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Human Papillomavirus and its impact on vulnerable populations

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Human Papillomavirus and its Impact on Vulnerable Populations

By

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A Dissertation

Presented to the faculty of

The University of Nebraska Graduate College

in partial fulfillment of the Requirements

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Epidemiology

Graduate Program

Under the Supervision of Professor Shinobu Watanabe-Galloway

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Human Papillomavirus and its Impact on Vulnerable Populations

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University of Nebraska, 2016

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Human papillomavirus (HPV) is the most common sexually transmitted infection. The infection is higher in certain racial/ethnic groups and those who are immunocompromised including pregnant women. Because immune system is suppressed during pregnancy, women are at higher risk of various types of infection including HPV, a known risk factor for pregnancy complications. However, its role in adverse pregnancy outcomes is unclear. Another high risk population is Northern Plain American Indian. In the Northern Plains region, American Indian women have significantly higher rate of HPV infection than white counterparts and are infected with different types of HPVs than the general population. Because the prevalence of infection with these HPV types are higher in American Indian population, the impact of HPV vaccine on cervical cancer cases is expected to vary from other populations.

The objectives of this study were to explore the relationship between HPV infection and adverse pregnancy outcomes and to estimate the number of cervical cancer cases reduced by 9-valent vaccine among Northern Plains American Indian women. To achieve these objectives, an analysis was conducted using Pregnancy Risk Assessment and Monitoring System (PRAMS), in a population-based survey of pregnant women from

2004 to 2011. In addition, a hospital-based data analysis was conducted on women who delivered a live birth at Nebraska Medical Center between 2012 and 2014. HPV infection was diagnosed on the basis of a Pap test report. PROC SURVEYLOGISTIC (or logistic) procedures were used to examine the relationship between HPV infection and adverse pregnancy outcomes such as low birth weight, preeclampsia, preterm birth, and premature rupture of membrane. Additionally, to project the impact of 9-valent vaccine on the American Indian population, a compartmental deterministic model was developed. Our study found low prevalence of HPV infection among pregnant women. Significant associations were found between HPV infection and adverse pregnancy outcomes, including preeclampsia, preterm birth, and low birth weight. In addition, this study found that the 9-valent vaccine is associated with a greater reduction of cervical cancer cases among white women than among American Indian women. Overall, this study fills various gaps in knowledge about the impact of HPV infection on two vulnerable populations.

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LIST OF ABBREVIATIONS

HPV	Human Papillomavirus
PROM	Premature Rupture of Membrane
BMI	Body Mass Index
Pap	Papanicolaou
CIN	Cervical Intraepithelial Neoplasia
U.S.	United States
SIL	squamous intraepithelial lesions
ACIS	Adenocarcinoma in situ
AdCA	Adenocarcinoma of the cervix
AIN	Anal intraepithelial neoplasia
DNA	Deoxyribonucleic Acid
IARC	International Agency for Research on Cancer
PRAMS	Pregnancy Risk Assessment Monitoring Systems
HIV	Human immunodeficiency virus
NHW	Non-Hispanic Whites
ASCUS	Atypical squamous cells of undetermined significance
USPSTF	United States Preventive Services Task force
VLPs	virus-like particles
FDA	Food and Drug Administration
LEEP	Loop electrosurgical excision procedure
AI/AN	American Indian/Alaska Native

OR	Odds Ratio
CI	Confidence Interval
AOR	Adjusted Odds Ratio
SE	Standard Error
HNC	Head and Neck Cancers
HR	High Risk
MAR	Missing At Random
AGW	Anogenital warts
FUTURE	Female United to Unilaterally Reduce Endo/Ectocervical Disease
PATRICIA	Papilloma Trail Against Cancer in Young Adults

CHAPTER 1

INTRODUCTION

1.1. Human Papillomavirus Overview

1.1.1 Discovery of HPV

Human papillomavirus (HPV) is a small (50–55 nm in diameter), nonenveloped, double-stranded, circular DNA virus that infects the skin or mucosal epithelium. Throughout evolution, diseases associated with HPV infection were well documented. Greek and Roman physicians were well aware of skin and genital warts. In those days, the term condyloma (a word of Greek origin), meaning “a round swelling around the anus,” was used for genital warts.¹ In 1842, an Italian physician, Rigoni-Stern, analyzed the death certificates of individuals who died as a result of cancer in Verona during the period 1760–1839. He found that deaths related to cervical cancer were rare among virgins and nuns, as compared to married women or widows. This study indicated the possible association of cervical cancer with sexually transmitted disease.¹

Since ancient times, genital warts have been considered a result of sexual promiscuity and have been regarded as infectious. However, their link to sexual behavior was not firmly established until 1954. At the end of the 19th century, the infectious nature of common warts was confirmed by Payne. Their infectiousness was also confirmed by Heidingsfield, who described a prostitute who had developed condyloma lesions on her tongue as a result of oral sex.² In 1907, Ciuffo demonstrated the infectious nature of human warts by using a cell filtrate of a common wart to transfer the infection.³ This experiment also established the viral nature of the responsible agent.

By the end of the 1960s, herpes simplex virus type 2 was thought to be the cause of cervical cancer, but further studies failed to confirm it.⁴ The interest of

researchers in HPV arose when HPV was visualized in HPV warts with the help of electron microscopy. The role of HPV in the development of cervical cancer was postulated and analyzed by Harald zur Hausen. In 1983–1984, the first HPV types, 16 and 18, were isolated from cancer biopsies of the cervix and were later cloned.⁵ In 2008, zur Hausen was awarded the Nobel Prize for Medicine, for the discovery of the infectious etiology of cervical cancer.

1.1.2 High- and Low-Risk HPV Types

During the 1970s, the multiplicity of HPV types became apparent. The plurality of HPV was established by a series of research studies by zur Hausen and his colleagues as well as by Gerard Orth's group in Paris. These researchers discovered the first four HPV types in cutaneous warts and numbered them 1 through 4.⁶⁻⁸ Soon, serological evidence was provided to support this plurality, because there seemed to be no link between HPV types 1–4 and the HPV types found in condylomata accuminata, laryngeal papillomas, or any of the malignant tumors tested.⁹ For the identification of new papillomavirus types, the most conserved region within the genome, L1 ORF, is used. If the DNA sequence of the L1 ORF differs by more than 10% from the closest types and the complete genome is cloned, then a new papillomavirus is recognized.¹⁰ Differences in homology ranging between 2% and 10% define a subtype, whereas those of less than 1% define a variant.¹¹

More than 100 types of HPV have been identified, and 40 of those types infect the genital tract.¹² HPV types are categorized as high-risk and low-risk groups. High-risk types are oncogenic and more persistent than low-risk types. High-risk types cause cervical intraepithelial lesions and cancers of the cervix, anus, head and neck, penis, and vulva. High-risk types currently include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82. High-risk types 16 and 18 are responsible for 70% of

cervical cancers. The remaining types are considered to be low risk because they do not cause cancer. These low-risk types can cause skin warts, or condylomata acuminata, on or around the genitals or anus. ¹³

1.1.3 Structure and life cycle of HPV

The HPV viral genome consists of approximately 8000 base pairs¹⁴ and is organized into three regions: the early region I, which incorporates E1, E2, and E4-E7 and constitutes 50% of the genome; the late region (L), consisting of the L1 and L2 region, which forms 40% of the genome; and the genomic regulatory region, which represents 10% of the genome.¹⁵ The early region is involved in the DNA replication (E1, E2), transcription (E5), and cell transformation (E5, E6, and E7), while the late region encodes structural proteins of the virion (Figure 1).¹⁶

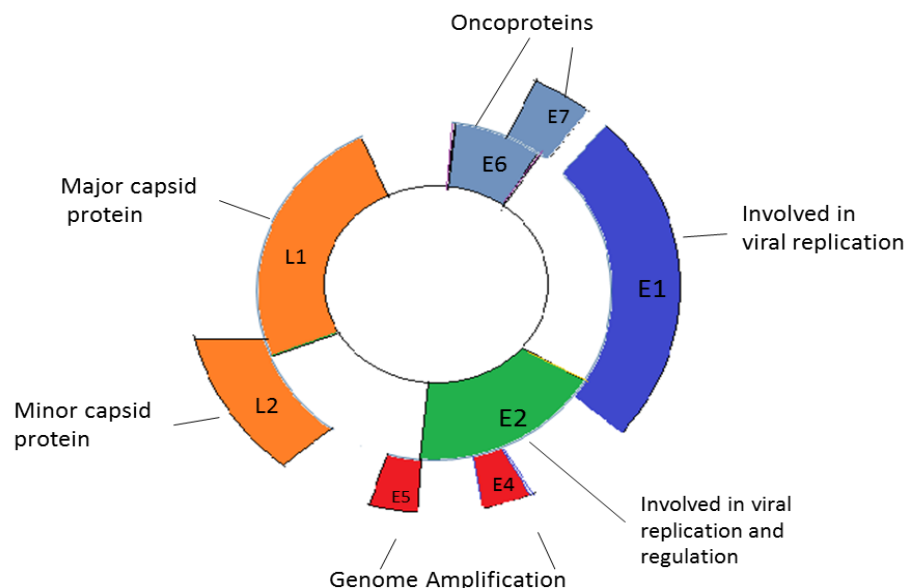


Figure1 Structure of HPV. Adapted from Malik H, *et al.* 2013.¹⁷

The papillomavirus structure does not contain any enzymes, lipids, or saccharides. The virus becomes inactivated at 70° Celsius, is stable at a pH of 3–7, and is killed after 30 minutes if kept at a temperature above 50° Celsius. HPV is resistant to solvents, acids, and X-rays.¹⁰ Because papillomaviruses initiate productive infections only within stratified epithelia of the skin, oral cavity, and anogenital tract, they are considered highly epitheliotropic. The life cycle of the virus is thought to begin when the basal epithelium cells become infected, probably at the site of injury.

1.1.4 Life cycle of HPV

The life cycle of HPV (Figure 2) begins when infecting viral particles reach the germinal cells in the basal layer through a small abrasion to the mucosa during sexual intercourse.¹⁸ The virus starts binding and then undergoes a conformational relaxation and enters the basal cell by endocytosis. This process of endocytosis takes about 2 to 4

hours. As soon as the virus enters the basal cells, the protein envelope is decomposed, and the viral DNA moves to the nucleus. Within the nucleus, the viral DNA exists in episomes but is separate from the host DNA. This is usually linked with the presence of low virus copy numbers and no cytological abnormalities.¹⁹

In the maturing squamous epithelium, viral assembly occurs as the virus amplifies its DNA to high copy numbers and synthesizes capsid proteins.²⁰ This in turn results in the release of amplified virus from terminally differentiated squamous cells. Next, the HPV early genes E6 and E7, which are required for malignant transformation, are produced in both the lower and the upper layers of the epithelium. The HPV L1 and L2 proteins form the viral capsid. These proteins are produced and assembled into virions that stimulates the immune response and are released only in the terminally differentiated outer epithelial layer.²¹ In very few scenarios, persistence, integration, and transformation occur. Usually, in order to integrate into the host cell DNA, the HPV DNA disrupts the E2 gene, enabling the circular genome to become linear. This disruption of E2 gene results in cessation of viral synthesis and also activates the deregulation of E6 and E7. The E6 gene binds and degrades p53 while the E7 gene inactivates the retinoblastoma gene. Retinoblastoma and p53 are both tumor suppressor genes, and inactivation of these genes causes genetic instability, prevention of apoptosis, and uncontrolled cellular proliferation, which may result in cancer.²¹

Unlike other infections, the life cycle of HPV is actually hidden from the host immune system. There is no systemic response, no viremia, and no blood-borne phase.

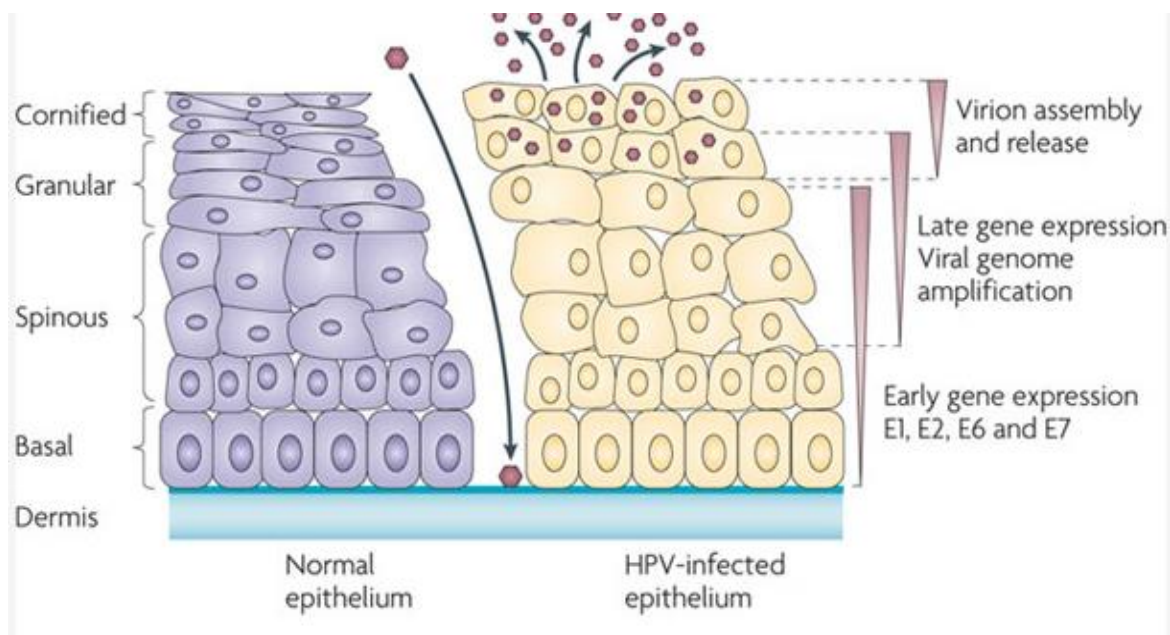


Figure 2. Life cycle of HPV. Adapted from Moody CA, *et al.*, 2010²²

1.1.5 HPV Risk Factors

Sexual activity is one of the major risk factors for acquiring HPV infection. Having multiple sex partners is associated with greater risk of infection. However, having sex with only one partner does not entirely eliminate the risk of procuring the infection.²³ Some of the other risk factors for HPV include co-infection with other sexually transmitted diseases, smoking, and a weakened immune system. In addition, use of hormonal contraceptives for longer duration is believed to be associated with increased risk of infection.²⁴

Age is another major risk factor, in that HPV infection is most common in sexually active men and women who are 21-24 years old. Although this association could be the result of risky behaviors among this age group, evidence indicates this

association may have biological causes.²³ Squamous cells are the most common type in adults, whereas columnar and metaplastic cells are predominant in adolescents.

Neonates are born with an abrupt squamo-columnar junction present on the ectocervix. At the time of puberty, the columnar epithelium gradually transforms into the squamous epithelium. This process is known as squamous metaplasia. During this process, large areas of transitional squamous, glandular, and metaplastic cells are formed, all of which support HPV replication.²⁵

1.1.6 Transmission of HPV

HPV is usually transmitted during sexual intercourse through contact with infected cervical, vaginal, vulvar, penile, or anal epithelium. However, it can also be transmitted through nonpenetrative sexual contact, such as oral-genital or digital-genital contact.²⁶ Inconsistent use of condoms also increases the risk of transmission of the virus. However, condom use is only 70% effective in preventing the transmission of HPV because there is still contact with genital skin.¹³

In addition to horizontal transmission, rarely vertical transmission of HPV from mother to fetus can also occur.²⁷ When transmitted vertically, HPV can cause juvenile-onset recurrent respiratory papillomatosis and laryngeal papillomatosis in infants.²⁸ A study conducted by Tenti et al. investigated HPV type-specific concordance between mother-infant pairs and observed that HPV types carried by HPV-positive newborns were identical to those found in their mothers.²⁹

1.1.7 Infectivity and Incubation

The probability of transmission of HPV infection per sexual act is independent of the type of HPV and is quite high. A previous study found that genital warts are highly infectious because of the high viral load, and up to 65% of sexual contacts develop an infection.³⁰ The incubation period of genital warts is usually 3 weeks to 8 months, with an

average of 2.9 months.³⁰ Longitudinal studies have indicated that most HPV infections are transient and no longer detectable within 1–2 years.³¹ High-risk infections usually persist longer than low-risk infections.³¹ In high-risk infections, HPV 16 seems to persist longer than other types. This indicates that high-risk HPV would spread at a greater rate than would low-risk HPV in populations with similar sexual patterns and transmissibility.²⁶

HPV infection can be in a latent, subclinical, or clinical phase. During the latent phase, the infection is inactive, there are no noticeable symptoms, and the infected site remains cytologically normal. In the subclinical phase, HPV infection is generally transient, and colposcopically detectable lesions develop that are usually low-grade cervical intraepithelial neoplasia (CIN)1.³² In most women the infection resolves by itself because of cell-mediated immunity. About 10% to 15% of women whose infection does not clear naturally remain HPV DNA positive and have persistent viral infection.²³ There is not yet a clear definition of persistence. However, follow-up strategies targeting abnormalities lasting 1–2 years seem to distinguish infections and associated lesions that put an individual at a greater risk of transient infections.³³ A study conducted by Moscicki et al. indicates that the risk of developing CIN3 is 14 times higher among women who have had at least three positive tests for high-risk HPV, compared to women with negative HPV test results.³⁴ Older women generally have higher persistence of HPV infection than younger women. One reason could be that the acquired infection is less likely to clear naturally in older women.³⁵ Additionally, this greater persistence could be due to the gradual predominance of longer-duration infection from earlier exposures, in comparison with more recent and more transient infection.³⁵

1.2 HPV and Cancer

1.2.1 HPV and cervical cancer

Virtually all cervical cancers are caused by HPV infection.³⁶ As mentioned earlier, HPV types 16 and 18 are responsible for nearly 70% of cervical cancer cases. The development of cervical cancer occurs in a series of four steps (Figure 1): HPV transmission, viral persistence, progression of a clone of persistently infected cells to pre-cancer, and invasion. Persistent HPV infection results in changes in the cervical cytology of squamous epithelia that may progress to noninvasive CIN2/3 and, many years later, to invasive cervical cancer.³⁶

Natural History of Cervical Cancer

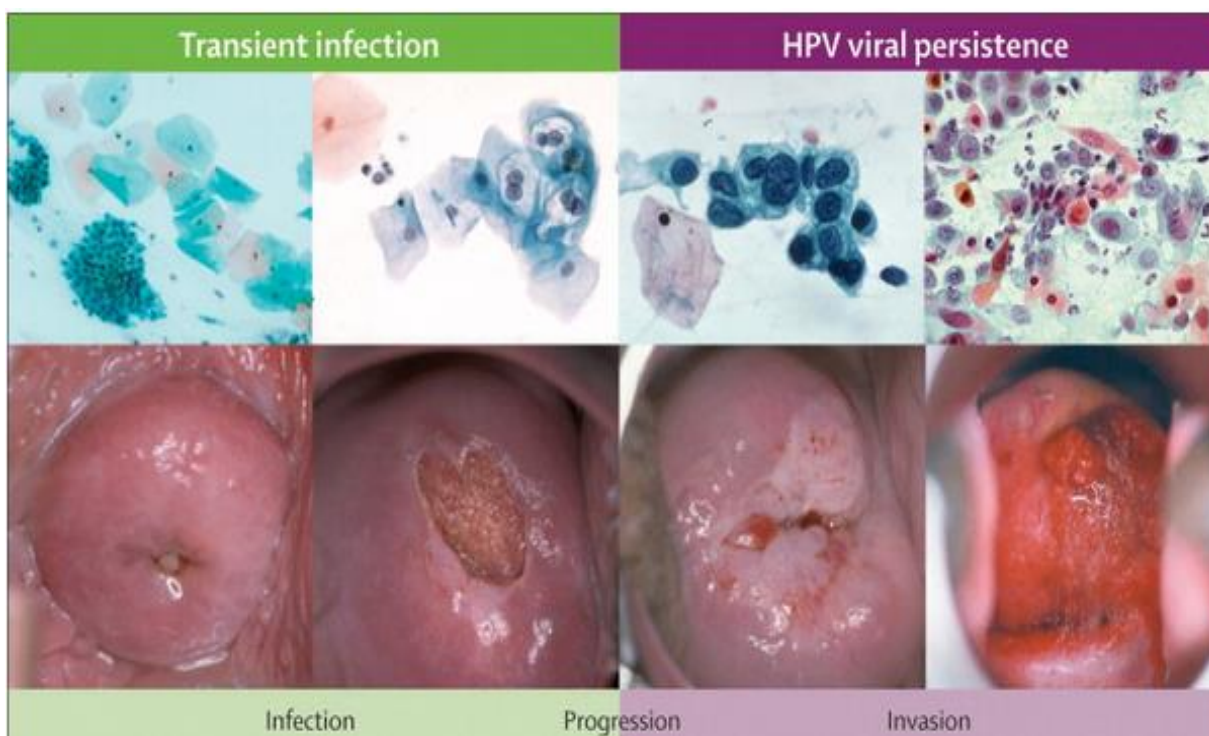


Figure 3: Steps in the development of cervical cancer. Adapted from Schiffman *et al*,2007.³³

HPV infection tends to cause cancer in areas known as the transformation zone. In this zone, one type of epithelium contacts and gradually replaces another by transforming itself through a process called metaplasia. Some examples of transformation zones that are prone to HPV infection include the cervix, anus, and tonsils. In the cervix, the transformation zone is the area of the columnar epithelium that transforms into the squamous epithelium.²³ The above process is comparatively inactive in children but becomes quite active around puberty.

In all HPV-related cancers, the stage of malignancy is set when HPV DNA integrates into the host cell genome. Viral oncoproteins E6 and E7 are released during the process. These proteins further bind and degrade host tumor suppressor genes TP53 and RB1.³⁷ Although HPV infection can cause various types of cancers, it is a primary concern for cervical cancer. Genotypes that cause cervical cancer include HPV 51 (alpha 5); HPV 56 and HPV 66 (alpha 6); HPV 18, HPV 39, HPV 45, and HPV 59 (alpha 7); and HPV 16, HPV 31, HPV 33, HPV 35, HPV 52, and HPV 58 (alpha 9).³⁸ All HPV genotypes that cause cervical cancer belong to the alpha genus.

Women who have a persistent infection of high-risk HPV types are at higher risk of developing high-grade intraepithelial disease and invasive cervical cancer.³⁹ High-risk HPV DNA can be detected in nearly 99.7% of squamous cell carcinomas⁴⁰ and in about 94% to 100% of cervical adenocarcinomas and adenosquamous carcinomas.⁴¹ Cervical squamous cell carcinomas are the most common histological types of cervical cancer that develop from pre-existing noninvasive squamous precursor lesions, also known as cervical intraepithelial neoplasias (CINs) or squamous intraepithelial lesions (SILs).⁴² Lesions are histologically classified based on the atypia of epithelial cells that continue to increase from the lower parabasal layers of squamous epithelium up to the whole epithelium. CIN1 and SIL correspond to mild dysplasia, CIN2 to moderate dysplasia, and

CIN3 to severe dysplasia.⁴² CIN2 and CIN3 are at high risk of progression or of cancer and are thus considered its precursor. The natural history of cervical carcinogenesis is shown in Figure 4.

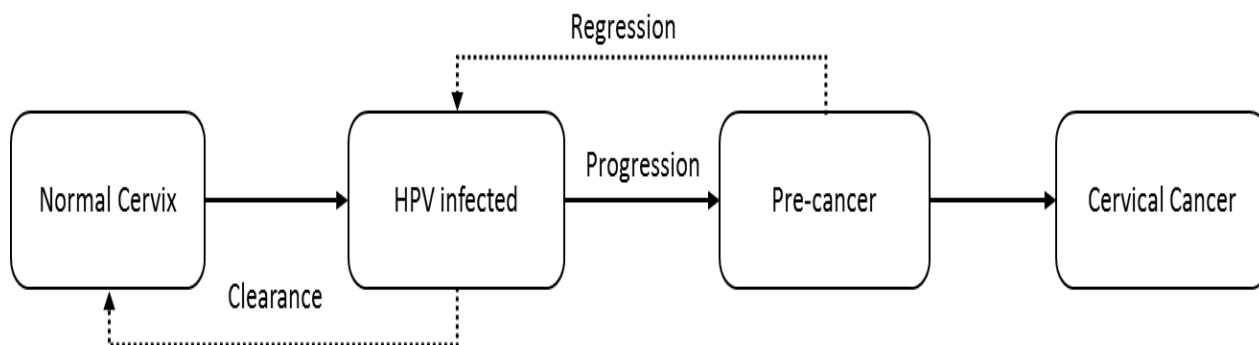


Figure 4: Natural history of cervical carcinogenesis. Adapted from Juckett G *et al.*, 2010.³⁷

Adenocarcinoma in situ (ACIS) and adenocarcinoma of the cervix (AdCA) are often not detected by Pap Smear, as they are located higher in the cervical canal and consequently are less accessible to the brush. Because of this, it might be beneficial to add testing for high-risk (HR)-HPV to the cervical cancer screening program in order to detect ACIS and AdCA.⁴¹

1.2.2 HPV and Penile Cancer

HPV plays an important role in the development of penile cancer. Although penile cancer is uncommon in developed countries, the incidence is much higher in developing countries such as Uganda (incidence, 4.4 per 100,000) or Paraguay (incidence, 4.2 per 100,000).⁴³ There are several different histological types of penile carcinomas. Most of the penile tumors are well-differentiated, keratinizing squamous cell carcinomas. Verrucous carcinoma is the second most common tumor subtype, and its variants are basaloid carcinoma and warty carcinoma. About 80% to 100% of basaloid and warty penile cancers are HPV positive. However, only a small fraction of verrucous penile

carcinomas are the result of HPV infection. Similar to cervical cancer, high-risk HPV expresses oncoproteins E6 and E7, which bind to p53 and inactivate the tumor suppressor protein Rb.⁴⁴

The pre-cancerous penile condition is known as penile intraepithelial neoplasia (PIN). Histologically, PIN is similar to CIN. However, the natural history of penile lesions is unknown, and therefore there are no standard protocols for diagnosis or management of penile cancer.⁴⁵

1.2.3 HPV and Head and Neck Cancers

Head and neck cancer (HNC) is the fifth most common cancer worldwide⁴⁶ and the eighth most common cause of cancer mortality.⁴⁷ HNC is a heterogeneous group of cancers, including cancers of the lip, oral cavity, nose, paranasal sinuses, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, and esophagus.⁴⁸ Although tobacco and alcohol are considered the two major risk factors for HNC^{49,50} about 25% of HNCs are associated with high-risk HPV. HPV-positive HNCs are usually less differentiated and of basaloid type.⁵¹ Although laryngeal and hypopharyngeal cancers are associated with smoking and alcohol consumption, oropharyngeal cancers involving tonsils, the pharyngeal wall, and the tongue base are mostly associated with HPV infection.^{52,53} The mechanisms of HPV oncogenesis in the oropharynx seems to be similar to those of cervical cancer. The differences are related to the anatomic, cellular, and immune environments. For instance, there is no transformation region in the oropharynx like that in the uterine cervix, in which malpighian epithelium of the exocervix joins the unistratified glandular epithelium of the endocervix, where most of the cancer develops. In the oropharynx, the tonsil is the most commonly affected anatomical region. So far, the exact mechanism of HPV infection in the nongenital region is unclear. However, easy

access to tonsillar crypts that have a favorable microenvironment may be the reason for the higher prevalence of HPV in this region.

1.2.4 HPV and Anal Cancer

Most of the anal squamous cell carcinomas are caused by HPV infection. Anal carcinoma is a rare malignancy with an incidence of 0.3 to 0.8 per 100,000 among men and 0.5 to 1.0 per 100,000 among women. However, since the 1970s there has been a 2% increase in the incidence of anal cancer in both men and women.⁵⁴ The exact reason for the increase is still unclear, but it may be the result of a change in sexual behavior.⁵⁴ Overall, the incidence of anal cancer is usually higher among men having sex with men and individuals who are immunosuppressed.⁵⁵

Invasive anal carcinoma develops from anal intraepithelial neoplasia (AIN). Similar to cervical intraepithelial neoplasia (CIN), AIN is classified into three categories: AIN1, AIN2, and AIN3. In AIN1, the lower third of the epithelium is affected, while in AIN2 and AIN3, two thirds of the epithelium and the entire epithelium, respectively, are affected.

