruceville, China Spring, Crawford, Eddy, Elm, Mott, Hewitt, Leroy, Lorena, Mart, McGregor, Moody, Riesel, Ross, Waco, West, and Woodway. Within McLennan County, 18.0% of citizens live under the poverty line compared to the 11.4% national average. In addition to this, 18.0% of the adults aged 18 to 65 live without health insurance, which is 7.8% above the national average. Furthermore, females aged 18-24, a key demographic for cervical cancer prevention, make up nearly 20% of the population living under the poverty line. HPV vaccination is recommended for individuals aged 9-26, and cervical cancer screening is recommended for people with a cervix aged 21-65, making this demographic group of uninsured females ages 18-24 at risk for missing both vaccination and screening (74).

While McLennan County contains a higher proportion of individuals living below the federal poverty line when compared to national averages, there are specific communities in the county where resources (i.e., financial, educational, and medical) are abundant. An income distribution map generated from census records of income

demonstrates this trend of wealth stratification by zip code. Median household incomes were mapped by zip code using 2019 US Census data.

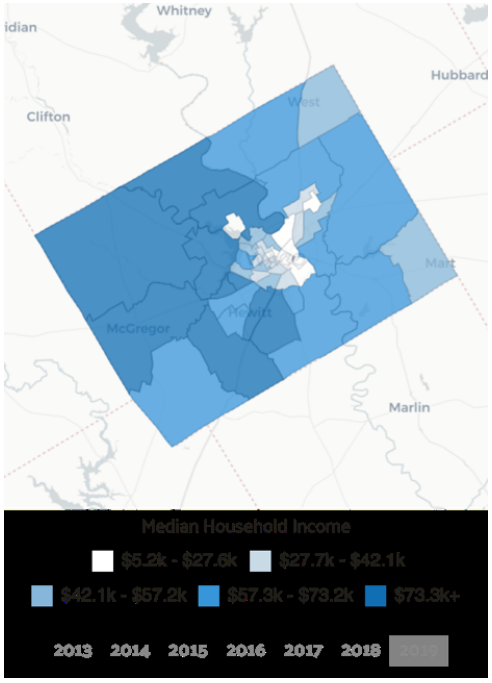

Figure 4: Map of Median Household Incomes in McLennan County by Zip Code Generated from US Census Data (74).

Awareness of the income and resource stratification within McLennan County inspired a 2019 study of life expectancy within the county. In this study, residents of Woodway were found to have an average life expectancy of 86 years. Meanwhile, Census records found the life expectancy for individuals living in East Waco as well as the areas bounded by US Highway 77 and the Brazos River to be 71 years. The conclusion that a few miles distance could prolong or shorten a lifespan by up to 15 years caught the attention of the McLennan community (75). The mapping of this increase in life expectancy strongly correlated with the mappings of increasing levels of income. Dr. Brenda Gray, director of the Waco McLennan County Public Health District, warned that

within McLennan County, “The disparities are not decreasing, so that means we have to have a different lens or a different paradigm of how we go about this work,” she said. “It’s very clear that place matters. ZIP code matters.”

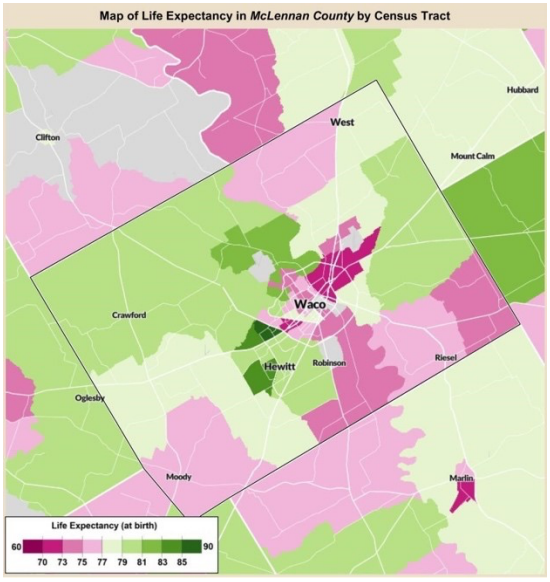

Figure 5: Map of Life Expectancies in McLennan County: This diagram is from 2019 Waco Tribune article raising awareness of health disparities in McLennan County (76) .

In conjunction with income and life expectancy measures, the Texas Hunger Initiative and the Baylor School of Social Work completed a survey of food availability in McLennan County in 2014. This study found that five zip codes (76701, 76704, 76706, & 76707) in the county did not have easy access to a grocery store, leaving convenience stores as the only readily available food source within walking distance. A comprehensive survey of food availability in these convenience stores concluded these five zip codes should be classified as food deserts. A food desert is defined by the US Department of Agriculture, Treasury, and Department of Health and Human Services as a low-income census tract where either a substantial number or share of residents has low access to a supermarket or large grocery store. Counties must meet two criteria to qualify census as food deserts: 1) The census tract has a poverty rate of ≥20% or a median

income ≤ 80% of the area median family income and 2) ≥500 persons and/or ≥33% of the census tract's population living more than one mile from a supermarket or large grocery store (77). Further research suggests, distribution of healthcare services in McLennan County mirrors this pattern of unequal access (78).

Healthcare Needs Assessment of McLennan County

The US Health Resources and Services Administration identifies medically underserved areas or populations (MUA) by systematically reviewing health resources. The main areas for qualification as medically underserved are threefold: having a shortage of primary medical care, high infant mortality, high poverty, and/or an abundant elderly population. These factors are taken into account and an index of medical underservice score is computed algorithmically. These values range from 0 (highest need) to 100 (lowest demonstrated need). To qualify as medically underserved, the index score of an area must be less than or equal to 62.0. McLennan County currently is qualified as a non-rural medically underserved area with an index score of 49.9 (71). Individuals living in the impoverished areas often are unable to receive transportation services to make quality healthcare readily available.

Access to Healthcare

In 2019, the Waco Center for Community Research and Development conducted a Community Health Needs Assessment of McLennan County using mixed-mode surveys and comparing the results with local health measures. The assessment results identified three significant areas of interest: access to healthcare, lifestyle and healthy behaviors, and women's health (72). The phrase women's health here refers to the specialized care

of individuals with primary and secondary sex characteristics of an individual assigned female at birth.

Access to care is a common barrier to successful entry into healthcare systems. Compared to national averages, researchers found that McLennan County housed a higher-than-average population of uninsured people when compared to national standards (18% compared to 10.2%). In addition to this, a higher-than-average number of people rely on government assistance for healthcare (22% compared to 17.8%). (73) In McLennan County, 41% of children were covered by CHIP (Medicaid) in 2016. 30% of McLennan County residents surveyed reported not receiving a wellness exam in over 12 months, and healthcare utilization surveys showed a strong reliance on emergency care received in an emergency room setting. 25% of survey participants responded that they had been to the ER at least once in the past year, oftentimes using this service because of a lack of a primary provider.

Additionally, significant racial/ethnic disparities were found in this report regarding specific healthcare access measures. For example, white adult residents were 160% more likely to have health insurance than African American adult residents. Moreover, white adult residents were 460% more likely to have health insurance than Hispanic adult residents. Income was also a significant indicator of insurance coverage. Participants making under $35,000 a year were 14% more likely to have lost insurance status within 12 months before taking the survey than higher-income participants.

Unhealthy Lifestyles

Unhealthy lifestyles were pervasive among survey respondents with low measures of both physical activity and balanced dietary practices. Healthy lifestyles were measured

by Healthy People 2020 guidelines which state that numerous epidemiological studies have shown that lifestyle behaviors such as lack of exercise, poor diet, and smoking are associated with higher risk of morbidity and mortality of several cancer types (74). Tobacco usage specifically has been shown to increase risk of cervical cancer development regardless of HPV infection status (75). Interestingly, the average daily smoking was 50% higher in McLennan County than the national average.

Women's Health

Women's health, the final area of needed improvement identified by this study is a key indicator for the need for intervention on the front of cervical cancer care. From survey data, it was shown that 26% of adult females in McLennan County had never received a well-woman exam or cervical cancer screening. Furthermore, 25% of respondents reported never having received information or education regarding a well-woman exam. This survey also analyzed the average age of first pregnancy, with 26% of child-bearing individuals in McLennan County becoming pregnant before their 18th birthday (72).

The aforementioned racial disparities in care pervade women's healthcare in McLennan County and are more severe in their impact. The distribution of teenage pregnancies was skewed toward Hispanic and Black populations who were more than twice as likely to experience a teen pregnancy than their white counterparts. Additionally, there was a 20-30% decrease in women of color reporting receiving prenatal care compared to white counterparts (76).

