Economic evaluation of a school based human papillomavirus (HPV) vaccination program in South Africa.

by

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Abstract

Introduction

Oncogenic human papillomavirus (HPV) types 16 and 18 pose the greatest risk for cervical cancer. Infection with HPV types 16 and 18, which cause 70% of cervical cancer worldwide, could be prevented with commercially available HPV 16 and 18 vaccines. A previous study in South Africa demonstrated that vaccination of 12 year old girls with a HPV vaccine, prior to sexual debut, is cost effective, however this was carried out prior to the roll-out of the HPV vaccination program. The aim of this study is to provide an up-dated cost effectiveness analysis of HPV 16 and 18 vaccination of nine year old school girls in South Africa, from a public sector healthcare provider perspective.

Methods

Treeage Pro Suite® software was used to create a lifetime static Markov model, to determine the cost effectiveness of a school based vaccination program in the public sector compared to cervical cancer screening alone. The time horizon was based on average life expectancy of 61 years of females in South Africa. The costs and effects of vaccination, screening and treatment compared to screening and treatment of precancerous lesions and cervical cancer were modelled with data obtained from published literature. Expert opinion was sought, where no published data was available. Cost and effects were discounted by 5% and a one way sensitivity analysis was performed on a range of parameters.

Results

Results of this study showed that HPV vaccination was more cost effective than screening alone. The incremental cost-effectiveness ratio (ICER) of adding HPV vaccination to the existing screening program was R10 567.79, and dominant for the HPV vaccination compared to screening alone from a public sector payer perspective.

The cost estimate of a two-dose schedule, school based HPV vaccination, is R636.75 per vaccinated girl. The vaccination cost to avert one case of cervical cancer stage 1 due to HPV 16 and/or 18 is R58 581.92 and over a lifetime, the number of new cervical cancer stage 1 cases averted due to HPV 16 and 18 vaccination of 507 073 nine year old girls is 5 538. The ICER for the exploratory model of HPV vaccination of HIV-infected nine year old girls also showed that HPV vaccine strategy with dominant with ICER of R2 375.62 per QALY.

Conclusions

A school based vaccination program of girls, prior to sexual debut, is a cost effective strategy to reduce the risk of cervical cancer when compared to screening alone in the public healthcare sector.

Keywords: HPV vaccination, cost effectiveness, cervical cancer, South Africa.

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Abbreviations and Definitions

Abbreviation	Definition
ASCUS	Atypical squamous cells of undetermined significance (slightly abnormal squamous cells, but the changes don't suggest that precancerous cells are present). Abnormality is not sufficient to constitute "dysplasia."
AS04	Adjuvant System 04. Is a trade name for combination of adjuvants used in various vaccine product by GlaxoSmithKline (GSK)
ASR	Age-standardised rate: a rate is the number of new cases or deaths per 100 000 persons per year. An age-standardised rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.
CANSA	The Cancer Association of South Africa
CD4	Cluster of differentiation 4 (refers to the cluster of proteins that make up a cell surface receptor)
CE	Cost Effectiveness
CEA	Cost Effectiveness Analysis Form of economic analysis that compares the relative costs and outcomes (effects) of two or more options. CEA is expressed as a ratio where the denominator is a gain in health (e.g. years of life gained) and the numerator is the cost associated with the health gain.
CIN 1	Cervical intraepithelial neoplasia grade 1 (mild dysplasia). Dysplastic squamous cells in the lower one-third of the epithelium with HPV changes in the rest of the superficial epithelium
CIN 2	Cervical intraepithelial neoplasia grade 2 (moderate to marked dysplasia). Dysplastic squamous cells in the basal two-thirds of the epithelium and the upper half of the epithelium shows HPV changes
CIN 3	Cervical intraepithelial neoplasia grade 3 (severe dysplasia to carcinoma in situ). Dysplastic squamous cells marked throughout the full thickness of the epithelium. HPV changes are confined to the superficial layer.
CIS	Carcinoma in situ: An early form of cancer that is defined by the absence of invasion of tumor cells into the surrounding tissue, usually before penetration through the basement membrane.
CKC	Cold knife conization
DOH	Department of Health
Dominance (ICER)	A dominant ICER indicates that one intervention is less costly with better benefits compared to another.
EPI	Expanded Programme on Immunisation