1.2.5 Risk Factors for HPV-Related Cancer

Tobacco Smoking

Smoking is one of the risk factors for HPV-related cancers. One possible mechanism by which smoking may contribute to cervical carcinogenesis is that there is direct exposure of DNA in the cervical epithelial cells to nicotine and cotinine.^{56,57} Another proposal is that exposure of DNA in cervical epithelial cells to metabolic products resulting from reactions among other components of cigarettes, such as aromatic polycyclic hydrocarbons and aromatic amines, may result in carcinogenesis.^{56,57} Studies have demonstrated measurable amounts of cigarette constituents and their metabolites such as benzopyrene,⁵⁸ nicotine, and nicotine-derived

nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are found in cervical mucus and DNA adducts in cervical tissues.⁵⁹ HPV infection genome amplification is increased by benzopyrene, which may in turn increase the probability of viral DNA integration into the host genome, which is a crucial step in the development of cervical cancer.⁶⁰ Additionally, aberrant HPV-induced methylation might be another mechanism of smoking-related cervical carcinogenesis. *In vitro* studies in untransformed and transformed cell lines have shown that there are changes in the expression of DNA methyltransferases, DNMT1, DNMT3A, and DNMT3B, when the cell lines are exposed to nicotine or tobacco smoke for a short period. Aberrant methylation of p16, a tumor suppressor gene, is strongly associated with current smoking in women with squamous-cell cervical cancers and high-grade CIN.⁶¹ Furthermore, tobacco smoking is believed to facilitate the acquisition or persistence of an HPV infection through a reduced number of Langerhans cells and CD4 lymphocytes,^{62,63} which are markers of local immune response in the cervix.^{64,205}

Immunosuppression

Previous studies have found that the prevalence of HPV infection is higher among those with immunosuppression.^{65,66} T-helper cells are part of the defense mechanism that acts against HPV-transformed cells. Individuals with immunosuppression have a lower number of T-helper cells, predisposing them to HPV infection. This is one of the major reasons that Human immunodeficiency virus (HIV)-positive individuals, pregnant women, and organ transplant recipients are at greater risk of HPV infection. Studies of HIV-positive women suggest that alteration in cell-mediated immunity plays a vital role in the development and progression of CIN, specifically in individuals with lower CD4+ T cell counts or with high HIV RNA plasma levels.⁶⁷⁻⁶⁹

Use of Oral Contraceptives

There has been a long debate on the risk of cervical cancer among users of oral contraceptives. A pooled analysis conducted by the International Agency for Research on Cancer (IARC) to study the association between oral contraceptives and risk of cervical cancer among HPV-positive women revealed no excess risk among women who had used oral contraceptives for ≤ 5 years. However, the study found that the relative risk of cervical cancer was 2.8 for those who had used oral contraceptives for 5–9 years and 4.0 for those who had used it for ≥ 10 years.⁷⁰ It is believed that oral contraceptives favor the progression of pre-cancerous lesions to cervical cancer.⁷¹

Parity

High parity has been associated with cervical cancer. The independent role of high parity has been confirmed by case-control studies of cervical carcinoma.⁷²⁻⁷⁴ A study conducted by IARC revealed that women with seven or more full-term pregnancies had 4 times the risk of developing squamous-cell carcinomas, compared to nulliparous women.⁷⁴ Similarly, another study conducted in Costa Rica showed an increased risk of HSIL/CC with increasing number of live births.⁷⁵

During pregnancy, the level of estrogens and progesterone in blood increases progressively.⁷⁶ The change in blood hormone levels results in a change in the junction between the squamous and columnar epithelium occurring during pregnancy. In early pregnancy, eversion of columnar epithelium onto the ectocervix begins and is more noticeable during the second and third trimesters. Since cervical ectopy increases with number of full pregnancies, it is believed that high parity might increase the risk of cervical carcinoma⁷⁷ because it maintains the transformation zone on the exocervix for a number of years, thus assisting the direct exposure to HPV.⁷⁴

1.2.6 Epidemiology of HPV and HPV-Related Cancers in the United States

HPV is the most common sexually transmitted infection and affects nearly 80% of women at some point in their lives.⁷⁸ In 2010, the prevalence of HPV among women in age group 18-59 years was 42.7% in the United States.⁷⁹ Although the prevalence of HPV varies geographically, the prevalence of both low-risk and high-risk HPV is highest in the age group of 21–24 years, compared to other age groups.⁷⁹ Additionally, the incidence of HPV infection is higher in certain racial/ ethnic groups. In the United States, non-Hispanic blacks have the highest prevalence of HPV (63.1%), followed by Mexican Americans (40.1%).⁷⁹ Furthermore, a study showed an HPV prevalence of 50.8% among women who had ≥3 lifetime partners. Moreover, the prevalence was found to be 74% among women who had >2 sexual partners in the past year.⁷⁹

HPV among Northern Plains American Indians

The Northern Plains region of the United States comprises Iowa, South Dakota, North Dakota, Minnesota, and Nebraska. In the Northern Plains, American Indian women have a significantly higher rate of HPV infection than their white counterparts and are infected with different types of HPV than the general population.⁸⁰ The incidence rate among Northern Plains American Indians is 11.3 per 100,000, which is 1.7 times higher than among non-Hispanic whites (7.5 per 100,000).⁸¹

Despite the fact that cervical cancer is preventable, it is the leading cause of cancer death among American Indian women. A study conducted by the Aberdeen Area Indian Health Services reported an age-adjusted cervical cancer mortality rate of 15.6 per 100,000, five times the rate reported in the general U.S. population (3 per 100,000).⁸² There is also disparity in the cervical cancer survival rates among American Indian women. In 2010, the 5-year survival rate for cervical cancer was reported to be 81% among American Indian women, compared to 84% among white women.⁸³

One of the major reasons for the disparity could be the higher prevalence of HPV types other than HPV 16 and 18, which are not covered by the two established vaccines (bivalent and quadrivalent). This explanation is supported by studies of infections among American Indian women that showed a broad variety and different patterns of HPV types, including a higher prevalence of mixed HPV infections.^{80,84}

1.2.7 Burden of HPV-related cancers

Worldwide, cervical cancer is the fourth most common cancer in women and the seventh overall.⁸⁵ However, the majority of the burden of cervical cancer is in developing nations. Cervical cancer is the most common cancer in women in Eastern and Middle Africa.⁸⁵ In 2012, there were an estimated 528,000 new cases and 266,000 deaths from cervical cancer worldwide, accounting for 7.5% of all female cancer deaths.⁸⁵ American cancer society estimates that in 2016 about 12,990 new cases of invasive cervical cancer will be diagnosed and 4120 women will die from cervical cancer.⁸⁶

Annually, there are approximately 97,215 cases of HPV noncervical cancers among men and women worldwide, including 50,780 cancers among men (13,485 anal cancers, 26,775 oropharyngeal cancers, and 10,520 penile cancers) and 46,435 cancers among women (14,787 anal cancers, 6,048 oropharyngeal cancers, and 25,600 vaginal/vulvar cancers).^{87,88}

1.3. Impact of HPV on Pregnancy

1.3.1 HPV among pregnant women

Pregnancy is a known risk factor for new or recurrent HPV infections.⁸⁹ In the state of pregnancy, the levels of progesterone are elevated, causing an increase in the replication of HPV DNA. HPV infection can increase the rate of trophoblast cell death,

which can further impair the extravillous trophoblast invasion into the maternal uterine wall. This could result in placental dysfunction and other adverse pregnancy outcomes.⁹⁰

HPV-related pregnancy outcomes

Adverse pregnancy outcomes that have been associated with bacterial or viral infection include preeclampsia, premature rupture of membrane (PROM), preterm birth, and low birth weight. However, little is known about their association with HPV infection.

Preeclampsia is characterized by high blood pressure and signs of damage to other organ systems during pregnancy and is a major cause of maternal and fetal mortality and morbidity.⁹¹ Preeclampsia generally begins after 20 weeks of pregnancy in a woman whose blood pressure had been normal. It complicates about 3% to 6% of pregnancies, and if left untreated, it can lead to serious and even fatal complications for both the mother and the unborn baby.⁹² Although the exact mechanism of preeclampsia is unknown, one suggested mechanism is defective placentation with reduced invasion of fetal extravillous trophoblast cells, in addition to reduced remodeling of maternal uteroplacental spiral arteries.⁹³ Additionally, it is believed that systemic inflammation—as illustrated by exaggerated leukocytosis, extensive platelet activation, and increased complement activation in preeclampsia—plays a vital role in the development of preeclampsia.⁹⁴⁻⁹⁶ It is widely accepted that cervicovaginal HPV infection causes chronic inflammation that may result in detrimental pregnancy outcomes. However, its association with preeclampsia is still elusive. Some of the known risk factors for preeclampsia include pre-existing hypertension, diabetes, older age, multiple pregnancies, and obesity.⁹⁷

Another adverse pregnancy outcome that may be associated with HPV infection is PROM, the rupture of fetal membrane before the onset of labor. It occurs in nearly 3% of pregnancies and can lead to respiratory distress syndrome, neonatal sepsis, umbilical

cord prolapse, placental abruption, and fetal death. It is a multifactorial disorder, but infection is one of the major causes of membrane damage. One possible mechanism for rupture as a result of infection is that the cytokines and metalloproteases (especially matrix metalloproteinase [MMP]-2) released by an organism can degrade collagen and also weaken the fetal membrane, resulting in membrane damage. Few studies have examined the association of PROM and MMP with HPV infection. However, because HPV in human invasive cervical carcinoma cell lines results in an increase in MMP-2 expression, HPV may play an important role in regulation of MMP.⁹⁸

Preterm birth is one of the leading causes of infant death and occurs in about 12% of all pregnancies in the United States.⁹⁹ Although the survival rate of preterm-birth babies is high, they are at increased risk of neurodevelopmental impairments and respiratory and other complications.¹⁰⁰ Some of the risk factors for preterm birth include maternal demographic characteristics such as low socioeconomic status, low and high maternal ages, infection, nutritional status, and pregnancy history.¹⁰⁰ Intrauterine infections account for 25% to 40% of preterm births, but this may be an underestimate since intrauterine infections can be difficult to detect with conventional techniques. Intrauterine infections activate the innate immune response that is believed to lead to preterm births.¹⁰¹⁻¹⁰³ In addition to preterm birth, intrauterine infections can also result in low birth weight, defined as less than 2500 grams. In the United States the prevalence of low birth weight is 7.7%.¹⁰⁴ Similar to preterm birth, the association of low birth weight and HPV infection has not been examined.

1.4. Prevention & Control of HPV

Cervical cancer and other HPV-related cancers are a burden on the health care system, yet they are preventable. The probability of acquiring HPV infection can be lowered with the help of HPV vaccines, regular HPV testing, and screening.

1.4.1 Pap test and HPV testing

Papanicolaou (Pap) test

The U.S. Preventive Services Task Force (USPSTF) recommends that women in the age group of 21 to 65 years be screened with a Pap smear test every three years. Pap test results are reported as normal, inconclusive, or conclusive. The test results are considered normal if no abnormal cells are detected in the cervix but are considered inconclusive if atypical squamous cells are detected. These cells are divided into two categories: atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells for which high-grade squamous intraepithelial lesions cannot be excluded (ASC-H). An ASCUS designation means that the squamous cells do not appear to be completely normal, but it is unclear what the cell changes indicate. ASCUS is similar to the ASC-H designation, except that ASC-H indicates a possibly higher risk of precancerous lesions. The changes could be the result of HPV infection or any other infection.

HPV testing

HPV testing is used to identify high-risk HPV types in the cervical cells. Since HPV cannot be cultured, HPV test depends on the detection of viral nucleic acids in the infected tissue. Most tests are based on direct hybridization or DNA-based amplification techniques.¹⁰⁵ In women 30 years and older, HPV testing has been shown to be more sensitive than Pap testing for the detection of cervical interstitial neoplasia (CIN) grade 2/3+.^{106,107} Various HPV tests have been approved for screening purposes. For example,

Hybrid Capture 2 is currently the only US FDA approved HPV test. It is a signal-amplified hybridization microplate-based assay.^{108,109} Most tests detect the DNA of high-risk HPV; however, one test detects the RNA of high-risk HPV. Currently the HPV test is only for women; there is no HPV test for men.

1.4.2 Screening guidelines

Women who want to increase the screening interval should be screened with both a combination of cytology (Pap smear) and HPV testing every five years. The USPSTF recommends against screening for cervical cancer in women younger than age 21.¹¹⁰ The reason for that is that women in their 20s who are sexually active are much more likely to have HPV infection that will clear off on its own. Currently, there is no recommended testing for HPV in pregnant women.¹¹¹

1.4.3 HPV Vaccines

There are currently three types of Food and Drug Administration (FDA)-approved HPV vaccines recommended for preteen males and females aged 11 or 12 years through 26 years.¹¹² All three vaccines consist of recombinant noninfectious virus-like particles (VLPs) formed by the HPV L1 capsid protein. The three vaccines that protect against certain types of HPV are Gardasil, Cervarix, and Gardasil 9. Whereas Cervarix is approved only for females, Gardasil can be given to both male and females. Gardasil is a quadrivalent vaccine that protects against HPV 6, 11, 16, and 18. Cervarix is bivalent and protects against two types of HPV: 16 and 18.¹¹² In US Gardasil was the only vaccine available from 2006 to late 2009.¹¹³

Mechanism of Action of Gardasil

Each Gardasil dose of 120 mg antigenic protein load comprises L1 VLPs specific to HPV 16 and 18 as well as genital warts. The recombinant vaccine is synthesized in *Saccharomyces cerevisiae*, and each 0.5 ml of Gardasil dose contains aluminum

hydroxy phosphate sulfate and polysorbate-80. Gardasil is a prophylactic vaccine. It induces high initial serum HPV-type specific antibodies.^{114,114} The antibodies prevent endocytosis into the epithelial cells, thus neutralizing the infecting HPV virion. There are two ways by which antibodies can reach the denuded basement membrane: via a constant transude from the dermal capillary network up through the intact basement membrane or via an exudate that is triggered by tissue injury to the cervical epithelium, exposing the basement membrane to HPV virions. To neutralize infective type-specific virions by any method, high antibody titers are necessary.¹¹⁴

Mechanism of Action of Cervarix vaccine

Cervarix is an AS04 adjuvant vaccine that contains recombinant L1 protein, the major antigenic protein of capsid and HPV types 16 and 18.¹¹⁵ Each 0.5-ml dose consists of 20 micrograms of HPV type 16 L1 protein, 20 micrograms of HPV type 18 L1 protein, 50 micrograms of the 3-O-desacyl-4'-monophosphoryl lipid A, and 0.5 mg of aluminum hydroxide. The efficacy of L1 VLP vaccine may be facilitated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid protein, produced as a result of vaccination.¹¹⁵

Both Gardasil and Cervarix vaccines are given intramuscularly in a series of three doses (scheduled for 0, 1 to 2, and 6 months) and are 90% to 100% effective against the respective HPV types.^{116,117} Gardasil and Cervarix were approved by the FDA in 2006 and 2009, respectively. In 2014, the FDA approved the Gardasil 9 vaccine by Merck, which consists of high-risk HPV types (HPV 31, 33, 45, 52, and 58) in addition to the pre-existing types in the Gardasil vaccine. Gardasil 9 included five additional types of HPV that are believed to account for nearly 20% or more of cervical cancer cases.¹¹⁸ Because these other types of HPV are more prevalent in the American Indian population

than in other populations, it is beneficial to study the impact of the 9-valent vaccine in that population.

1.4.4 HPV treatment

If a woman is found to have an abnormal Pap test result and a positive HPV test result, colposcopy (use of an instrument called a colposcope to examine the vagina and the cervix) and follow-up testing are usually recommended. If biopsy of cells from the affected area shows CIN2 or more severe abnormality, then a Loop Electrosurgical Excision Procedure (LEEP), cryotherapy, laser therapy, or conization is performed.

1.5 Gaps in Knowledge

Although wide research on etiology of cervical cancer has been conducted recently, there have been few population-based studies on prevalence of HPV among pregnant women in the United States and on the possible adverse health outcomes, especially with regard to active HPV infections and adverse pregnancy outcomes. U.S. studies have shown that the HPV infection rates among adolescent girls and nonpregnant women range from 8.8% to 42.7% among women 14-59 years.^{79,119-122} However, the prevalence of HPV among pregnant women since the introduction of vaccines is still unknown. It is also important to note that previous research studies among pregnant women were mostly conducted before the introduction of the HPV vaccine, which should already have a measurable impact on the current population. It is essential to estimate the current prevalence of HPV among pregnant women in the post-vaccination era and to further study the effect of HPV on current pregnancies or later pregnancies.

Recent studies indicate that the prevalence of HPV infection increases drastically among pregnant women, because of the immune suppression that occurs during

pregnancy. Additionally, the role of other sexually transmitted diseases such as chlamydia and gonorrhea in causing adverse pregnancy outcomes is well documented. However, there is little knowledge about the role of HPV infection in adverse pregnancy outcomes. It is crucial to understand that role, because HPV affects nearly 80% of sexually active women.

Another major gap in knowledge is related to the impact of Gardasil 9 vaccine on Northern Plains American Indian women. To date, no study has projected the impact of HPV vaccine specifically on Northern Plains American Indians. As mentioned in section 1.2.6, the prevalence of certain types of HPV is higher among American Indian women than among white women. It is crucial to know the significance of using Gardasil 9 compared to the established Gardasil (4-valent) vaccine among Northern Plains American Indians, because Gardasil 9 is more expensive.

OBJECTIVE OF DISSERTATION

This dissertation is focused on two high-risk populations: pregnant women and Northern Plains American Indian women. The long-term goal of this dissertation is to reduce adverse consequences of HPV infection in high-risk population groups. The dissertation has three specific aims.

Aim 1: To examine the association of HPV infection with adverse pregnancy outcomes by using hospital data from 2012 to 2014.

Aim 2: To examine HPV infection prevalence and its association with perinatal outcomes among singleton mothers, by using Pregnancy Risk Assessment Monitoring System (PRAMS) data from 2004 to 2010.

Aim 3: To project the potential public health impact of the Gardasil 9 vaccine on cervical cancer cases in Northern Plains American Indians.

Chapter 2

Does HPV affect pregnancy outcomes?

2.1 HPV and Adverse Pregnancy Outcomes Overview

HPV is a huge health problem because of its high prevalence and transmissibility.¹²³ Studies conducted in the United States and other countries indicate that pregnant women are at higher risk of acquiring HPV infection.¹²⁴ During pregnancy, major physiological and immunological changes take place that regulate the functioning of the immune system and may cause alteration in HPV replication.¹²⁵ These changes make clearance of HPV much more difficult.⁷⁸ Extravillous or invasive trophoblast cells facilitate placental attachment to the maternal uterine wall and are responsible for establishing a high-flow, low-resistance maternal circulation supplying the placenta and the fetus.⁹⁰ HPV infection can impair extravillous trophoblast invasion into the uterine wall by increasing the rate of trophoblast cell deaths, causing placental dysfunction. As a consequence of this placental dysfunction, adverse pregnancy outcomes may occur.⁹⁰

Preeclampsia is one potential adverse pregnancy outcome. It is a main cause of maternal and fetal morbidity and mortality. In the last two decades, the rate of preeclampsia has increased by 25%.¹²⁶ Although, age, obesity, and history of preeclampsia are some of the known risk factors, the underlying cause of preeclampsia is not well understood. However, a study conducted by Redman and Sargent suggests that the probability of developing preeclampsia increases when the level of systemic inflammatory burden, which is an integral part of pregnancy, transcends the maternal capability to compensate for this added stress.¹²⁷ The researchers believe if this is true, then it is possible to hypothesize that infections that increase systemic inflammatory burden could result in increased risk of preeclampsia.¹²⁷ In the past, various

epidemiological studies have examined the association between maternal infection and preeclampsia,¹²⁸⁻¹³¹ but few focused on its association with HPV.⁷⁸ A recent study report by McDonnold et al. noted that risk of developing preeclampsia was nearly twofold among women infected with HR-HPV.⁷⁸ However, these findings were contrary to the study findings of Cho et al., which showed no significant association between HPV and preeclampsia.⁸⁹ These inconsistent results suggest a need to further investigate this association.

Another adverse pregnancy outcome is preterm birth. An estimated 12% to 13% of pregnancies in the United States are preterm.¹⁰⁰ Nearly 25% to 40% of these preterm births are due to intrauterine infections that activate the inflammatory pathways; however, this may be an underestimate, because intrauterine infections are not easily detected with conventional culture techniques.^{132,133} To date, few studies have examined the relation of cervical cytology during pregnancy and HPV infection.¹³⁴⁻¹³⁶ Also, previous study results were inconclusive regarding the impact of HPV on pregnancy outcomes, highlighting the importance of our study. In addition to preterm birth, intrauterine infections can affect fetal development and cause intrauterine growth restriction that results in low birth weight.¹³⁷ Though the association of bacterial infections, including gonorrhea and chlamydia, with adverse pregnancy outcomes has been studied before, no previous studies have focused on their association with HPV.

Premature rupture of membrane (PROM), before the onset of labor, is another probable adverse pregnancy outcome.¹³⁸ PROM is a multifactorial condition, with infection being one of the major causes of membrane damage.¹³⁹ One possible mechanism suggested by previous researchers is that cytokines such as metalloproteases secreted by various organisms degrade the collagen and weaken the fetal membrane, causing the membrane to rupture.¹³² Specifically, MMP-2 degrades the

extracellular matrix of the fetal membrane, resulting in PROM. Interestingly, the increase in MMP-2 is associated with the presence of HPV in human invasive cervical carcinoma cell lines, suggesting the possible role of HPV in regulation of MMP.⁹⁸ Recent epidemiological research has found an association between PROM and colonization of the genital tract with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and group B streptococci.^{140,141} However, the relationship between HPV and PROM remains ambiguous. Bopegamage et al. reported no association between viral genomes and preterm rupture of membrane (rupturing before 37 weeks),¹⁴² whereas another study showed that the risk of PROM among women with HR-HPV infection was twofold the risk for noninfected women.⁸⁹

The ambiguity in the results of the previous studies may be due to confounding factors such as smoking or co-infection with chlamydia or gonorrhea that were not controlled for in some studies. In the present study, we controlled for the necessary confounders to examine whether the association would still be significant. The objective was to determine if HPV infection is associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, low birth weight, and PROM.

2.2 Material and Methods

In this study, hospital data on adult women (18 years and older) who delivered a live birth at Nebraska Medical Center between 2012 and 2014 was analyzed.¹⁴³ The potential subjects were identified based from a query of the hospital patient database, and analysis was restricted to women who had a Pap test during pregnancy. Because the data were unidentifiable, this study was exempted from Institutional Review Board approval.¹⁴³ Women with multipara were included, with each pregnancy considered individually. However, women with multiple births (e.g. twins, triplets, etc) were excluded

from our study, because multiple births are more likely to have adverse pregnancy outcomes.^{100,144} This resulted in a total of 4,824 women (5,022 births) in the sample.

Patients with low/high-grade squamous intraepithelial lesions or atypical squamous cells of undetermined significance (ASCUS) on Pap smear were considered to be HPV-positive. The outcomes studied in this study were preterm birth, PROM, low birth weight, and preeclampsia. Preterm birth was defined as birth before 37 weeks of gestation. PROM was defined as rupture of the membrane prior to the onset of labor. Low birth weight was characterized as infant weight of less than 2500 gram at the time of birth. Preeclampsia was defined by a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg on two occasions at least 6 hours apart, along with proteinuria (an abnormal amount of protein in urine).

Bivariate analysis was conducted to assess the relationship between HPV infection and demographic and clinical variables. Additionally, logistic regression was performed to determine the association between HPV infection and each of following pregnancy outcomes, after adjustment for demographic and clinical variables: preterm birth, PROM, low birth weight, and preeclampsia. The demographic and clinical variables were those that were significantly different between the infected and noninfected groups or were based on prior knowledge of their association with both HPV infection and the outcome. These variables included age, race, smoking, mode of delivery, previous preterm birth, infection with chlamydia and gonorrhea, obesity prior to pregnancy and previous abortions.

A two-sided *p* value of less than 0.05 was considered significant.

2.3 Results

Of the total sample of 5,022 observations, 221 (4.4%) tested positive for HPV. Significant differences in demographic and clinical characteristics between HPV-infected and noninfected groups are shown in Table 1.¹⁴³ Over 40% of HPV-infected women were in the age group of 20 to 24 years, compared to only 23.3% of uninfected women in that age category.¹⁴³ About 30% of women with HPV infection were black, compared to 16% of women who were not infected. Close to 20% of HPV-infected women were smokers, compared to 6.9% of uninfected women. HPV-infected women were also at higher risk of chlamydia and gonorrhea, compared to noninfected women. The HPV-infected group had a statistically higher percentage of vaginal delivery than did the noninfected group (87.8% vs. 81.9%; $p = 0.025$). Finally, the percentages of women with previous preterm delivery and previous abortion were higher in the HPV-infected group than in the noninfected group (13.8% vs. 8.1% for preterm delivery; 28.6% vs. 22.5% for abortion).¹⁴³

Pregnancy outcomes and odds ratios (ORs) are shown in Table 2. The crude ORs were significant for preeclampsia (OR: 2.37; 95% confidence interval [CI]: 1.11–5.06), preterm birth (OR: 1.64; 95% CI: 1.15–2.32), and low birth weight (OR: 2.71; 95% CI: 1.86–3.94) and remained significant after adjusting for demographic and other variables that were believed to confound the association, on the basis of prior studies.¹⁴³ HPV-positive women were 2.83 times more likely to develop preeclampsia, compared to HPV-negative women (adjusted OR: 2.83; 95% CI: 1.28–6.26), after adjustment for age, race, previous preterm birth, gestational age, infection with chlamydia and gonorrhea, previous abortions, and delivery type. Women with HPV infection were 1.8 times more likely to deliver preterm (adjusted OR: 1.81; 95% CI: 1.15–2.83) and 2.58 times more likely to deliver low-birth-weight infants (adjusted OR: 2.58; 95% CI: 1.56–4.27) than

were uninfected women, after adjustment for other covariates. Although the odds of developing PROM were higher among infected women than among uninfected women, the association was not statistically significant (OR: 1.39; 95% CI: 0.54–3.52).¹⁴³

Characteristics	Infected (%)	Uninfected (%)	P value
Total	221 (4.4)	4801 (95.6)	-
Age			<0.001
≤19	12 (5.4)	392 (8.2)	
20–24	91 (41.2)	1119 (23.3)	
25–29	57 (25.8)	1536 (31.9)	
30–34	35 (15.8)	1215 (25.3)	
≥35	26 (11.8)	539 (11.2)	
Race/Ethnicity			<0.001
White/Caucasian	113 (51.6)	3140 (67.1)	
Black/African American	69 (31.5)	751 (16.0)	
AI/AN/PI	11 (5.0)	84 (1.8)	
Hispanic	4 (1.8)	139 (2.9)	
Other	21 (9.6)	435 (9.3)	
Unknown	1 (0.5)	133 (2.8)	
Smoking			<0.001
Yes	39 (17.7)	332 (6.9)	
No	182 (82.4)	4469 (93.1)	
Obese			0.462
Yes	95 (7.5)	1165 (92.5)	
No	67 (6.5)	963 (93.5)	

Chlamydia and Gonorrhea			0.002
Yes	8 (15.7)	43 (84.3)	
No	213 (4.3)	4758 (95.7)	
Mode of delivery			0.025
Vaginal	194 (4.7)	3930 (95.3)	
Cesarean (C-section)	27 (3.0)	871 (96.9)	
Previous preterm delivery			0.008
Yes	30 (7.2)	383 (92.7)	
No	188 (4.1)	4370 (95.9)	
Previous abortion			0.047
Yes	57 (5.5)	989 (94.5)	
No	142 (4.0)	3400 (95.9)	

Outcomes	Total Sample size	Prevalence of HPV (%)	Crude OR	95% CI	Adjusted OR^o	95% CI
PROM	94	5.3	0.94	0.38–2.34	1.39	0.54–3.52
Preeclampsia	66	12.1	2.37	1.11–5.06	2.83*	1.28–6.26
Preterm birth	626	4.1	1.64	1.15–2.32	1.81[†]	1.15–2.83
Low birth weight	357	10.1	2.71	1.86–3.94	2.58	1.56–4.27

^o Adjusted for age, race, smoking, previous preterm, gestational age, infection with Chlamydia and Gonorrhea, previous abortions, delivery type, gestational diabetes and chronic hypertension

[†] Preterm birth was not adjusted for gestational age

* Except for preeclampsia all other outcomes were additionally adjusted for preeclampsia

2.4 Discussion

This study investigated the association of HPV infection with adverse pregnancy outcomes. The overall prevalence of HPV among pregnant women in this study was 4.4%, remarkably lower than in previous studies conducted in United States.^{145,146} One reason could be that previous studies that showed a higher prevalence of HPV among pregnant women were conducted before the inception of HPV vaccination. Additionally, there is no recommended screening for HPV among pregnant women.¹¹¹ Another possible factor is the difference in HPV prevalence by geographic regions. For example, a study conducted in Austria showed HPV in 24.6% of pregnant women, whereas a study conducted in Spain showed a lower HPV infection rate, of 6.5%.¹⁴⁷ Interestingly, in this study, the prevalence of HPV among whites was higher than among other ethnic/racial groups, contrary to the national rates (51.6% vs. 31.5%). A study conducted by Dinh et al. indicated that there is a higher prevalence of genital warts among whites than among blacks.¹⁴⁸ Because most genital warts are the result of HPV, the presence of these in pregnant women would likely prompt healthcare professionals to test them for HPV. This might be the reason for the higher prevalence of HPV infection among whites in our study data.

Our study results indicate that HPV infection is significantly associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, and low birth weight, but not with premature rupture of membrane. After controlling for demographic and clinical variables, we observed that HPV-positive women were 2.83 times more likely to develop preeclampsia, compared to HPV-negative women. The association remained significant after adjusting for confounding factors. Our study results were consistent with those of other studies that revealed HPV as a risk factor for preeclampsia.^{78,149} A study conducted by McDonnold et al.⁷⁸ was scrutinized for not

adjusting for co-infections, leading to concern that HPV may not be the main cause of the adverse outcome, but rather a contributing factor to other infections.¹⁵⁰ In our study, we adjusted for co-infection with chlamydia and gonorrhea and still observed a significant association. However, our study results were contradictory to the results of a case-control study that found no difference in the detection of HR-HPV from placentas of women with preterm severe preeclampsia and controls.⁹⁰ This could be possible if HPV infection present in uterine decidua can still affect uteroplacental function.⁷⁸

In addition, we found that HPV-positive women were 1.8 times more likely to deliver preterm than were HPV-negative women. Our study results were consistent with the results of a previous study conducted by Zhuang Zuo that revealed a significant association between HPV and preterm birth.¹⁵¹ Though the pathophysiology of preterm birth is not well understood, systemic and/or local inflammation has been suggested as an independent etiological risk factor for preterm birth. According to a study conducted by Gomez et al., HPV can infect and replicate in invasive trophoblast cells, and that infection by HPV induces pathological sequelae that are associated with placental dysfunction and spontaneous preterm delivery.⁹⁰ Additionally, some in vitro studies have shown that HPV can infect a fetus through transplacental transmission.^{152,153} Trophoblasts are integral cell types of the placenta. It is believed that trophoblasts infected with HPV may alter the cellular characteristics and lead to compromised gestation.¹⁵⁴ Racicot *et al.* proposed that preterm birth is a polymicrobial disease and demonstrated that a viral infection of the cervix during pregnancy reduces the ability of the lower reproductive tract to prevent bacterial infection of the pregnant uterus. In the study model, pregnancy and sex hormones are responsible for increasing the susceptibility of the cervix to the viral infection. As a consequence of viral infection, the

protection against ascending bacteria is decreased. This decrease in protection in turn leads to intrauterine inflammation, in response to bacteria, and preterm birth (Figure 5).

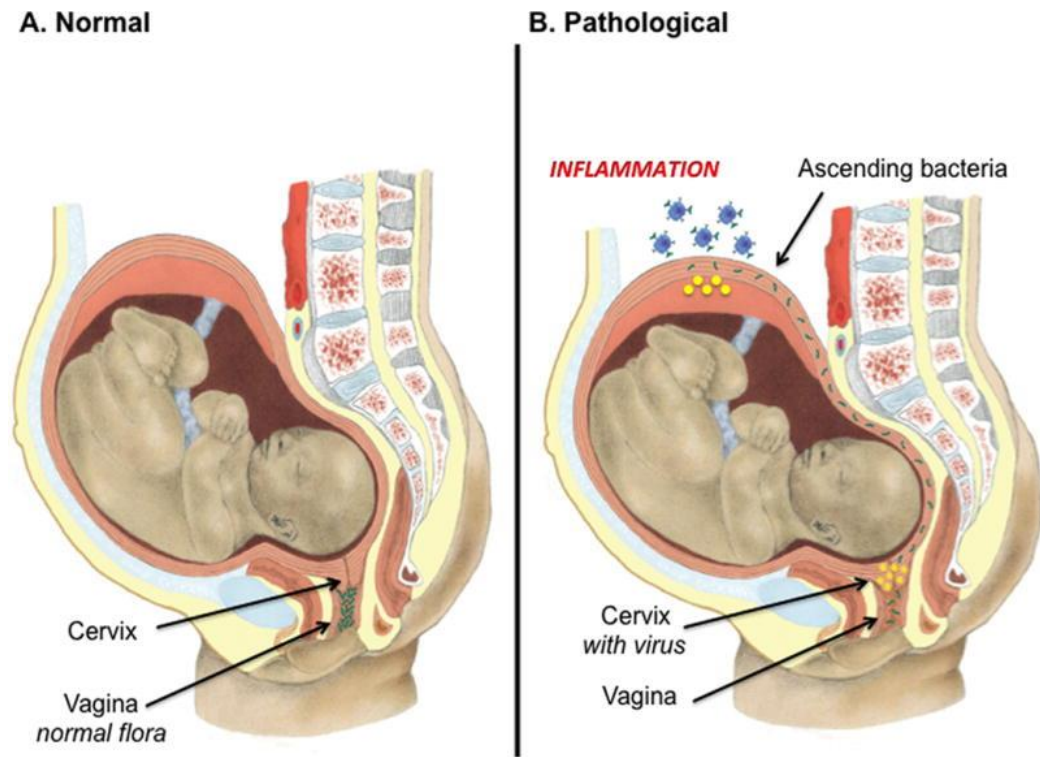


Figure 5. Model of polymicrobial disease during pregnancy. Racicot *et al.*, 2013.¹⁵⁵

Furthermore, our results indicate that HPV-infected women were 2.58 times more likely to deliver low-birth-weight infants than were women not infected with HPV.

Although low birth weight has been associated with other sexually transmitted diseases,^{156,157} to our knowledge no other study has examined the association of HPV and low birth weight. HPV infection could occur by ascending from the maternal birth canal,¹⁵² or it may cross the placenta and cause infection in the fetus. If HPV infection occurs at a crucial moment during the development of the fetus, it may affect the fetal cells and cause intrauterine growth retardation. In our study, we did not find any

significant association between HPV and PROM, even after controlling for other covariates. Our study results were contrary to those of a study conducted by Cho et al., who reported a significant association between HR-HPV and PROM. One reason for this disagreement with results could be that the other study was conducted in Korea, and the study sample had a high prevalence of HR-HPV compared to our study (14.1% vs. 4.4%) The difference in prevalence could also be because of the difference in the HPV test detection methods. Additionally, the study does not mention what HR-HPV types were included. Furthermore, the study did not adjust for smoking, which has been reported to be a strong risk factor for both PROM and HPV.¹⁵⁸⁻¹⁶⁰

Our study findings are important because currently there is no vaccination or recommended screening for HPV among pregnant women. Our study results indicate that the presence of HPV during pregnancy may cause adverse pregnancy outcomes, suggesting the need for understanding the impact of HPV vaccination on pregnant women. A number of limitations should be considered when interpreting the results of this study. First, in this findings of ASCUS were assumed to be a result of HPV infection, though they could be a result of other factors such as bacterial infection. This may have caused misclassification of cases, resulting in overestimation. Second, although we had information on current smoking status, we did not know the smoking status prior to pregnancy; that missing information may have concealed the true exposure to tobacco.