Increasing Provider Education for the Prevention of Cervical Cancer

Cervical cancer is a preventable disease that persists because of differences in both opportunities to access care and education on cervical cancer prevention, creating vast cervical-cancer-related healthcare disparities. The role of the healthcare industry, ranging from community healthcare workers to physicians and hospital stakeholders, is explored in regard to the role of the provider in the prevention of cervical cancer. These findings will establish the value of increased provider education regarding cervical cancer prevention.

McLennan County Health Officials analyzed opinions regarding patients' ability to receive care among hospital staff and hospital stakeholders in McLennan County through a Baylor Scott and White focus group. Providers identified several concrete barriers to care within McLennan County, including cultural and language barriers, education-related barriers, cost of care, physician availability, and transportation to and from care. 6% of McLennan County residents report not speaking English in the home, with the primary language of these respondents being Spanish, and participants in this focus group did not feel this language barrier was well accounted for in the current standard of care. When asked about disproportionate access to care in the county, participants often suggest low socio-economic patients are unable to understand information regarding healthy lifestyle choices. Additionally, one focus group participant was cited as saying, "In poor [neighborhoods], health is not valued." Topics of additional barriers to care mirrored similar sentiments, with much of the burden of care being placed on the patient (76). To combat this, comprehensive education ranging from provider to patient is necessary in successful intervention clinics. Specifically, given the 2 to 3 shot series required for HPV vaccination and the need for repeated Pap testing throughout a

person with a cervix's lifetime, providers could be trained in effective means to educate medically indigent populations on the importance of clinical compliance for the prevention of cervical cancer.

Gynecologic Provider and Specialty Care Availability

HPV vaccination and cervical cancer screening can be accessed on the level of primary care, however, subsequent treatment for invasive disease or cancer in the case of an abnormal screening result requires the availability of specialized, secondary care. When asked what the preferred method was of receiving gynecologic care, most participants indicated a preference for care from General or Family Physicians. Available providers at the primary and specialized secondary levels are crucial in diagnosing and treating cervical pre-cancer and cancer. Screening measures that employ cytology require specialized training in pathology for the test to be accurate. Screening measures are only helpful if follow-up care and treatment are readily available, and patients are not lost to follow-up. However, there is both a shortage of primary care physicians in this area and subsequent specialty care as measured by the MUA index of need previously mentioned (71). In addition to the less-than-ideal proportion of people with a cervix receiving well-women exams, many are then lost to follow-up, not receiving additional diagnostic or therapeutic care.

Availability of public hospitals for the uninsured or underinsured populations is primarily provided by Federally Qualified Health Centers (FQHCs), with federal and state funds available for cervical cancer screening and prevention. There are currently only 12 FQHC's serving McLennan County. Waco Family Medicine (WFM) is a highly productive primary care clinic that received FQHC status in 1999. Since gaining this title

and associated government aid, WFM has quadrupled its number of patients, and it is estimated that 1 in 5 Waco residents rely on WFM for healthcare. Much of this ability to expand and provide comes from WFM's enhanced Medicaid payments. This additional resource has made it possible for patients to see any WFM clinician if insured with Medicaid (77).

As of a 2013 comprehensive study, there were 76 American College of Surgeons Commission on Cancer (CoC) accredited institutions in Texas. These centers are responsible for 80% of the cancer care received in the state of Texas. In addition, four cancer centers in Texas are accredited by the National Cancer Institute (NCI). Despite these institutions' large size and infrastructure, gynecologic oncology care level is often unavailable to McLennan County residents. Out of the 76 CoC accredited institutions and four NCI accredited institutions in Texas, only one resides within McLennan County, with many surrounding counties also relying on this institution to receive care. There are three gynecologic oncologists in McLennan County, with only one practicing at an accredited CoC (78).

Several Texas-based programs are focused on combatting these problems as they present within rural and low-resource communities within the state. The goals of these initiatives are to A) increase the number of people with a cervix receiving pelvic exams and Pap tests, B) improve treatment for pre-cancerous cervical lesions, and C) increase HPV vaccine uptake. The primary mechanism by which these organizations hope to achieve stated goals is by increasing provider education on patient perspectives and increasing the proportion of physicians accepting Medicaid for Breast and Cervical Care (79).

Vaccination Rates in the McLennan County versus the State of Texas and National Averages

Texas is one of the states with the lowest HPV vaccination rates, with 54.9% of boys and girls receiving >1 dose of the vaccine. This is about 15 points lower than other high-ranking states like Massachusetts and Colorado, with 85.2% and 77.2% vaccination respectively (80). Within the state of Texas, state-wide rates of HPV vaccinations are calculated based off of sampling estimates. Comprehensive data for vaccination distribution has become publicly available as recently as 2019.This comprehensive dataset tracks only new occurrences of vaccinations.

While comprehensive measures of HPV vaccination rates among individuals in McLennan County are not available, a new public reporting of HPV vaccine distribution by county was started in 2019 to address this knowledge gap. ImmTrac2 is a program sponsored and run by the Texas Department of State Health Services. This service offers the Texas Immunization Registry to all Texans free of charge and consolidates vaccination records to be shared between healthcare providers, schools, and other authorized entities. Imm2Trac also provides aggregate data, reporting monthly numbers of vaccinations (e.g., MMR, HOV, etc.) given by each county. Because of the newness of the program, measures of total vaccination rates are not available, with Imm2trac aggregate data only representing new vaccinations after the 2019 start date (81).

A preliminary analysis of the number of HPV vaccinations distributed and counted in McLennan County by the Imm2trac system was performed using RStudio modeling.

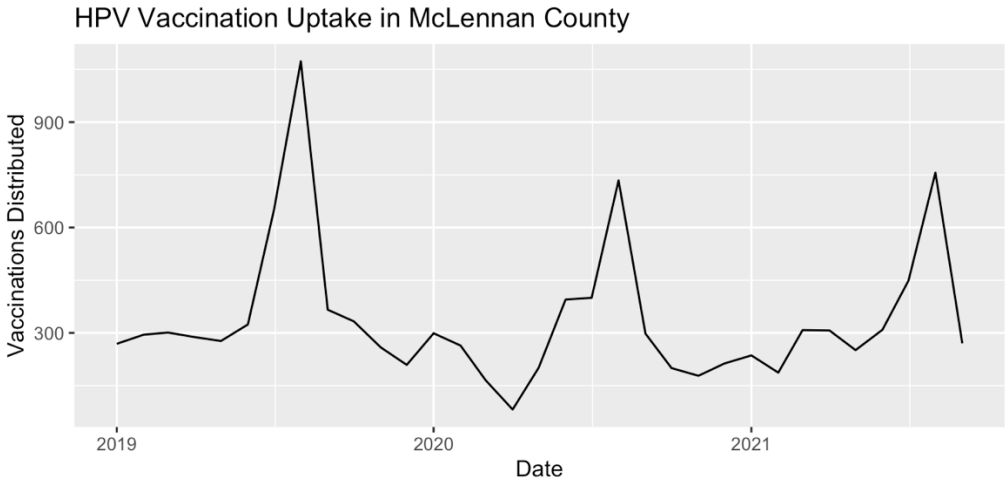

Figure 6: Mapping of HPV Vaccinations Disseminated in McLennan County was performed. Imm2Trac data does not include designation on vaccination number within the series.

Figure 5 displays aggregate data of HPV vaccinations distributed in McLennan County by month with no additional designation of vaccination number within the series. Seasonal vaccination trends in figure 5 are noted with pattern of increasing vaccinations in the summer months, the month of August in particular. An interesting trend to note is the sharp decrease in vaccination beginning in March of 2020, corresponding to the advent of widespread COVID-19 infections and associated restrictions in the United States (82) . Despite these restrictions on non-emergent medical visits, McLennan County has managed to increase vaccination post-COVID, but levels of vaccinations have not returned to pre-pandemic levels.

Larger counties, such as Harris County show similar patterns of vaccinations with large spike in the number of HPV vaccinations distributed in the month of August. It can also be noted that Harris County experienced a similar pattern of a drop in vaccinations surrounding the start of the COVID-19 pandemic.

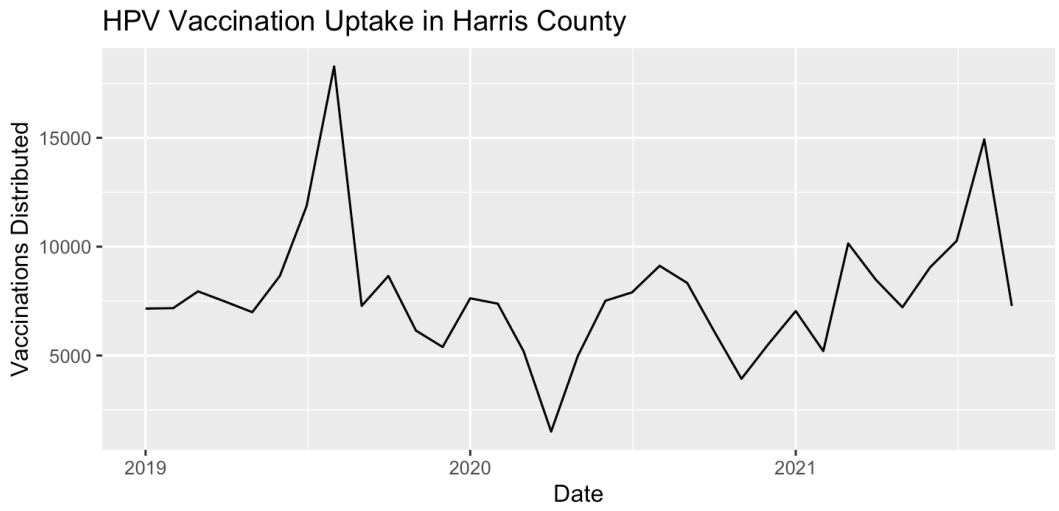

Figure 7: Mapping of HPV Vaccination Distributed in Harris County was performed. Imm2Trac data does not include designation on vaccination number within the series.