GAVI alliance	Global Alliance for Vaccines and Immunization is a public-private global health partnership committed to increasing immunization in poor countries.
GMTs	Geometric mean titers
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV 16	Human Papillomavirus type 16
HPV 18	Human Papillomavirus type 18
HRQL	Health-related quality of life (HRQL)
HSIL	High grade squamous intraepithelial lesion (moderate or severe dysplasia or carcinoma in situ)
ICER	Incremental cost effectiveness ratio. ICER is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment. The equation for ICER is: ICER = (C1 – C2) / (E1 – E2)
JORRP	Juvenile-Onset Recurrent Respiratory Papillomatosis
LEEP/LLETZ	Large loop excision of the transformation zone
LSIL	Low grade squamous intraepithelial lesion (mild dysplasia) Is a cytology diagnosis using the Bethesda system
LMICs	Low and Middle Income Countries (LMICs)
Pap (test)	Papanicolaou test. A cytological test that detects abnormal cervical cells.
TVC	Total Vaccinated Cohort
Unknown cervical cancer	Cases of cervical cancer not detected due to absence of symptoms
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

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1. Introduction

1.1. Background to research

Cervical cancer is the leading cause of cancer death in the African Region. In South Africa cervical cancer ranks as the second most frequent cancer among women (15 to 44 years) and at any given time about 21% of women are infected with cervical HPV. Two HPV strains 16 and 18 are responsible for about two thirds of cervical cancers caused by HPV.[1]

1.2. Research problem and hypotheses

The public health strategy, for managing cervical cancer, at the time of undertaking this research, was to screen women for cervical cancer every ten years. This strategy reaches mainly younger women who are screened for cervical cancer when they seek other maternal or family planning services[2]. Unstructured cervical cancer screening is not effective in reaching all women at risk of cervical cancer hence the introduction of the HPV vaccines may provide a more comprehensive approach to reducing the burden of cervical cancer.[3]

Vaccines (Cervarix® and Gardasil®) that offer protection against human papillomavirus (types 16 and 18) are registered in South Africa, for females nine to 45 years old, for protection against disease caused by HPV 16 and 18. Gardasil® is also registered for protection against genital warts caused by HPV 6 and 11 in women aged nine to 45 years old, and disease caused by HPV 31, 33, 35, 52 and 58 in women aged nine to 26 years old.[4] Brown et al. reported that the cross-protective efficacy was most apparent and consistent for members of the A9 species which includes 6 cancer-causing types (16, 31, 33, 35, 52, and 58).[4] The combined incidence of HPV-31/33/35/52/58 related CIN1 to 3/AIS was reduced by 31.9% (95% CI, 11.8% to 47.6%). It is hypothesized (due to the polyclonal nature of the immune response to vaccination), that anti–HPV-16 and anti–HPV-18 may be able to bind to and possibly neutralize virions of HPV types closely related to 16 and/or 18, thereby

preventing infection and disease associated with these other types (cross-protection).[4]

These vaccines were initially not adopted by government as part of a national vaccination program despite the high burden of cervical cancer, largely due to the cost of the vaccines at R630.04 for a single dose of Cervarix® and R617.88 for a single dose of Gardasil® (MIMS September 2014).[5] In March 2014, the Minister of Health in South Africa announced that government will launch a school based HPV vaccination program for grade four girls.[6] This decision was influenced by the low vaccine prices which the Department of Health and other agencies such as Global Alliance for Vaccines and Immunization (GAVI) have been able to achieve.

This study was undertaken to determine the cost effectiveness analysis of a HPV vaccination program versus screening and treatment of cervical cancer to assess the feasibility of introducing such a program for policy makers in South Africa.

1.3. Justification for the research

A previous study in South Africa proposed vaccination of 12 year old girls and used 2007 costs. This study aimed to calculate the cost effectiveness of HPV vaccination of nine year old girls as proposed in the national vaccination plan, using updated (2013) costs. The results of this study will be beneficial to decision makers to assess budget implications for future budget planning and to monitor areas of uncertainty.