Previous researchers have found that the prevalence of HPV varies by gestational age.^{27,161} Lee et al. detected HPV DNA in 14% of pregnant women in the first trimester, 18% in the second trimester, and 10% in the third trimester.²⁷ This indicates that the HPV infection may be triggered by hormonal or other effects of pregnancy, such as immunosuppression.¹⁶¹ Although our study was unable to account for gestational age of infection, future studies might take into account the time point of

HPV infection. Despite these limitations, the study has a number of strengths. Because the exposure and outcome status were based on obstetric records/ laboratory tests, this information was more reliable than self-reported data.

2.5 Conclusion

The data from this study suggest that HPV infection is associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, and low birth weight. From a clinical standpoint, this may highlight the health benefits of HPV vaccination for young girls and adolescent females prior to pregnancy as well as for young boys and men. Also, one priority should be to improve HPV vaccination rates through better education and awareness campaigns among the patient population. In addition, policymakers should consider mandating HPV testing of pregnant women. Concurrently, there should be a close follow-up of HPV-positive women and their fetuses. However, it appears that mandating HPV vaccination may be challenging, in light of the experience in Texas. Although Governor Rick Perry mandated HPV vaccination for young girls, Texas legislators passed H.B. 1098 to override the executive order. Future studies should involve larger, more diverse samples of women to enable us to understand the impact of HPV infection.

Chapter 3

Examining the Relationship between HPV and Adverse Pregnancy Outcomes at the Population Level

3.1 Introduction

HPV infection is the most common sexually transmitted disease in the United States.¹⁶² Some of the known risk factors for HPV infection include early first sexual intercourse, multiple sex partners, co-infection with other sexually transmitted diseases, and smoking or any form of immune suppression.¹¹⁹ In addition, pregnancy is a risk factor for new or recurrent HPV infections.⁸⁹ During pregnancy, the immune system is suppressed, which decreases the ability to resist infections.^{163, 78} In addition, the level of HPV DNA replication is increased in pregnancy because of elevated levels of pregnancy hormones such as progesterone. Because of these factors, pregnant women may be more susceptible to HPV infection than nonpregnant women.

There is a lack of population-based data on HPV infection prevalence among pregnant women in the United States and on the possible adverse health outcomes related to active HPV infections, especially adverse pregnancy outcomes. U.S. studies have shown HPV infection rates among adolescent girls and nonpregnant women ranging from 8.8% to 42.7% among women in the age group of 18-59 years.^{79,119-122} It is also important to note that previous research on pregnant women was mostly conducted before introduction of the HPV vaccine, which may already have a measurable impact on the current population. It is essential to estimate the current prevalence of HPV among pregnant women in the post-vaccination era and to further examine its effect on pregnancy.

HPV causes genital warts, cervical cancer, head and neck cancer, anal cancer, juvenile-onset recurrent respiratory papillomatosis, and laryngeal papillomatosis.²⁸ However, little is known about the potential link between HPV infection and adverse pregnancy outcomes such as preterm birth, low birth weight, preeclampsia, and PROM. The etiology of such outcomes is still unclear, and the literature on their association with HPV infection is contradictory.^{78,89} It is important to research and learn more about the association between HPV infection and adverse pregnancy outcomes, since the little information available now is not conclusive. The inconsistencies in the results of the previous studies regarding adverse pregnancy outcomes and their association with HPV infection necessitate further research.^{78,89}

Previous studies were based on small sample sizes, which may have caused underestimation of the results. Use of the Pregnancy Risk Assessment Monitoring System (PRAMS) is the standardized data collection methodology. It includes a questionnaire completed by mothers that can provide population-based prevalence estimates of HPV infection. Additionally, along with information from birth certificates, the PRAMS database can allow us to elucidate the association of HPV with adverse pregnancy outcomes. The primary purpose of this study was to estimate the prevalence of HPV infection among pregnant women, with use of the most recent data available. The secondary purpose was to examine the association of HPV with adverse pregnancy outcomes, including preeclampsia, preterm birth, low birth weight, and PROM.

3.2 Methods

This study used data from the 2004–2011 multi-state PRAMS. The current study used PRAMS data from multiple states: Delaware, Florida, Missouri, Mississippi, New York, Tennessee, and Utah.

3.2.1 PRAMS

PRAMS is a state-specific population-based surveillance system that collects data from women who delivered live-born infants about their experiences before, during, and after pregnancy.¹⁶⁴ This database uses a multistage, complex sampling strategy and is a mixed-mode surveillance system with standardized data collection methodology. Each month, a list of mothers who delivered a live infant in the past 2 to 4 months is randomly generated from a file of birth certificate records. Mothers are sent a 14-page self-administered questionnaire. Each mother's response is linked to extracted items from the birth certificate file, such as infant's birth weight, type of delivery, and mother's marital status, race, age, education, and smoking status. The response rate of PRAMS is nearly 70%.

The PRAMS database includes core questions for all states' surveys and optional standard and state-developed questions. In the present study, only states that had questions on HPV infection were included.

3.2.2 Study Definitions

HPV Infection: The question used to assess HPV infection among pregnant women was "During your most recent pregnancy, did a doctor, nurse, or other health care worker tell you that you had any of the following diseases?" HPV was defined by a 'yes' in the Genital warts (HPV) category.

Perinatal Outcomes: Preeclampsia is a disease characterized by high blood pressure during pregnancy and signs of damage to other organ systems and is a major cause of maternal and fetal mortality and morbidity.⁹¹ Preeclampsia generally begins after 20 weeks of pregnancy in a woman whose blood pressure had been normal. For this study, it was measured by response to the question "Did you have any of the following problems during your most recent pregnancy?" Preeclampsia was defined by a 'yes'

response in the preeclampsia category. Preterm birth was based on the gestational age variable available in the birth certificate file. It was defined as the birth of an infant before 37 weeks of pregnancy. Low birth weight was defined as a weight less than 2500 grams at the time of birth. PROM was defined as the rupture of membrane before the onset of labor. Both low birth weight and PROM were obtained from birth certificate files.

Covariates: Candidate covariates for the statistical models derived from PRAMS questionnaire included the following: mother's age at delivery, mother's race/ethnicity, mother's education level, marital status, smoking, gestational age, body mass index (BMI) prior to pregnancy, gestational diabetes, high blood pressure before pregnancy and co-infection with gonorrhea and chlamydia, and previous preterm deliveries. Race was divided into three categories: white, black, and other. BMI prior to pregnancy was classified as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (≥ 30). Mother's smoking status was categorized as 'yes' or 'no.'

3.3 Data analysis

We limited our study to singleton births since multiples are more likely to have an adverse outcome such as low birth weight or preterm birth.^{100,144} To account for the complex sampling design of the PRAMS, analyses were completed with SAS Survey procedures, software version 9.3. Data were weighted with sampling weights to produce population-based estimates. Bivariate analyses were performed to assess the relationship between each perinatal outcome and HPV infection. Logistic regression was performed to assess the relationship between each perinatal outcome (PROM, preterm birth, low birth weight, and preeclampsia) and HPV infection. Multivariable models for each of the primary independent variables were built to adjust for confounding variables based on the previous literature.

Multiple imputation technique was used to impute observations missing at random for HPV exposure (n = 200) since HPV information was not missing completely at random. This Monte Carlo process involves repeated imputation of each missing value and then averaging over imputations. Multiple imputation assumes that data is missing at random (MAR), and it creates several copies of the data set, each containing different imputed values. A separate analysis was carried out on each dataset that yielded multiple sets of parameter estimates and standard errors. For this study, we used five multiple imputed datasets to combine into a single set as a result. Multiple imputation was conducted in three phases: imputation, analysis, and pooling. The multiple imputation process was performed with SAS 9.3. Statistical significance was assessed at $\alpha = 0.05$. Multiple imputation was performed on the database with the PROC MI procedure in SAS. To impute HPV status, variables such as smoking status, education level, age, bleeding of the mother, and preterm birth were used.

3.4 Results

Table 3 exhibits the demographic and obstetric characteristics of pregnant women infected with HPV. HPV was present in 1.4% of the PRAMS survey participants (N = 26,085). The prevalence of HPV was significantly higher among women ≤ 19 years old (2.7%) than in all other age groups. Additionally, the prevalence was notably higher among these groups: smokers (3.5%) versus nonsmokers (1.2%), women who had high blood pressure before pregnancy (2.5%) versus those who did not (1.3%), and those who were not married (2.5%) versus those who were (0.8%). Furthermore, the prevalence of HPV was significantly higher among women who were co-infected with chlamydia or gonorrhea (6.4%) than among women with no such co-infection (1.3%). No significant differences in age, pre-pregnancy BMI, previous preterm delivery, or

gestational diabetes were observed between women with HPV infection and those without.

Additional analysis was conducted to examine the prevalence of other sexually transmitted infections by HPV status. As shown in Table 4, we found that there were significant differences in the prevalence of other sexually transmitted infections by HPV status. For instance, the prevalence of chlamydia was 9.2% among HPV-positive women, compared to 2.1% among HPV-negative women. Similarly, the prevalence of Group B streptococci was 21.7% among HPV-positive women, compared to only 10% among HPV-negative women.

Table 5 shows the weighted prevalence, ORs, and 95% CIs for the perinatal outcomes among pregnant women. The overall weighted prevalence of low birth weight among women who delivered was 7.3%. In the crude analysis, no association was found between HPV infection and low birth weight. After adjustment for demographic and obstetric characteristics, low birth weight was not significantly associated with HPV infection (adjusted OR: 1.00; 95% CI: 0.83–1.21). However, low birth weight was significantly associated with HPV in the nonimputed data (OR: 1.91; 95% CI: 1.13–3.24). As shown in Table 6, no significant association was found between HPV infection and PROM, pre-eclampsia, or preterm birth in the nonimputed data. In addition, the weighted prevalence among women who delivered preterm was 9.4%. The crude OR and adjusted OR were not significant for the association between HPV infection and preterm birth (OR: 0.98; 95% CI: 0.81–1.19). Furthermore, the weighted prevalence among women who had premature rupture of membrane was 2.9%. Although the odds of having PROM was higher among HPV-positive versus HPV-negative women, this was not statistically significant after adjustment for confounding variables (adjusted OR: 1.46, 95% CI: 0.53–4.01). The weighted prevalence of preeclampsia among pregnant women

was 6.2%. Similar to PROM, the adjusted OR for preeclampsia was higher among those infected with HPV versus the uninfected; this was not statistically significant (OR: 1.31; 95% CI: 0.95–1.80)

Table3. Demographic and obstetric characteristics of pregnant women who self-reported HPV exposure status			
Characteristics	Unweighted Sample Size	Weighted Prevalence of HPV (% , SE)^a	P value^b
Total	26085	1.44 (0.07)	
Age			<.001
≤19	2772	2.7 (0.10)	
20–24	7107	2.3 (0.09)	
25–34	13194	0.9 (0.05)	
35+	3011	0.8 (0.05)	
Race/Ethnicity			0.19
Non-Hispanic white	16688	1.6 (0.07)	
Non-Hispanic black	3866	1.3 (0.08)	
Non-Hispanic American Indian/Alaskan Native	160	2.2 (0.09)	
Hispanic	4230	0.9 (0.06)	
Non-Hispanic other	997	1.6 (0.07)	
Married			<.001
Yes	16395	0.8 (0.05)	
No	9686	2.5 (0.10)	
Education, years			.13
≤11	5560	1.7 (0.09)	
12	7589	1.9 (0.09)	
13–15	6243	1.5 (0.08)	
≥16	6235	0.7 (0.05)	
Smoking			<.001
Yes	3122	3.5 (0.19)	
No	22768	1.2 (0.06)	
Pre-pregnancy BMI			.48
Underweight	1523	1.9 (0.10)	
Normal	12433	1.3 (0.06)	
Overweight	5489	1.6 (0.07)	
Obese	4889	1.5 (0.07)	
Pre-high blood pressure			.019
Yes	926	2.5 (0.58)	
No	8255	1.3 (0.08)	
Previous preterm delivery			.31
Yes	488	2.4 (0.59)	
No	12245	1.4 (0.07)	
Co-infection (chlamydia and/or gonorrhea)			<.001

Yes	639	6.4 (0.15)	
No	25446	1.3 (0.07)	
Gestational diabetes			.57
Yes	755	1.5 (0.33)	
No	8378	1.4 (0.07)	

^a Based on imputed data

^b Chi-square test was used to compute the p value. P value of <0.05 was considered significant.

Type of Infection	HPV+ (n = 380)	HPV- (n = 25704)	P value ^a
Chlamydia	33 (9.23%)	556 (2.12%)	<.0001
Herpes	33 (7.17%)	229 (1.07%)	<.0001
Syphilis	11 (2.95%)	13 (0.04%)	<.0001
Gonorrhea	15 (5.54%)	93 (0.31%)	<.0001
Group B streptococci	64 (21.7%)	2451 (10.04%)	<.0001
Trichomonas	10 (2.34%)	190 (0.69%)	.011
Yeast	87 (26.21%)	2006 (7.76%)	<.0001

^a Chi-square test was used to compute the p value.

Table 5. Weighted prevalence (%), ORs, and 95% CIs of perinatal outcomes among pregnant women by HPV exposure, PRAMS, 2004–2011 (based on imputed data)

Outcomes	Weighted Prevalence (SE)	Crude OR ^d	95% CI ^d	AOR ^{a,d}	95% CI
Low birth weight ^b	7.27 (0.03)	1.09	0.95–1.24	1.08	0.74–1.57
Preeclampsia ^c	6.20 (0.21)	0.90	0.67–1.21	1.31	0.95–1.80
PROM ^b	2.91 (0.15)	1.12	0.79–1.59	1.08	0.74–1.57
Preterm birth	9.36 (0.20)	0.96	0.80–1.16	1.01	0.84–1.20

^a Adjusted for age, race, co-infection (with chlamydia or gonorrhea), BMI, smoking, gestational age (preterm birth not adjusted for gestational age), married, gestational diabetes.

^b In addition to above confounders, preterm birth, PROM, and low birth weight were adjusted for previous preterm birth and preeclampsia.

^c In addition to above confounders, preeclampsia was also adjusted for hypertension before pregnancy.

^d Based on imputed database.

Table 6. ORs and 95% CIs of perinatal outcomes among pregnant women by HPV exposure, PRAMS, 2004–2011 (based on nonimputed data)

Outcomes	Crude OR	95% CI	AOR ^a	95% CI
Low birth weight ^b	1.18	0.90–1.54	1.91	1.13–3.24
Preeclampsia ^c	0.82	0.45–1.48	0.58	0.19–1.71
PROM ^b	1.25	0.62–2.55	1.46	0.53–4.01
Preterm birth	1.08	0.75–1.56	0.54	0.31–0.95

^a Adjusted for age, race, co-infection (with chlamydia or gonorrhea), BMI, smoking, gestational age (preterm birth not adjusted for gestational age), married, gestational diabetes.

^b In addition to above confounders, preterm birth, PROM, and low birth weight were adjusted for previous preterm birth and preeclampsia.

^c In addition to above confounders, preeclampsia was also adjusted for hypertension before pregnancy.

3.5 Discussion

To our knowledge, this is the first study to utilize a multi-state PRAMS database to study the prevalence of HPV and its impact on pregnancy outcomes. The prevalence of HPV exposure in our study sample was only 1.4%, which varies drastically from a meta-analysis that revealed a much higher prevalence of 16.8% among pregnant women.¹²⁴ One of the reasons could be that our study was based on self-reported HPV exposure status. Because HPV testing is not recommended for pregnant women,¹⁶⁵ most women may be unaware of their status. This may have underestimated the true prevalence of HPV among these women. Additionally, lower prevalence could be due to the impact of HPV vaccination.

In the present study, we found that HPV-positive women had higher prevalence of other sexually transmitted infections. Because this is a cross-sectional study, we cannot infer that HPV infection predisposes women to other sexually transmitted infections. However, Racicot et al. reported that viral infection of the cervix during pregnancy decreases the ability of the lower reproductive tract to prevent bacterial infections.¹⁵⁵ In the future, prospective studies may explore the relation of HPV infection with other sexually transmitted diseases. Also, it would be interesting to know if specific types of HPV may be responsible for putting pregnant women at risk for other sexually transmitted infections.

On the basis of nonimputed data, women with HPV infection were 1.91 times more likely to have a low-birth-weight infant (Table 4). Although low birth weight has been associated with other sexually transmitted diseases,^{166,167} no studies have examined the association of HPV and low birth weight. It is believed that some infections can affect fetal cells and restrict intrauterine growth if they occur at a critical moment in fetal development.¹³⁷ If infection occurs during the first trimester, then the consequences

of the infection on pregnancy are more serious.¹³⁷ Future studies should consider the time of infection to better understand the role of HPV in adverse outcomes.

In this study, we did not find any significant association between HPV infection and pregnancy outcomes, which is contrary to the findings of previous studies. One possible explanation is that in our study the prevalence of HPV infection was low among pregnant women (1.4%), in comparison with its prevalence in previous studies that examined the association of HPV with pregnancy outcomes such as low birth weight, PROM, preeclampsia, and preterm birth.^{78,89,90,168} Additionally, one study that showed a significant association between HPV infection and preterm birth did not control for smoking, which can confound the association.⁹⁰ Although there is no clear process by which HPV infection can result in these adverse pregnancy outcomes, some mechanisms have been proposed. It is thought that infection with HPV can result in chronic cervicovaginal inflammation that may put the pregnancy at higher risk of an adverse outcome.¹⁶⁹ Additionally, HPV releases cytokines and metalloprotease (specifically MMP-2), which can degrade collagen and also weaken the fetal membrane, resulting in membrane damage.^{98,170,171}

This study has a few limitations, such as those that apply to PRAMS as a whole. Because the study was cross-sectional, we cannot infer causality of the relationship between self-reported HPV and perinatal outcomes. Also, the infection information available through PRAMS was limited to seven states that included questions related to HPV infection in their state questionnaire. Additionally, selection bias could have occurred if women who were educated or had an infant of normal birth weight were more likely to respond to the PRAMS survey. Furthermore, the question used to assess HPV infection among pregnant women is non-specific that might be difficult to comprehend. In the PRAMS survey questionnaire, HPV infection was measured on the

basis of a single multicategorical question: “What disease or infection were you told you had?” One of the response options for this question is “Genital Warts (HPV),” which may not be comprehensive for all women. Except for the above question, there is no other question related to high-risk HPV or low-risk HPV. Genital warts are the result of low-risk HPV such as types 6 or 11 and not the cancer-causing HPV types such as HPV 16 or 18. So it might be that some women with high-risk HPV did not report their status.

Despite these limitations, this study has a number of strengths. First, the data come from a large population-based survey of maternal attitudes and experiences before, during, and shortly after pregnancy. Second, the PRAMS survey has a high response rate of 70%, reducing the potential for biased estimates. Third, all of the outcomes (except for preeclampsia) for this study were derived from birth certificate files, which are based on medical information (not self-reported).

To the best of our knowledge, this is the first study to utilize PRAMS data to analyze the prevalence of HPV infection and its relationship with pregnancy outcomes. On the basis of this multi-state population-based survey, the prevalence of HPV infection was found to be 1.4%. The low prevalence of HPV infection among PRAMS participants may be due to the lack of consistent HPV testing among pregnant women. The low prevalence of HPV infection may have skewed the results significantly. Although we did not find significant associations between HPV and perinatal outcomes, further research with use of a large population database is needed. So far, only 7 of 40 states in the PRAMS database collect information on HPV. We recommend that other states consider including questions on HPV, which would allow researchers to study HPV among pregnant women in large population-based investigations and would provide data that are more representative of the population. In the future, researchers should also

consider conducting longitudinal studies of HPV among pregnant women that would allow them to take into account the time of infection.

Chapter 4

Projecting the potential impact of 9-valent vaccine among Northern Plains American Indian women and white women

4.1 Introduction

Cervical cancer is the second most common cancer in women worldwide. In 2015, approximately 12,900 women were diagnosed with invasive cervical cancer in the United States, and 4,100 died from it.¹⁷² With widespread use of an effective screening test (i.e., Pap smear), there was a large decline in incidence rates over the last 30 years; however, the decline gradually tapered off in the past decade, especially among younger women.¹⁷³ Also, after decades of rapid declines, mortality rates have leveled off, and no significant decline was observed for both women younger than 50 years and those 50 years and older.¹⁷³

In addition to the lack of progress in decreasing the burden of cervical cancer in the overall population, another concern is a persisting disparity among certain population groups in the United States. One group at particularly high risk of developing and dying from cervical cancer is American Indians/Alaska Natives in the Northern and Southern Plains regions. For instance, the incidence rate among Northern Plains American Indians/Alaska Natives was 12.5 per 100,000, which put them at 1.7 times higher risk of developing cervical cancer than non-Hispanic white women in the same region.⁸¹ Other publications have documented an incidence rate of cervical cancer among American Indian/Alaska Native women in South Dakota as high as 16.2 per 100,000, compared to 6.1 per 100,000 among non-Hispanic white women in the state, and an age-adjusted cervical cancer mortality in the Dakotas of 4.5 per 100,000.¹⁷⁴

HPV is a primary cause of cervical cancer and is responsible for anal, oropharyngeal, and vulvar cancer.¹⁶² More than 40 types of HPV are considered to be

high-risk or can cause cancer. Together, HPV 16 and 18 account for 70% of cervical cancer in the United States.¹³ Five additional high-risk types, HPV 31, 33, 45, 52, and 58, are believed to account for nearly 20% or more of cervical cancer cases.¹¹⁸ In 2006, Gardasil was introduced in the United States as the first prophylactic HPV vaccine. Gardasil, a quadrivalent vaccine, protects against HPV 16, 18, 6, and 11 and is licensed for administration to individuals between ages 13 and 26. Cervarix, a bivalent vaccine subsequently licensed in 2009, protects against HPV 16 and 18 only. Both vaccines are 90% to 100% effective against the respective HPV types.^{116,117,175}

In December 2014, Gardasil 9, a 9-valent vaccine including HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58, was launched. The 9 types included in the vaccine are considered responsible for 90% of cervical cancers worldwide.^{118,176} A recent study by Velde predicted that changing from quadrivalent to a 9-valent vaccine will reduce the cumulative number of episodes of anogenital warts by an additional 6.6% over 70 years. In addition, the study showed that switching to 9-valent vaccine could further reduce precancerous lesions and cervical cancer.¹⁷⁷

Previous research indicated variation in the HPV type distribution among population groups within the United States.¹²¹ Because of the differences in HPV infection, varying degrees of impact are expected from HPV vaccination. Mathematical modeling, which incorporates results from epidemiological and clinical studies, has been used in public health to project potential benefits of population-level interventions.¹⁷⁷⁻¹⁷⁹ Previously, modelling has been employed to investigate HPV vaccine effectiveness and cost effectiveness.¹⁷⁸⁻¹⁸⁰ However, none of the published studies have examined the potential impact of 9-valent vaccine in high-risk population such as Northern Plains American Indians. In addition, of particular interest is the effect that varying vaccination rates have in decreasing cervical cancer incidence and mortality. The HPV vaccination

completion rate remains low, around 39.7% as of 2014, among female adolescents in the United States.¹⁸¹ Given the considerable effort and time it will take to increase the vaccine completion rate; it is of interest to estimate with a mathematical model the potential benefit of increasing vaccine coverage.

The purpose of the present study was to estimate the potential impact of 9-valent vaccine on cervical cancer cases in the American Indian population. Two specific questions were explored: (1) Among American Indian compared with white women, how many cases of invasive cervical cancer and cervical dysplasia (CIN2/CIN3) would be prevented because of the 5 additional types (HPV 31, 33, 45, 52, and 58) incorporated in the 9-valent vaccine? (2) If the 4-valent vaccine coverage rate of three doses among Northern Plains American Indian women increased from about 23% currently to 80%, how many cases of invasive cervical cancer and cervical dysplasia could be prevented in that population? To our knowledge, this is the first study to use mathematical modeling to assess the impact of 9-valent vaccine in this high-risk population of Northern Plains American Indian women.

4.2 Materials and Methods

We developed a deterministic compartmental model to evaluate the effects of 9-valent versus 4-valent vaccine on cervical cancer cases. We modeled 4-valent vaccine (not bivalent) because 4-valent vaccine was the sole vaccine from 2006 to late 2009 in US.¹¹³ Also, it contains HPV types 16 and 18 that are covered by bivalent HPV vaccine. The model depicted an open population that begins in 2005, a year before the start of HPV vaccination, and ends after 70 years from the start. Because HPV 6 and 11 are low-risk viruses that cause genital warts and do not lead to cervical cancer, these were not included in any of our models. The population of susceptible women in the Northern

Plains (Iowa, Nebraska, Minnesota, South Dakota, and North Dakota) was based on the 2010 U.S. census. Because the CDC recommends that females aged 12–26 be vaccinated, the model population was categorized into three groups: <12 years old, 12–26 years and 27 years and above. There were 37,836 American Indians and 976,958 whites in the 12–26 age group and 99,205 American Indians and 3,458,063 whites in the age group 27 and above.¹⁸²

In our study, susceptible women were defined as nonvaccinated women at risk of getting infected with HPV. HPV-infected women were defined as women who contracted HPV infection from their male sex partners. Although in many individuals the HPV infection clears naturally, HPV can also avoid attack by the immune system¹⁸³ and in some cases can regress to any of the initial stages. In the absence of regression, persistent HPV infection progresses from precancerous lesions (CIN1, CIN2, and CIN3) to cervical cancer.^{184,185} We did not model males in our study, in order to reduce the complexity of the model. However, the contact and transmission rate parameter was based on heterosexual contact rates.

4.2.1 Mathematical Model

On the basis of the biology of HPV and cervical cancer, we developed a system of differential equations that captures the dynamics of HPV and cervical cancer (see Appendix for model equations). Figure 1 displays the natural history model flow diagram as well as the measures taken to mitigate the progression. This epidemiologic model begins with 12-year-old females entering the susceptible category. Once HPV transmission occurs, susceptible females enter the category of infected females. In accordance with mathematical epidemiology convention, the hazard rate at which these women contract infection is termed the force of infection. Individuals leave this category when the infectious period for HPV ends, and they start entering the cervical

intraepithelial neoplasia (CIN) stages. CIN, also known as cervical dysplasia, is the premalignant transformation and abnormal growth of squamous cells on the surface of the cervix. In a fraction of females, the infection clears naturally, and they will be immune for 5 years from the infection. After 5 years, these women will return to the susceptible stage, while the rest will either suffer mortality move to the CIN2 stage. Similar to CIN1, in some women at CIN2 and CIN3, the infection will clear, and in others it will regress back to CIN1 and CIN2, respectively. In addition, some females in these three stages undergoing treatment will leave their categories, become immune for 5 years, and then be susceptible after the immunity wanes. Some at the CIN3 stage will acquire cervical cancer. To reduce the complexity of the model, we assumed that women treated for cervical cancer will become immune and not susceptible to HPV infection.

A fraction of susceptible females in the age group of 12–26 years will be vaccinated and thus moved to the vaccination category, and nearly 90% will later be immune. However, females in any age group can also acquire other high-risk HPVs, and a proportion of them become infected with HPV 31/33/45/52/58, which all follow the same natural history as HPV 16/18.

Specifically, within each population, the model tracks the changing number of susceptible, HPV infected, CIN1, CIN2, CIN3, cervical cancer, treatment, vaccinated, and immune females. In light of the lower mixing rates between populations, each population was stimulated separately. Additionally, within each population model, a different model used for HPV types 16/18 and 5-additional types. Population-level vaccine-efficacy predictions are presented for the primary outcome: cervical cancer and CIN over time. Outcomes were modeled over 70 years post vaccination because this horizon allows enough time to reach a stable post-vaccination equilibrium and shows maximum differences in efficacy between the different vaccines.¹⁷⁷ However, the results

were reported after 15 and 30 years of vaccination in order to highlight the medium-term impact of the vaccine.

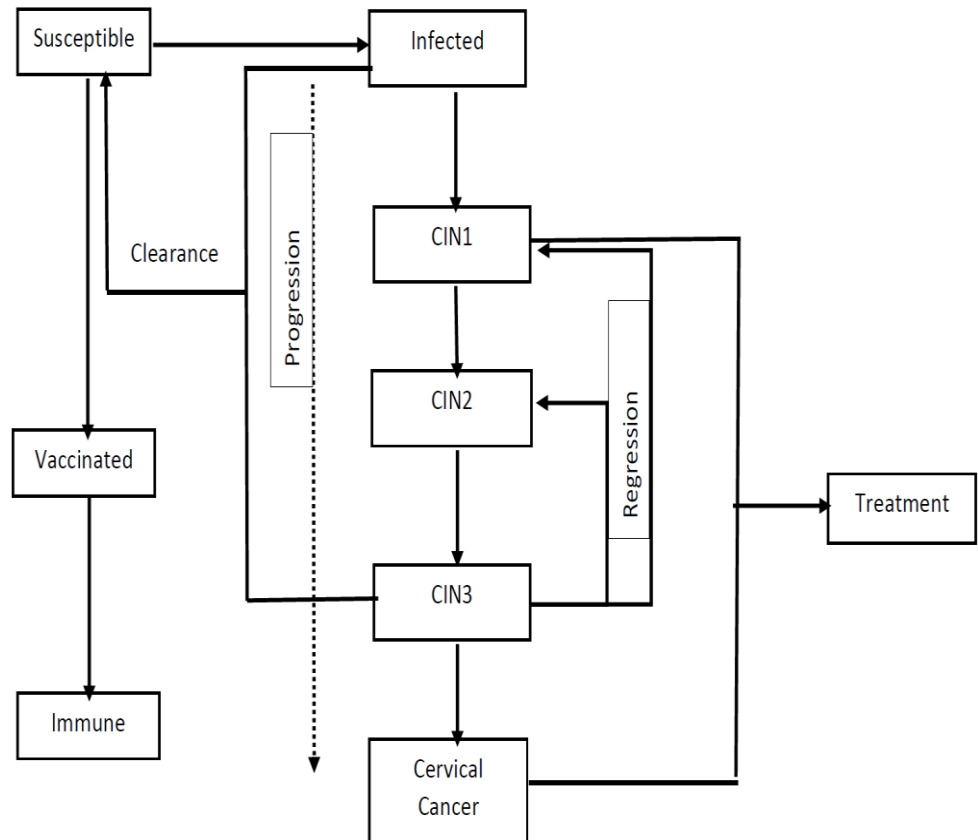


Figure 6. Model Flow Diagram

4.2.3 Model Assumptions

We assumed homogeneous mixing between the age groups within each population and used parameter estimates based on the literature. Rates of progression and regression to HPV and cancer were assumed to be independent of age.^{35,186,187} We followed¹⁸⁶ in assuming lifelong immunity in those vaccinated against the infection and no therapeutic effect of current vaccines (i.e., it cannot cure the virus or related infection). Additionally, we took into account neither cross-protectivity (in which

immunization with a certain vaccine type provides clinically significant protection against infection or disease, or both, due to another HPV type¹⁸⁸) nor cross-neutralization (in which antibodies elicited by vaccination with an HPV type neutralize virions of another HPV type at a variable degree in vitro). One reason for not taking cross-protectivity into account was that a comparison of two clinical trials—Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II of the quadrivalent vaccine and Papilloma Trial Against Cancer in Young Adults (PATRICIA) of the bivalent vaccine—suggested that estimates of cross-protectivity of vaccines against infections and lesions associated with HPV 31, 33, and 45 were usually higher for the bivalent vaccine than the quadrivalent vaccine.¹⁸⁹

4.2.4 Model Parameters

Table 1 summarizes the parameter estimates and references. A comprehensive search of the literature was performed to find parameter estimates. Prevalence rates for both American Indian women (HPV 16/18: 11.3%; HPV 16/18/31/33/45/52:14.8%) and white women (HPV 16/18: 5.9%; HPV 16/18/31/33/45/52: 8.3%) were based on unpublished data collected among Northern Plains American Indians and whites.¹⁹⁰ Progression rate, eradication with treatment rate, clearance rate, sensitivity, and vaccine efficacy for HPV were derived from several published studies.^{186,191-193} Because of the lack of race-specific rates, all the above rates were assumed to be the same for both the American Indian and the white population (except for the calibrated values). Screening rates for the year 2010 were obtained from CDC.¹⁹⁴ A sensitivity analysis was performed for various parameters in the model because different values were noted in the literature.^{186,195,196} Sensitivity and elasticity analysis was conducted on multiple parameters to determine the most influential inputs (Table 10). The baseline parameters were increased by 10% to determine the percent change in the baseline values for

susceptible, HPV infected, CIN3, and cumulative cervical cancer cases. To determine the sensitivity, the outcomes were measured at year 2035 (after 30 years from the start of the model).