To compare the rate of vaccination in McLennan County relative to other counties, county population data was taken from US Census Bureau Data and merged with existing Imm2Trac data to provide a percentage of the population being vaccinated every month in order to compare across counties in a more meaningful way. When comparing the percentage of the population receiving a dose of the HPV vaccine on a monthly basis, McLennan County performed at or above vaccination rates of other large counties (Harris, Dallas, and Travis), nearby counties (Bell), and counties with notably high rates of vaccination (Hidalgo).

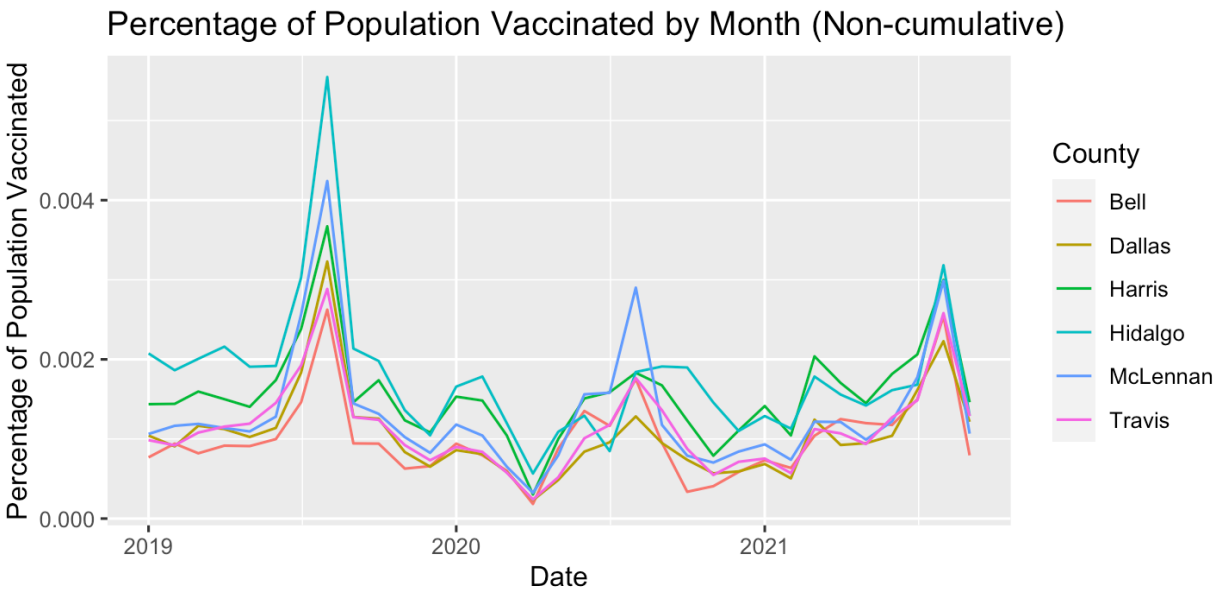

Figure 8:Percentage of Target Population Receiving Vaccinations Per Month: Number of individuals receiving an HPV vaccination by county by month were divided by total population counts provided by 2020 census information.

In this graphic, McLennan County holds up very well against other counties when comparing the percentage of the population receiving a dose of the HPV vaccination each month. McLennan county was superseded by only Hidalgo County during peak vaccination times, suggesting the presence of effective intervention methods in McLennan happening annually corresponding with the start of the school year. However, the vaccination percentage drops off between these highly productive periods, with McLennan County performing near the bottom of the distribution between the summer months.

It is important to note that the start date of the data collection for the Imm2Trac system is after the release of the needs assessment of McLennan County mentioned previously that calls attention to the need for women's health, specifically HPV prevention, to be a public health priority. While McLennan County is performing well with regard to the percentage of the population receiving a dose of the HPV vaccine on a

monthly basis, the data does not address issues of access to care that may have prevented older individuals from receiving the HPV vaccine series in its entirety. Additionally, because of the aggregate form of the data, it is not possible to track HPV vaccine series completion. No indicators of zip code or further geographic identifiers were provided through the Imm2Trac data to further stratify the data by location.

Target Populations for Intervention within McLennan County

Although all of McLennan County is designated as medically underserved, specific populations are disproportionately affected, as seen in the proportion of minority women without insurance and access to reproductive healthcare. To assess why particular populations of individuals requiring cervical cancer care do not receive cervical cancer prevention care at equal rates to the general population, exploratory data analysis of a dataset coming from the University of Utah's 2013 survey given to women 18 to 26 years of age was conducted. This survey details the demographic and attitudinal factors that may be associated with HPV vaccine initiation and completion (83). This analysis models overall attitudes of vaccine safety, HPV-specific vaccination attitudes, and the effect of perception on vaccination initiation and completion. The results show that educational attainment and racial identity play a significant role in participants' perceptions and knowledge of HPV and cervical cancer prevention.

In this mode of data collection, patients were prompted with a survey and were asked to rank their agreement or disagreement with various HPV and vaccine-related statements. Responses were measured on a Likert scale with 1 denoting strong disagreement with a given statement, and 6 denoting strong agreement.

The perceptions of vaccinations in general among the selected cohort were analyzed. The purpose of this preliminary analysis was to discover whether or not there were baseline differences in vaccination attitudes of racial groups and education levels.

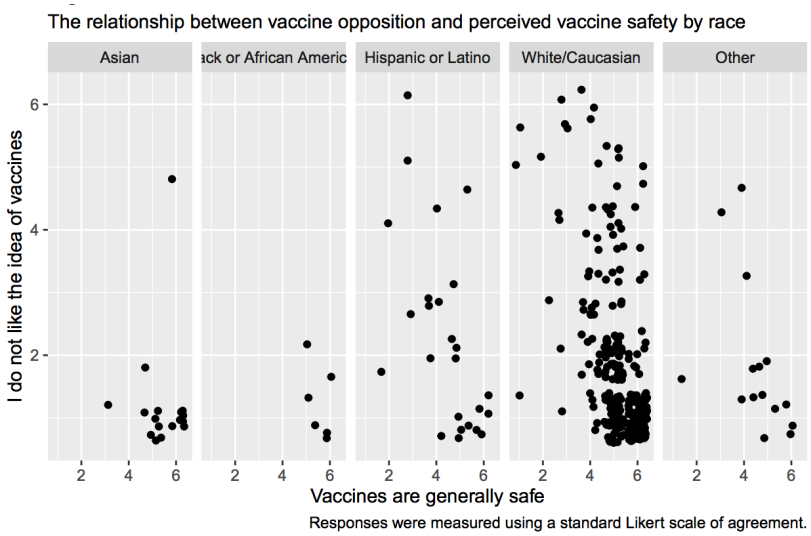

Figure 9: Responses were measured on a Likert scale with 1 denoting strong disagreement with a given statement, and 6 denoting strong agreement. Statements are provided on the left of the graphic. Data is taken from 2013 study conducted by the University of Utah (83).

Upon visualization of response distribution, there appears to be a consensus that vaccines are safe, with most of the survey data clustering between moderately and strongly agree (Fig.8). There is, however, more variation in the perceived safety in minority groups, specifically Hispanics and Latinos, as they are more inclined to be cautious of vaccinations. When analyzing these results concerning a disapproving opinion of vaccines, it is clear that most who believed vaccines to be safe also have a

positive or neutral view of vaccines.