2. Literature Review

2.1. Introduction

HPV vaccination has been introduced in many developed countries following country specific cost effectiveness evaluations. . HPV vaccination introduction in low and middle income countries (LMICs) is more limited and there are fewer cost effectiveness studies to inform decision makers in these countries.[7]

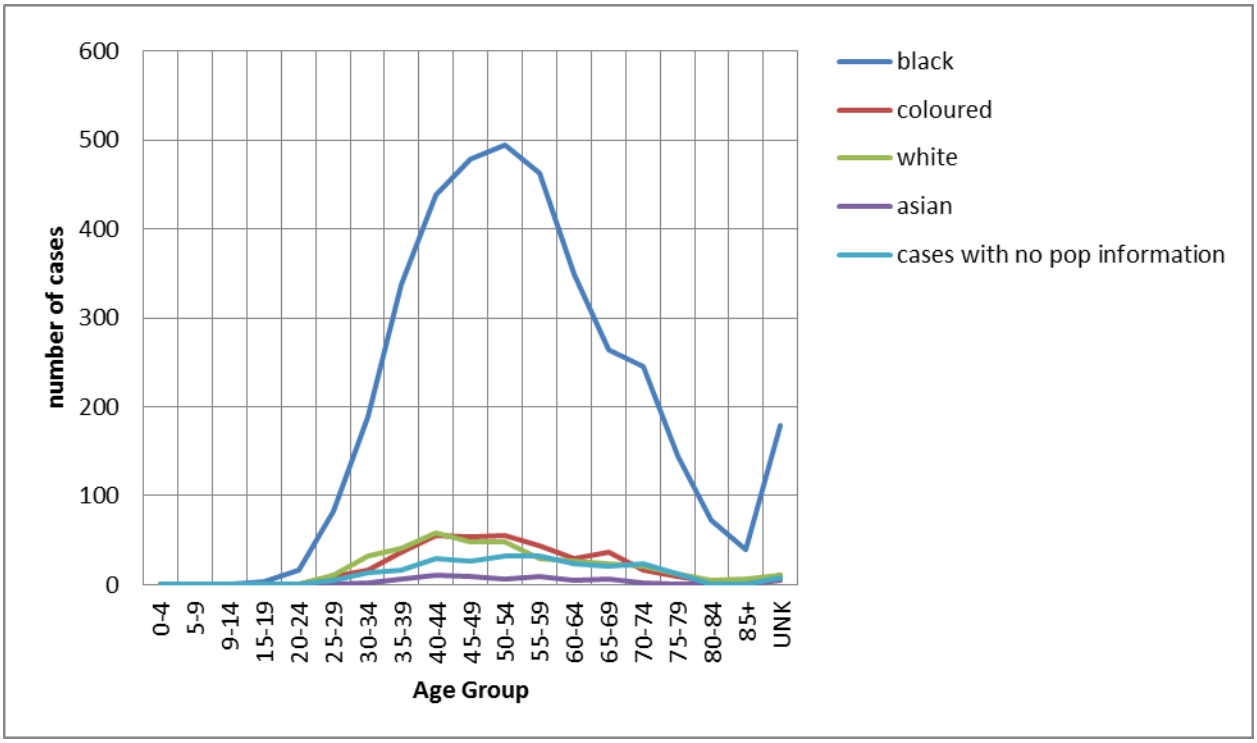
2.2. Epidemiology and Burden of Human Papillomavirus (HPV) disease

Cervical cancer, globally, is the fourth most common cancer in women, with an estimated 528 000 new cases in 2012. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.[8] In South Africa in 2012, the estimated incidence was 7 735 cases (19.3% of all female cancers).[9]

Worldwide an estimated 266 000 deaths from cervical cancer occurred in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions.[8] In South Africa the estimated deaths in 2012 due to cervical cancer was 4 248 (17.6% of all female cancer deaths).[9]

Cervical HPV persistence is known to cause development of cervical cancer.[10] The peak rate of HPV infection is seen in women less than 25 years of age. About fifty percent of HPV infections clear within six months and about 90 percent within a few years.[10] Persistent HPV infection with one or more carcinogenic types can result in progression to cervical precancerous lesions and thereafter invasion to cervical carcinogenesis.[10]

Figure 2.1: Cervical cancer in South Africa (2005) by age and population group.[10]



In South Africa the peak incidence of cervical cancer occurs between ages of 40 and 44 (see Figure 2.1) for, Asian, Coloured and White and between 50 and 54 years for Black population.