Table 7. Parameter estimates for HPV disease categories			
Parameters in the model	American Indians	Whites	References
Number of susceptible			
12–26	38,736	976,958	177,182
27 and above	67313	3,438,989	
Ratio of males to females	0.96	0.98	182
Infected with oncogenic HPV types	13,945	205,161	
Transmission probability	0.7 (0.4)*	0.7 (0.4)*	195
Progression hazards per year			
HPV Infected to CIN1	0.09 (0.16)*	0.09	186
CIN1 to CIN2	0.13 (0.24)*	0.13	186
CIN2 to CIN3	0.14	0.14	186
CIN3 to cervical cancer	0.42	0.42	186
Fraction of eradications of infection with treatment			
CIN1	0.96	0.96	186
CIN2	0.92	0.92	186
CIN3	0.92	0.92	186
Localized cervical cancer	0.92	0.92	186
Clearance hazards rate			
CIN1 to Normal	0.32 (0.46)*	0.32 (0.48)*	186
CIN2 to Normal	0.21	0.21	186
CIN3 to Normal	0.11	0.11	186
Regression			
CIN2 to CIN1	0.133	0.133	186
CIN3 to CIN2	0.03	0.03	186
CIN3 to CIN1	0.03	0.03	186
Fraction of women screened each year	0.73	0.72	194
Sensitivity			
CIN1	0.28	0.28	197
CIN2 and CIN3	0.59	0.59	197
Vaccine efficacy	0.90	0.90	198
Current vaccination hazard	0.03	0.05	(IHS, unpublished data, 2015)

* The values in parentheses () are calibrated values.

Parameter	American Indians	Whites	Reference
Prevalence of any oncogenic types	36%	21%	
Prevalence of HPV 16/18 among ages 12–26 years	11.5%	8.9%	¹⁹⁰
Prevalence of HPV 16/18 among ages 27 and above	5.3%	8.2%	¹⁹⁰
Prevalence of HPV 16, 18, 31, 33, 45, 52, or 58	14.8%	8.3%	¹⁹⁰
Prevalence of HPV 31, 33, 45, 52, or 58 among ages 12–26 years	23.5%	9.8%	¹⁹⁰
Prevalence of HPV 31, 33, 45, 52, or 58 among 27 and above	6.3%	0.94%	¹⁹⁰
Fraction of women vaccinated (vaccination coverage rate)	0.23	0.40	IHS and South Dakota Health Department

4.3 Results

4.3.1 Sensitivity and Elasticity Analysis

The baseline parameters were increased by 10% to determine the percent change in the baseline values for susceptible, HPV infected, CIN3, and cumulative cervical cancer cases. For instance, a 10% increase in transmission rate resulted in a 6.49% increase in cumulative cervical cancer cases. Similar results for sensitivity and elasticity analysis were obtained for American Indian women (data not shown). Overall, the 10% change in transmission rate, screening rate, CIN 1 to CIN2 hazard rate, and CIN2 to CIN3 caused the parameter values to deflect more than 5% from the original value.

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Parameter	Percent change (Elasticity)* in:			<i>Cumulative Cervical Cancer</i>
	Susceptible White Women	HPV infected	CIN3	
Transmission rate	-6.57 (0.6)	15.6 (1.5)	12.49 (1.2)	<i>6.49 (0.6)</i>
Screening rate	0.14 (1.4)	-2.7 (0.2)	-12.5 (1.2)	<i>-9.87 (0.9)</i>
CIN1 to CIN2 hazard rate	-0.26 (0.02)	-1.64 (0.1)	7.95 (0.7)	<i>8.41 (0.8)</i>
CIN2 to CIN3 hazard rate	-0.26 (0.02)	-1.63 (0.1)	7.87 (0.7)	<i>8.34 (0.8)</i>
CIN3 to cervical cancer hazard rate	-0.25 (0.02)	1.68 (0.1)	-4.60 (0.4)	<i>5.88 (0.5)</i>
Vaccination rate	-0.61 (0.06)	-3.25 (0.3)	-0.68 (0.06)	<i>-0.10 (0.01)</i>
Rate of regression, CIN2 to CIN1	-0.26 (0.02)	-1.66 (0.01)	-1.45 (0.1)	<i>-1.18 (0.1)</i>
Rate of regression, CIN3 to CIN2	-0.26 (0.02)	-1.65 (0.1)	-0.26 (0.02)	<i>-0.19 (0.01)</i>
Fraction of CIN1 cured	0.12 (0.01)	-2.40 (0.2)	-3.56 (0.3)	<i>-2.51 (0.2)</i>
Fraction of CIN2 cured	0.09 (0.009)	-1.91 (0.1)	-5.24 (0.5)	<i>-4.11 (0.4)</i>
Fraction of CIN3 cured	-0.25 (0.02)	-1.72 (0.1)	-4.35 (0.4)	<i>-3.56 (0.3)</i>

**After 30 years of vaccination*

4.3.2 Model Fit and Validation

The predictive validity of the model was evaluated by comparing model results with epidemiologic data from populations in the United States. Table 11 shows the comparison of our model predictions with the reference model. Predictions of the model

were similar to the values reported in the literature. The prediction for HPV prevalence of five additional types among white women 27 years old and above is different from the epidemiological data because the prevalence obtained from the real data seems too low to be true. Based on the other population studies in the literature it seems plausible to have prevalence of 0.06 instead of 0.0094.

Parameter	Base model Value	Reference Value	Reference
Fraction of American Indian women 12 to 26 who have been vaccinated	0.224	0.23	Unpublished data from Indian Health Services
Fraction of White women 12 to 26 who have been vaccinated	0.39	0.40	¹⁷⁸
HPV 16/18 prevalence among American Indian women 12–26 years old	0.1144	0.115	¹⁹⁰
HPV 16/18 prevalence among American Indian women 27 years old and above	0.07	0.053	¹⁹⁰
HPV prevalence of five additional types among American Indian women 12–26 years old	0.209	0.235	¹⁹⁰
HPV prevalence of five additional types among American Indian women 27 years old and above	0.078	0.063	¹⁹⁰
HPV 16/18 prevalence among white women 12–26 years old	0.09	0.089	¹⁹⁰
HPV prevalence of five additional types among white women 12–26 years old	0.095	0.098	¹⁹⁰
HPV 16/18 prevalence among white women 27 years old and above	0.094	0.082	¹⁹⁰
HPV prevalence of five additional types among white women 27 years old and above	0.06	0.0094	¹⁹⁰

4.3.3 Model Scenarios

In this study we examined two different scenarios. The first scenario examined the number of CIN3 cases reduced by 9-valent versus 4-valent vaccine among American

Indian and White women in the Northern Plains. Table 11 shows the estimated number of CIN2/3 cases reduced per 100,000 by vaccine type since the reference year (2014, when the 9-valent vaccine was introduced), assuming 20% of cervical cancer cases are attributable to the 5 additional types of HPV included in the 9-valent vaccine. The model projects that after 30 years of vaccination, 371.4 per 100,000 CIN2 prevalent cases will be reduced at that time due to 4-valent vaccine among American Indian women, compared to 536 per 100,000 CIN 2 prevalent cases reduced at that time due to the 9-valent vaccine. Similarly, 132 per 100,000 cases among white women will be reduced by 4-valent vaccine compared to 284.1 per 100,000 cases that will be reduced by the 9-valent vaccine. Overall, there is a higher reduction in absolute terms in prevalent cases of CIN2 and CIN3 due to 4-valent and 9-valent vaccine among American Indian women compared to White women. Table 11 shows similar results for CIN3. Because the prevalent cases of CIN3 are much smaller than CIN2, this highlights that the magnitude of the impact of HPV vaccines to reduce CIN3 cases will be smaller.

	4-Valent				9-Valent			
	American Indians		Whites		American Indians		Whites	
Year*	15	30	15	30	15	30	15	30
CIN2	249.67	371.4	74.4	132.0	323.82	536.3	166.5	284.1
CIN3	71.6	112.5	13.5	27.6	88.9	153.1	35.1	63.9

* Years since the reference year of vaccination

As shown in Table 12, the model further projects that after 30 years from the reference year, 16.34 cumulative cervical cancer cases per 100,000 life years lived will be avoided by the 4-valent vaccine among American Indian women, while 18.41 cumulative cervical cancer cases per 100,000 life years lived will be avoided by the 9-valent vaccine among American Indian women. Similarly, the model predicts that 3.64 per 100,000 life years lived cumulative cervical cancer cases per 100,000 life years lived will be avoided by 4-valent vaccine among white women while 5.53 cumulative cervical cancer cases per 100,000 life years lived will be avoided by the 9-valent vaccine.

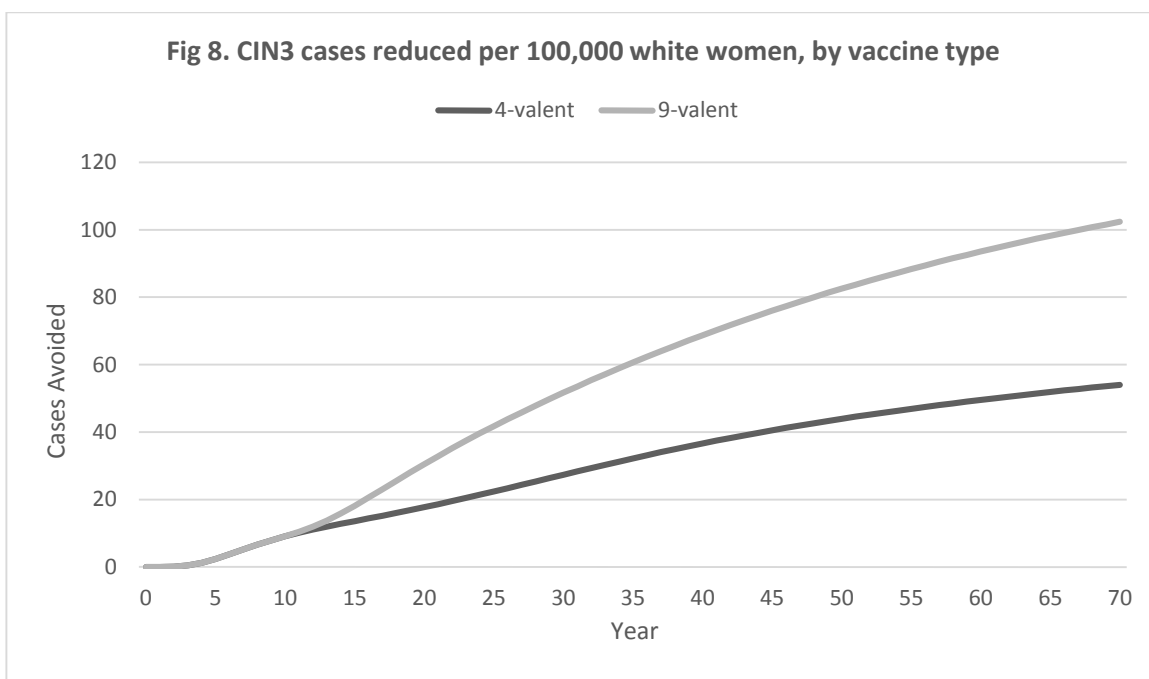
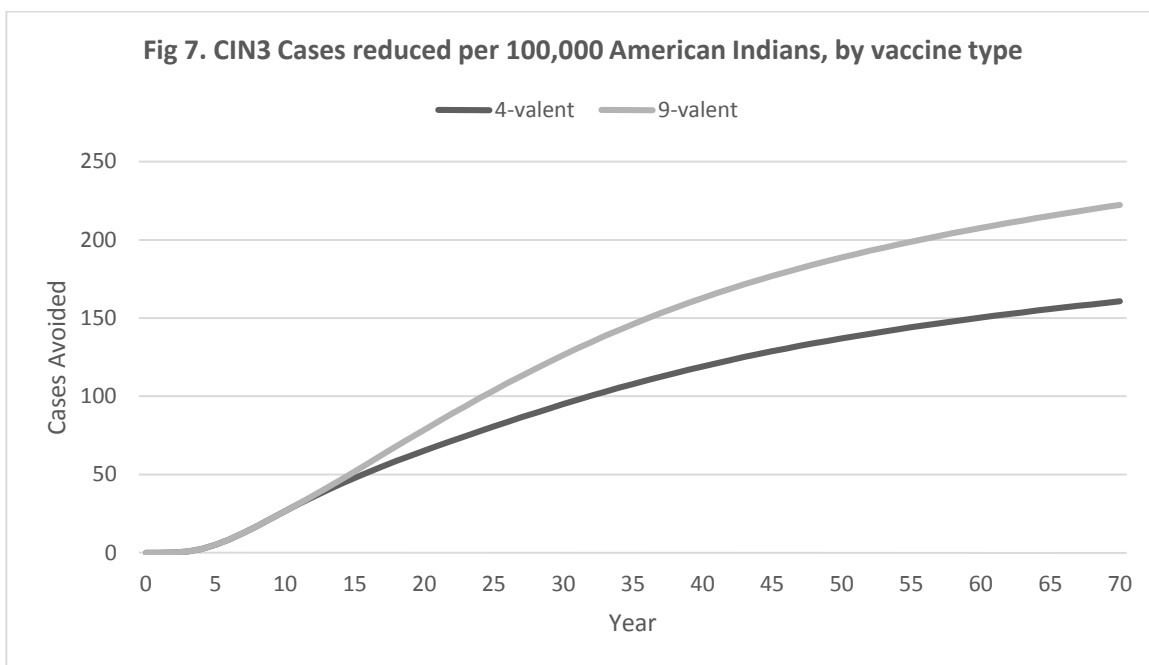
Table 12. Cumulative Cervical Cancer Cases avoided per 100,000 life years lived among American Indian women and White women								
	4-valent				9-valent			
	AI		White		AI		White	
Year since the reference year of vaccination	15	30	15	30	15	30	15	30
Cumulative cervical cancer cases avoided per 100,000 life years lived	8.51	16.34	1.74	3.64	9.05	18.41	2.25	5.53

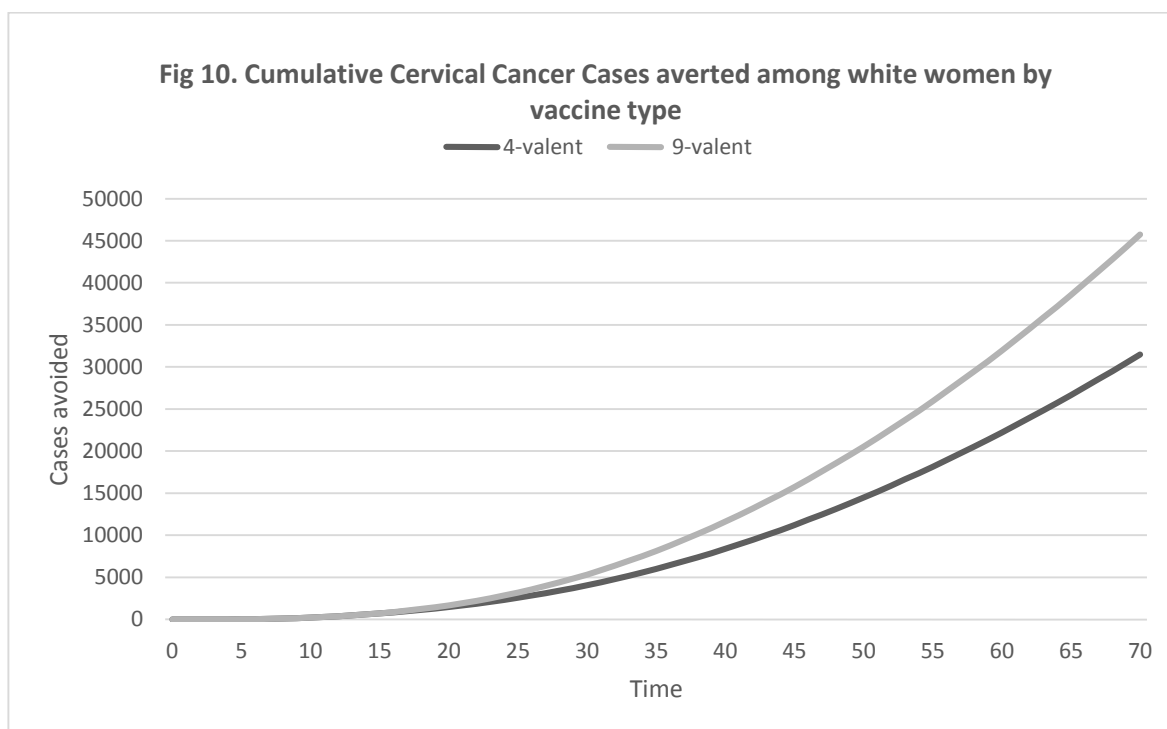
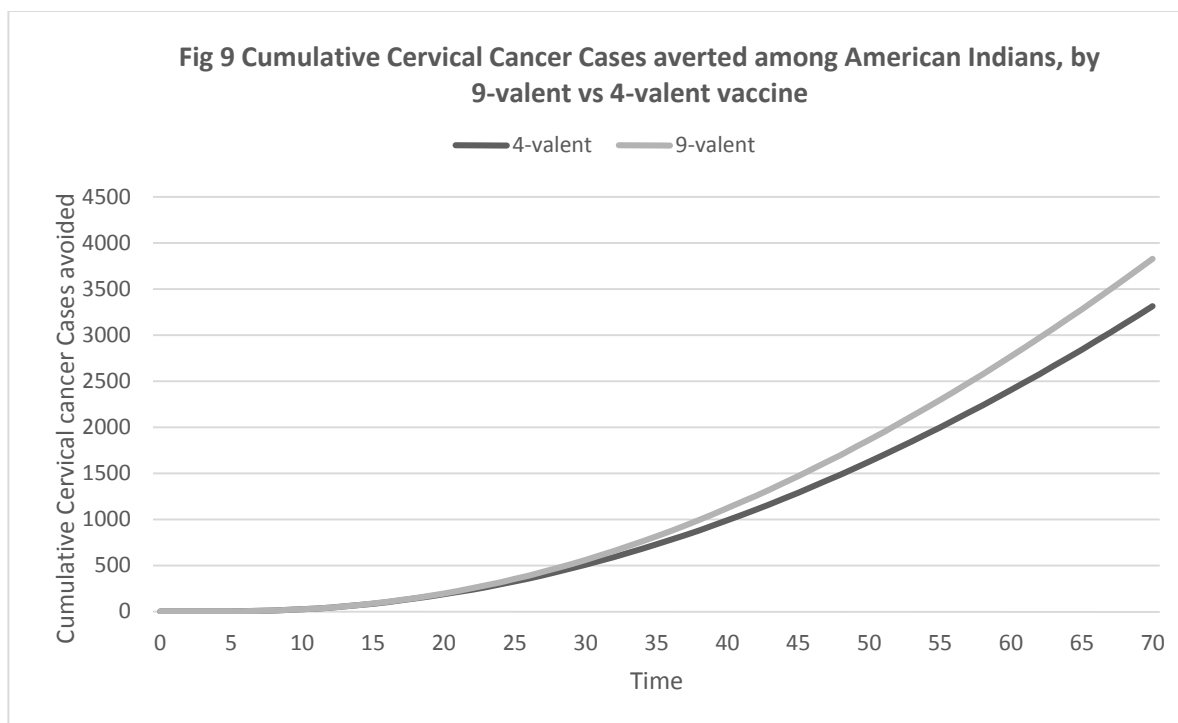
Figures 7 and 8 represent the CIN3 cases reduced per 100,000 by vaccine type among American Indian women and white women. In absolute terms, the switch to 9-valent vaccine from 4-valent vaccine further reduced the occurrence of CIN3, from a reduction of 112.5 per 100,000 women to a reduction of 153.1 per 100,000 women. This is an absolute difference of 40.6 per 100,000 women among American Indian. Among whites, the switch to 9-valent from 4-valent vaccine further reduced the occurrence of CIN3, from a reduction of 27.6 per 100,000 people to a reduction of 63.9 per 100,000 women. This is an absolute difference of 36.3 per 100,000 women. From the above results, it is clear that American Indian women benefit more from the 9-valent vaccine compared to the 4-valent vaccine.

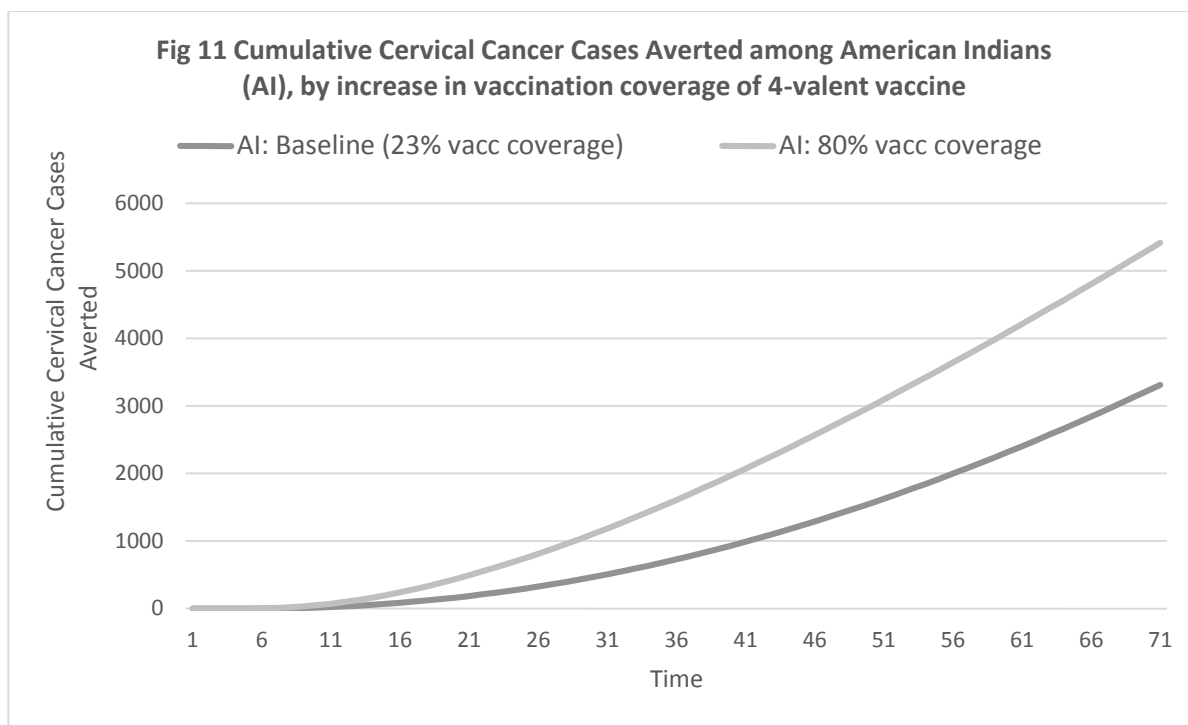
Figures 9 and 10 represent the cumulative cervical cancer cases averted over time, by vaccine status, among American Indian and white women. Caution should be taken in interpreting the results; the scales of the graphs are different because of the large difference in population size of American Indians and whites and thus are not

comparable. However, it does provide a picture of cumulative cervical cancer cases that would result per vaccination status.

The second scenario noted the number of cervical cancer cases averted by the 4-valent vaccine when the vaccination coverage is increased to 80%. The model predicts that after 30 years, with an increase in the current vaccination coverage from 23% to 80%, there will be a 25% decrease in the cumulative cervical cancer cases (Figure 11).

Model Scenarios





4.4 Discussion

The main aim of this study was to investigate the potential impact of the 9-valent vaccine in a high-risk population, using Northern Plain American Indians as an example. We used a mathematical model and considered two different scenarios. The first scenario examined the cervical cancer cases averted by 4-valent and 9-valent vaccine among American Indian and white women in the Northern Plains. The second scenario examined the cervical cancer cases reduced among American Indian women if the vaccination coverage was increased from 23% to 80%.

Our study result indicates that incremental gains from introducing 9-valent vaccine are higher among American Indian versus white women. The larger gains from 9-valent vaccination compared to 4-valent vaccination extends to both CIN3 and cervical cancer. We believe that these results could still be an underestimate because we were

unable to account for certain risk factors, such as the smoking rate.¹⁹⁹ Previous studies have indicated that persistent HPV infection is strongly associated with higher risk of cervical cancer.²⁰⁰ Persistent HPV infection results in inactivation of p53 and pRb tumor suppressor genes by the E6 and E7 proteins on the HPV genome. This, in turn, leads gradually to severe intraepithelial neoplasia and ultimately to cervical cancer.¹⁹¹

Because smoking is a major risk factor for HPV persistence, it may be causing the 5 additional types to persist longer among American Indian women compared to white women, resulting in a higher number of cervical cancer cases due to these types.

Additionally, another factor that needs to be taken into consideration is that there are still certain types of HPV that are not included in the 9-valent vaccine (such as HPV 59, 39, and 73) that are more prevalent in the American Indian population,²⁰¹ which raises an important concern about whether the implementation of universal vaccine is the best method in managing HPV infection and cervical cancer in specific populations such as American Indians. Geographic variation in the HPV distribution can play an important role in the effectiveness of the vaccination programs and policy development. On the other hand, if future studies after taking into account all the above factors find significant reduction in cervical cancer cases among American Indian women, then revaccinating the American Indian women with the 9-valent vaccine should be taken into consideration. Revaccinating might be more cost-effective, considering the small population size.

Another interesting finding of our study was that with the increase in the current vaccination coverage of 4-valent vaccine among American Indian women to 80% (a Healthy People 2020 goal), we would be able to reduce 25% of the cumulative cervical cancer cases after 30 years of vaccination. This is not a dramatic reduction in cumulative

cervical cancer cases, indicating that vaccinating against HPV 16 and 18 alone may not be sufficient, thus highlighting the benefit of 9-valent vaccine.

4.4.1 Strengths and Limitations

One of the major challenges we faced in conducting this study was lack of data on certain parameters (e.g., transmission rate, progression rate, and regression rate), specifically for the American Indian population. However, we did use calibrated values for certain parameters, as predicted by the model. Another impediment in modelling infectious disease is that it is difficult to include all relevant factors. For instance, we were unable to take smoking into account. Smoking is a major risk factor for HPV persistence and may be responsible for the higher rate of cervical cancer among American Indian women. Tobacco smoking is believed to facilitate the acquisition or persistence of an HPV infection through a reduced number of Langerhans cells and CD4 lymphocytes,^{62,63} which are markers of local immune response in the cervix.^{64,205} Although we were unable to account for this in our current study, future studies should include smoking in their model to make the predictions closer to the reality. Second, we assumed no cross-protection in our study, which may have affected the predicted results. However, this may not be true, since recent studies on HPV vaccine have demonstrated cross-protection against related HPV strains.^{189,202} Third, we did not account for HIV in our model, which is a potential modifier of the HPV natural history. We believe that since these factors were not taken into account, the results might be underestimated. Fourth, the model was not stratified by HPV types and ethnicity but instead done separately. This imposed several limitations including the omission of mixing between ethnic groups, inability to quantify death over time, unable to take into account multiple infections in an individual. Additionally, we were unable to understand the effects of death due to one HPV type on the prevalence of the other HPV type. In

addition, imprecise biological and behavioral measurements and the extreme sensitivity of the systems to small changes in the parameter values are frequently challenging for accurate quantitative predictions. Vaccination against HPV not only reduces the incidence of the disease in those immunized but also indirectly protects nonvaccinated susceptible persons against infection (called herd immunity). However, due to the static nature of this model, we could not take herd immunity into account. Our model is based on assumption of life-long immunity from the vaccine, which may not be the case in reality. If the immunity against the infection is lost, HPV-infected women may move back into the susceptible class, and the epidemiology of the HPV infection would be very different; high observed prevalence and sero-prevalence would be possible, with much lower basic reproductive number and transmission probability. This may further result in reduced vaccine efficacy and coverage required for elimination with a vaccine that did generate immune protection.²⁰³

We believe that our modeling approach has several strengths. First, this is the first study to project the impact of HPV vaccine on American Indian women. Second, for the validation, model results were compared to the data specific to American Indian women and white women in the Northern Plains. Third, the vaccination coverage rate used in this study was obtained from Indian Health Services and the Department of Health, South Dakota, which makes the results more reliable. Finally, the model is available to facilitate replication of findings and independent review of the model.

4.5 Conclusion

In summary, our model shows that 9-valent vaccine will substantially reduce the cumulative cervical cancer cases among both American Indian and white women, with larger gains among American Indian women. Currently, there is need for more specific

data for the American Indian population to have more robust results. Future studies should be conducted to collect more data on the Northern Plains American Indian population, and a stochastic model should be developed that would allow random variation in the inputs over time.

Chapter 5

DISCUSSION

5.1 Current Research

The burden and cost of HPV-associated diseases and cancer remain a major public health problem.¹⁶² The total medical cost of HPV infection for both men and women aged 15-24 is estimated to be \$2.9 billion, making HPV the second most expensive STI after HIV.²⁰⁴ To reduce this burden, we identified two vulnerable populations for our study: pregnant women and Northern Plain American Indian women, both high-risk groups. Two aims of this project were centered on understanding the role of HPV infection among pregnant women, as they are at higher risk of getting infected than nonpregnant women. The third aim was focused on projecting the impact of 9-valent HPV vaccine compared to 4-valent vaccine among American Indian women, since the prevalence of certain HPV types is much higher among this group.

5.1.1 HPV infection and its role in pregnancy

There is limited research on HPV infection and its association with adverse pregnancy outcomes. Recent research indicates that during pregnancy, the immune system is suppressed and major physiological changes take place that may result in increased HPV DNA replication.¹²⁵ In an animal model study, a murine form of herpes virus, MHV68, induced significant changes in the capacity of the trophoblast to respond to additional danger signals. When lipopolysaccharide (at a dose level that has no effect on pregnancy outcome) was injected into pregnant mice that were pre-exposed to MHV68, the study demonstrated that viral infection modulates the capacity of the trophoblast to cause increased inflammatory mediators in response to lipopolysaccharides such as MCP-1, G-CSF, and IL-6.¹⁵⁰ It is believed that HPV infection

impairs the extravillous trophoblast invasion into the uterine wall by increasing the rate of trophoblast cell deaths and causes placental dysfunction. As a consequence of this placental dysfunction, adverse pregnancy outcomes may occur. To understand the role of HPV infection in adverse pregnancy outcomes, the two main objectives of this project were (1) to examine the HPV infection prevalence and its association with perinatal outcomes among singleton mothers, with use of PRAMS data, and (2) to examine the association of HPV infection with adverse pregnancy outcomes, with use of hospital data. The results from these objectives will add to the existing body of HPV infection knowledge, aid in the development of better future studies, and help to identify adverse pregnancy outcomes that may be caused by HPV infection.