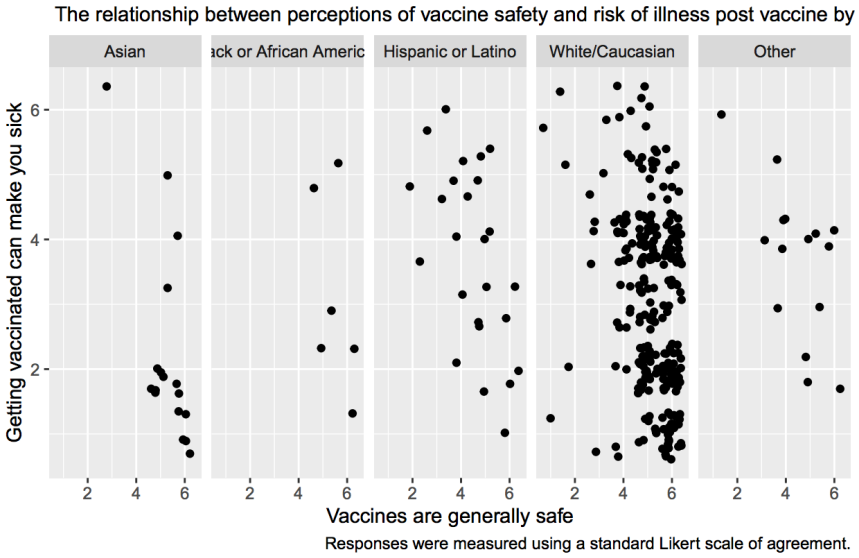

Figure 10: Responses were measured on a Likert scale with 1 denoting strong disagreement with a given statement, and 6 denoting strong agreement. Statements are provided on the left of the graphic. Data is taken from 2013 study conducted by the University of Utah (83).

To understand why there were differences in levels of vaccine opposition among racial groups, the responses focused on whether or not people believe vaccines make you sick were analyzed (Fig. 9). The relationship between vaccine safety perceptions and risk of illness after vaccination showed more variability between different racial groups than in the first figure, with many people agreeing with both of these statements. Again, more significant variation in responses among Hispanic and Latino populations and Asian populations is seen. This speaks to the complexity of understanding vaccinations and the beneficial immune response which they elicit.

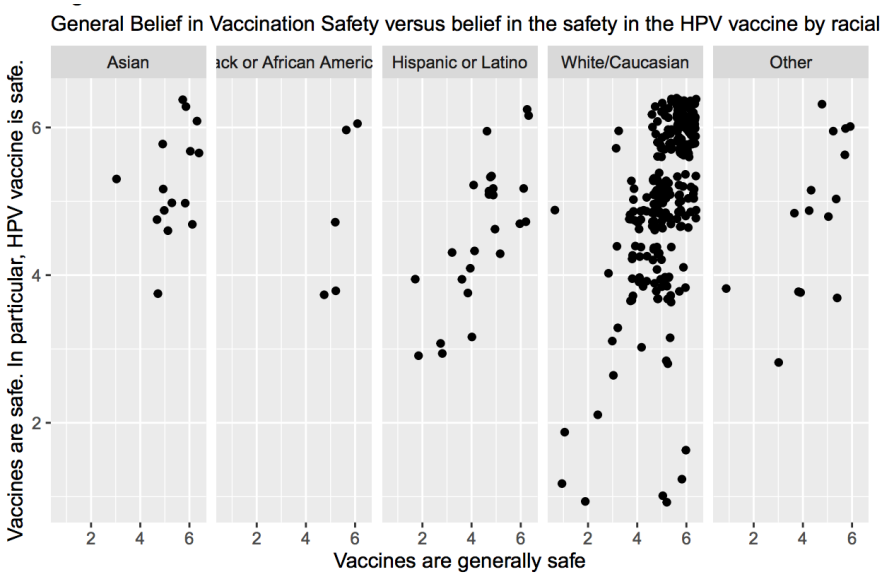

Figure 11 : Responses were measured on a Likert scale with 1 denoting strong disagreement with a given statement, and 6 denoting strong agreement. Statements are provided on the left of the graphic. Data is taken from 2013 study conducted by the University of Utah (83).

Significant proportions of Hispanic populations surveyed display distrust in the HPV vaccine compared to other ethnic groups (Fig.10). Surprisingly, there did not seem to be a significant difference between attitudes specific to the HPV vaccine compared to overall vaccine attitudes. This is opposed to the assumption that HPV vaccination perceptions would be, on average, more damaging due to its relative newness to the market and its ties to STI prevention.

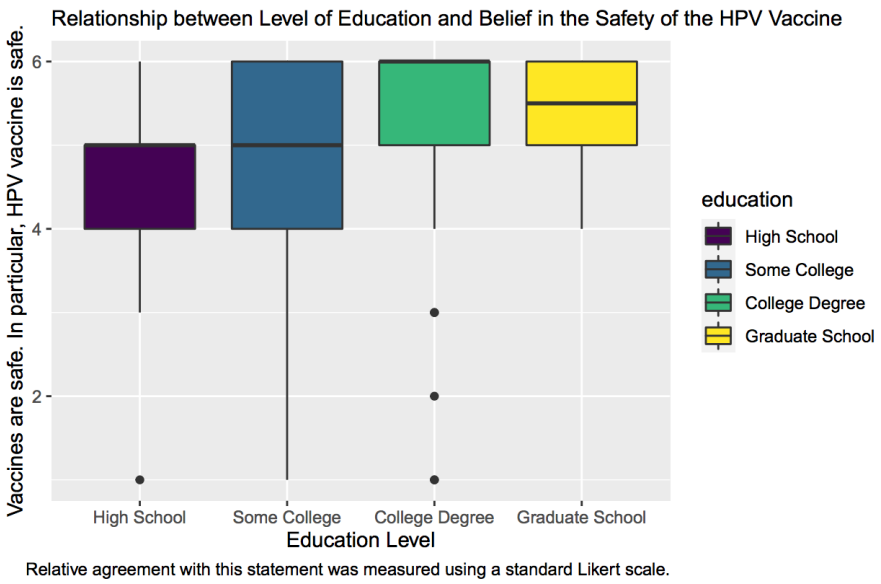

Figure 12: Levels of agreement with the statement, "Vaccines are safe. In particular the HPV vaccine is safe," was measured using a Likert scale of agreement with a score of 1 denoting strong disagreement and 6 denoting strong agreement. Data was subset by levels of educational attainment. Data is taken from 2013 study conducted by the University of Utah (83).

Survey responses concerning HPV vaccine safety across different education levels were analyzed (Fig.11). Among those with a college degree, the majority strongly agreed that HPV vaccines were safe. Those with a graduate degree moderately to strongly agreed, while those with some college had a more comprehensive array of beliefs, slightly agreeing to agree strongly. Lastly, it was noted, those with only a high school education were less likely to view the HPV vaccine as safe. Thus, it could be suggested that higher levels of education correlate with having greater trust in the HPV vaccine.

Negative vaccine-related attitudes are a strong indicator of vaccine utilization (84). These attitudes must be taken into account when determining which populations are at risk for not initiating the HPV vaccine series. Additional data from Waco residents would have to be collected in order to provide a more comprehensive and area specific

analysis of difficult to reach populations. None-the-less, target groups can be identified for customized intervention within McLennan County based on this information.

Within McLennan County, the following zip-codes have been identified as areas of high need for intervention based on healthcare access challenges: 76704, 76705, 76707, 76710, and 76711. Within the aforementioned areas, there are only 10 clinical locations available for patients to receive HPV vaccinations or cervical cancer screenings, all of which are branches of Waco Family Medicine. Further restrictions are placed on available clinical locations based on the insurance status of people seeking care. It is estimated that 22% of McLennan County residents rely on Medicaid to receive care. An additional 18% of the McLennan County population reports not having any form of health insurance. Both scarce clinical availability and below-average rates of insured persons stagnate the effort to prevent cervical cancer. These two factors are identified as underlying causes for the 54.9% rate of HPV vaccinations within the state of Texas and the sharp decline in vaccination rates between the months of September through July.

By addressing both disparities in vaccination availability and perception, the proposed clinic intervention will work to eliminate HPV infection and cervical cancer within McLennan County. Extrapolating data from McLennan County needs assessments allows for the proposed clinic to target areas and zip codes disproportionately affected by disparities in healthcare. Application of survey data can further narrow the target population of the clinic to include individuals of minority populations and lower educational attainment to receive educational material and counseling thereby, increasing trust in the HPV vaccine.

CHAPTER THREE

Cervical Cancer Intervention Clinical Proposal for McLennan County

Clinic Proposal

To meet the challenge of elimination of cervical cancer in McLennan County, intensive interventions are required. Promotion of HPV vaccination uptake and cervical cancer screening through the use of short-term clinics has the capacity to greatly increase treatment-seeking and treatment-compliant behaviors among patient (85)(86). Semi-annual clinic events are proposed herein to increase the rate of HPV vaccination initiation and completion in McLennan County as well as to address to the needs of the unvaccinated populations through screening. The proposed clinic will occur biannually in partnership with Baylor Health services and will include HPV vaccination and cervical cancer screening for all pre-enrolled individuals. We predict that annual clinics of this nature over a period of 5 years will result in 1500 unique individuals receiving at least 1 dose of the HPV vaccine series and 500 unique individuals receiving cervical cancer screening. The following sections outline the rationale for qualification for clinical enrollment, approaches to health education, cultural awareness in care, and insurance coverage for clinic participants.