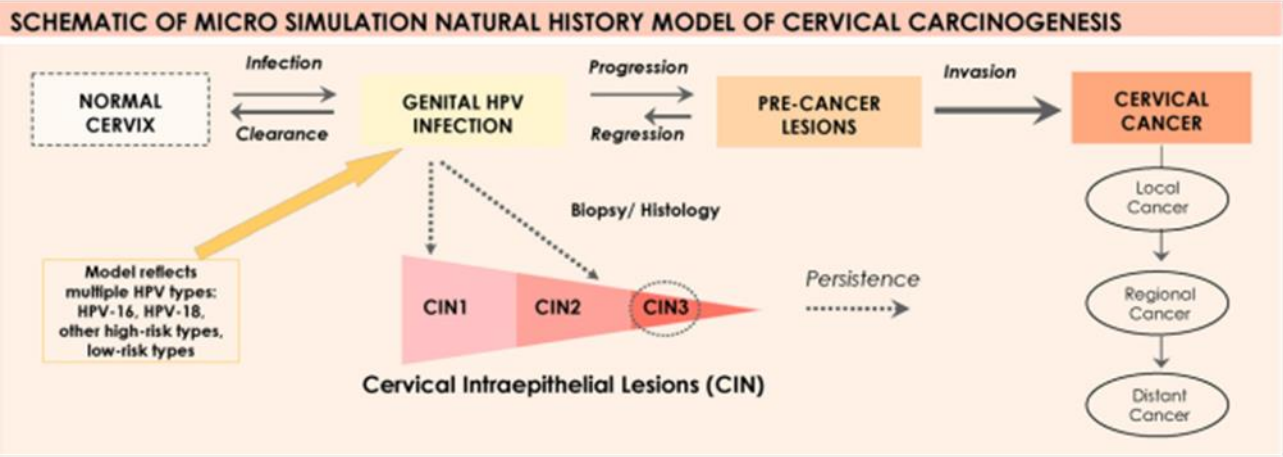
There are over 150 million human HPV types which can be divided, based on DNA sequence analysis, into five genera (Beta, Gamma, Alpha, Mu and Nu). The World Health Organization (WHO) has defined 12 HPV alpha types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) as high risk cancer-causing types.[12] The high risk alpha HPV types are linked to squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the cervix.[12]

The three most common HPV types found in women with invasive cervical cancer are HPV type 16 (63%), 18 (16%) and 45 (5%).[13] In a recent study in sub-Saharan Africa (Ghana, Nigeria, and South Africa), the most commonly detected HPV types, in cervical biopsy specimens, were HPV16 (51.2%), HPV18 (17.2%), HPV35 (8.7%), HPV45 (7.4%) and HPV33 (4.0%).[14] The most common HPV types in South African women,

with histologically confirmed invasive cervical cancer, infected with a single HPV type was HPV16 (47.5%), HPV18 (18.2%), HPV35 (9.9%), HPV45 (7.7%) and HPV33 (6.6%).[14]

HPV types 16 and 18 account for the majority of all cervical cancers worldwide, 41 to 67% of high-grade squamous intraepithelial lesions (HSIL), 16 to 32% of low-grade squamous intraepithelial lesions (LSIL) and 6 to 27% of atypical squamous cells of undetermined significance (ASCUS).[15]

Figure 2.2. Schematic model of cervical cancer natural history.[16]



In South Africa at any point in time about 21.0% of women in the general population have cervical HPV infection. A World Health Organization (WHO) report on HPV in South Africa states that the majority (62.8%) of invasive cervical cancers are due to HPV types 16 or 18.[1]

***Table 2.1: Prevalence of HPV type 16 and 18 in women in South Africa.*[1]**

HPV type	Normal Cytology (n=1216)	Low grade cervical lesions (LSIL/CIN-1) (n=15)	High Grade Cervical Lesions (HSIL/ CIN-2 / CIN-3 / CIS) (n=168)	Cervical Cancer (n=307)
16	1.9%	13.3%	52.4%	52.1%
18	1.7%	13.3%	6%	10.7%
Total	**3.6%**	**26.6%**	**58.4%**	**62.8%**

HPV 16 is more prevalent among women with precancerous cervical lesions and invasive cervical cancer in South Africa (Table 2.1).