Overall, in both the PRAMS and hospital database studies, we found the prevalence of HPV infection among pregnant women was lower than what has been previously reported. However, the prevalence of HPV infection was even lower in the PRAMS study (1.4%). This might be an underestimate because of certain limitations associated with the data collection. This study was based on self-reported HPV exposure status, whereas the other studies that have reported higher prevalence of HPV infection were based on laboratory test results. Self-reported data are subject to recall bias or may be under-reported or over-reported. Another factor that should be taken into consideration is that out of 40 states that collect PRAMS data, only seven ask for HPV information. HPV prevalence varies geographically, so it could be that the prevalence in those seven states is lower than in some other states. Additionally, in the PRAMS survey questionnaire, HPV infection is measured on the basis of a single multicategorical question: "What disease or infection were you told you had?" One of the response options for this question is "Genital Warts (HPV)," which may not be comprehensive for all women. Except for the above question, there is no other question related to high-risk

HPV or low-risk HPV. Genital warts are the result of low-risk HPV such as types 6 or 11 and not the cancer-causing HPV types such as HPV 16 or 18. So it might be that some women with high-risk HPV did not report their status.

On the contrary, our hospital-based study involved laboratory-tested HPV infection. The prevalence was found to be 4.4% in the total sample of 5,022 women. Although the prevalence in this study was also lower than in previous studies (where it ranges from 5.5% to 65%),²⁰⁵ it was still higher than what we found in the PRAMS database. This suggests that further exploration is needed. The previous studies that reported higher prevalence were conducted in the pre-vaccination era, so the decline in the HPV prevalence noted in our study could be the result of vaccination program effectiveness. Furthermore, we found that the prevalence of HPV among whites was higher than in other ethnic/racial groups (including Black, American Indian, and Hispanic), contrary to the national rates (51.6% vs. 31.5%). A study conducted by Dinh et al. indicated that there is a higher prevalence of genital warts among whites compared to blacks.¹⁴⁸ Because most genital warts are the result of HPV, the presence of these in pregnant women would likely prompt healthcare professionals to perform HPV testing on these women. This might be the reason for the higher prevalence of HPV infection among white women in our study data.

Another component of both these studies was to examine the relationship between HPV infection and adverse pregnancy outcomes, including preterm birth, preeclampsia, low birth weight, and PROM. Our study based on the PRAMS database did not find any significant association between HPV infection and adverse pregnancy outcomes. However, in our hospital based study, we did find significant association between HPV infection and adverse pregnancy outcomes, including preeclampsia, preterm birth, and low birth weight. After controlling for demographic and clinical variables, we observed that HPV-positive women were 2.80 times more likely to develop

preeclampsia, 1.80 times more likely to have a preterm birth, and 2.58 times more likely to deliver a low-birth-weight infant. In these studies, we controlled for co-infection with chlamydia and gonorrhea, which wasn't adjusted for in some of the previous studies, raising some concerns related to the reliability of those results.

Our study findings also indicate that there is a significant difference in the prevalence of other sexually transmitted infections by HPV status. For instance, the prevalence of chlamydia was 9.2% among HPV-positive women, compared to 2.1% among HPV-negative women. Similarly, prevalence of Group B streptococci was 21.7% among HPV-positive women, compared to only 10% among HPV-negative women. Although the specific role of these sexually transmitted infections in the natural history of HPV is not clear, several mechanisms have been suggested. The most likely mechanism is the initiation of cervical inflammation that may lead to genotoxic damage through oxidative metabolites.²⁰⁶ Previous studies have found an association between chlamydia and HPV.²⁰⁷ Some studies have suggested that co-infection with chlamydia reduces the ability of the host to clear HPV infection. The chronic cervical inflammation influences HPV persistence through increased production of free radicals and a reduction of host-cell-mediated immunity.^{208,209} Chlamydia is believed to induce a shift in the immune response, and the unresolved infections have been associated with a humoral immune response, while clearance of HPV lesions have been associated with cellular immune response. Thus, modulation of cervical immune response by chlamydia may influence the clearance of HPV lesions.²⁰⁹ Because both HPV and chlamydia are related to sexual behaviors, they may synergize in inducing cervical epithelium alterations.^{18,210}

Although this study did not examine the relationship between HPV and chlamydia among pregnant women, we believe that it is beneficial to understand the association and its direction (casual inference) among pregnant women in future studies.

5.1.2 Impact of 9-valent HPV vaccine on Cervical Cancer

To our knowledge, this is the first published study to project the impact of 9-valent HPV vaccine among Northern Plains American Indian women. The reason for examining the impact on an American Indian population was that Northern Plains American Indian/Alaska Native women are at 1.7 times greater risk of developing cervical cancer than Non-Hispanic white women in the same region.⁸¹ Because the prevalence of HPV differs among population groups in the United States, varying degree of impact of HPV vaccine is expected. Gardasil 9, a 9-valent vaccine, was introduced in December 2014. This vaccine seems to have greater potential to reduce cervical cancer cases because it provides immunity against five additional types of HPV: 31, 33, 45, 52, and 58.

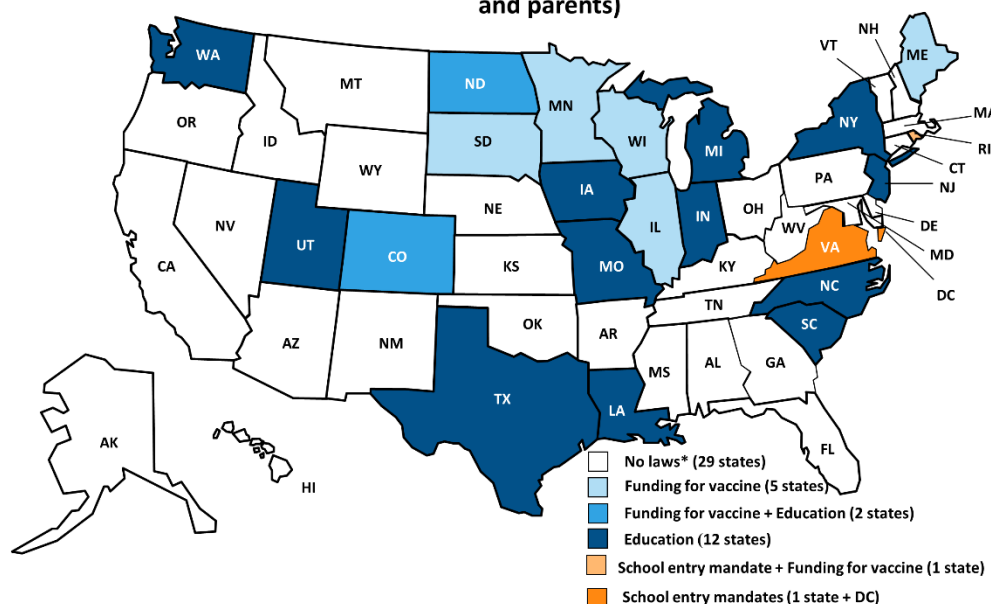
Our study indicates that the incremental gains from introducing 9-valent vaccine are higher among American Indian women compared to White women. The larger gains from 9-valent vaccine compared to 4-valent vaccine extends to both CIN3 and cervical cancer. The model predicted that after 30 years from the reference year, 16.34 cumulative cervical cancer cases per 100,000 life year lived will be avoided by the 4-valent vaccine among American Indian women, while 18.41 cumulative cervical cancer cases per 100,000 life year lived will be avoided by the 9-valent vaccine among American Indian women. Similarly, the model predicts that 3.64 per 100,000 cumulative cervical cancer cases per 100,000 life years lived will be avoided by 4-valent vaccine among white women while 5.53 cumulative cervical cancer cases per 100,000 life years lived will be avoided by the 9-valent vaccine. Additionally, the model predicted that in

absolute terms the switch to 9-valent vaccine from 4-valent vaccine would further reduce the occurrence of CIN3, from a reduction of 112.5 per 100,000 women to a reduction of 153.1 per 100,000 women, an absolute difference of 40.6 per 100,000 women among American Indian. Among whites, the switch to 9-valent from 4-valent vaccine further reduces the occurrence of CIN3, from a reduction of 27.6 per 100,000 people to a reduction of 63.9 per 100,000 women. This is an absolute difference of 36.3 per 100,000 women.

In this study we also estimated the percent decrease in the cumulative cervical cancer cases if the vaccination coverage is increased. The vaccination coverage of HPV vaccine is much lower compared to other vaccines such as Tdap and meningococcal conjugate vaccine.¹⁸¹ Some of the barriers to vaccination are higher cost of the vaccine,²¹¹ parent's negative perception about vaccine,²¹² health care providers not strongly recommending HPV vaccine for young adolescents,^{213,214} and low vaccine acceptance among adolescents.²¹² Parents are usually influenced by denial of risk (believing that their child is not sexually active and therefore is not at risk of HPV²¹²), concerns about vaccine safety, and feeling that a vaccine is too new if it was approved less than 10 years ago.²¹³ Moreover, currently only 21 states and D.C. have laws that either require HPV vaccination for school entry, provide funding to cover the cost of vaccines or support public education about HPV and vaccine (as shown in figure 12).²¹⁵

HPV Vaccination Policies- Mandates, Education, and Funding

State laws requiring HPV vaccinations for school entry, providing funding to cover the cost of the vaccine, or requiring public education (including for school children and parents)



NOTES: *States may have other laws relating to the HPV vaccine, such as insurance coverage mandates and research initiatives.
SOURCE: National Conference of State Legislatures. (2014). HPV vaccine: state legislation and statutes.
State of Rhode Island Department of Health (2015). Immunization Information for Schools and Child Care Workers.



Figure 12. HPV Vaccination Policies- Mandates, Education, and Funding. Adapted from The Henry J. Kaiser Family Foundation, 2015.²¹⁵

Because of the low coverage of the HPV vaccine, it is one of the goals of Healthy People 2020 to increase the HPV vaccination coverage to 80%. This study finding shows that if the vaccination coverage among American Indian women with 4-valent vaccine is increased from 23% to 80%, then after 30 years there will be a 25% decrease in the cumulative cervical cancer cases.

Our study results show that 9-valent vaccine will have a greater impact in the American Indian population. However, there are few things that need to be taken into consideration when interpreting the results of the study. Our model was challenged by the lack of parameter values specific to the American Indian population. For our study, we had to assume that the parameter values for American Indian women were the same

as for white women, which in reality may not be true, considering the environment as well as genetic and behavioral differences. For instance, the smoking rates are much higher in the American Indian population. Tobacco smoking is believed to facilitate the acquisition or persistence of an HPV infection through a reduced number of Langerhans cells and CD4 lymphocytes,^{62,63} which are markers of local immune response in the cervix.^{64,205}

Additionally, the activity of natural killer cells can be affected by tobacco smoking, which may affect the innate immune response.⁶⁴ Thus, the progression rate, regression rate, and clearance rate might vary drastically from what we see in the white population. For the treatment rate we also had to rely on data for the white population. However, to reduce the error, we conducted sensitivity analysis and validated our model by comparing our model values to historical values. Additionally, in our study, we were not able to account for smoking and HIV, which can modify the natural history of HPV infection. Furthermore, we did not consider the effect of circumcision among males in the model which may have an effect on the transmission probability of HPV infection from males to females. Circumcision has been associated with a reduced prevalence and persistence of oncogenic HPV infections.²¹⁶ Since circumcision rates are much lower in American Indian women compared to Whites, the transmission rate of HPV infection is expected to be very different in the two populations.²¹⁷ Because we were unable to consider these factors in our model, we believe that our results might be underestimated, especially among American Indian women. Another key limitation of this study was that the model was not stratified by HPV types and ethnicity, but instead done separately. This imposed several limitations including omission of mixing between ethnic groups, inability to quantify death over time, unable to take into account multiple

infections in an individual. Additionally, we were unable to understand the effects of death due to one type of HPV on prevalence of the other type of HPV.

5.2 Future Directions

5.2.1 Future Directions Based On Research of HPV among Pregnant Women

We found that there is a relationship between HPV infection and adverse pregnancy outcomes, including preterm birth, low birth weight, and preeclampsia. However, there is a need for future prospective studies to study these relationships in more depth. For instance, a cohort of women who are planning to get pregnant within the next 2 years can be selected randomly from the community. The cohort then can be divided into two groups: women who have been exposed to HPV and those who have not been exposed. These women could be followed up until their delivery. This type of study would allow us to analyze behavioral factors along with other factors before and during the pregnancy. This would be helpful because women tend to change certain behaviors (e.g., smoking, alcohol consumption, physical activity) during pregnancy, which may influence their self-reported responses. Additionally, there is a need for a population-based database that collects HPV information on pregnant women. We recommend that other states collecting PRAMS data should include HPV-related questions in their questionnaire that would allow researchers to explore the relationship at a population level. Also, new questions related to HPV infection should be included in the questionnaire, since currently there is only one question, which is very narrow. To get a clear picture of HPV infection among pregnant women questions like: “Were you ever told by a physician that you have HPV?” or “Were you ever diagnosed with genital warts?” or a more specific question like: “When you were pregnant, were you informed by your healthcare provider that you have HPV?” might be useful.

In addition, our study identified factors that should be considered when conducting similar research. First, we recommend future studies exclude ASCUS specimens. Although 50% of ASCUS specimens demonstrate HR-HPV,²¹⁸ other infections can also result in ASCUS. Second, gestational age of infection is an important factor that we think should be considered. Previous studies have reported that HPV prevalence varies by gestational age. Third, vaccination status should be considered since it could confound the association between HPV and adverse obstetrics outcomes. Fourth, in addition to chlamydia and gonorrhea, bacterial vaginosis should be taken into consideration, as it is associated with poor pregnancy outcomes.

5.2.2 Future Directions Based On HPV Modelling Research

We found that the 9-valent HPV vaccine will have a larger impact on American Indian women than white. However, our study identified gaps in knowledge that may have caused underestimation of cervical cancer cases among American Indian women in the Northern Plains. Further epidemiological studies should be conducted in the Northern Plain American Indian population to collect information on the sexual behaviors, screening rate, cervical intraepithelial neoplasia treatment rate, transmission rate of HPV from men to women and vice versa, progression rate, regression rate, and clearance rate of HPV among these women. Information on sexual behaviors can be collected with the help of surveys, and for certain parameters such as progression/regression/clearance rate, it might be useful to conduct a prospective study. This could be done by recruiting a randomly selected cohort of women with HPV infection. The cohort can then be divided into two groups (HR-HPV type and LR-HPV type), since the rates of progression, regression, and clearance may vary by HPV type. Then these women could be followed over time, for 5 years, a time period that would allow us to see the necessary changes. Women receiving treatment should also be

recorded. Although, this would be the best approach to gather all the necessary information, it might be difficult considering the challenges associated with conducting research among American Indian populations. Acknowledging this fact, the other approach is to conduct a mixed method research. A random sample of women receiving care at Indian Health Services should be obtained. All those women who provides their consent to participate in the study should be given surveys to gather information on their sexual behavior. This information should be later linked to the past health records of an individual from the clinic.

It was challenging for us to conduct a study without population-specific parameters, and we believe that this is a void that should be filled for better understanding of HPV vaccination. For example, it would be beneficial to study sexual behaviors and calculate the transmission rate, based on the sexual activity level. Because not every person has the same level of sexual activity, the transmission rate would not be the same across the population. Additionally, we recommend that future studies should include smoking as one of the parameters because it is known to cause modification in the natural history of HPV. Another important factor that should be considered is waning immunity. Given the significance of the duration of protection on the effectiveness of HPV vaccination, it would be essential to conduct post-vaccination surveillance. If the vaccine immunity does wane, then from the health policy standpoint it would be essential to consider booster shots, which would help in maintaining vaccine-induced immunity. For simplicity of the model and based on previous literature, we assumed life-long immunity after vaccination and assumed that after clearance of HPV infection the immunity wanes after 5 years in both American Indian and white population. However, this assumption may not be valid in reality. It could be possible that due to gene-environment interaction the

immunity wanes sooner in American Indian than white women. Hence, more studies are needed to explore this research area.

Furthermore, future studies are recommended to stratify the model by HPV types and ethnicity instead of creating a separate model. By doing so, various limitations associated with the current model such as the omission of mixing between ethnic groups, inability to quantify death over time, inability to account for multiple infections in an individual could be avoided.

5.3 Conclusion

Overall, this dissertation fills gaps in knowledge about the impact of HPV on two vulnerable populations; pregnant women and Northern Plains American Indian women. This is the first population based study that estimated HPV prevalence among pregnant women and examined its role in adverse pregnancy outcomes. In addition, this project identified the need for consistent HPV testing among pregnant women. In regard to American Indian population, this project emphasized the need of epidemiological data that would help in making future predictions using mathematical modeling techniques. These modeling techniques could also be applied to other vulnerable populations such as Black and Hispanics. Because of limitations, the findings of this study cannot be used to provide clinical recommendations, but they do provide knowledge that will be useful to the advancement of future research.

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APPENDIX

HPV Model Equations for American Indian Population

- "Cancer cases lived per year per 100,000 with five additional types"=Cancer cases lived per year five additional types*100000
- "Cancer cases lived per life year per 100,000 nona"= "Cancer Cases lived per life year (nona)"*100000
- Cancer cases lived per life year per 100000= "Cancer cases lived per year (quad)"*100000
- "vacc rate (FiveAdditionalTypes)"= IF THEN ELSE (Time < 8, 0 , Prospective nona vaccination rate)
- Prospective nona vaccination rate=0.03
- total population of women nona=total population of women quadrivalent
- Cumulative count cancer cases nona= Cumulative cervical cancer cases 12 to 26 FiveAdditionalTypes+Cumulative cervical cancer cases 12 to 26 quad +Cumulative Cervical Cancer cases 27 and above FiveAdditionalTypes+"cumulative cervical cancer cases quad 27&above"
- cumulative count of cervical cancer cases five additional types= Cumulative cervical cancer cases 12 to 26 FiveAdditionalTypes+Cumulative Cervical Cancer cases 27 and above FiveAdditionalTypes
- Cumulative count of cervical cancer cases quad= Cumulative cervical cancer cases 12 to 26 quad+" cumulative cervical cancer cases quad 27&above"
- Cancer cases lived per year five additional types= zidz(cumulative count of cervical cancer cases five additional types,life years lived five additional types)
- "Cancer Cases lived per life year (nona)"= zidz(cumulative count cancer cases nona,Life years lived nona)

- "Cancer cases lived per year (quad)"= $\text{zidz}(\text{cumulative count of cervical cancer cases quad, life years lived quad})$
- Life years lived nona= $\text{INTEG}(\text{total population of women nona}, 0)$
- total population of women quad= total population of women quadrivalent
- Total population of five additional types= total population of women 12 to 26 quadrivalent+ total population of women 27 and above FiveAdditionalTypesvalent
- total population of women five additional types= Total population of five additional types
- life years lived quad= $\text{INTEG}(\text{total population of women quad}, 1)$
- life years lived five additional types= $\text{INTEG}(\text{total population of women five additional types}, 0)$
- Ref rate of clearance of HPV infected quad 27 and above= 0.5922
- $\text{reg1 } 12 \text{ to } 26 \text{ FiveAdditionalTypes} = \text{Rate of regression CIN2 to CIN1 five additional types} * \text{CIN2 } 12 \text{ to } 26 \text{ FiveAdditionalTypes}$
- $\text{clearance2 FiveAdditionalTypes} = \text{"Rate of clearance of CIN2 five additional types 27\&above"} * \text{CIN2 } 27 \text{ and above FiveAdditionalTypes}$
- $\text{"reg1 } 27 \&\text{above FiveAdditionalTypes"} = \text{Rate of regression CIN2 to CIN1 five additional types} * \text{CIN2 } 27 \text{ and above FiveAdditionalTypes}$
- $\text{clearance3 among } 12 \text{ to } 26 \text{ quad} = \text{Ref Rate of clearance of CIN3 quad } 12 \text{ to } 26 * \text{CIN3 } 12 \text{ to } 26 \text{ quad} * \text{Coefficient of clearance for quad}$
- $\text{clearance3 FiveAdditionalTypes} = \text{Rate of clearance of CIN3 five additional types } 27 \text{ and above} * \text{CIN3 } 27 \text{ and above FiveAdditionalTypes}$
- $\text{"reg2 } 27 \&\text{above FiveAdditionalTypes"} = \text{Rate of Regression CIN3 to CIN2 five additional types} * \text{CIN3 } 27 \text{ and above FiveAdditionalTypes}$
- $\text{reg3 } 12 \text{ to } 26 \text{ FiveAdditionalTypes} = \text{Rate of regression CIN3 to CIN1 five additional types} * \text{CIN3 } 12 \text{ to } 26 \text{ FiveAdditionalTypes}$

- Ref rate of clearance of CIN2 quad 27 and above= 0.21
- "reg3 27&above FiveAdditionalTypes"= Rate of regression CIN3 to CIN1 five additional types*CIN3 27 and above FiveAdditionalTypes
- "clearance1 27&above quad"= Ref rate of clearance of CIN1 quad 27 and above*CIN1 27 and above quad*Coefficient of clearance for quad
- Rate of regression CIN3 to CIN1 five additional types= 0.03
- Rate of Regression CIN3 to CIN2 five additional types= 0.03
- "clear2 27 & above quad"= Ref rate of clearance of CIN2 quad 27 and above*CIN2 27 and above quad*Coefficient of clearance for quad
- "clear3 27&above quad"= Ref rate of clearance of CIN3 quad 27 and above*CIN3 27 and above quad*Coefficient of clearance for quad
- Rate of clearance of HPV infected five additional types 27 and above= 0.47705
- clearance of HPV infected 27 and above quad= HPV infected 27and above quad*Ref rate of clearance of HPV infected quad 27 and above *Coefficient of clearance for quad
- "clearance of infection 27&above FiveAdditionalTypes"= Rate of clearance of HPV infected five additional types 27 and above*HPV infected 27 and above FiveAdditionalTypes
- Ref rate of clearance of CIN1 quad 27 and above= 0.4606
- Rate of clearance of CIN1 five additional types 27 and above= 0.329
- Rate of regression CIN2 to CIN1 five additional types= 0.133
- "Rate of clearance of CIN2 five additional types 27&above"= 0.21
- reg2 26no= Rate of Regression CIN3 to CIN2 five additional types*CIN3 12to26 FiveAdditionalTypes
- Rate of clearance of CIN3 five additional types 27 and above= 0.11

- "clearance1 27 & above FiveAdditionalTypes"= Rate of clearance of CIN1 five additional types 27 and above*CIN1 27 and above FiveAdditionalTypes
- Ref rate of clearance of CIN3 quad 27 and above= 0.11
- rx1 12to26 FiveAdditionalTypes= Fraction of CIN1 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN1 *CIN1 12 to26 FiveAdditionalTypes
- "rx3 27&above quad"= Fraction of CIN3 successfully cured*sensitivity CIN2and CIN3*screening rate*CIN3 27 and above quad
- "rx2 27&above quad"= screening rate*Fraction of CIN2 successfully cured*sensitivity CIN2and CIN3*CIN2 27 and above quad
- "rx1 27&above quad"= Fraction of CIN1 successfully cured*screening rate*sensitivity CIN1*CIN1 27 and above quad
- rx2 12to26 FiveAdditionalTypes= Fraction of CIN2 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN2and CIN3*CIN2 12to 26 FiveAdditionalTypes
- rx3 12to26 FiveAdditionalTypes= Fraction of CIN3 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN2and CIN3 *CIN3 12to26 FiveAdditionalTypes
- clearance1 among 12to26 quad= Ref Rate of clearance of CIN1 quad 12 to 26*CIN1 12 to 26 quad*Coefficient of clearance for quad
- clearance2 among 12to26 quad= Ref Rate of clearance of CIN2 quad 12 to 26*CIN2 12 to 26 quad*Coefficient of clearance for quad
- Coefficient of clearance for quad= 0.68
- HPV infected clearance rate 12 to 26 quad= HPV infected 12 to 26 quad*Ref Rate of clearance of HPV infected quad 12 to 26*Coefficient of clearance for quad
- prog2 12to26FiveAdditionalTypes=CIN1 to CIN2 hazard rate FiveAdditionalTypes*CIN1 12 to26 FiveAdditionalTypes

- "prog2 27& above FiveAdditionalTypes"= CIN1 to CIN2 hazard rate
FiveAdditionalTypes*CIN1 27 and above FiveAdditionalTypes
- clearance2 12to 26 FiveAdditionalTypes= Rate of clearance of CIN2
FiveAdditionalTypes 12 to 26*CIN2 12to 26 FiveAdditionalTypes
- prog3 12 to 26FiveAdditionalTypes= CIN2 to CIN3 hazard rate
FiveAdditionalTypes*CIN2 12to 26 FiveAdditionalTypes
- clearance3 12to26 FiveAdditionalTypes= Rate of clearance of CIN3
FiveAdditionalTypes 12 to 26*CIN3 12to26 FiveAdditionalTypes
- "prog1 27 & above FiveAdditionalTypes"= HPV infected to CIN1 hazard rate
FiveAdditionalTypes*HPV infected 27 and above FiveAdditionalTypes
- Rate of clearance of CIN3 FiveAdditionalTypes 12 to 26= 0.11
- clearance hpv infected 12 to 26FiveAdditionalTypes= Rate of clearance of HPV
infected FiveAdditionalTypes 12 to 26*HPV infected 12to26 FiveAdditionalTypes
- Rate of clearance of HPV infected FiveAdditionalTypes 12 to 26= 0.1316
- CIN3 to cervical cancer hazard rate FiveAdditionalTypes= 0.42
- CIN1 12 to26 FiveAdditionalTypes= INTEG (prog1 12 to
26FiveAdditionalTypes+reg1 12 to 26FiveAdditionalTypes+reg3 12 to
26FiveAdditionalTypes-CIN1 12 to 26 FiveAdditionalTypes aging-CIN1 deaths 12to
26FiveAdditionalTypes-clearance1 12to26 FiveAdditionalTypes-prog2
12to26FiveAdditionalTypes-rx1 12to26 FiveAdditionalTypes, Initially HPV infected
12 to 26 women with FiveAdditionalTypes who are at CIN1)
- "prog3 27& above FiveAdditionalTypes"= CIN2 to CIN3 hazard rate
FiveAdditionalTypes*CIN2 27 and above FiveAdditionalTypes
- rate of clearance of CIN1 FiveAdditionalTypes 12 to 26= 0.329
- CIN2 to CIN3 hazard rate FiveAdditionalTypes= 0.14

- "prog4 27&above FiveAdditionalTypes"= CIN3 to cervical cancer hazard rate
FiveAdditionalTypes*CIN3 27 and above FiveAdditionalTypes
- HPV infected to CIN1 hazard rate FiveAdditionalTypes= 0.094
- CIN1 to CIN2 hazard rate FiveAdditionalTypes=0.136
- progression4 12to26 FiveAdditionalTypes= CIN3 12to26 FiveAdditionalTypes*CIN3
to cervical cancer hazard rate FiveAdditionalTypes
- HPV infected 12to26 FiveAdditionalTypes= INTEG (infection
12to26FiveAdditionalTypes-clearance hpv infected 12 to 26FiveAdditionalTypes-
deaths infected 12to 26 FiveAdditionalTypes-hpv infected 12 to
26FiveAdditionalTypes aging-prog1 12 to 26FiveAdditionalTypes initially infected
HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1)
- clearance1 12to26 FiveAdditionalTypes= rate of clearance of CIN1
FiveAdditionalTypes 12 to 26*CIN1 12 to26 FiveAdditionalTypes
- Rate of clearance of CIN2 FiveAdditionalTypes 12 to 26= 0.21
- prog1 12 to 26FiveAdditionalTypes= HPV infected to CIN1 hazard rate
FiveAdditionalTypes*HPV infected 12to26 FiveAdditionalTypes
- total cumulative cervical cancer cases 5 additional types= Cumulative cervical
cancer cases 12 to 26 FiveAdditionalTypes+Cumulative Cervical Cancer cases 27
and above FiveAdditionalTypes
- total cumulative cervical cancer cases quad= Cumulative cervical cancer cases 12
to 26 quad+"cumulative cervical cancer cases quad 27&above"
- women 27 and above who have been vaccinated quad= INTEG (aging into women
27 and above who have been vaccinated quad-death of women 27 and above who
have been vaccinated quad, 0)
- aging into women 27 and above who have been vaccinated FiveAdditionalTypes=
aging women 12 to 26 who have been vaccinated FiveAdditionalTypes

- aging into women 27 and above who have been vaccinated quad= aging number of women 12 to 26 who are vaccinated quad
- death of women 27 and above who have been vaccinated quad= women 27 and above who have been vaccinated quad*"death rate for 27&above"
- death of number of women 12 to 26 who are vaccinated FiveAdditionalTypes= women 12 to 26 FiveAdditionalTypes who have been vaccinated*death rate 12 to 26
- new vaccination of 12to 26 FiveAdditionalTypes=total population of women 12 to 26 FiveAdditionalTypesvalent*"vacc rate (FiveAdditionalTypes)"
- death of women 27 and above who have been vaccinated FiveAdditionalTypes= Women 27 and above who have been vaccinated FiveAdditionalTypes*"death rate for 27&above"
- Women 27 and above who have been vaccinated FiveAdditionalTypes= INTEG (aging into women 27 and above who have been vaccinated FiveAdditionalTypes- death of women 27 and above who have been vaccinated FiveAdditionalTypes, 0)
- fraction of women 12 to 26 who have been vaccinated= women 12 to 26 FiveAdditionalTypes who have been vaccinated/total population of women 12 to 26 FiveAdditionalTypesvalent
- aging women 12 to 26 who have been vaccinated FiveAdditionalTypes= women 12 to 26 FiveAdditionalTypes who have been vaccinated/mean years until aging
- women 12 to 26 FiveAdditionalTypes who have been vaccinated= INTEG (new vaccination of 12to 26 FiveAdditionalTypes-death of number of women 12 to 26 who are vaccinated FiveAdditionalTypes-aging women 12 to 26 who have been vaccinated FiveAdditionalTypes,0)

- Women 12 to 26 who have been vaccinated quad= INTEG (new vaccinations of 12 to 26 women-aging number of women 12 to 26 who are vaccinated quad-death of number of women 12 to 26 who are vaccinated,0)
- new vaccinations of 12 to 26 women= total population of women 12 to 26 quadrivalent*vacc rate
- aging number of women 12 to 26 who are vaccinated quad= Women 12 to 26 who have been vaccinated quad/mean years until aging
- death of number of women 12 to 26 who are vaccinated= Women 12 to 26 who have been vaccinated quad*death rate 12 to 26
- vacc quad= Susceptible12to26 quad*vacc rate*vaccine efficacy
- fraction of women 12 to 26 who have been vaccinated quad= Women 12 to 26 who have been vaccinated quad/total population of women 12 to 26 quadrivalent
- vacc rate= 0.03
- fraction of susceptible women 27 and above FiveAdditionalTypes= Susceptible 27and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent
- Fraction of women susceptible 12 to 26 quad= Susceptible12to26 quad/total population of women 12 to 26 quadrivalent
- Fraction of women susceptible 12 to 26 FiveAdditionalTypes= susceptible 12 to26 FiveAdditionalTypes/total population of women 12 to 26 FiveAdditionalTypesvalent
- fraction of women that are susceptible for 27 and above quad= Susceptible 27and above quad/total population of women 27 and above quadrivalent
- Inital 27 and above CIN1 infected women from HPV quad infected= fraction of women 27 and above who were infected with quad and are CIN1*Initial 27 and above HPV quad infected women from US census including CIN1

- HPV infected 27 and above FiveAdditionalTypes= INTEG (aging into hpv infected FiveAdditionalTypes+"infection 27&above FiveAdditionalTypes"- "clearance of infection 27&above FiveAdditionalTypes"-infected 27 and above deaths FiveAdditionalTypes-"prog1 27 & above FiveAdditionalTypes", initially HPV infected women 27 and above not CIN1 FiveAdditionalTypes)
- fraction of women 27 from US census who are infected with HPV quad strain= $(0.0528 \times 0) + 0.1$
- initially infected HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1=Initially infected HPV women 12 to 26 from US census including CIN1 for FiveAdditionalTypes-Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1
- Initially susceptible women 12 to 26 from US census= Total initial population 12 to 26 from US census-(Initially CIN1 infected women from HPV infected women+Initially HPV infected women from US census for quad not CIN1)
- HPV infected 12 to 26 quad= INTEG (infection rate among 12to26 quad-aging hpv infected 12 to 26 quad-deaths of infected 12 to 26 quad-HPV infected clearance rate 12 to 26 quad-progression1 among 12 to 26 quad, Initially HPV infected women from US census for quad not CIN1)
- Initially susceptible women 12 to 26 from US census for FiveAdditionalTypes= Total initial population 12 to 26 from US census-(Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1+initially infected HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1)
- Initially HPV infected women 27 and above from US census for quad not CIN1= Initial 27 and above HPV quad infected women from US census including CIN1- Initial 27 and above CIN1 infected women from HPV quad infected