Model for Clinical Design

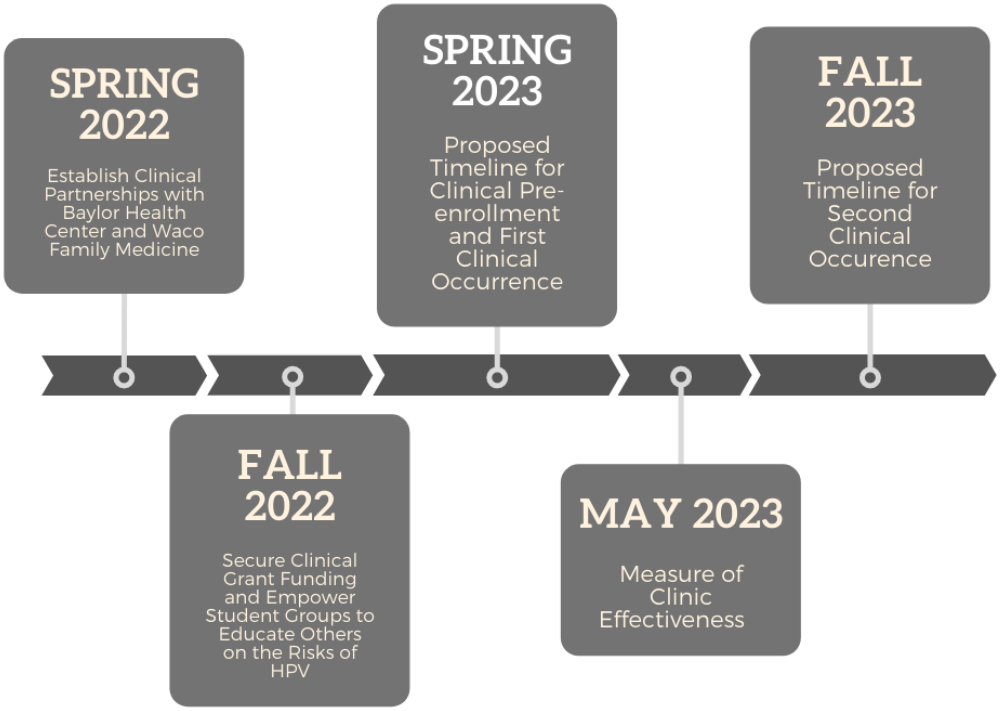

Figure 13: Model for Clinical Design with Projected Timeline

Combination of Services Strategy for Clinic Target Populations

The proposed clinical design combines HPV vaccination and cervical cancer screening in a single-visit clinical program. These two methods of cervical cancer prevention are often implemented as non-coordinated programs, but the combination of services reduces travel and insurance-related barriers to care by providing a singular clinical visit free of charge to participants (87). A combined of offering of services strategy has been successfully implemented in several clinical settings, often referenced as the "HPV-Faster Protocol" (88). In this treatment protocol, all vaccination-aged

participants not previously initiating or completing the vaccination series will receive the first or subsequent dose of the HPV vaccine (Gardasil 9) to continue or complete the series (89). Each clinic will A) offer HPV vaccination only to individuals aged 9-26 who do not have a current HPV infection and B) provide HPV testing and cytology via Pap testing for all people with a cervix due for screening according to national guidelines. Finally, any patient presenting with a screening result indicating HPV infection or cytologic abnormalities will then be offered a follow-up diagnostic test and treatment in accordance with recommended guidelines (90).

Core Tenets Clinical Design

The complex nature of HPV and cervical cancer awareness among patients has been explored at great length, and persistently low screening and vaccination measures demonstrate the need for intervention (91). Understanding the complexity of medical indigence in relation to cervical cancer prevention requires healthcare providers to recognize and combat biologic, social, and psychological risk factors which lead to poor health outcomes and low levels of treatment compliance. Efficient cervical cancer care begins with an understanding of predisposing and perpetuating risk factors that form a patient's understanding of HPV and cervical cancer (85). Understanding health-related risk factors greatly impacts a patient's perceived risk of contracting HPV as well as treatment-seeking behaviors in the case of HPV infection (92). The need for comprehensive programs combating disparities in health outcomes has been identified by several government agencies, and the elimination of these disparities is the goal of a four-step plan proposed by the Affordable Care Act of 2010 (93). This plan identifies the need for A) prevention and early detection of disease, B) healthcare access and coordination,

C) insurance coverage and continuity, and D) cultural competency in the effort to reduce healthcare disparities in the United States (94). Low measures of clinical access and educational attainment in McLennan County make this location an ideal subject for aforementioned interventions. The proposed clinic's design keeps these four goals at the forefront of the program.

I. Education for Prevention and Early Detection

Educational components to HPV vaccination efforts have been shown to increase both vaccination uptake rates as well as rates of vaccination series completion in several clinical settings (95). However, the gaps in effectiveness between different programs suggested that not all educational efforts achieve the same impact (96)(97)(98). Clinical effectiveness is measured by both subjective measures of patient satisfaction as well as objective measures of increased vaccination knowledge, increased rates of vaccination uptake and completion, and increased rates of cervical cancer screenings. The goal of the educative component of the proposed clinic is to equip patients with the knowledge needed to positively receive messages encouraging vaccination and screening (99). This will occur via tabling at community events and parent education during school-based events.

Under this framework, program materials should be designed with the goal of bringing all participants to a level of understanding where messages as to their role in HPV and cervical cancer prevention can be positively received. Education for prevention and early detection is a voluntary first step toward enrollment in the proposed clinic. Community members will be able to enroll in the clinic program regardless of attendance at these educational events. However,

following each of the educational efforts, information on how to enroll as well as live support will be available to all participants to encourage participation in the clinic program.

II. Healthcare Access and Coordination

With regard to healthcare coordination, following the availability of preliminary educational programs, continuity of education and support will be provided to all patients through the use of patient navigators to improve healthcare access via coordination of care. A patient navigator is a trained person who assists and advises patients, families, and caregivers along the care continuum. Navigators need not be certified medical professionals, but some entry-level practitioners serve as patient navigators. Navigators serve to decrease healthcare system barriers, including but not limited to, insurance coverage gaps, barriers of travel, and issues of understanding in medically complex cases, efficiently and effectively, at any point along the care continuum. With 25% of Waco residents reporting a lack of a primary provider, navigators have potential to be highly effective in regard to increasing patient enrollment into a healthcare system following initial enrollment. Although there is no singular model for effective patient navigation, navigation in this context will be focused more on reducing concrete barriers to care rather than an emotionally inclusive approach to care as seen in other settings (100). The utilization of patient navigators in medically indigent populations as well as in medically underserved areas has been shown to significantly increase the number of healthcare-seeking behaviors in these groups (101). Here, healthcare-seeking behavior is defined as "any activity

undertaken by individuals who perceived themselves to have a health problem or to be ill for the purposes of finding an appropriate remedy"(102).

The patient navigation program was designed for a cancer care setting, and several studies have shown that navigators significantly increase the rates of healthcare-seeking behaviors after cancer screenings. In a recent study following a cohort of female patients receiving breast cancer screenings, of those navigated, 87.5% completed recommended breast biopsies, compared with 56.6% of the non-navigated patients (103).

Coordination through patient navigators served to increase entry into and subsequent use of the healthcare system, referred to here as healthcare access (104). Effective access to healthcare requires continued contact with providers after the day of the clinic. Encouraging participants to enroll as patients with the partnering Federally Qualified Healthcare Center allows for a record of care to be established for all participants. Following the day of the clinic and subsequent enrollment with the partnering FQHC, patient navigators will provide patients with information leading up to the day of the vaccination and screening clinic, making themselves available as a resource for patients. Following the day of the clinic, navigators will serve to increase the proportion of patients receiving follow-up care for continuation of vaccine schedule or additional care in the case of an abnormal screening result.

III. Insurance Coverage and Continuity

Grant funding for the proposed clinic covers only clinical costs incurred on the day of the event. Coverage for care required after the clinic requires

enrollment in a health insurance program (105). According to the most recent United States Census Bureau information, 18% of people aged 0-65 are uninsured in McLennan County, 9.2% higher than the national average. Furthermore, this measure demonstrates a 3% increase in the proportion of the population in McLennan County living without health insurance compared to 2016. As of 2016, 35% of McLennan County residents reported receiving insurance through Medicaid or other public aid.