***Table 2.2: Prevalence of HPV type 16 and 18 among invasive cervical cancer cases in South Africa by histology.*[1]**

HPV type	Any Histology (n=307)	Squamous Cell Cancer (n=249)	Adenocarcinoma (n=8)	Unspecified (n=50)
16	52.1%	46.2%	50%	82%
18	10.7%	11.2%	0%	10%
Total	**62.8%**	**57.4%**	**50%**	**92%**

Histology data for South Africa show that HPV 16 is more prevalent in cervical cancer of any histology type and 62.8% of invasive cervical cancers are attributed to HPV 16 or 18 (Table 2.2).

2.3. Co-factors contributing to cervical cancer in women in South Africa

HPV is a necessary cause of cervical cancer, but it is not a sufficient cause. Other co-factors are necessary for progression from cervical HPV infection to cancer. Tobacco smoking, high parity, long-term hormonal contraceptive use, and co-infection with HIV have been identified as established co-factors and South Africa data is presented below:

- Smoking, of any tobacco type, prevalence (8.9%): 2008 data
- Total fertility rate (2.9 live births per women): 2001 data
- Oral contraceptive use prevalence (11.1%) : 2003 data

- The rate of HIV in young females aged 15 to 24yrs(12.7%): 2007 data.[1]

Other probable co-factors are co-infection with Chlamydia trachomatis (CT) and herpes simplex virus type-2 (HSV-2), immunosuppression and certain dietary deficiencies.[17]

2.4. HPV in HIV positive women

Human immunodeficiency virus (HIV) infection in women increases the risk of HPV infection and developing cervical cancer.[18] A study in the United States of America showed that HIV positive women were 1.8 times more likely to have high risk HPV (types 16, 18, 31, 45) infections compared to HIV negative women.[19] Another study showed that among all women who were HPV positive, the number of individual HPV types detected was higher among HIV positive women compared to HIV negative women ($P<0.0001$).[20] Thirty-six percent of HIV-positive women with HPV infection were infected with two or more types compared with twelve percent of HIV-negative women with HPV infection ($P<0.0001$). Among HIV-positive women with HPV infection with multiple HPV types, was most common among those with lower CD4 levels ($P<0.0001$), and twenty eight percent of women with CD4 counts less than 200/mm^3 were infected with three or more HPV types.[20]

In Africa approximately 57% of HIV positive women are HPV positive.[18] In South Africa HIV prevalence in women (2012 data) was 14.4%.[21] Persistent HPV infection in HIV positive women is due to increased susceptibility, decreased ability to clear infection due to impaired cell mediated immunity and reactivation of latent HPV infection associated with immunosuppression. Immunocompromised people are also resistant to treatment of HPV related diseases and prone to accelerated development of HPV associated cancer.[18]

A study in Sub Sahara Africa countries (Ghana, Nigeria, and South Africa) showed that the prevalence of single and multiple HPV infections was higher among HIV-positive women, indicating that HPV infections were more common in HIV-positive women.[14] The results for the South Africa arm of the study, where the HIV status of

almost 90% of women was known, showed that 96.4% of HIV positive women, 91.2% of HIV negative women were HPV-positive and 14.8% HIV-positive and 9.0% HIV-negative women had multiple HPV infections.[14]

Some studies show patients on Highly Active Antiretroviral Therapy (HAART) have regression of HPV infection while other studies show no impact of HAART on HPV associated disease. It is unclear if HPV infection affects the risk of acquiring HIV.[18]

2.5. Screening for Cervical Cancer

The South African government's policy allows for women attending public sector services to have three Papanicolaou cytology tests (Pap tests) per lifetime at ten-year intervals, starting at age 30. This decision was informed by various factors including the WHO recommendations.