- Initial susceptible women 27 and above from US census $\text{FiveAdditionalTypes} = \text{total initial population 27 and above from US census} - (\text{initially HPV infected women 27 and above not CIN1} + \text{FiveAdditionalTypes} + \text{Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain})$
- total population of women 27 and above quadrivalent = HPV infected 27 and above quad + Susceptible 27 and above quad + CIN1 27 and above quad + CIN2 27 and above quad + CIN3 27 and above quad + Immune via vaccination 27 and above quad + Immune after HPV clearance 27 and above quad
- Initially susceptible women 27 and above from US census = total initial population 27 and above from US census - (Initially HPV infected women 27 and above from US census for quad not CIN1 + Initial 27 and above CIN1 infected women from HPV quad infected)
- Initial 27 and above HPV quad infected women from US census including CIN1 = fraction of women 27 from US census who are infected with HPV quad strain * total initial population 27 and above from US census
- initially HPV infected women 27 and above not CIN1 $\text{FiveAdditionalTypes} = \text{Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1} - \text{Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain}$
- total population of women 12 to 26 quadrivalent = HPV infected 12 to 26 quad + Susceptible 12 to 26 quad + CIN1 12 to 26 quad + CIN2 12 to 26 quad + CIN3 12 to 26 quad + Immune via vaccination 12 to 26 quad + Immune after HPV infection clearance 12 to 26 quad
- total population of women 12 to 26 $\text{FiveAdditionalTypes valent} = \text{CIN1 12 to 26 FiveAdditionalTypes} + \text{CIN2 12 to 26 FiveAdditionalTypes} + \text{CIN3 12 to 26 FiveAdditionalTypes} + \text{HPV infected 12 to 26 FiveAdditionalTypes} + \text{susceptible 12}$

to26 FiveAdditionalTypes+ immune via vacc 12 to 26 FiveAdditionalTypes
 +Immune after HPV infection 12 to26 FiveAdditionalTypes

- Initially HPV infected women from US census for quad not CIN1= Initially HPV infected women from US census for quad including CIN1-Initially CIN1 infected women from HPV infected women
- total population of women 27 and above FiveAdditionalTypesvalent= CIN1 27 and above FiveAdditionalTypes+CIN2 27 and above FiveAdditionalTypes+CIN3 27 and above FiveAdditionalTypes +HPV infected 27 and above FiveAdditionalTypes+ Susceptible 27and above FiveAdditionalTypes +immune via vaccination 27 and above FiveAdditionalTypes +Immune after HPV infection 27and above FiveAdditionalTypes
- HPV infected 27and above quad= INTEG (Aging into HPV infected 27+"infection 27&above quad"-clearance of HPV infected 27 and above quad-"deaths of infected 27&above quad"-prog1 27and above quad, Initially HPV infected women 27 and above from US census for quad not CIN1)
- Immune after HPV clearance 27 and above quad= INTEG (aging into immune after HPV clearance 27 and above quad+"clear2 27 & above quad"+"clear3 27&above quad"+ clearance of HPV infected 27 and above quad+"clearance1 27&above quad"+"rx1 27&above quad"+"rx2 27&above quad"+"rx3 27&above quad"-death of immune after HPV clearance 27 and above-waning immunity after infection among 27 and above quad,0)
- Susceptible 27and above quad= INTEG (Aging into susceptible 27+waning immunity after infection among 27 and above quad-"infection 27&above quad"-susceptible27 deaths+"waning immunity among 27 and above (quad)", Initially susceptible women 27 and above from US census)

- Immune after HPV infection 27 and above FiveAdditionalTypes= INTEG (aging into immune after HPV infection 27 and above FiveAdditionalTypes+"clearance of infection 27&above FiveAdditionalTypes"+"clearance1 27 & above FiveAdditionalTypes"+"clearance2 FiveAdditionalTypes+clearance3 FiveAdditionalTypes+"rx1 27& above FiveAdditionalTypes"+"rx2 27& above FiveAdditionalTypes"+"rx3 27&above FiveAdditionalTypes" -Deaths of immune after vaccination 27 and above FiveAdditionalTypes-waning immunity after infection 27 and above nano,0)
- susceptible 12 to26 FiveAdditionalTypes= INTEG ("Aging females <12 FiveAdditionalTypes"+waning immunity after vaccination 12to 26 nano +waning immunity of 27 and above FiveAdditionalTypes-death of susceptibles 12to 26no-infection 12to26FiveAdditionalTypes-Susceptible 12 to 26 FiveAdditionalTypes aging-vacc FiveAdditionalTypes, Initially susceptible women 12 to 26 from US census for FiveAdditionalTypes)
- immune via vacc 12 to 26 FiveAdditionalTypes= INTEG (vacc FiveAdditionalTypes-aging of immune 12 to 26 FiveAdditionalTypes-deaths of immune 12 to 26 FiveAdditionalTypes-waning immunity after vaccination 12to 26 nano-waning immunity after vaccination 12to 26 nano,0)
- "rx2 27& above FiveAdditionalTypes"=Fraction of CIN2 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN2and CIN3*CIN2 27 and above FiveAdditionalTypes
- Immune via vaccination 12to26 quad= INTEG (vacc quad-aging immune via vaccination 12 to 26 quad-deaths of immune 12 to 26 quad-waning immunity after vaccination among 12to26quad,0)
- Susceptible12to26 quad= INTEG ("Aging of female <12"-aging susceptible 12to 26 quad-deaths of susceptible 12 to 26 quad-infection rate among 12to26 quad-

vacc quad+ Waning immunity after infection 12 to 26 quad+ waning immunity after vaccination among 12to26quad, Initially susceptible women 12 to 26 from US census)

- waning immunity after infection among 27 and above quad=Immune after HPV clearance 27 and above quad/Time until waning immunity after infection
- Susceptible 27and above FiveAdditionalTypes= INTEG (aging into susceptible 27 and FiveAdditionalTypes+waning immunity after infection 27 and above nano-"infection 27&above FiveAdditionalTypes"-susceptible 27 and above deaths+waning immunity after vaccination 27 and above FiveAdditionalTypes, Initial susceptible women 27 and above from US census FiveAdditionalTypes)
- time until waning immunity after vaccination=10
- waning immunity after vaccination among 12to26quad= (Immune via vaccination 12to26 quad/time until waning immunity after vaccination)*"enable waning immunity after vaccination?"
- "enable waning immunity after vaccination?"=0
- waning immunity after vaccination 12to 26 nano=(immune via vacc 12 to 26 FiveAdditionalTypes/time until waning immunity after vaccination)*"enable waning immunity after vaccination?"
- rx2 12to26 quad= screening rate*sensitivity CIN2and CIN3*Fraction of CIN2 successfully cured*CIN2 12 to 26 quad
- waning immunity after vaccination 27 and above FiveAdditionalTypes= (immune via vaccination 27 and above FiveAdditionalTypes/time until waning immunity after vaccination)* "enable waning immunity after vaccination?"
- waning immunity after infection 27 and above nano= Immune after HPV infection 27and above FiveAdditionalTypes/Time until waning immunity after infection

- "waning immunity among 27 and above (quad)"= (Immune via vaccination 27 and above quad/time until waning immunity after vaccination) *"enable waning immunity after vaccination?"
- fraction of women 12to26 immune via vaccination quad= Immune via vaccination 12to26 quad/total population of women 12 to 26 quadrivalent
- waning immunity of 27 and above FiveAdditionalTypes= Immune after HPV infection 12 to26 FiveAdditionalTypes/Time until waning immunity after infection
- aging of immune after HPV infection 12 to 26 FiveAdditionalTypes=
- Immune after HPV infection 12 to26 FiveAdditionalTypes/mean years until aging
- aging into immune after HPV clearance 27 and above quad= aging of immune after HPV infection clearance 12 to 26 quad
- Immune after HPV infection 12 to26 FiveAdditionalTypes= INTEG (clearance1 12to26 FiveAdditionalTypes+clearance2 12to 26 FiveAdditionalTypes+clearance3 12to26 FiveAdditionalTypes+rx1 12to26 FiveAdditionalTypes+rx2 12to26 FiveAdditionalTypes+rx3 12to26 FiveAdditionalTypes-deaths of immune after HPV infection 12 to 26 FiveAdditionalTypes-waning immunity of 27 and above FiveAdditionalTypes-aging of immune after HPV infection 12 to 26 FiveAdditionalTypes+ clearance hpv infected 12 to 26FiveAdditionalTypes,0)
- deaths of immune after HPV infection 12 to 26 FiveAdditionalTypes= death rate 12 to 26*Immune after HPV infection 12 to26 FiveAdditionalTypes
- Deaths of immune after vaccination 27 and above FiveAdditionalTypes= "death rate for 27&above"*Immune after HPV infection 27and above FiveAdditionalTypes

- aging into immune after HPV infection 27 and above $\text{FiveAdditionalTypes} = \text{aging of immune after HPV infection 12 to 26 FiveAdditionalTypes}$
- Waning immunity after infection 12 to 26 $\text{quad} = \text{Immune after HPV infection clearance 12 to 26 quad} / \text{Time until waning immunity after infection}$
- Time until waning immunity after infection = 5
- incidence of cc per 100000 12to26 = $(\text{Progression4 among 12 to 26 quad} / \text{total population of women 12 to 26 quadrivalent}) * 100000$
- aging of immune after HPV infection clearance 12 to 26 $\text{quad} = \text{Immune after HPV infection clearance 12 to 26 quad} / \text{mean years until aging}$
- deaths of immune after HPV infection clearance = $\text{Immune after HPV infection clearance 12 to 26 quad} * \text{death rate 12 to 26}$
- death of immune after HPV clearance 27 and above = $\text{Immune after HPV clearance 27 and above quad} * \text{"death rate for 27\&above"}$
- Immune after HPV infection clearance 12 to 26 $\text{quad} = \text{INTEG} (\text{HPV infected clearance rate 12 to 26 quad} + \text{clearance1 among 12to26 quad} + \text{clearance2 among 12to26 quad} + \text{clearance3 among 12 to 26 quad} + \text{rx1 12to26 quad} + \text{rx2 12to26 quad} + \text{rx3 12 to 26 quad} - \text{Waning immunity after infection 12 to 26 quad} - \text{aging of immune after HPV infection clearance 12 to 26 quad} - \text{deaths of immune after HPV infection clearance}, 0)$
- force of infection 12to26 $\text{quad} = \text{mean partner acquisition 12 to 26} * (\text{Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age} * \text{HPV prevalence 12 to 26 quad} + (1 - \text{Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age}) * \text{HPV prevalence 27 and above quad}) * \text{transmission rate 12to26}$
- force of infection 12 to 26 $\text{FiveAdditionalTypes} = \text{mean partner acquisition 12 to 26} * (\text{Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of$

age* HPV prevalence 12to26FiveAdditionalTypes+ (1-Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age) * HPV prevalence 27 and above FiveAdditionalTypes)* transmission rate 12to26

- transmission rate 12to26= 0.4
- CIN3 27 and above deaths FiveAdditionalTypes= "death rate for 27&above"*CIN3 27 and above FiveAdditionalTypes
- CIN3 12to26 FiveAdditionalTypes= INTEG (prog3 12 to 26FiveAdditionalTypes-CIN3 12 to 26 FiveAdditionalTypes aging-CIN3 deaths 12to26FiveAdditionalTypes-clearance3 12to26 FiveAdditionalTypes-reg2 26no-reg3 12 to 26FiveAdditionalTypes-rx3 12to26 FiveAdditionalTypes +prog3 12 to 26FiveAdditionalTypes-progression4 12to26 FiveAdditionalTypes,0)
- "CIN3 27 & above death quad"= "death rate for 27&above"*CIN3 27 and above quad
- CIN3 27 and above FiveAdditionalTypes= INTEG (aging into cin3 FiveAdditionalTypes+"prog3 27& above FiveAdditionalTypes"-CIN3 27 and above deaths FiveAdditionalTypes-clearance3 FiveAdditionalTypes-"prog4 27&above FiveAdditionalTypes"- "reg2 27 &above FiveAdditionalTypes"- "reg3 27&above FiveAdditionalTypes"- "rx3 27&above FiveAdditionalTypes"+"prog3 27& above FiveAdditionalTypes"- "prog4 27&above FiveAdditionalTypes", 0)
- CIN3 27 and above quad= INTEG ("Aging into CIN3 27&above quad"+prog3 27and above quad-"CIN3 27 & above death quad"- "clear3 27&above quad"- "reg2 27&above quad"-reg3 27 and above quad-"rx3 27&above quad"+prog3 27and above quad-prog4 27and above quad,0)
- "CIN1 27&above deaths quad"= "death rate for 27&above"*CIN1 27 and above quad

- immune via vacc deaths quad= Immune via vaccination 27 and above
quad*"death rate for 27&above"
- Cumulative cervical cancer cases 12 to 26 FiveAdditionalTypes= INTEG
(progression4 12to26 FiveAdditionalTypes,0)
- Cumulative Cervical Cancer cases 27 and above FiveAdditionalTypes= INTEG
("prog4 27&above FiveAdditionalTypes", 0)
- "cumulative cervical cancer cases quad 27&above"= INTEG (prog4 27and above
quad,0)
- infected 27 and above deaths FiveAdditionalTypes= "death rate for
27&above"*HPV infected 27 and above FiveAdditionalTypes
- prog4 27and above quad= CIN3 27 and above quad*CIN3 to cervical cancer
hazard rate quad
- "death rate for 27&above"= 0.005417
- Progression4 among 12 to 26 quad= CIN3 to cervical cancer hazard rate
quad*CIN3 12 to 26 quad
- "CIN1 27 &above deaths FiveAdditionalTypes"= CIN1 27 and above
FiveAdditionalTypes*"death rate for 27&above"
- susceptible27 deaths= Susceptible 27and above quad*"death rate for 27&above"
- "CIN2 27&above deaths FiveAdditionalTypes"= CIN2 27 and above
FiveAdditionalTypes*"death rate for 27&above"
- deaths of immune 27 and above FiveAdditionalTypes="death rate for
27&above"*immune via vaccination 27 and above FiveAdditionalTypes
- susceptible 27 and above deaths="death rate for 27&above"*Susceptible 27and
above FiveAdditionalTypes
- prog4 27 and above quad per 100000= (prog4 27and above quad/total
population of women 27 and above quadrivalent)*100000

- CIN3 12 to 26 quad= INTEG (-Aging CIN3 12 to 26 FiveAdditionalTypes-clearance3 among 12 to 26 quad-deaths of CIN3 12 to 26 quad-regression2 12to26 quad-Regression3 12to26 quad-rx3 12 to 26 quad+progression3 among 12 to 26 quad-Progression4 among 12 to 26 quad,0)
- CIN2 deaths among 27 and above quad= CIN2 27 and above quad*"death rate for 27&above"
- "deaths of infected 27&above quad"= HPV infected 27and above quad*"death rate for 27&above"
- Cumulative cervical cancer cases 12 to 26 quad= INTEG (Progression4 among 12 to 26 quad,0)
- total population of men and women FiveAdditionalTypes= total population of women FiveAdditionalTypesvalent*(1+Ratio of male to female population)
- "Initial susceptible women <12 years FiveAdditionalTypesvalent"= 37112
- "Female <12 FiveAdditionalTypes"= INTEG (birth FiveAdditionalTypes-"Aging females <12 FiveAdditionalTypes"- "death of females <12 years", "Initial susceptible women <12 years FiveAdditionalTypesvalent")
- total population of men and women quad= total population of women quadrivalent*(1+Ratio of male to female population)
- birth FiveAdditionalTypes= birth rate for female babies*total population of men and women FiveAdditionalTypes
- birth quad= total population of men and women quad*birth rate for female babies
- Ratio of male to female population= 0.96
- rx3 12 to 26 quad= screening rate*sensitivity CIN2and CIN3*Fraction of CIN3 successfully cured*CIN3 12 to 26 quad

- "rx3 27&above FiveAdditionalTypes"= Fraction of CIN3 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN2and CIN3*CIN3 27 and above FiveAdditionalTypes
- "rx1 27& above FiveAdditionalTypes"= Fraction of CIN1 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN1*CIN1 27 and above FiveAdditionalTypes
- rx1 12to26 quad= sensitivity CIN1*screening rate*Fraction of CIN1 successfully cured*CIN1 12 to 26 quad
- HPV infected FiveAdditionalTypes per 100000= (HPV infected 27 and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent)*100000
- CIN3 among 12 to 26 per 100000 quad= (CIN3 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- CIN2 12to26 quad per 100000= (CIN2 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- CIN3 FiveAdditionalTypes per 100000= (CIN3 27 and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent)*100000
- CIN2 27 and above per 100000 quad=(CIN2 27 and above quad/total population of women 27 and above quadrivalent)*100000
- CIN1 12to26 per 100000 quad= (CIN1 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- CIN1 26FiveAdditionalTypes per 100000= (CIN1 12 to26 FiveAdditionalTypes/total population of women 12 to 26 FiveAdditionalTypesvalent)*100000

- $\text{hpv infected 27 and above per 100000 quad} = (\text{HPV infected 27 and above quad} / \text{total population of women 27 and above quadrivalent}) * 100000$
- $\text{"CIN1 27\& above FiveAdditionalTypes per 100000"} = (\text{CIN1 27 and above FiveAdditionalTypes} / \text{total population of women 27 and above FiveAdditionalTypesvalent}) * 100000$
- $\text{CIN3 12 to 26 per 100000 FiveAdditionalTypes} = (\text{CIN3 12to26 FiveAdditionalTypes} / \text{total population of women 12 to 26 FiveAdditionalTypesvalent}) * 100000$
- $\text{"CIN1 27\&above per 100000 quad"} = (\text{CIN1 27 and above quad} / \text{total population of women 27 and above quadrivalent}) * 100000$
- $\text{CIN3 27 and above per 100000 quad} = (\text{CIN3 27 and above quad} / \text{total population of women 27 and above quadrivalent}) * 100000$
- $\text{CIN2 12 to 26per 100000 FiveAdditionalTypes} = (\text{CIN2 12to 26 FiveAdditionalTypes} / \text{total population of women 12 to 26 FiveAdditionalTypesvalent}) * 100000$
- $\text{"total population of women (quad+FiveAdditionalTypes)"} = \text{total population of women 12 to 26 FiveAdditionalTypesvalent} + \text{total population of women 12 to 26 quadrivalent} + \text{total population of women 27 and above FiveAdditionalTypesvalent} + \text{total population of women 27 and above quadrivalent}$
- $\text{total population} = \text{"total population of women (quad+FiveAdditionalTypes)"} * \text{ratio of total population to total population of women}$
- $\text{"CIN2 27\&above FiveAdditionalTypes per 100000"} = (\text{CIN2 27 and above FiveAdditionalTypes} / \text{total population of women 27 and above FiveAdditionalTypesvalent}) * 100000$
- $\text{HPV infected 12 to 26 per 100000 quad} = (\text{HPV infected 12 to 26 quad} / \text{total population of women 12 to 26 quadrivalent}) * 100000$

- $\text{hpv infected 12 to 26} \times \text{FiveAdditionalTypes per 100000} = (\text{HPV infected 12 to 26} \times \text{FiveAdditionalTypes} / \text{total population of women 12 to 26} \times \text{FiveAdditionalTypesvalent}) \times 100000$
- Aging into HPV infected 27 = aging hpv infected 12 to 26 quad
- "Females <12 quad" = INTEG (birth quad - "Aging of female <12" - "death of females < 12 years of age", "Initial susceptible females <12 quad")
- "Initial susceptible females <12 quad" = 37112
- $\text{total population of women FiveAdditionalTypesvalent} = \text{total population of women 12 to 26 FiveAdditionalTypesvalent} + \text{total population of women 27 and above FiveAdditionalTypesvalent}$
- "HPV Infection (quad) among 12 to 26 count" = CIN1 12 to 26 quad + CIN2 12 to 26 quad + CIN3 12 to 26 quad + HPV infected 12 to 26 quad
- $\text{HPV prevalence 27 and above FiveAdditionalTypes} = (\text{"HPV infection among 27 and above (FiveAdditionalTypes) count"} / \text{total population of women 27 and above FiveAdditionalTypesvalent})$
- $\text{HPV prevalence 12 to 26 quad} = (\text{"HPV Infection (quad) among 12 to 26 count"} / \text{total population of women 12 to 26 quadrivalent})$
- "HPV infection among 12 to 26 (FiveAdditionalTypes) count" = CIN1 12 to 26 FiveAdditionalTypes + CIN2 12 to 26 FiveAdditionalTypes + CIN3 12 to 26 FiveAdditionalTypes + HPV infected 12 to 26 FiveAdditionalTypes
- "HPV infection among 27 and above (FiveAdditionalTypes) count" = HPV infected 27 and above FiveAdditionalTypes + CIN1 27 and above FiveAdditionalTypes + CIN2 27 and above FiveAdditionalTypes + CIN3 27 and above FiveAdditionalTypes

- "HPV infection among 27 and above (quad) count"= CIN1 27 and above quad+CIN2 27 and above quad+CIN3 27 and above quad+HPV infected 27and above quad
- HPV prevalence 12to26FiveAdditionalTypes= ("HPV infection among 12 to 26 (FiveAdditionalTypes) count")/total population of women 12 to 26 FiveAdditionalTypesvalent
- HPV prevalence 27 and above quad= ("HPV infection among 27 and above (quad) count")/total population of women 27 and above quadrivalent
- CIN1 12 to 26 quad= INTEG (progression1 among 12 to 26 quad+regression1 12to26 quad+Regression3 12to26 quad-aging CIN1 12to26 quad-clearance1 among 12to26 quad-deaths of CIN1 12to26 quad-progression2 among 12 to 26 quad-rx1 12to26 quad, Initially CIN1 infected women from HPV infected women)
- CIN1 27 and above FiveAdditionalTypes= INTEG (aging into CIN1 FiveAdditionalTypes+"prog1 27 & above FiveAdditionalTypes"+"reg1 27&above FiveAdditionalTypes"+"reg3 27&above FiveAdditionalTypes"- "CIN1 27 &above deaths FiveAdditionalTypes"- "clearance1 27 & above FiveAdditionalTypes"- "prog2 27& above FiveAdditionalTypes"- "rx1 27& above FiveAdditionalTypes", Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain)
- total population of women quadrivalent= total population of women 12 to 26 quadrivalent+total population of women 27 and above quadrivalent
- deaths of immune 12 to 26 FiveAdditionalTypes= death rate 12 to 26*immune via vacc 12 to 26 FiveAdditionalTypes
- aging into immune via vaccination 27 and above quad= aging immune via vaccination 12 to 26 quad

- $\text{deaths of immune 12 to 26 FiveAdditionalTypes} = \text{death rate 12 to 26} * \text{immune via vacc 12 to 26 FiveAdditionalTypes}$
- $\text{aging immune via vaccination 12 to 26 quad} = \text{Immune via vaccination 12 to 26 quad} / \text{mean years until aging}$
- $\text{aging into immune via vacc 27 and above FiveAdditionalTypes} = \text{aging of immune 12 to 26 FiveAdditionalTypes}$
- $\text{immune via vaccination 27 and above FiveAdditionalTypes} = \text{INTEG} (\text{aging into immune via vacc 27 and above FiveAdditionalTypes} - \text{deaths of immune 27 and above FiveAdditionalTypes} - \text{waning immunity after vaccination 27 and above FiveAdditionalTypes}, 0)$
- $\text{Immune via vaccination 27 and above quad} = \text{INTEG} (\text{aging into immune via vaccination 27 and above quad} - \text{"waning immunity among 27 and above (quad)" - immune via vacc deaths quad}, 0)$
- $\text{aging of immune 12 to 26 FiveAdditionalTypes} = \text{immune via vacc 12 to 26 FiveAdditionalTypes} / \text{mean years until aging}$
- $\text{vacc FiveAdditionalTypes} = \text{susceptible 12 to 26 FiveAdditionalTypes} * \text{"vacc rate (FiveAdditionalTypes)" * vaccine efficacy}$
- $\text{HPV prevalence 27 and above per 100 quad} = \text{HPV prevalence 27 and above quad} * 100$
- $\text{HPV prevalence 12 to 26 per 100 FiveAdditionalTypes} = \text{HPV prevalence 12 to 26 FiveAdditionalTypes} * 100$
- $\text{HPV prevalence 27 and above FiveAdditionalTypes per 100} = \text{HPV prevalence 27 and above FiveAdditionalTypes} * 100$
- $\text{HPV prevalence 12 to 26 quad per 100} = \text{HPV prevalence 12 to 26 quad} * 100$
- $\text{CIN1 27 and above quad} = \text{INTEG} (\text{"Aging into CIN1 27 \& above quad"} + \text{prog1 27 and above quad} + \text{reg1 27 and above quad} + \text{reg3 27 and above quad} - \text{"CIN1$

27&above deaths quad"- "clearance1 27&above quad"-prog2 27and above quad-
 "rx1 27&above quad", Initial 27 and above CIN1 infected women from HPV quad
 infected)

- fraction of women 27 and above who were infected with quad and are CIN1=
 0.09
- Total initial population 12 to 26 from US census= 38736
- total initial population 27 and above from US census=67313
- Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1=
 Initially infected HPV women 12 to 26 from US census including CIN1 for
 FiveAdditionalTypes*Fraction of 12 to 26 years who are initially infected with
 HPV FiveAdditionalTypes who have CIN1
- Initially HPV infected women from US census for quad including CIN1=Total
 initial population 12 to 26 from US census*Fraction of women 12 to 26 from US
 census who are HPV infected for quad strain
- Initially infected HPV women 12 to 26 from US census including CIN1 for
 FiveAdditionalTypes = Fraction of US 12 to 26 census population that is initially
 infected with FiveAdditionalTypes strain of HPV *Total initial population 12 to 26
 from US census
- Fraction of women 27 and above from HPV FiveAdditionalTypes infected that are
 CIN1= 0.1184
- fraction of women 27 and above from susceptible that are infected with HPV
 FiveAdditionalTypes=0.08
- Fraction of 12 to 26 years old who are initially infected with quad strains of HPV
 who have CIN1=0.09

- Initially CIN1 infected women from HPV infected women= Initially HPV infected women from US census for quad including CIN1*Fraction of 12 to 26 years old who are initially infected with quad strains of HPV who have CIN1
- Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1= fraction of women 27 and above from susceptible that are infected with HPV FiveAdditionalTypes*total initial population 27 and above from US census
- Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain= Fraction of women 27 and above from HPV FiveAdditionalTypes infected that are CIN1*Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1
- Fraction of women 12 to 26 from US census who are HPV infected for quad strain= 0.15
- Fraction of 12 to 26 years who are initially infected with HPV FiveAdditionalTypes who have CIN1=0.09
- Fraction of US 12 to 26 census population that is initially infected with FiveAdditionalTypes strain of HPV= 0.27
- death of susceptible 12to 26no= susceptible 12 to26 FiveAdditionalTypes*death rate 12 to 26
- CIN1 deaths 12to 26FiveAdditionalTypes= CIN1 12 to26 FiveAdditionalTypes*death rate 12 to 26
- deaths of CIN3 12 to 26 quad= death rate 12 to 26*CIN3 12 to 26 quad
- deaths of immune 12 to 26 quad= Immune via vaccination 12to26 quad*death rate 12 to 26
- deaths of infected 12 to 26 quad= death rate 12 to 26*HPV infected 12 to 26 quad

- CIN3 deaths 12to26FiveAdditionalTypes= CIN3 12to26
FiveAdditionalTypes*death rate 12 to 26
- CIN2 deaths 12to 26 FiveAdditionalTypes= CIN2 12to 26
FiveAdditionalTypes*death rate 12 to 26
- CIN2 27 and above quad= INTEG (Aging into CIN2 27 and above quad-"clear2
27 & above quad"+prog2 27and above quad-prog3 27and above quad +"reg2
27&above quad"-CIN2 deaths among 27 and above quad-reg1 27 and above
quad-"rx2 27&above quad",0)
- deaths infected 12to 26 FiveAdditionalTypes= HPV infected 12to26
FiveAdditionalTypes*death rate 12 to 26
- deaths of CIN2 12 to 26 quad= death rate 12 to 26*CIN2 12 to 26 quad
- CIN2 27 and above FiveAdditionalTypes= INTEG (aging into cin2
FiveAdditionalTypes+"prog2 27& above FiveAdditionalTypes"+"reg2 27 &above
FiveAdditionalTypes"-CIN2 27&above deaths FiveAdditionalTypes"-clearance2
FiveAdditionalTypes-"prog3 27& above FiveAdditionalTypes"-reg1 27&above
FiveAdditionalTypes"-rx2 27& above FiveAdditionalTypes",0)
- deaths of CIN1 12to26 quad= CIN1 12 to 26 quad*death rate 12 to 26
- deaths of susceptible 12 to 26 quad= Susceptible12to26 quad*death rate 12 to
26
- Ref Rate of clearance of CIN1 quad 12 to 26= 0.4606
- Ref Rate of clearance of CIN2 quad 12 to 26= 0.21
- Ref Rate of clearance of CIN3 quad 12 to 26= 0.11
- vaccine efficacy= 0.9
- "death of females< 12 years of age"= "death rate of females <12
years""Females <12 quad"
- "death rate of females <12 years"= 0.0002195

- "death of females <12 years"= "death rate of females <12 years"*"Female <12 FiveAdditionalTypes"
- force of infection 27 and above quad= mean partner acquisition rate 27 and above*(fraction of partners 27 years and older women that are in 27 years and older *HPV prevalence 27 and above quad +(1-fraction of partners 27 years and older women that are in 27 years and older)* HPV prevalence 12 to 26 quad)*transmission rate 27 and above
- force of infection 27 and above FiveAdditionalTypes= mean partner acquisition rate 27 and above * (fraction of partners 27 years and older women that are in 27 years and older * HPV prevalence 27 and above FiveAdditionalTypes + (1-fraction of partners 27 years and older women that are in 27 years and older) * HPV prevalence 12to26FiveAdditionalTypes)*transmission rate 27 and above
- fraction of partners 27 years and older women that are in 27 years and older= 0.915
- Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age= 0.33
- "Aging females <12 FiveAdditionalTypes"= "Female <12 FiveAdditionalTypes"/"mean years of aging for <12 years old"
- "Aging of female <12"= "Females <12 quad"/"mean years of aging for <12 years old"
- "mean years of aging for <12 years old"= 12
- reg3 27 and above quad= CIN3 27 and above quad*Rate of Reg CIN3 to CIN1 quad
- Fraction of CIN1 successfully cured= 0.96
- "reg2 27&above quad"= Rate of Reg CIN3 to CIN2 quad*CIN3 27 and above quad

- regression2 12to26 quad= Rate of Reg CIN3 to CIN2 quad*CIN3 12 to 26 quad
- Regression3 12to26 quad= Rate of Reg CIN3 to CIN1 quad*CIN3 12 to 26 quad
- Rate of Reg CIN3 to CIN2 quad= 0.03
- regression1 12to26 quad= Rate of regression CIN2 to CIN1 quad*CIN2 12 to 26 quad
- reg1 27 and above quad= CIN2 27 and above quad*Rate of regression CIN2 to CIN1 quad
- Rate of Reg CIN3 to CIN1 quad= 0.03
- Fraction of CIN3 successfully cured= 0.92
- Rate of regression CIN2 to CIN1 quad= 0.133
- Fraction of CIN2 successfully cured= 0.92
- CIN3 to cervical cancer hazard rate quad= 0.546
- progression1 among 12 to 26 quad= HPV infected to CIN1 hazard rate quad*HPV infected 12 to 26 quad
- progression2 among 12 to 26 quad= CIN1 to CIN2 hazard rate quad*CIN1 12 to 26 quad
- progression3 among 12 to 26 quad= CIN2 to CIN3 hazard rate quad*CIN2 12 to 26 quad
- HPV infected to CIN1 hazard rate quad= 0.1692
- prog2 27and above quad= CIN1 to CIN2 hazard rate quad*CIN1 27 and above quad
- prog3 27and above quad= CIN2 to CIN3 hazard rate quad*CIN2 27 and above quad
- CIN2 to CIN3 hazard rate quad=0.252
- prog1 27and above quad= HPV infected to CIN1 hazard rate quad*HPV infected 27and above quad