Medicaid was made widely accessible with the Affordable Care Act (ACA) of 2010. The ACA includes provisions to expand both Medicaid and private coverage, with the goal of reaching the large uninsured population in 2010 when the law was enacted. At the time of the introduction of the Affordable Care Act, nearly 50 million people living in the United States were uninsured. Prior to the ACA, states covered low-income children and their families through Medicaid and the Children's Health Insurance Program. However, state coverage often did not include non-elderly adults without children. There were additional adult parent populations that were excluded from care even once their children qualified for coverage. Since the advent of the Affordable Care Act, Medicaid has been expanded in many states to cover most people up to 133% of the federal poverty level compared to the original standard of 400% of the federal poverty level. However, Texas remains one of the few states left to continue to block the previously mentioned expansion of coverage, rendering it the state with the highest levels of uninsured adults in the nation (106). Additionally, important exceptions to ACA coverage apply to noncitizens. Undocumented immigrants are

excluded from the ACA's major coverage expansions. On the basis of laws that preceded the ACA, some groups of lawfully present noncitizens are also ineligible for full Medicaid coverage, including most legal permanent residents who have resided in the United States for less than 5 years (93).

The Children's Health Insurance Program (CHIP) was created through an amendment to the Social Security Act to provide health care coverage to uninsured children not already eligible for Medicaid. Like Medicaid, CHIP is jointly financed by states and the federal government. States have the option of using CHIP funds to expand their existing Medicaid program, create a separate stand-alone CHIP, or do a combination of both (107). In 2013, Texas Children's Health Plan (CHIP) enrollment in McLennan County was 0.2%. Of the more than 30,000 children living below the poverty line in McLennan County, 99.8% receive health insurance through Children's Medicaid.

Navigators can play an important role in not only helping patients gain consistent access to insurance through programs such as Medicaid and other publicly-funded programs but also in helping them to remain consistently insured. The role of the navigator extends beyond insurance access to include explanation of policies and policy options to patients. Patient navigators also work as advocates for the rights of groups who have been historically excluded from coverage or care. Furthermore, navigators will be vital in prompting patients to receive additional vaccinations and follow-up screening. Finally, navigators may play a role in advising patients, especially medically complex patients, in their choice of health insurance plans (108).

IV. Cultural Competency

As shown through ethnic differences in cervical cancer perceptions in Chapter 2, culture plays a compelling role in levels of trust in health-care as well as the likelihood to seek out healthcare, especially when considering HPV and cervical cancer. The proposed clinic suggests the use of patient navigators not only for the provision of clinic and insurance information to patients but also the provision of culturally-nuanced education on the topics of HPV and cervical cancer. Adaptation of patient navigators to this role has been shown to be effective in Hispanic/ Latino populations, a key demographic for intervention in McLennan County. Partnering members of clinical target populations will be sought to conduct cultural inclusive educational events. One such program, the AMIGAS educational effort is a bilingual intervention designed to increase acceptance of cervical cancer screening among Latina women of Mexican descent. This educational effort led by navigators of similar ethnic and cultural backgrounds, referred to here as promotoras, included educational videos, body diagrams, and bilingual educational activities. Pap testing increased in all three AMIGAS intervention groups tested as compared to control groups. (109)

Funding

Funding for this project will be provided either by The University of Texas M.D. Anderson Cancer Center's cervical cancer prevention grant awarded through the Cancer Prevention & Research Institute of Texas (CPRIT) or by additional funds jointly secured by the partnering institutions. The goal of this work is to create interventions combining cervical cancer screening and HPV vaccination, which will result in increased rates of

detection and treatment of preinvasive cervical disease. This early detection will ultimately decrease cervical cancer incidence and mortality in the state of Texas if the combined interventions can be further refined and disseminated across Texas (110). (111). Partnership with Baylor University serves to increase efficiency of labor in advertising partnerships and in making logistical arrangements to create a clinical location in central Texas. Participating Baylor students will gain exposure to the field of gynecologic oncology as well as incidental education through the clinical experiences of conducting health promotions events to encourage enrollment, assisting with welcoming patients to the clinic, and shadowing physicians in screening and patient education efforts.

Local Partnerships and Clinic Logistics

Baylor Student Health Advisory Council (SHAC) is a student led initiative to develop health outreach programs within the Baylor community. Partnership with this organization serves to provide a physical location for clinical events and answers to logistical necessities including refrigeration for vaccines and private areas to conduct screenings on the day of the clinic. Additional partnerships with local healthcare providers to provide staffing for the event are required. Requirements of partnering institutions include the provisions of a physical location for clinical occurrences and staffing for clinic events as well as the hosting of educational pre-enrollment events. CPRIT grant funding would cover costs associated with acquisition of HPV vaccinations.

Continuity of Care Post-Clinic

Both vaccination and screening services provided at this clinic require the availability of a continued source of care to complete the series of HPV vaccinations or receive diagnostic care in the instance of an abnormal Pap test. There is a linear trend in increasing cervical cancer screening rates when one goes from having no usual source of care, to having a usual source, and to having a regular clinician at that usual source(112). Emphasis on continuity of care, especially on a usual source of care, may help to bridge the gap in access to cancer prevention services faced by medically underserved populations (113). Continuity of care will be achieved by introducing medically underserved populations to FQHCs that are focused on expanding insurance coverage and care to include target clinical populations. Key-informant interviews at similarly designed single-occurrence clinics revealed that patients were more motivated through their participation in the clinic to read educational materials or discuss screening with providers, suggesting there are continued benefits following one-time clinics (43).

Evaluation of Clinic Effectiveness

Clinic effectiveness will be measured using both qualitative and quantitative measures of success. The number of individuals beginning the HPV vaccination series, receiving a second dose of the vaccine, or completing the vaccination series will be tracked and reported in aggregate to measure the impact of the clinic on overall county vaccination rates. Data for people with a cervix receiving cervical cancer screening tests will also be collected and reported correspondingly. Surveys measuring clinic effectiveness will be given at the end of the visit to all patients or guardians (if the patient is a minor) measuring program satisfaction. Measures to be included in the survey of satisfaction

include perceptions of provider helpfulness, measures of provider trust, and overall ease of program access. In addition to this feedback, knowledge of HPV/cervical cancer, willingness to screen or vaccinate, as well as knowledge of healthcare resources will be measured before and after clinical visit to measure the impact of patient education. All collected data will be analyzed using chi-square measures of aggregate differences between groups before and after the clinic.

Additionally, the level of vaccination schedule compliance and the proportion of patients receiving follow-up diagnostic care, if indicated, among clinic participants will be measured up to 18 months after participation in the clinic event. For reasons indicated previously, follow-up care and continued access to medical care are vital to eliminating cervical cancer at a local level. These measures of medical compliance will serve to further test the effectiveness of the clinic design.

Evaluation of Cost-Effectiveness of Proposed Clinic

Approximately 30-40 of the HPV viral types infect the genital tract, conferring a gradation of symptoms. Within these 30-40 viral types, there are several identified oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, and 58); persistent infections with these viral types are associated with the development of cervical, vulvar, vaginal, and anal cancers (9). In addition to oncogenic viruses, several non-oncogenic HPV types which infect the genital tract (6, 11, 40, 42, 43, 44, and 54) are associated with the development of benign genital warts (10).

The economic costs of HPV-related genital warts and cervical cancer, including screening to prevent cervical cancer, are estimated to be at least $4 billion annually in the United States. When performing cost-benefit analysis on HPV vaccination of 12-year-old

females in the United States, it was estimated that individual vaccination improves life expectancy by 2.8 days at a cost of $246. Furthermore, modeling suggests that if the present cohort of 12-year-old girls living in the United States were to all receive the HPV vaccine, more than 1,300 deaths due to cervical cancer could be averted throughout the cohort's lifetime. Despite different methodologies and various assumptions, most studies were consistent in their conclusion that multiple age cohort vaccination was economically viable (114). Vaccination of girls against HPV is considered highly cost-effective, and even when the indicial benefits are small, the population level benefits are significant (115).

CHAPTER FOUR

Predictive Modeling for Local Elimination of Cervical Cancer in McLennan County

In the effort to achieve local elimination of cervical cancer, HPV vaccination and screening clinics will serve to decrease the rate of persistent HPV infections and subsequent cervical cancer development within McLennan County. The achievement of elimination of cervical cancer is predicted to require a 90% vaccination rate and 70% of people with a cervix receiving a pap smear before the age of 35 and again by age 45. Predictive modeling in regions receiving long-term cervical cancer care interventions forecast that local elimination of cervical cancer is a goal achievable within the next 30 years (116). Pre-intervention predictive modeling of HPV vaccination rates in McLennan County was performed to provide further justification for clinical intervention. Furthermore, prognostic modeling was run on data, including simulated data points, to anticipate the effect of a single clinic occurrence on vaccination uptake in McLennan County. Together, these projections suggest that a single clinic, alone, will not result in elimination of cervical cancer in McLennan County; however, the effects of increased intervention serve to provide benefit at the level of the individual, with the hopes of exponentiating the effect of vaccination clinics through education and social change.