Sankaranarayanan et al. reported that programs, either organised or opportunistic, with frequently repeated cytology screening, have led to a large decline in cervical cancer incidence and mortality in developed countries. Organised screening programs with systematic call, recall, follow-up and surveillance systems have shown the greatest effect in reducing cervical cancer incidence and mortality.[22] Sherris et al. concluded that the optimal age-group, in low resource settings for cervical cancer screening, to achieve the greatest public health impact is 30 to 39 year old women.[23]

In developed countries where the screening coverage is more than 70%, the maximum impact of decreasing the incidence of cervical cancer and cervical cancer deaths becomes apparent and reaches a plateau at 84% coverage.[24] In developing countries the objectives are very different. The WHO advocates at least one Pap test between 30 and 35 years old be performed. Never having a Pap test remains one of the highest risk factors for the development of cervical cancer.[24]

***Table 2.3: Reduction in the cumulative incidence of invasive cervical cancer with different frequencies of screening.*[25]**

Frequency of screening (years)	Reduction in cumulative incidence (%)	Number of Tests
1	93	30
2	93	15
3	91	10
5	84	6
10	64	3

These results (Table 2.3), based on a report by the World Health Organization demonstrate that screening every year or every two years has an insignificant effect on the percentage reduction in cervical cancer. While screening every three years is probably more effective, screening every five years offers substantial benefits. These estimates assume total coverage of the population.[25]

***Table 2.4: Reduction in the cumulative incidence of invasive cervical cancer, by different proportions of the population screened, and different frequencies of screening.*[25]**

Frequency of screening (years)	Proportion screened (%)	Reduction in cumulative incidence (%)	Number of Tests
1	20	19	6
2	30	28	4.5
3	40	37	4
5	50	42	3
10	80	51	2.4

Table 2.4 data indicates that it is probably more cost-effective to screen a greater percentage of the population infrequently, especially high-risk populations, than to recruit a low proportion and screen them often.[25]

The cervical cancer screening program in South Africa is reported to be less than optimal. Denny et al. comment that the cervical cancer screening policy in South Africa has been implemented in a fragmented and uncoordinated manner and has not yet had a significant impact on cervical cancer incidence. Accurate data on

cervical cancer incidence and the impact of sporadic or current screening activity in South Africa is lacking.[26] A study in South Africa by Moodley et al.; on challenges in implementing a cervical screening program, also showed that the coverage of cervical cancer screening is not optimal.[27]

***Table 2.5: Reduction in the cumulative incidence of invasive cervical cancer for different ages at initiation of screening.*[25]**

Age screening initiated (years)	Frequency of screening (years)	Percentage reduction in cumulative incidence	Number of Tests
20	5	84	9
25	5	84	8
35	5	77	6
20	2	52	10

Moodley[25] reported that it appears that it is more cost-effective to screen older women than younger women, because a lower number of older women would need to be screened to detect one cervical cancer case. However, among HIV-positive women, the age incidence of invasive cervical cancer shows that women are presenting with invasive cancers at younger ages.[25]

Since cervical cancer has been classified as an AIDs defining illness, the frequency of screening for cervical cancer in HIV positive women, who are also HPV positive, should be increased for early detection and treatment of suspicious lesions.[24] The National Institute of Health (NIH) recommends that HIV positive women should have a first Pap test at aged 18 and older or when first sexually active, repeat the Pap test 6 months later and thereafter annually.[28] In South Africa, in 2013, the United Nations AIDs (UNAIDs) estimated the number of people living with HIV to be 6.3 million.