- CIN1 to CIN2 hazard rate quad= 0.2448
- "Aging into CIN1 27&above quad"= aging CIN1 12to26 quad
- aging into CIN1 FiveAdditionalTypes= CIN1 12 to 26 FiveAdditionalTypes aging
- Aging into CIN2 27 and above quad= aging CIN2 12to 26 quad
- aging into cin2 FiveAdditionalTypes= CIN2 12to26 FiveAdditionalTypes aging
- "Aging into CIN3 27&above quad"= Aging CIN3 12 to 26 FiveAdditionalTypes
- aging into cin3 FiveAdditionalTypes= CIN3 12 to 26 FiveAdditionalTypes aging
- aging into hpv infected FiveAdditionalTypes= hpv infected 12 to 26FiveAdditionalTypes aging
- Aging into susceptible 27= aging susceptible 12to 26 quad
- aging into susceptible 27 and FiveAdditionalTypes= Susceptible 12 to 26 FiveAdditionalTypes aging
- CIN1 12 to 26 FiveAdditionalTypes aging= CIN1 12 to26 FiveAdditionalTypes/mean years until aging
- ratio of total population to total population of women=2
- mean partner acquisition 12 to 26= 1.64
- aging CIN1 12to26 quad= CIN1 12 to 26 quad/mean years until aging
- aging CIN2 12to 26 quad= CIN2 12 to 26 quad/mean years until aging
- aging hpv infected 12 to 26 quad= HPV infected 12 to 26 quad/mean years until aging
- aging susceptible 12to 26 quad=Susceptible12to26 quad/mean years until aging
- Susceptible 12 to 26 FiveAdditionalTypes aging= susceptible 12 to26 FiveAdditionalTypes/mean years until aging
- CIN2 12to 26 FiveAdditionalTypes= INTEG (prog2 12to26FiveAdditionalTypes+reg2 26no-CIN2 deaths 12to 26 FiveAdditionalTypes-clearance2 12to 26 FiveAdditionalTypes-prog3 12 to

26FiveAdditionalTypes-reg1 12 to 26FiveAdditionalTypes-rx2 12to26

FiveAdditionalTypes-CIN2 12to26 FiveAdditionalTypes aging,0)

- CIN2 12to26 FiveAdditionalTypes aging= CIN2 12to 26
FiveAdditionalTypes/mean years until aging
- hpv infected 12 to 26FiveAdditionalTypes aging= HPV infected 12to26
FiveAdditionalTypes/mean years until aging
- CIN3 12 to 26 FiveAdditionalTypes aging= CIN3 12to26
FiveAdditionalTypes/mean years until aging
- CIN2 12 to 26 quad= INTEG (+progression2 among 12 to 26 quad+regression2
12to26 quad-clearance2 among 12to26 quad-progression3 among 12 to 26
quad-regression1 12to26 quad-rx2 12to26 quad-aging CIN2 12to 26 quad-deaths
of CIN2 12 to 26 quad,0)
- Aging CIN3 12 to 26 FiveAdditionalTypes= CIN3 12 to 26 quad/mean years until
aging
- mean years until aging= 15
- birth rate for female babies= (0.0124 / 2)
- death rate 12 to 26= 0.000647
- "total infected HPV 16 &18"= HPV infected 12 to 26 per 100000 quad+hpv
infected 27 and above per 100000 quad
- "total infected (5 additional types)"= hpv infected 12 to 26FiveAdditionalTypes per
100000+HPV infected FiveAdditionalTypes per 100000
- "total CIN1 HPV 16&18"= CIN1 12to26 per 100000 quad+"CIN1 27&above per
100000 quad"
- "total CIN1 (5 additional types)"= CIN1 26FiveAdditionalTypes per 100000+"CIN1
27& above FiveAdditionalTypes per 100000"

- "total CIN2 HPV 16 &18"= CIN2 12to26 quad per 100000+CIN2 27 and above per 100000 quad
- "total CIN2 (5 additional types)"= CIN2 12 to 26per 100000 FiveAdditionalTypes+"CIN2 27&above FiveAdditionalTypes per 100000"
- "total CIN3 HPV 16&18"= CIN3 among 12 to 26 per 100000 quad+CIN3 27 and above per 100000 quad
- "total CIN3 (5 additional types)"= CIN3 12 to 26 per 100000 FiveAdditionalTypes+CIN3 FiveAdditionalTypes per 100000
- total infected= HPV infected FiveAdditionalTypes per 100000+HPV infected 12 to 26 per 100000 quad+ hpv infected 12 to 26FiveAdditionalTypes per 100000+hpv infected 27 and above per 100000 quad
- total CIN 1= CIN1 12to26 per 100000 quad+"CIN1 27& above FiveAdditionalTypes per 100000"+CIN1 26FiveAdditionalTypes per 100000+"CIN1 27&above per 100000 quad"
- "infection 27&above quad"= force of infection 27 and above quad*Susceptible 27and above quad
- infection 12to26FiveAdditionalTypes= force of infection 12 to 26 FiveAdditionalTypes*susceptible 12 to26 FiveAdditionalTypes
- total CIN2= "CIN2 27&above FiveAdditionalTypes per 100000"+CIN2 12to26 quad per 100000+CIN2 12 to 26per 100000 FiveAdditionalTypes+CIN2 27 and above per 100000 quad
- total CIN3= CIN3 FiveAdditionalTypes per 100000+CIN3 among 12 to 26 per 100000 quad+CIN3 12 to 26 per 100000 FiveAdditionalTypes+CIN3 27 and above per 100000 quad
- screening rate FiveAdditionalTypes= 0.73

- "infection 27&above FiveAdditionalTypes"= force of infection 27 and above
FiveAdditionalTypes*Susceptible 27and above FiveAdditionalTypes
- infection rate among 12to26 quad= force of infection 12to26
quad*Susceptible12to26 quad
- Ref Rate of clearance of HPV infected quad 12 to 26= 0.3619
- mean partner acquisition rate 27 and above= 1.19
- screening rate= 0.73
- sensitivity CIN1= 0.28
- sensitivity CIN2and CIN3= 0.59
- transmission rate 27 and above= 0.4

HPV Model Equations for White Population

- cumulative count of cancer cases nonavalent= Cumulative cervical cancer cases
12 to 26 FiveAdditionalTypes+Cumulative Cervical Cancer cases 27 and above
FiveAdditionalTypes+Cumulative cervical cancer cases 12 to 26
quad+"cumulative cervical cancer cases quad 27&above"
- "Cancer cases lived per life year per 100000(five additional types)"= cancer
cases lived per life year five additional types*100000
- "Cancer cases lived per life year per 100,000 (nona)"= cancer cases lived per life
year nonavalent*100000
- "Cancer cases lived per life year per 100,000 quad"= Cancer cases lived per life
year quad*100000
- prospective nona vaccination rate= 0.053

- "vacc rate (FiveAdditionalTypes)"= IF THEN ELSE(Time <8, 0 , prospective nona vaccination rate)
- cumulative life years lived five additional types= INTEG (total population five additional types,0)
- cumulative cervical cancer cases count five additional types= Cumulative cervical cancer cases 12 to 26 FiveAdditionalTypes+Cumulative Cervical Cancer cases 27 and above FiveAdditionalTypes
- cancer cases lived per life year five additional types= zidz(cumulative cervical cancer cases count five additional types,cumulative life years lived five additional types)
- total population of women quad= total population of women quadrivalent
- cumulative count of cervical cancer cases of quad= Cumulative cervical cancer cases 12 to 26 quad+"cumulative cervical cancer cases quad 27&above"
- total population nona= total population nonavalent
- cumulative life years lived nonavalent= INTEG (total population nona, 0)
- cumulative life years lived quad= INTEG (total population of women quad,0)
- Cancer cases lived per life year quad=zidz(cumulative count of cervical cancer cases of quad, cumulative life years lived quad)
- total population five additional types=total population of women FiveAdditionalTypesvalent
- total population nonavalent= total population of women 12 to 26 FiveAdditionalTypesvalent+ total population of women 27 and above FiveAdditionalTypesvalent
- cancer cases lived per life year nonavalent= zidz(cumulative count of cancer cases nonavalent,cumulative life years lived nonavalent)
- Ref Rate of clearance of HPV infected quad 27 and above= 0.483

- $\text{clearance3 FiveAdditionalTypes} = \text{Rate of clearance of CIN3 five additional types 27 and above} * \text{CIN3 27 and above FiveAdditionalTypes}$
- $\text{"clearance of infection 27\&above FiveAdditionalTypes"} = \text{Rate of clearance of HPV infected five additional types 27 and above} * \text{HPV infected 27 and above FiveAdditionalTypes}$
- $\text{clearance2 FiveAdditionalTypes} = \text{Rate of clearance of CIN2 five additional types 27 and above} * \text{CIN2 27 and above FiveAdditionalTypes}$
- $\text{Rate of clearance of CIN3 five additional types 27 and above} = 0.11$
- $\text{Ref rate of clearance of CIN1 quad 27 and above} = 0.483$
- $\text{clearance of HPV infected 27 and above quad} = \text{HPV infected 27 and above quad} * \text{Ref Rate of clearance of HPV infected quad 27 and above} * \text{Coefficient of clearance for quad}$
- $\text{"clearance1 27 \& above FiveAdditionalTypes"} = \text{Rate of clearance of CIN1 five additional types 27 and above} * \text{CIN1 27 and above FiveAdditionalTypes}$
- $\text{Ref rate of clearance of CIN3 quad 27 and above} = 0.11$
- $\text{Rate of clearance of HPV infected five additional types 27 and above} = 0.41125$
- $\text{Rate of clearance of CIN1 five additional types 27 and above} = 0.329$
- $\text{"clear2 27 \& above quad"} = \text{Ref rate of clearance of CIN2 quad 27 and above} * \text{CIN2 27 and above quad} * \text{Coefficient of clearance for quad}$
- $\text{"clear3 27\&above quad"} = \text{Ref rate of clearance of CIN3 quad 27 and above} * \text{CIN3 27 and above quad} * \text{Coefficient of clearance for quad}$
- $\text{"clearance1 27\&above quad"} = \text{Ref rate of clearance of CIN1 quad 27 and above} * \text{CIN1 27 and above quad} * \text{Coefficient of clearance for quad}$
- $\text{Ref rate of clearance of CIN2 quad 27 and above} = 0.21$
- $\text{Rate of clearance of CIN2 five additional types 27 and above} = 0.21$

- $\text{rx1}_{12\text{to}26\text{FiveAdditionalTypes}} = \text{Fraction of CIN1 successfully cured} * \text{screening rate}_{\text{FiveAdditionalTypes}} * \text{sensitivity}_{\text{CIN1}} * \text{CIN1}_{12\text{ to}26\text{FiveAdditionalTypes}}$
- $\text{"rx3}_{27\&\text{above quad}} = \text{Fraction of CIN3 successfully cured} * \text{sensitivity}_{\text{CIN2and CIN3}} * \text{screening rate} * \text{CIN3}_{27\text{ and above quad}}$
- $\text{"rx2}_{27\&\text{above quad}} = \text{screening rate} * \text{Fraction of CIN2 successfully cured} * \text{sensitivity}_{\text{CIN2and CIN3}} * \text{CIN2}_{27\text{ and above quad}}$
- $\text{"rx1}_{27\&\text{above quad}} = \text{Fraction of CIN1 successfully cured} * \text{screening rate} * \text{sensitivity}_{\text{CIN1}} * \text{CIN1}_{27\text{ and above quad}}$
- $\text{rx2}_{12\text{to}26\text{FiveAdditionalTypes}} = \text{Fraction of CIN2 successfully cured} * \text{screening rate}_{\text{FiveAdditionalTypes}} * \text{sensitivity}_{\text{CIN2and CIN3}} * \text{CIN2}_{12\text{ to }26\text{FiveAdditionalTypes}}$
- $\text{rx3}_{12\text{to}26\text{FiveAdditionalTypes}} = \text{Fraction of CIN3 successfully cured} * \text{screening rate}_{\text{FiveAdditionalTypes}} * \text{sensitivity}_{\text{CIN2and CIN3}} * \text{CIN3}_{12\text{to}26\text{FiveAdditionalTypes}}$
- $\text{clearance1 among}_{12\text{to}26\text{quad}} = \text{Ref Rate of clearance of CIN1 quad}_{12\text{ to }26} * \text{CIN1}_{12\text{ to }26\text{quad}} * \text{Coefficient of clearance for quad}$
- $\text{clearance3 among}_{12\text{ to }26\text{quad}} = \text{Ref Rate of clearance of CIN3 quad}_{12\text{ to }26} * \text{CIN3}_{12\text{ to }26\text{quad}} * \text{Coefficient of clearance for quad}$
- $\text{clearance2 among}_{12\text{to}26\text{quad}} = \text{Ref Rate of clearance of CIN2 quad}_{12\text{ to }26} * \text{CIN2}_{12\text{ to }26\text{quad}} * \text{Coefficient of clearance for quad}$
- $\text{Coefficient of clearance for quad} = 0.74$
- $\text{HPV infected clearance rate}_{12\text{ to }26\text{quad}} = \text{HPV infected}_{12\text{ to }26\text{quad}} * \text{Ref Rate of clearance of HPV infected quad}_{12\text{ to }26} * \text{Coefficient of clearance for quad}$
- $\text{prog2}_{12\text{to}26\text{FiveAdditionalTypes}} = \text{CIN1 to CIN2 hazard rate}_{\text{FiveAdditionalTypes}} * \text{CIN1}_{12\text{ to}26\text{FiveAdditionalTypes}}$

- "prog2 27& above FiveAdditionalTypes"= CIN1 to CIN2 hazard rate
FiveAdditionalTypes*CIN1 27 and above FiveAdditionalTypes
- clearance2 12to 26 FiveAdditionalTypes= Rate of clearance of CIN2
FiveAdditionalTypes 12 to 26*CIN2 12to 26 FiveAdditionalTypes
- prog3 12 to 26FiveAdditionalTypes= CIN2 to CIN3 hazard rate
FiveAdditionalTypes*CIN2 12to 26 FiveAdditionalTypes
- clearance3 12to26 FiveAdditionalTypes= Rate of clearance of CIN3
FiveAdditionalTypes 12 to 26*CIN3 12to26 FiveAdditionalTypes
- "prog1 27 & above FiveAdditionalTypes"= HPV infected to CIN1 hazard rate
FiveAdditionalTypes*HPV infected 27 and above FiveAdditionalTypes
- Rate of clearance of CIN3 FiveAdditionalTypes 12 to 26= 0.11
- clearance hpv infected 12 to 26FiveAdditionalTypes= Rate of clearance of HPV
infected FiveAdditionalTypes 12 to 26*HPV infected 12to26 FiveAdditionalTypes
- Rate of clearance of HPV infected FiveAdditionalTypes 12 to 26= 0.27965
- CIN3 to cervical cancer hazard rate FiveAdditionalTypes= 0.42
- CIN1 12 to26 FiveAdditionalTypes= INTEG (prog1 12 to
26FiveAdditionalTypes+reg1 12 to 26FiveAdditionalTypes+reg3 12 to
26FiveAdditionalTypes-CIN1 12 to 26 FiveAdditionalTypes aging-CIN1 deaths
12to 26FiveAdditionalTypes-clearance1 12to26 FiveAdditionalTypes -prog2
12to26FiveAdditionalTypes-rx1 12to26 FiveAdditionalTypes, Initially HPV
infected 12 to 26 women with FiveAdditionalTypes who are at CIN1)
- "prog3 27& above FiveAdditionalTypes"= CIN2 to CIN3 hazard rate
FiveAdditionalTypes*CIN2 27 and above FiveAdditionalTypes
- Rate of clearance of CIN1 FiveAdditionalTypes 12 to 26=0.329
- CIN2 to CIN3 hazard rate FiveAdditionalTypes= 0.14

- "prog4 27&above FiveAdditionalTypes"= CIN3 to cervical cancer hazard rate
FiveAdditionalTypes*CIN3 27 and above FiveAdditionalTypes
- HPV infected to CIN1 hazard rate FiveAdditionalTypes= 0.094
- CIN1 to CIN2 hazard rate FiveAdditionalTypes= 0.136
- progression4 12to26 FiveAdditionalTypes= CIN3 12to26
FiveAdditionalTypes*CIN3 to cervical cancer hazard rate FiveAdditionalTypes
- HPV infected 12to26 FiveAdditionalTypes= INTEG (infection
12to26FiveAdditionalTypes-clearance hpv infected 12 to 26FiveAdditionalTypes-
deaths infected 12to 26 FiveAdditionalTypes-hpv infected 12 to
26FiveAdditionalTypes aging-prog1 12 to 26FiveAdditionalTypes, initially infected
HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1)
- clearance1 12to26 FiveAdditionalTypes= Rate of clearance of CIN1
FiveAdditionalTypes 12 to 26*CIN1 12 to26 FiveAdditionalTypes
- Rate of clearance of CIN2 FiveAdditionalTypes 12 to 26= 0.21
- prog1 12 to 26FiveAdditionalTypes= HPV infected to CIN1 hazard rate
FiveAdditionalTypes*HPV infected 12to26 FiveAdditionalTypes
- total cumulative cervical cancer cases 5 additional types= Cumulative cervical
cancer cases 12 to 26 FiveAdditionalTypes+Cumulative Cervical Cancer cases
27 and above FiveAdditionalTypes
- total cumulative cervical cancer cases quad= Cumulative cervical cancer cases
12 to 26 quad+"cumulative cervical cancer cases quad 27&above"
- Total cumulative cervical cancer nona=Cumulative cervical cancer cases 12 to
26 FiveAdditionalTypes+Cumulative cervical cancer cases 12 to 26
quad+Cumulative Cervical Cancer cases 27 and above
FiveAdditionalTypes+"cumulative cervical cancer cases quad 27&above"

- women 27 and above who have been vaccinated quad= INTEG (aging into women 27 and above who have been vaccinated quad-death of women 27 and above who have been vaccinated quad,0)
- aging into women 27 and above who have been vaccinated
FiveAdditionalTypes= aging women 12 to 26 who have been vaccinated
FiveAdditionalTypes
- aging into women 27 and above who have been vaccinated quad= aging number of women 12 to 26 who are vaccinated quad
- death of women 27 and above who have been vaccinated quad= women 27 and above who have been vaccinated quad*"death rate for 27&above"
- death of number of women 12 to 26 who are vaccinated FiveAdditionalTypes=
women 12 to 26 FiveAdditionalTypes who have been vaccinated*death rate 12 to 26
- new vaccination of 12to 26 FiveAdditionalTypes= total population of women 12 to 26 FiveAdditionalTypesvalent*"vacc rate (FiveAdditionalTypes)"
- death of women 27 and above who have been vaccinated FiveAdditionalTypes=
- Women 27 and above who have been vaccinated FiveAdditionalTypes*"death rate for 27&above"
- Women 27 and above who have been vaccinated FiveAdditionalTypes= INTEG (aging into women 27 and above who have been vaccinated
FiveAdditionalTypes-death of women 27 and above who have been vaccinated
FiveAdditionalTypes, 0)
- fraction of women 12 to 26 who have been vaccinated = women 12 to 26
FiveAdditionalTypes who have been vaccinated/total population of women 12 to 26
FiveAdditionalTypesvalent

- aging women 12 to 26 who have been vaccinated $\text{FiveAdditionalTypes} = \text{women 12 to 26 FiveAdditionalTypes who have been vaccinated} / \text{mean years until aging}$
- women 12 to 26 $\text{FiveAdditionalTypes}$ who have been vaccinated = INTEG (new vaccination of 12 to 26 $\text{FiveAdditionalTypes}$ - death of number of women 12 to 26 who are vaccinated $\text{FiveAdditionalTypes}$ - aging women 12 to 26 who have been vaccinated $\text{FiveAdditionalTypes}$, 0)
- Women 12 to 26 who have been vaccinated quad = INTEG (new vaccinations of 12 to 26 women - aging number of women 12 to 26 who are vaccinated quad - death of number of women 12 to 26 who are vaccinated, 0)
- new vaccinations of 12 to 26 women = total population of women 12 to 26 quadrivalent * vacc rate
- aging number of women 12 to 26 who are vaccinated quad = Women 12 to 26 who have been vaccinated quad / mean years until aging
- death of number of women 12 to 26 who are vaccinated = Women 12 to 26 who have been vaccinated quad * death rate 12 to 26
- vacc quad = Susceptible12to26 quad * vacc rate * vaccine efficacy
- fraction of women 12 to 26 who have been vaccinated quad =
- Women 12 to 26 who have been vaccinated quad / total population of women 12 to 26 quadrivalent
- vacc rate = 0.053
- fraction of susceptible women 27 and above $\text{FiveAdditionalTypes}$ = Susceptible 27 and above $\text{FiveAdditionalTypes}$ / total population of women 27 and above $\text{FiveAdditionalTypes}$ valent
- Fraction of women susceptible 12 to 26 quad = Susceptible12to26 quad / total population of women 12 to 26 quadrivalent

- Fraction of women susceptible 12 to 26 FiveAdditionalTypes= susceptible 12 to 26 FiveAdditionalTypes/total population of women 12 to 26 FiveAdditionalTypesvalent
- fraction of women that are susceptible for 27 and above quad= Susceptible 27and above quad/total population of women 27 and above quadrivalent
- Inital 27 and above CIN1 infected women from HPV quad infected= fraction of women 27 and above who were infected with quad and are CIN1*Initial 27 and above HPV quad infected women from US census including CIN1
- HPV infected 27 and above FiveAdditionalTypes= INTEG (aging into hpv infected FiveAdditionalTypes+"infection 27&above FiveAdditionalTypes"- "clearance of infection 27&above FiveAdditionalTypes"-infected 27 and above deaths FiveAdditionalTypes-"prog1 27 & above FiveAdditionalTypes", initially HPV infected women 27 and above not CIN1 FiveAdditionalTypes)
- fraction of women 27 from US census who are infected with HPV quad strain= 0.24
- initially infected HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1= Initially infected HPV women 12 to 26 from US census including CIN1 for FiveAdditionalTypes-Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1
- Initially susceptible women 12 to 26 from US census=Total initial population 12 to 26 from US census-(Initially CIN1 infected women from HPV infected women+Initially HPV infected women from US census for quad not CIN1)
- HPV infected 12 to 26 quad= INTEG (infection rate among 12to26 quad-aging hpv infected 12 to 26 quad-deaths of infected 12 to 26 quad-HPV infected clearance rate 12 to 26 quad-progression1 among 12 to 26 quad, Initially HPV infected women from US census for quad not CIN1)

- Initially susceptible women 12 to 26 from US census for FiveAdditionalTypes=
Total initial population 12 to 26 from US census-(Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1+initially infected HPV women 12 to 26 from US census for FiveAdditionalTypes that are not CIN1)
- Initially HPV infected women 27 and above from US census for quad not CIN1=
Initial 27 and above HPV quad infected women from US census including CIN1-Initial 27 and above CIN1 infected women from HPV quad infected
- Initial susceptible women 27 and above from US census FiveAdditionalTypes=
total initial population 27 and above from US census-(initially HPV infected women 27 and above not CIN1 FiveAdditionalTypes +Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain)
- total population of women 27 and above quadrivalent= HPV infected 27and above quad+ Susceptible 27and above quad+CIN1 27 and above quad +CIN2 27 and above quad+CIN3 27 and above quad+ Immune via vaccination 27 and above quad+ Immune after HPV clearance 27 and above quad
- Initially susceptible women 27 and above from US census= total initial population 27 and above from US census-(Initially HPV infected women 27 and above from US census for quad not CIN1+Initial 27 and above CIN1 infected women from HPV quad infected)
- Initial 27 and above HPV quad infected women from US census including CIN1=
fraction of women 27 from US census who are infected with HPV quad strain*total initial population 27 and above from US census
- initially HPV infected women 27 and above not CIN1 FiveAdditionalTypes=
Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1-Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain

- total population of women 12 to 26 quadrivalent= HPV infected 12 to 26 quad+ Susceptible12to26 quad+CIN1 12 to 26 quad+ CIN2 12 to 26 quad+CIN3 12 to 26 quad+ Immune via vaccination 12to26 quad+ Immune after HPV infection clearance 12 to 26 quad
- total population of women 12 to 26 FiveAdditionalTypesvalent= CIN1 12 to26 FiveAdditionalTypes+CIN2 12to 26 FiveAdditionalTypes+CIN3 12to26 FiveAdditionalTypes+HPV infected 12to26 FiveAdditionalTypes +susceptible 12 to26 FiveAdditionalTypes+immune via vacc 12 to 26 FiveAdditionalTypes +Immune after HPV infection 12 to26 FiveAdditionalTypes
- Initially HPV infected women from US census for quad not CIN1= Initially HPV infected women from US census for quad including CIN1-Initially CIN1 infected women from HPV infected women
- total population of women 27 and above FiveAdditionalTypesvalent= CIN1 27 and above FiveAdditionalTypes+CIN2 27 and above FiveAdditionalTypes+CIN3 27 and above FiveAdditionalTypes +HPV infected 27 and aboveFiveAdditionalTypes+ Susceptible 27and above FiveAdditionalTypes +immune via vaccination 27 and above FiveAdditionalTypes +Immune after HPV infection 27and above FiveAdditionalTypes
- HPV infected 27and above quad= INTEG (Aging into HPV infected 27+"infection 27&above quad"-clearance of HPV infected 27 and above quad-"deaths of infected 27&above quad"-prog1 27and above quad, Initially HPV infected women 27 and above from US census for quad not CIN1)
- Immune after HPV clearance 27 and above quad= INTEG (aging into immune after HPV clearance 27 and above quad+"clear2 27 & above quad"+"clear3 27&above quad"+clearance of HPV infected 27 and above quad+"clearance1 27&above quad"+"rx1 27&above quad"+"rx2 27&above quad"+"rx3 27&above

- quad"-death of immune after HPV clearance 27 and above-waning immunity after infection among 27 and above quad,0)
- Susceptible 27and above quad= INTEG (Aging into susceptible 27+waning immunity after infection among 27 and above quad-"infection 27&above quad" - susceptible27 deaths+ "waning immunity among 27 and above (quad)", Initially susceptible women 27 and above from US census)
 - Immune after HPV infection 27and above FiveAdditionalTypes= INTEG (aging into immune after HPV infection 27 and above FiveAdditionalTypes+"clearance of infection 27&above FiveAdditionalTypes"+"clearance1 27 & above FiveAdditionalTypes"+clearance2 FiveAdditionalTypes+clearance3 FiveAdditionalTypes+"rx1 27& above FiveAdditionalTypes"+"rx2 27& above FiveAdditionalTypes"+"rx3 27&above FiveAdditionalTypes"-Deaths of immune after vaccination 27 and above FiveAdditionalTypes-waning immunity after infection 27 and above nano, 0)
 - susceptible 12 to26 FiveAdditionalTypes= INTEG ("Aging females <12 FiveAdditionalTypes"+waning immunity after vaccination 12to 26 nano +waning immunity of 27 and above FiveAdditionalTypes-death of susceptible 12to 26no-infection 12to26FiveAdditionalTypes-Susceptible 12 to 26 FiveAdditionalTypes aging-vacc FiveAdditionalTypes, Initially susceptible women 12 to 26 from US census for FiveAdditionalTypes)
 - immune via vacc 12 to 26 FiveAdditionalTypes= INTEG (vacc FiveAdditionalTypes-aging of immune 12 to 26 FiveAdditionalTypes-deaths of immune 12 to 26 FiveAdditionalTypes -waning immunity after vaccination 12to 26 nano-waning immunity after vaccination 12to 26 nano,0)

- "rx2 27 & above FiveAdditionalTypes" = Fraction of CIN2 successfully cured * screening rate FiveAdditionalTypes * sensitivity CIN2 and CIN3 * CIN2 27 and above FiveAdditionalTypes
- Immune via vaccination 12to26 quad = INTEG (vacc quad - aging immune via vaccination 12 to 26 quad - deaths of immune 12 to 26 quad - waning immunity after vaccination among 12to26quad, 0)
- Susceptible12to26 quad = INTEG ("Aging of female <12" - aging susceptible 12to26 quad - deaths of susceptible 12 to 26 quad - infection rate among 12to26 quad - vacc quad + Waning immunity after infection 12 to 26 quad + waning immunity after vaccination among 12to26quad, Initially susceptible women 12 to 26 from US census)
- waning immunity after infection among 27 and above quad = Immune after HPV clearance 27 and above quad / Time until waning immunity after infection
- Susceptible 27 and above FiveAdditionalTypes = INTEG (aging into susceptible 27 and FiveAdditionalTypes + waning immunity after infection 27 and above nano - "infection 27 & above FiveAdditionalTypes" - susceptible 27 and above deaths + waning immunity after vaccination 27 and above FiveAdditionalTypes, Initial susceptible women 27 and above from US census FiveAdditionalTypes)
- time until waning immunity after vaccination = 10
- waning immunity after vaccination among 12to26quad = (Immune via vaccination 12to26 quad / time until waning immunity after vaccination) * "enable waning immunity after vaccination?"
- "enable waning immunity after vaccination?" = 0
- waning immunity after vaccination 12to 26 nano = (immune via vacc 12 to 26 FiveAdditionalTypes / time until waning immunity after vaccination) * "enable waning immunity after vaccination?"