Parameters for Local Elimination of Cervical Cancer

In 2020, the World Health Organization set goals designed to assist communities in achieving local elimination of cervical cancer, as well as parameters to define achievement of cervical cancer elimination (117). A case maximum of 4 cases of cervical

cancer per 100,000 of individuals with a cervix has to be maintained within the designated area to achieve elimination of cervical cancer. The WHO suggests a three-part approach to ensure this goal is met. Firstly, vaccination series completion of 90% of all girls must be achieved by the age of 12. Secondly, 70% of people with a cervix must be screened for cervical cancer by age 35 and again by age 45. Lastly, 90% of individuals with cervical precancer must receive regular treatment and screenings as outlined in the most recent American Cancer Society guidelines (118). Due to a lack of public data availability, measures of the percentage of individuals with a cervix receiving cervical cancer screenings or treatment for cervical pre-cancer in McLennan County are not available. Therefore, progress toward 70% screening cannot be estimated, nor clinic impact on this front be accurately measured. However, vaccination rate data, made publicly available through the Imm2Trac vaccination tracking system, serves to model the current progress toward the goal of 90% of adolescent people with a cervix completing vaccination series against HPV. Bayesian time-series forecasting is used to predict the rate of HPV vaccination within the next two years, providing insight to the rate at which local elimination can be achieved within McLennan County.

Methods

Achieving Stationarity

Aggregate data of vaccinations (beginning in January 2019) in McLennan County provided by the Imm2Trac data system was used to perform Bayesian state space time analysis. Time series analysis uses data that is marked by equally spaced increments of time (e.g., minutes, hours or weeks) to model trends and forecast future outcomes. The existing Imm2TracHPV vaccination data included monthly measures of HPV vaccination

dissemination by county (81). Due to the discrete nature of time series data, it is possible to have a seasonal trend element built into a starting dataset. (119). As seen in figure 6, a highly seasonal trend can be visualized with peaks in vaccinations occurring in summer months, followed by rapid decline in vaccination rates in the months between peaks. To model using time series analysis, data must be made stationary by accounting for existing seasonal trends. The removal of strong seasonal patterns to vaccination schedules as noted in Chapter 2 was the first step in the time series predictive modeling process; it functioned to prepare the data prior to model creation. By creating stationary data, the mean and variance of the series are no longer a function of time. To achieve stationarity, a linear regression model was applied to McLennan County HPV vaccination data taken from the Imm2Trac data set. This linear regression removes the seasonal nature of both mean and variance to provide the model with stationary data.

Model Selection

To account for the seasonal trend seen in the Imm2Trac data, a seasonal exponential smoothing model was selected as the best fit for a base level modeling of expected numbers vaccinations being distributed in McLennan County by month with projections into the year 2024 (120). This base model weights the most recent observation most heavily, with the weighting of previous observations decreasing exponentially with time. Consequently, the vaccination data from years 2021 and 2020 are most influential in predicting the number of vaccinations dispensed in the coming two years with no clinical intervention. Exponential smoothing allows for seasonal trends to be incorporated into the predictive model without skewing predictive results. Limitations to this form of modeling surround the inability of the model to account for correlation

that the variable of interest has with itself throughout the time-frame of data collection. This internal correlation is referred to within time-series analysis as autocorrelation (121).

Analysis of Model Accuracy

After output generation, the model accuracy was calculated using the Akaike Information Criterion (AIC). An AIC score is assigned to the model to estimate the prediction error of a generated model. This score allows for comparison of the accuracy of generated models. A lower AIC score suggests a more powerful and accurate predictive model. Effective use of the AIC tool requires the generation of several models for comparison. Differences in model techniques when generating outputs for comparison for this project were two-fold. Firstly, differences in seasonal variability measures were used to see the effects on predictions. This is because the spikes in vaccination trends were not exactly 12 months (or time units) apart. The first spike visualized is in July of 2019. The second spike is in August of 2020, and the third is in August of 2021. Seasonal variability values of both 11 and 12 (denoting an expected repetition of seasonal variation every 11 or 12 months respectively) were used. A twelve-month seasonal variability measure was determined to increase the predictive power of the model. The second variable manipulated in the generation of these models was the amount of sub-set data for both training and testing. In order to complete any form of statistical modeling, data must be separated into categories of testing and training. Training data (usually around 80% of total dataset material) is randomly sampled and subset from the total dataset and used to generate a pattern. The remaining data, referred to as test data, is then used as a comparison to training data predictions. The closer the model algorithm is to predicting test data values, the more accurate the model is considered to be. Figures 13, 14, and 15,

produced AIC scores of 420.9, 447.7 , and 449.8 respectively (in comparison to AIC > 720 of rejected models). While these values can be helpful in comparing the effectiveness of proposed models, they are relative and do not reflect how well the model fits the data itself.

To predict the effects of a clinical intervention, a simulated data point was added to the most recent spike in vaccination distribution (August 2021) representing the predicted impact of the clinic effort proposed herein. The goal of each clinical event is to vaccinate 150 unique individuals, and the simulated data was produced to reflect this progress. The most recent spike from August 2021 reported 756 individuals receiving a dose of the HPV vaccine, so a simulated point of 906 was used in place of reported vaccinations. Predictive modeling was then run again, using the same parameters identified as described in the previous paragraph, to forecast the effects of a single intervention clinic (mock intervention added to existing vaccination rates in August of 2021) on overall rates of HPV vaccination in McLennan County projecting into October of 2024. Projections were made using the TBATS package in R, an exponential smoothing state-space model which allows for non-integer seasonality cycles.

Results

Predictive Modeling of McLennan County HPV Vaccination Without Clinical Intervention

Modeling suggests that, without intervention, vaccination rates in McLennan County will not increase within the next two years (Fig.13). The annual number of Imm2Tract documented vaccinations will remain at ~ 4,000 doses administered

according to calculated predictions. Furthermore, the selected model does not project improved maintenance-level vaccination (vaccinations given between seasonal spikes) within this two-year period. This trend suggests a stagnation in growth of HPV vaccination from the already below- average state-wide level of 54.9% of Texas residents receiving an initial dose of the vaccine.

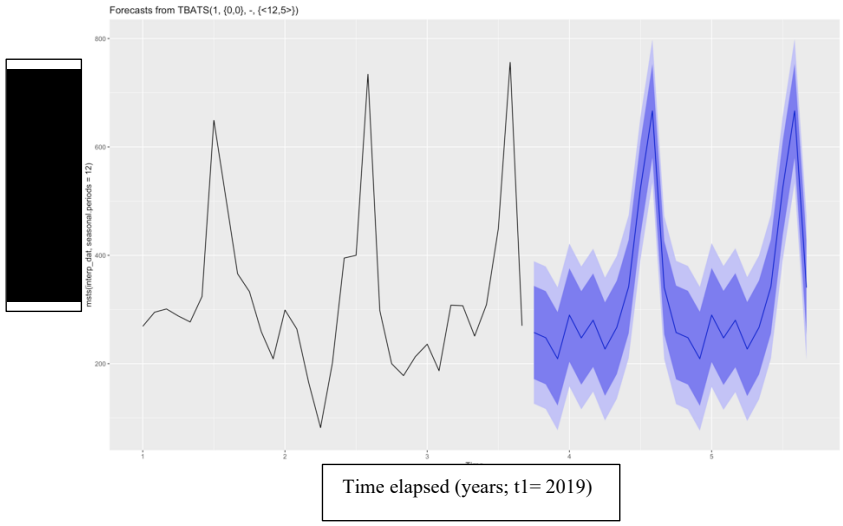

Figure 14: Bayesian time series analysis was performed on the Imm2Trac data set for HPV Vaccinations in McLennan County with no intervention. Time 1 represents October of 2019, and yearly time increments follow, projecting into October of 2024.

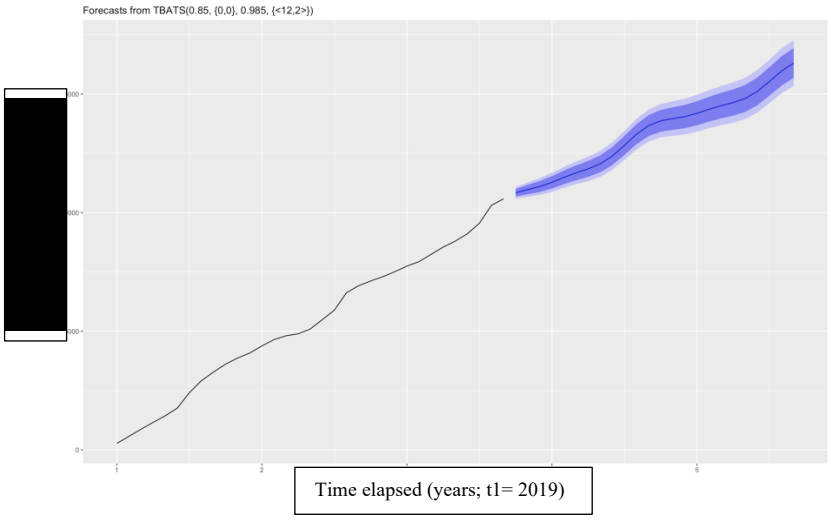

Figure 15: Forecasting was performed on cumulative vaccination measures to model growth of vaccination rates over time in McLennan County. Time 1 represents the number of vaccinations distributed in October

of 2019, and yearly time increments follow, accumulating vaccination numbers and projecting into October of 2024.