- $rx2_{12to26\ quad} = screening\ rate * sensitivity\ CIN2\ and\ CIN3 * Fraction\ of\ CIN2\ successfully\ cured * CIN2_{12\ to\ 26\ quad}$
- $waning\ immunity\ after\ vaccination\ 27\ and\ above\ FiveAdditionalTypes = (immune\ via\ vaccination\ 27\ and\ above\ FiveAdditionalTypes / time\ until\ waning\ immunity\ after\ vaccination) * "enable\ waning\ immunity\ after\ vaccination?"$
- $waning\ immunity\ after\ infection\ 27\ and\ above\ nano = Immune\ after\ HPV\ infection\ 27\ and\ above\ FiveAdditionalTypes / Time\ until\ waning\ immunity\ after\ infection$
- $"waning\ immunity\ among\ 27\ and\ above\ (quad)" = (Immune\ via\ vaccination\ 27\ and\ above\ quad / time\ until\ waning\ immunity\ after\ vaccination) * "enable\ waning\ immunity\ after\ vaccination?"$
- $fraction\ of\ women\ 12to26\ immune\ via\ vaccination\ quad = Immune\ via\ vaccination\ 12to26\ quad / total\ population\ of\ women\ 12\ to\ 26\ quadrivalent$
- $waning\ immunity\ of\ 27\ and\ above\ FiveAdditionalTypes = Immune\ after\ HPV\ infection\ 12\ to26\ FiveAdditionalTypes / Time\ until\ waning\ immunity\ after\ infection$
- $aging\ of\ immune\ after\ HPV\ infection\ 12\ to\ 26\ FiveAdditionalTypes = Immune\ after\ HPV\ infection\ 12\ to26\ FiveAdditionalTypes / mean\ years\ until\ aging$
- $aging\ into\ immune\ after\ HPV\ clearance\ 27\ and\ above\ quad = aging\ of\ immune\ after\ HPV\ infection\ clearance\ 12\ to\ 26\ quad$
- $Immune\ after\ HPV\ infection\ 12\ to26\ FiveAdditionalTypes = INTEG (clearance1_{12to26\ FiveAdditionalTypes} + clearance2_{12to\ 26FiveAdditionalTypes} + clearance3_{12to26\ FiveAdditionalTypes} + rx1_{12to26\ FiveAdditionalTypes} + rx2_{12to26\ FiveAdditionalTypes} + rx3_{12to26\ FiveAdditionalTypes} - deaths\ of\ immune\ after\ HPV\ infection\ 12\ to\ 26\ FiveAdditionalTypes - waning\ immunity\ of\ 27\ and\ above\ FiveAdditionalTypes - aging\ of\ immune\ after\ HPV\ infection\ 12\ to\ 26\ FiveAdditionalTypes + clearance\ hpv\ infected\ 12\ to\ 26FiveAdditionalTypes, 0)$

- $\text{deaths of immune after HPV infection 12 to 26 FiveAdditionalTypes} = \text{death rate 12 to 26} * \text{Immune after HPV infection 12 to 26 FiveAdditionalTypes}$
- $\text{Deaths of immune after vaccination 27 and above FiveAdditionalTypes} = \text{"death rate for 27\&above"} * \text{Immune after HPV infection 27 and above FiveAdditionalTypes}$
- $\text{aging into immune after HPV infection 27 and above FiveAdditionalTypes} = \text{aging of immune after HPV infection 12 to 26 FiveAdditionalTypes}$
- $\text{Waning immunity after infection 12 to 26 quad} = \text{Immune after HPV infection clearance 12 to 26 quad} / \text{Time until waning immunity after infection}$
- $\text{Time until waning immunity after infection} = 5$
- $\text{incidence of cc per 100000 12to26} = (\text{Progression4 among 12 to 26 quad} / \text{total population of women 12 to 26 quadrivalent}) * 100000$
- $\text{aging of immune after HPV infection clearance 12 to 26 quad} = \text{Immune after HPV infection clearance 12 to 26 quad} / \text{mean years until aging}$
- $\text{deaths of immune after HPV infection clearance} = \text{Immune after HPV infection clearance 12 to 26 quad} * \text{death rate 12 to 26}$
- $\text{death of immune after HPV clearance 27 and above} = \text{Immune after HPV clearance 27 and above quad} * \text{"death rate for 27\&above"}$
- $\text{Immune after HPV infection clearance 12 to 26 quad} = \text{INTEG (HPV infected clearance rate 12 to 26 quad} + \text{clearance1 among 12to26 quad} + \text{clearance2 among 12to26 quad} + \text{clearance3 among 12 to 26 quad} + \text{rx1 12to26 quad} + \text{rx2 12to26 quad} + \text{rx3 12 to 26 quad} - \text{Waning immunity after infection 12 to 26 quad} - \text{aging of immune after HPV infection clearance 12 to 26 quad} - \text{deaths of immune after HPV infection clearance, 0})$

- force of infection 12to26 quad= mean partner acquisition 12 to 26*(Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age* HPV prevalence 12 to 26 quad + (1-Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age) * HPV prevalence 27 and above quad)
*transmission rate 12to26
- force of infection 12 to 26 FiveAdditionalTypes= mean partner acquisition 12 to 26*(Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age* HPV prevalence 12to26FiveAdditionalTypes + (1-Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age) * HPV prevalence 27 and above FiveAdditionalTypes)* transmission rate 12to26
- transmission rate 12to26= 0.4
- CIN3 27 and above deaths FiveAdditionalTypes= "death rate for 27&above"*CIN3 27 and above FiveAdditionalTypes
- CIN3 12to26 FiveAdditionalTypes= INTEG (prog3 12 to 26FiveAdditionalTypes-CIN3 12 to 26 FiveAdditionalTypes aging-CIN3 deaths 12to26FiveAdditionalTypes-clearance3 12to26 FiveAdditionalTypes-reg2 26no-reg3 12 to 26FiveAdditionalTypes-rx3 12to26 FiveAdditionalTypes+prog3 12 to 26FiveAdditionalTypes-progression4 12to26 FiveAdditionalTypes,0)
- "CIN3 27 & above death quad"= "death rate for 27&above"*CIN3 27 and above quad
- CIN3 27 and above FiveAdditionalTypes= INTEG (aging into cin3 FiveAdditionalTypes+"prog3 27& above FiveAdditionalTypes"-CIN3 27 and above deaths FiveAdditionalTypes-clearance3 FiveAdditionalTypes-"prog4 27&above FiveAdditionalTypes"- "reg2 27 &above FiveAdditionalTypes" -"reg3 27&above FiveAdditionalTypes"- "rx3 27&above FiveAdditionalTypes"+"prog3 27& above FiveAdditionalTypes"- "prog4 27&above FiveAdditionalTypes", 0)

- CIN3 27 and above quad= INTEG ("Aging into CIN3 27&above quad"+prog3 27and above quad-"CIN3 27 & above death quad"- "clear3 27&above quad"- "reg2 27&above quad"-reg3 27 and above quad-"rx3 27&above quad"+prog3 27and above quad-prog4 27and above quad, 0)
- "CIN1 27&above deaths quad"= "death rate for 27&above"*CIN1 27 and above quad
- immune via vacc deaths quad= Immune via vaccination 27 and above quad*"death rate for 27&above"
- Cumulative cervical cancer cases 12 to 26 FiveAdditionalTypes= INTEG (progression4 12to26 FiveAdditionalTypes,0)
- Cumulative Cervical Cancer cases 27 and above FiveAdditionalTypes= INTEG ("prog4 27&above FiveAdditionalTypes",0)
- "cumulative cervical cancer cases quad 27&above"= INTEG (prog4 27and above quad,0)
- infected 27 and above deaths FiveAdditionalTypes= "death rate for 27&above"*HPV infected 27 and above FiveAdditionalTypes
- prog4 27and above quad= CIN3 27 and above quad*CIN3 to cervical cancer hazard rate
- "death rate for 27&above"= 0.00541
- Progression4 among 12 to 26 quad= CIN3 to cervical cancer hazard rate*CIN3 12 to 26 quad
- "CIN1 27 &above deaths FiveAdditionalTypes"=CIN1 27 and above FiveAdditionalTypes*"death rate for 27&above"
- susceptible27 deaths=Susceptible 27and above quad*"death rate for 27&above"
- "CIN2 27&above deaths FiveAdditionalTypes"=CIN2 27 and above FiveAdditionalTypes*"death rate for 27&above"

- deaths of immune 27 and above $\text{FiveAdditionalTypes} = \text{"death rate for 27\&above"} * \text{immune via vaccination 27 and above FiveAdditionalTypes}$
- susceptible 27 and above deaths $= \text{"death rate for 27\&above"} * \text{Susceptible 27 and above FiveAdditionalTypes}$
- prog4 27 and above quad per 100000 $= (\text{prog4 27 and above quad} / \text{total population of women 27 and above quadrivalent}) * 100000$
- CIN3 12 to 26 quad $= \text{INTEG} (-\text{Aging CIN3 12 to 26 FiveAdditionalTypes} - \text{clearance3 among 12 to 26 quad} - \text{deaths of CIN3 12 to 26 quad} - \text{regression2 12to26 quad} - \text{Regression3 12to26 quad} - \text{rx3 12 to 26 quad} + \text{progression3 among 12 to 26 quad} - \text{Progression4 among 12 to 26 quad}, 0)$
- CIN2 deaths among 27 and above quad $= \text{CIN2 27 and above quad} * \text{"death rate for 27\&above"}$
- "deaths of infected 27\&above quad" $= \text{HPV infected 27 and above quad} * \text{"death rate for 27\&above"}$
- Cumulative cervical cancer cases 12 to 26 quad $= \text{INTEG} (\text{Progression4 among 12 to 26 quad}, 0)$
- total population of men and women $\text{FiveAdditionalTypes} = \text{total population of women FiveAdditionalTypesvalent} * (1 + \text{Ratio of male to female population})$
- "Initial susceptible women <12 years $\text{FiveAdditionalTypesvalent}$ " $= 37112$
- "Female <12 $\text{FiveAdditionalTypes}$ " $= \text{INTEG} (\text{birth FiveAdditionalTypes} - \text{"Aging females <12 FiveAdditionalTypes"} - \text{"death of females <12 years"}, \text{"Initial susceptible women <12 years FiveAdditionalTypesvalent"})$
- total population of men and women quad $= \text{total population of women quadrivalent} * (1 + \text{Ratio of male to female population})$
- birth $\text{FiveAdditionalTypes} = \text{birth rate for female babies} * \text{total population of men and women FiveAdditionalTypes}$

- birth quad= total population of men and women quad*birth rate for female babies
- Ratio of male to female population= 0.98
- rx3 12 to 26 quad= screening rate*sensitivity CIN2and CIN3*Fraction of CIN3 successfully cured*CIN3 12 to 26 quad
- "rx3 27&above FiveAdditionalTypes"= Fraction of CIN3 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN2and CIN3*CIN3 27 and above FiveAdditionalTypes
- "rx1 27& above FiveAdditionalTypes"= Fraction of CIN1 successfully cured*screening rate FiveAdditionalTypes*sensitivity CIN1*CIN1 27 and above FiveAdditionalTypes
- rx1 12to26 quad= sensitivity CIN1*screening rate*Fraction of CIN1 successfully cured*CIN1 12 to 26 quad
- HPV infected FiveAdditionalTypes per 100000= (HPV infected 27 and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent)*100000
- CIN3 among 12 to 26 per 100000 quad= (CIN3 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- CIN2 12to26 quad per 100000=(CIN2 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- CIN3 FiveAdditionalTypes per 100000= (CIN3 27 and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent)*100000
- CIN2 27 and above per 100000 quad= (CIN2 27 and above quad/total population of women 27 and above quadrivalent)*100000
- CIN1 12to26 per 100000 quad= (CIN1 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000

- $\text{CIN1 26FiveAdditionalTypes per 100000} = \left(\frac{\text{CIN1 12 to 26 FiveAdditionalTypes}}{\text{total population of women 12 to 26 FiveAdditionalTypesvalent}} \right) * 100000$
- $\text{hpv infected 27 and above per 100000 quad} = \left(\frac{\text{HPV infected 27 and above quad}}{\text{total population of women 27 and above quadrivalent}} \right) * 100000$
- $\text{"CIN1 27\& above FiveAdditionalTypes per 100000"} = \left(\frac{\text{CIN1 27 and above FiveAdditionalTypes}}{\text{total population of women 27 and above FiveAdditionalTypesvalent}} \right) * 100000$
- $\text{CIN3 12 to 26 per 100000 FiveAdditionalTypes} = \left(\frac{\text{CIN3 12 to 26 FiveAdditionalTypes}}{\text{total population of women 12 to 26 FiveAdditionalTypesvalent}} \right) * 100000$
- $\text{"CIN1 27\& above per 100000 quad"} = \left(\frac{\text{CIN1 27 and above quad}}{\text{total population of women 27 and above quadrivalent}} \right) * 100000$
- $\text{CIN3 27 and above per 100000 quad} = \left(\frac{\text{CIN3 27 and above quad}}{\text{total population of women 27 and above quadrivalent}} \right) * 100000$
- $\text{CIN2 12 to 26 per 100000 FiveAdditionalTypes} = \left(\frac{\text{CIN2 12 to 26 FiveAdditionalTypes}}{\text{total population of women 12 to 26 FiveAdditionalTypesvalent}} \right) * 100000$
- $\text{"total population of women (quad+FiveAdditionalTypes)} = \text{total population of women 12 to 26 FiveAdditionalTypesvalent} + \text{total population of women 12 to 26 quadrivalent} + \text{total population of women 27 and above FiveAdditionalTypesvalent} + \text{total population of women 27 and above quadrivalent}$
- $\text{total population} = \text{"total population of women (quad+FiveAdditionalTypes)" * ratio of total population to total population of women}$

- "CIN2 27&above FiveAdditionalTypes per 100000"= (CIN2 27 and above FiveAdditionalTypes/total population of women 27 and above FiveAdditionalTypesvalent)*100000
- HPV infected 12 to 26 per 100000 quad= (HPV infected 12 to 26 quad/total population of women 12 to 26 quadrivalent)*100000
- hpv infected 12 to 26FiveAdditionalTypes per 100000= (HPV infected 12to26 FiveAdditionalTypes/total population of women 12 to 26 FiveAdditionalTypesvalent)*100000
- Aging into HPV infected 27= aging hpv infected 12 to 26 quad
- "Females <12 quad"= INTEG (birth quad-"Aging of female <12"-"death of females< 12 years of age", "Initial susceptible females <12 quad")
- "Initial susceptible females <12 quad"= 724633
- total population of women FiveAdditionalTypesvalent= total population of women 12 to 26 FiveAdditionalTypesvalent+total population of women 27 and above FiveAdditionalTypesvalent
- "HPV Infection (quad) among 12 to 26 count"= CIN1 12 to 26 quad+CIN2 12 to 26 quad+CIN3 12 to 26 quad+HPV infected 12 to 26 quad
- HPV prevalence 27 and above FiveAdditionalTypes= ("HPV infection among 27 and above (FiveAdditionalTypes) count")/total population of women 27 and above FiveAdditionalTypesvalent
- HPV prevalence 12 to 26 quad=("HPV Infection (quad) among 12 to 26 count")/total population of women 12 to 26 quadrivalent
- "HPV infection among 12 to 26 (FiveAdditionalTypes) count"= CIN1 12 to26 FiveAdditionalTypes+CIN2 12to 26 FiveAdditionalTypes+CIN3 12to26 FiveAdditionalTypes+HPV infected 12to26 FiveAdditionalTypes

- "HPV infection among 27 and above (FiveAdditionalTypes) count"= HPV infected 27 and above FiveAdditionalTypes+CIN1 27 and above FiveAdditionalTypes+CIN2 27 and above FiveAdditionalTypes+CIN3 27 and above FiveAdditionalTypes
- "HPV infection among 27 and above (quad) count"= CIN1 27 and above quad+CIN2 27 and above quad+CIN3 27 and above quad+HPV infected 27 and above quad
- HPV prevalence 12to26FiveAdditionalTypes= ("HPV infection among 12 to 26 (FiveAdditionalTypes) count")/total population of women 12 to 26 FiveAdditionalTypesvalent
- HPV prevalence 27 and above quad= ("HPV infection among 27 and above (quad) count")/total population of women 27 and above quadrivalent
- CIN1 12 to 26 quad= INTEG (progression1 among 12 to 26 quad+regression1 12to26 quad+Regression3 12to26 quad-aging CIN1 12to26 quad-clearance1 among 12to26 quad-deaths of CIN1 12to26 quad-progression2 among 12 to 26 quad-rx1 12to26 quad, Initially CIN1 infected women from HPV infected women)
- CIN1 27 and above FiveAdditionalTypes= INTEG (aging into CIN1 FiveAdditionalTypes+"prog1 27 & above FiveAdditionalTypes"+"reg1 27&above FiveAdditionalTypes"+"reg3 27&above FiveAdditionalTypes"-CIN1 27 &above deaths FiveAdditionalTypes"-clearance1 27 & above FiveAdditionalTypes"- "prog2 27& above FiveAdditionalTypes"-rx1 27& above FiveAdditionalTypes", Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain)
- total population of women quadrivalent= total population of women 12 to 26 quadrivalent+total population of women 27 and above quadrivalent

- $\text{deaths of immune 12 to 26 FiveAdditionalTypes} = \text{death rate 12 to 26} * \text{immune via vacc 12 to 26 FiveAdditionalTypes}$
- $\text{aging into immune via vaccination 27 and above quad} = \text{aging immune via vaccination 12 to 26 quad}$
- $\text{deaths of immune 12to 26 FiveAdditionalTypes} = \text{death rate 12 to 26} * \text{immune via vacc 12 to 26 FiveAdditionalTypes}$
- $\text{aging immune via vaccination 12 to 26 quad} = \text{Immune via vaccination 12to26 quad} / \text{mean years until aging}$
- $\text{aging into immune via vacc 27 and above FiveAdditionalTypes} = \text{aging of immune 12 to 26 FiveAdditionalTypes}$
- $\text{immune via vaccination 27 and above FiveAdditionalTypes} = \text{INTEG} (\text{aging into immune via vacc 27 and above FiveAdditionalTypes} - \text{deaths of immune 27 and above FiveAdditionalTypes} - \text{waning immunity after vaccination 27 and above FiveAdditionalTypes}, 0)$
- $\text{Immune via vaccination 27 and above quad} = \text{INTEG} (\text{aging into immune via vaccination 27 and above quad} - \text{"waning immunity among 27 and above (quad)" - immune via vacc deaths quad}, 0)$
- $\text{aging of immune 12 to 26 FiveAdditionalTypes} = \text{immune via vacc 12 to 26 FiveAdditionalTypes} / \text{mean years until aging}$
- $\text{vacc FiveAdditionalTypes} = \text{susceptible 12 to 26 FiveAdditionalTypes} * \text{"vacc rate (FiveAdditionalTypes)" * vaccine efficacy}$
- $\text{HPV prevalence 27 and above per 100 quad} = \text{HPV prevalence 27 and above quad} * 100$
- $\text{HPV prevalence 12 to 26 per 100 FiveAdditionalTypes} = \text{HPV prevalence 12to26FiveAdditionalTypes} * 100$

- HPV prevalence 27 and above FiveAdditionalTypes per 100= HPV prevalence 27 and above FiveAdditionalTypes*100
- HPV prevalence 12 to 26 quad per 100= HPV prevalence 12 to 26 quad*100
- CIN1 27 and above quad= INTEG ("Aging into CIN1 27&above quad"+prog1 27and above quad+reg1 27 and above quad+reg3 27 and above quad-"CIN1 27&above deaths quad"- "clearance1 27&above quad"-prog2 27and above quad-"rx1 27&above quad", Initial 27 and above CIN1 infected women from HPV quad infected)
- fraction of women 27 and above who were infected with quad and are CIN1=0.1
- Total initial population 12 to 26 from US census=976958
- total initial population 27 and above from US census=3.43899e+006
- Initially HPV infected 12 to 26 women with FiveAdditionalTypes who are at CIN1= Initially infected HPV women 12 to 26 from US census including CIN1 forFiveAdditionalTypes *Fraction of 12 to 26 years who are intially infected with HPV FiveAdditionalTypes who have CIN1
- Initially HPV infected women from US census for quad including CIN1=Total initial population 12 to 26 from US census*Fraction of women 12 to 26 from US census who are HPV infected for quad strain
- Initially infected HPV women 12 to 26 from US census including CIN1 for FiveAdditionalTypes= Fraction of US 12 to 26 census population that is initially infected with FiveAdditionalTypes strain of HPV*Total initial population 12 to 26 from US census
- Fraction of women 27 and above from HPV FiveAdditionalTypes infected that are CIN1=0.1184
- fraction of women 27 and above from susceptible that are infected with HPV FiveAdditionalTypes= 0.04

- Fraction of 12 to 26 years old who are initially infected with quad strains of HPV who have CIN1= 0.09
- Initially CIN1 infected women from HPV infected women= Initially HPV infected women from US census for quad including CIN1*Fraction of 12 to 26 years old who are initially infected with quad strains of HPV who have CIN1
- Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1= fraction of women 27 and above from susceptible that are infected with HPV FiveAdditionalTypes *total initial population 27 and above from US census
- Initial 27 and above at CIN1 from HPV infected women with FiveAdditionalTypes strain= Fraction of women 27 and above from HPV FiveAdditionalTypes infected that are CIN1*Initially infected 27 and above with HPV FiveAdditionalTypes including CIN1
- Fraction of women 12 to 26 from US census who are HPV infected for quad strain= 0.18
- Fraction of 12 to 26 years who are initially infected with HPV FiveAdditionalTypes who have CIN1= 0.09
- Fraction of US 12 to 26 census population that is initially infected with FiveAdditionalTypes strain of HPV=0.12
- death of susceptible 12to 26no= susceptible 12 to26 FiveAdditionalTypes*death rate 12 to 26
- CIN1 deaths 12to 26FiveAdditionalTypes= CIN1 12 to26 FiveAdditionalTypes*death rate 12 to 26
- deaths of CIN3 12 to 26 quad= death rate 12 to 26*CIN3 12 to 26 quad
- deaths of immune 12 to 26 quad= Immune via vaccination 12to26 quad*death rate 12 to 26

- deaths of infected 12 to 26 quad= death rate 12 to 26*HPV infected 12 to 26 quad
- CIN3 deaths 12to26FiveAdditionalTypes= CIN3 12to26 FiveAdditionalTypes*death rate 12 to 26
- CIN2 deaths 12to 26 FiveAdditionalTypes= CIN2 12to 26 FiveAdditionalTypes*death rate 12 to 26
- CIN2 27 and above quad= INTEG (Aging into CIN2 27 and above quad-"clear2 27 & above quad"+prog2 27and above quad-prog3 27and above quad+"reg2 27&above quad"-CIN2 deaths among 27 and above quad-reg1 27 and above quad-"rx2 27&above quad",0)
- deaths infected 12to 26 FiveAdditionalTypes= HPV infected 12to26 FiveAdditionalTypes*death rate 12 to 26
- deaths of CIN2 12 to 26 quad=death rate 12 to 26*CIN2 12 to 26 quad
- CIN2 27 and above FiveAdditionalTypes= INTEG (aging into cin2 FiveAdditionalTypes+"prog2 27& above FiveAdditionalTypes"+"reg2 27 &above FiveAdditionalTypes"-CIN2 27&above deaths FiveAdditionalTypes"-clearance2 FiveAdditionalTypes"-prog3 27& above FiveAdditionalTypes"-reg1 27&above FiveAdditionalTypes"-rx2 27& above FiveAdditionalTypes", 0)
- deaths of CIN1 12to26 quad= CIN1 12 to 26 quad*death rate 12 to 26
- deaths of susceptible 12 to 26 quad=Susceptible12to26 quad*death rate 12 to 26
- Ref Rate of clearance of CIN1 quad 12 to 26= 0.483
- Ref Rate of clearance of CIN2 quad 12 to 26= 0.21
- Ref Rate of clearance of CIN3 quad 12 to 26= 0.11
- vaccine efficacy= 0.9
- "death of females< 12 years of age"= "death rate of females <12 years""Females <12 quad"

- "death rate of females <12 years"= 0.0002195
- "death of females <12 years"= "death rate of females <12 years"*"Female <12 FiveAdditionalTypes"
- force of infection 27 and above quad= mean partner acquisition rate 27 and above*(fraction of partners 27 years and older women that are in 27 years and older *HPV prevalence 27 and above quad +(1-fraction of partners 27 years and older women that are in 27 years and older) *HPV prevalence 12 to 26 quad)*transmission rate 27 and above
- force of infection 27 and above FiveAdditionalTypes= mean partner acquisition rate 27 and above * (fraction of partners 27 years and older women that are in 27 years and older * HPV prevalence 27 and above FiveAdditionalTypes + (1-fraction of partners 27 years and older women that are in 27 years and older) * HPV prevalence 12to26FiveAdditionalTypes)*transmission rate 27 and above
- fraction of partners 27 years and older women that are in 27 years and older= 0.915
- Fraction of partners of 12 to 26 year old women that are in 12 to 26 year of age= 0.33
- "Aging females <12 FiveAdditionalTypes"= "Female <12 FiveAdditionalTypes"/"mean years of aging for <12 years old"
- "Aging of female <12"= "Females <12 quad"/"mean years of aging for <12 years old"
- "mean years of aging for <12 years old"= 12
- reg3 27 and above quad= CIN3 27 and above quad*Rate of Reg CIN3 to CIN1
- Fraction of CIN1 sucessfully cured=0.96
- reg1 12 to 26FiveAdditionalTypes= Rate of regression CIN2 to CIN1*CIN2 12to 26 FiveAdditionalTypes

- $\text{reg2 26no} = \text{Rate of Reg CIN3 to CIN2} * \text{CIN3 12to26 FiveAdditionalTypes}$
- $\text{"reg2 27\&above quad"} = \text{Rate of Reg CIN3 to CIN2} * \text{CIN3 27 and above quad}$
- $\text{"reg2 27 \&above FiveAdditionalTypes"} = \text{Rate of Reg CIN3 to CIN2} * \text{CIN3 27 and above FiveAdditionalTypes}$
- $\text{reg3 12 to 26FiveAdditionalTypes} = \text{Rate of Reg CIN3 to CIN1} * \text{CIN3 12to26 FiveAdditionalTypes}$
- $\text{regression2 12to26 quad} = \text{Rate of Reg CIN3 to CIN2} * \text{CIN3 12 to 26 quad}$
- $\text{Regression3 12to26 quad} = \text{Rate of Reg CIN3 to CIN1} * \text{CIN3 12 to 26 quad}$
- $\text{Rate of Reg CIN3 to CIN2} = 0.03$
- $\text{regression1 12to26 quad} = \text{Rate of regression CIN2 to CIN1} * \text{CIN2 12 to 26 quad}$
- $\text{"reg1 27\&above FiveAdditionalTypes"} = \text{Rate of regression CIN2 to CIN1} * \text{CIN2 27 and above FiveAdditionalTypes}$
- $\text{reg1 27 and above quad} = \text{CIN2 27 and above quad} * \text{Rate of regression CIN2 to CIN1}$
- $\text{Rate of Reg CIN3 to CIN1} = 0.03$
- $\text{Fraction of CIN3 successfully cured} = 0.92$
- $\text{Rate of regression CIN2 to CIN1} = 0.133$
- $\text{"reg3 27\&above FiveAdditionalTypes"} = \text{Rate of Reg CIN3 to CIN1} * \text{CIN3 27 and above FiveAdditionalTypes}$
- $\text{Fraction of CIN2 successfully cured} = 0.92$
- $\text{CIN3 to cervical cancer hazard rate} = 0.42$
- $\text{progression1 among 12 to 26 quad} = \text{HPV infected to CIN1 hazard rate} * \text{HPV infected 12 to 26 quad}$
- $\text{progression2 among 12 to 26 quad} = \text{CIN1 to CIN2 hazard rate} * \text{CIN1 12 to 26 quad}$

- progression3 among 12 to 26 quad= CIN2 to CIN3 hazard rate*CIN2 12 to 26 quad
- HPV infected to CIN1 hazard rate= 0.094
- prog2 27and above quad= CIN1 to CIN2 hazard rate*CIN1 27 and above quad
- prog3 27and above quad= CIN2 to CIN3 hazard rate*CIN2 27 and above quad
- CIN2 to CIN3 hazard rate= 0.154
- prog1 27and above quad=HPV infected to CIN1 hazard rate*HPV infected 27and above quad
- CIN1 to CIN2 hazard rate= 0.136
- "Aging into CIN1 27&above quad"= aging CIN1 12to26 quad
- aging into CIN1 FiveAdditionalTypes= CIN1 12 to 26 FiveAdditionalTypes aging
- Aging into CIN2 27 and above quad= aging CIN2 12to 26 quad
- aging into cin2 FiveAdditionalTypes= CIN2 12to26 FiveAdditionalTypes aging
- "Aging into CIN3 27&above quad"=Aging CIN3 12 to 26 FiveAdditionalTypes
- aging into cin3 FiveAdditionalTypes= CIN3 12 to 26 FiveAdditionalTypes aging
- aging into hpv infected FiveAdditionalTypes= hpv infected 12 to 26FiveAdditionalTypes aging
- Aging into susceptible 27= aging susceptible 12to 26 quad
- aging into susceptible 27 and FiveAdditionalTypes= Susceptible 12 to 26 FiveAdditionalTypes aging
- CIN1 12 to 26 FiveAdditionalTypes aging= CIN1 12 to26 FiveAdditionalTypes/mean years until aging
- ratio of total population to total population of women= 2
- mean partner acquisition 12 to 26=1.64
- aging CIN1 12to26 quad= CIN1 12 to 26 quad/mean years until aging
- aging CIN2 12to 26 quad= CIN2 12 to 26 quad/mean years until aging

- aging hpv infected 12 to 26 quad= HPV infected 12 to 26 quad/mean years until aging
- aging susceptible 12to 26 quad= Susceptible12to26 quad/mean years until aging
- Susceptible 12 to 26 FiveAdditionalTypes aging= susceptible 12 to26 FiveAdditionalTypes/mean years until aging
- CIN2 12to 26 FiveAdditionalTypes= INTEG (prog2 12to26FiveAdditionalTypes+reg2 26no-CIN2 deaths 12to 26 FiveAdditionalTypes-clearance2 12to 26 FiveAdditionalTypes -prog3 12 to 26FiveAdditionalTypes-reg1 12 to 26FiveAdditionalTypes-rx2 12to26 FiveAdditionalTypes -CIN2 12to26 FiveAdditionalTypes aging, 0)
- CIN2 12to26 FiveAdditionalTypes aging= CIN2 12to 26 FiveAdditionalTypes/mean years until aging
- hpv infected 12 to 26FiveAdditionalTypes aging= HPV infected 12to26 FiveAdditionalTypes/mean years until aging
- CIN3 12 to 26 FiveAdditionalTypes aging= CIN3 12to26 FiveAdditionalTypes/mean years until aging
- CIN2 12 to 26 quad= INTEG (+progression2 among 12 to 26 quad+regression2 12to26 quad-clearance2 among 12to26 quad-progression3 among 12 to 26 quad-regression1 12to26 quad-rx2 12to26 quad-aging CIN2 12to 26 quad-deaths of CIN2 12 to 26 quad,0)
- Aging CIN3 12 to 26 FiveAdditionalTypes= CIN3 12 to 26 quad/mean years until aging
- mean years until aging= 15
- birth rate for female babies= (0.0124 / 2)
- death rate 12 to 26= 0.000647

- "total infected HPV 16 &18"= HPV infected 12 to 26 per 100000 quad+hpv infected 27 and above per 100000 quad
- "total infected (5 additional types)"= hpv infected 12 to 26FiveAdditionalTypes per 100000+HPV infected FiveAdditionalTypes per 100000
- "total CIN1 HPV 16&18"= CIN1 12to26 per 100000 quad+"CIN1 27&above per 100000 quad"
- "total CIN1 (5 additional types)"= CIN1 26FiveAdditionalTypes per 100000+"CIN1 27& above FiveAdditionalTypes per 100000"
- "total CIN2 HPV 16 &18"= CIN2 12to26 quad per 100000+CIN2 27 and above per 100000 quad
- "total CIN2 (5 additional types)"= CIN2 12 to 26per 100000 FiveAdditionalTypes+"CIN2 27&above FiveAdditionalTypes per 100000"
- "total CIN3 HPV 16&18"= CIN3 among 12 to 26 per 100000 quad+CIN3 27 and above per 100000 quad
- "total CIN3 (5 additional types)"= CIN3 12 to 26 per 100000 FiveAdditionalTypes+CIN3 FiveAdditionalTypes per 100000
- total infected= HPV infected FiveAdditionalTypes per 100000+HPV infected 12 to 26 per 100000 quad+hpv infected 12 to 26FiveAdditionalTypes per 100000+hpv infected 27 and above per 100000 quad
- total CIN 1= CIN1 12to26 per 100000 quad+"CIN1 27& above FiveAdditionalTypes per 100000"+CIN1 26FiveAdditionalTypes per 100000 +"CIN1 27&above per 100000 quad"
- "infection 27&above quad"= force of infection 27 and above quad*Susceptible 27and above quad
- infection 12to26FiveAdditionalTypes=force of infection 12 to 26 FiveAdditionalTypes*susceptible 12 to26 FiveAdditionalTypes

- total CIN2= "CIN2 27&above FiveAdditionalTypes per 100000"+CIN2 12to26 quad per 100000+CIN2 12 to 26per 100000 FiveAdditionalTypes+CIN2 27 and above per 100000 quad
- total CIN3=CIN3 FiveAdditionalTypes per 100000+CIN3 among 12 to 26 per 100000 quad+CIN3 12 to 26 per 100000 FiveAdditionalTypes+CIN3 27 and above per 100000 quad
- screening rate FiveAdditionalTypes=0.728
- "infection 27&above FiveAdditionalTypes"= force of infection 27 and above FiveAdditionalTypes*Susceptible 27and above FiveAdditionalTypes
- infection rate among 12to26 quad= force of infection 12to26 quad*Susceptible12to26 quad
- Ref Rate of clearance of HPV infected quad 12 to 26= 0.483
- mean partner acquisition rate 27 and above= 1.19
- screening rate=0.728
- sensitivity CIN1= 0.28
- sensitivity CIN2and CIN3=0.59
- transmission rate 27 and above= 0.4