Cumulative vaccination data modeling demonstrates the changes in growth rate of vaccination from 2019 projecting into October of 2024 (Fig 14). The slope of the line tangent to the curve demonstrates only periodic variability. The results of this model reveal that without intervention, rates of HPV vaccination are projected to be subject to the same seasonal variability but with little to no improvement to the overall rate of vaccination in McLennan County. Because available vaccination data does not begin until the year 2019, this figure does not serve to model the current cumulative total of vaccinations disseminated. Furthermore, participation in the Imm2Trac program is optional, further reducing the power of the model. None-the-less, the model permits visualization of the rate of growth of vaccination distribution under the assumptions that Imm2Trac enrollment levels are high enough to accurately represent the target population.

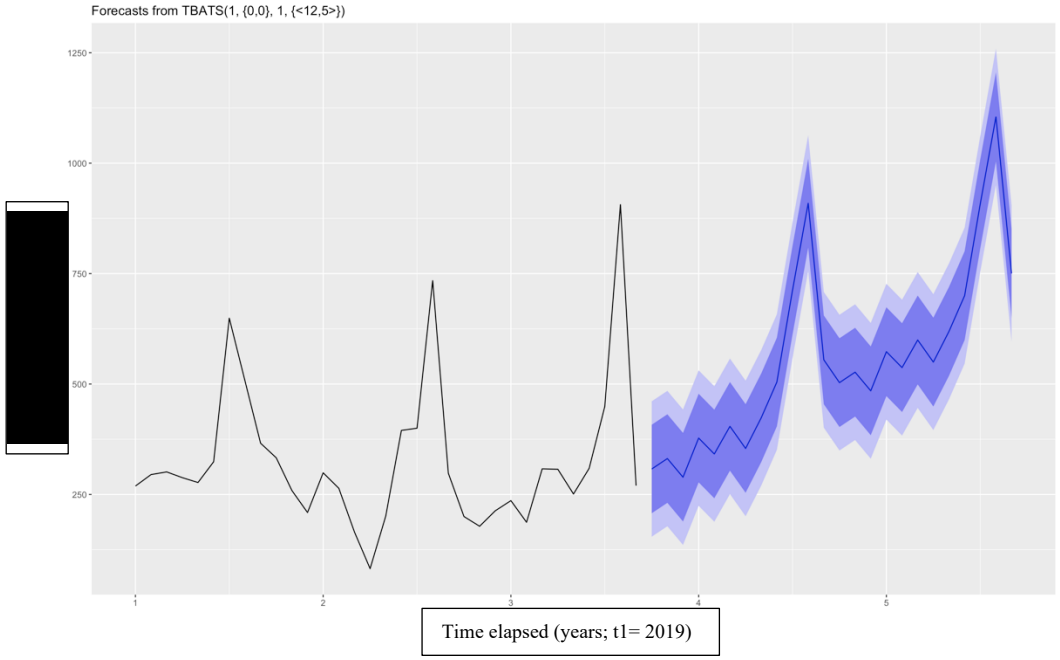

Figure 16: Bayesian time series analysis was performed on Imm2Trac data set for HPV Vaccinations in McLennan County, including a simulated data point representing the proposed clinical intervention. Time 1 represents the number of vaccinations in October of 2019, and yearly time increments follow, projecting into October of 2024.

Forecasting models were developed that included 150 additional HPV vaccinations being distributed in August of 2021; these models were used to represent the introduction of clinical intervention like that proposed herein continuing into 2022. The projections of this adjusted forecast show predicted improvement in the vaccination rates within McLennan County. The significance of this model's output lies in the positive trending seen in outside of seasonal variation. This represents not only an improvement in maintenance level vaccination between August spikes but also influences future vaccination rates due to continued clinic occurrences. This improvement, using the uppermost confidence limit of projections with and without intervention, predicts a ~ 3% increase in the percentage of the population receiving a dose of the HPV vaccine compared to pre-intervention predictions. Assumptions of target population size were

required given the lack of age specificity in available census data. Using the parameters of a targeted age range of 9 to 12 years of age and assumptions of equal age-distributions of the population aged 5 to 18, the estimate for target population size was determined to be ~14,967 individuals. The two-part design of intervention and education as seen in the clinical proposal suggests impacts could be greater than the 3% projected. It can be posited that success in the education of women and children regarding HPV vaccination will grow the impact of the program beyond what is projected here due to mothers who receive education regarding HPV vaccination and cervical cancer choosing to vaccinate future children regardless of participation in future clinics.

A limitation of this analysis is that an estimate of the percentage of individuals vaccinated in the county cannot be made. Very little data is published or made publicly available regarding McLennan County's current vaccination or screening efforts. Therefore, future projections for local elimination of cervical cancer using previously mentioned WHO parameters would be based on state-level vaccination rates. Furthermore, the rates of vaccination in the state of Texas are measured by two immunization tracking survey groups, The Behavioral Risk Factor Surveillance System and the National Immunization Survey (122). The use of surveys places predictions of vaccination dissemination farther from actual measures of vaccinations being distributed. In order to achieve the goal of local elimination of cervical cancer, comprehensive county-specific data measures of all three WHO measures of elimination must be collected and made publicly available (123)

Discussion

Predictive modeling suggests the introduction of intervention clinics, even after a single occurrence, will have positive impacts on the rate of vaccination uptake within McLennan County into October of 2024 and beyond. The predicted 3% of individuals receiving a dose of the HPV vaccination per year who otherwise would not have access to such care represents 450 children who have a 98% reduction in the likelihood to ever be infected with HPV. This reduction in infection can be translated in to a 98% reduction in the likelihood that these children will ever be confronted with a diagnosis of cervical cancer. This also represents an average of 3,150 possible sexual partners who themselves will not pass on the virus to others. This reduction in the incidence of HPV infection represents savings to the individual and to the healthcare system in the instance of abnormal Pap results and subsequent diagnosis and treatment. The proposed bi-annual clinical partnership, lasting 5 years in duration, will serve to further intensify the positive effects demonstrated through Bayesian time series forecasting.

Limitations of this form of projection can be primarily attributed to the need for long periods of discrete data upon which to base the model for accurate time-series projections. Therefore, although a 5-year projection rate would have been ideal given the duration of the proposed clinic, due to a limited 36 entries of data ranging from 2019 to 2022, only two years of projections were able to be calculated. Best practices for time-series forecasting suggest projecting no further than the duration of supplied data to preserve model accuracy. Further limitations to this form of modeling include the inability to further stratify vaccination rates by zip code or people group within McLennan County to further comment on the trend of differential healthcare outcomes in high-resource areas of the county. It is possible that improvements are move dramatic in

local communities with more barriers to care access. Additionally, assumptions were made to calculate the proportion of children aged 9 to 12 given current census information. The age range of 9 to 12 was calculated using an assumption of equal age distribution within the provided census data. Furthermore, given the assumptions for the very narrow targeted age-range, it can be assumed that the increase to the proportion of individuals (9 to 26) receiving a dose of the HPV vaccine that otherwise would not have received care is significantly lower than the 3% increase seen under the assumption that all vaccinations were given to children aged 9 to 12.

Summary

Cervical cancer has been demonstrated to be a completely preventable disease with available resources of vaccination and screenings. Up to 98% of persistent infections with HPV can be prevented through vaccination, and 91% of breakthrough infections or infections in unvaccinated populations can be treated before progression to cervical cancer through screening. McLennan County, TX currently houses a higher-than-average proportion of uninsured individuals as well as individuals living under the federal poverty line. Survey analysis of the area revealed only ~26% of women receiving a well-woman exam within their lifetime, and state-wide rates of vaccination against HPV (54.9%) fall far from goals of elimination (76). A proposed clinic-based intervention in McLennan County serves to increase rates of HPV vaccination and cervical cancer screening within the county. Finally, the positive effects of these intervention clinics have been modeled to bolster support for efficacy of the clinic.

The goals of increased HPV vaccination and local cervical cancer elimination require long-term, persistent intervention such as the biannual vaccination and screening clinic proposed herein. While modeling does not suggest local elimination of cervical cancer through HPV vaccination to be likely in the near future, uppermost predictions of a 3% increase the proportion of individuals in the target population receiving a dose of the HPV vaccine due to clinical intervention represent an additional 450 unique individuals per year receiving HPV vaccination compared to basal rates of vaccine uptake. The proposed clinical intervention serves to progress efforts toward local elimination of cervical cancer, with the immediate positive impacts being seen on an individual level. The work of this clinical intervention nor others is complete until no person dies of cervical cancer.

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