2.6. Treatment of precancerous cervical lesions

A WHO guideline outlines ‘screen-and-treat’ approaches in which the treatment decision is based on a screening test and treatment is provided soon or, ideally,

immediately after a positive screening test. Available screening tests include a HPV test, visual inspection with acetic acid (VIA), and cytology (Pap test). Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), and cold knife conization (CKC).[29] Flowcharts for screen (with cytology) and-treat strategies (negative or unknown HIV status) are provided in the guideline for program managers.[29]

2.7. Treatment of cervical cancer

Treatment of early-stage cervical cancer may include:

- Cervical Conisation which involves removing a cone-shaped piece of tissue from the cervix and cervical canal. The overall size of the tissue removed varies depending on the severity of the cancer.
- Loop Electrosurgical Excision Procedure (LEEP) which is made of a thin, low-voltage electrified wire loop to cut out abnormal tissue.
- Cryosurgery is used for cervical dysplasia or abnormal cells on the cervix. If left untreated, these abnormal cells may develop into cervical cancer. Cryosurgery kills pre-cancerous and cancerous cells by freezing them.
- Total hysterectomy.
- Internal Radiation Therapy (Brachytherapy).[30]

Treatment for more advanced cervical cancer may include:

- Radical hysterectomy, where the uterus and much of the surrounding tissue, including lymph nodes and the upper part of the vagina is surgically removed.
- Pelvic exenteration, where all of the organs of the pelvis, including the bladder and rectum, are surgically removed.
- Radiation Therapy may be used to treat cancer that has spread beyond the pelvis, or cancer that has returned:
    - Internal radiation therapy, where a device filled with radioactive material is placed inside the woman's vagina next to the cervical cancer. The device is removed before patient is discharged from hospital.

- External radiation therapy (also called brachytherapy) where a high-powered energy beam of radiation is focused onto the body where the cancer is located.[30]

2.8. Prophylactic HPV vaccines

HPV vaccines (Cervarix® and Gardasil®) have been commercially available in South Africa since 2008. The characteristics of both vaccines are presented in Table 2.6.

Table 2.6: Characteristics of HPV vaccines and clinical trial populations' details. [31]

Manufacturer and trade name	**Quadrivalent vaccine Merck (Gardasil®)**	**Bivalent vaccine GlaxoSmithKline (Cervarix®)**
Virus-like particles [VLPs] of genotypes	6, 11, 16, 18	16, 18
Substrate	Yeast [S. cerevisiae]	Baculovirus expression system
Adjuvant	Proprietary aluminium hydroxyphosphate sulfate (225µg) (Merck aluminium adjuvant)	Proprietary aluminium hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)
Schedule used in trials: 3 intramuscular doses of 0.5 ml with intervals of:	Two months between doses 1 and 2; six months between doses 1 and 3	One month between doses 1 and 2; six months between doses 1 and 3
Countries/regions included in phase II trials	Brazil (34%); Europe (21%); USA (45%)	Brazil and North America (over 50% of women were from Brazil)
Countries/regions included in phase III trials	N. America (25%); Latin America (27%); Europe (44%): Asia-Pacific (4%)	N. America (12%); Latin America (34%); Europe (30%); Asia-Pacific (25%)
Adolescent safety/immunogenicity bridging	Females and males 9 to15 years	Females 10 to14 years trials Males 10 to18 years
Other trials in progress or due to start	Efficacy, immunogenicity bridging and safety in women 25 to45 years; studies of administration at the same time as other vaccines; safety and immunogenicity in HIV-infected persons and other immunocompromised groups; Efficacy study in males	Efficacy, immunogenicity bridging and safety studies in women > 26 years; studies of administration at the same time as other vaccines; safety and immunogenicity in African populations, including HIV-infected women

Cervarix® (a bivalent vaccine) is composed of HPV immunogens of genotypes 16 and 18) and Gardasil® (a quadrivalent vaccine) comprises of four subtypes of HPV immunogens of genotypes 16, 18 and 6 and 11, are the only prophylactic HPV vaccines currently registered in South Africa. HPV genotypes 6 and 11 cause genital warts and HPV genotypes 16 and 18, cause cervical malignancy.

2.9. Immune Responses

Prophylactic HPV Virus Like Particle (VLP) vaccines are highly effective in producing an antibody response. The available evidence suggests that a neutralising antibody is the mechanism of protection against HPV infection. However despite the robust humoral response elicited by VLP vaccines, there is no immune correlate, no minimum level of antibody, or any other immune parameter, that predicts protection against infection or disease.[32] Only long term follow up of vaccinated cohorts in human populations can answer such questions unequivocally.[32] HPV vaccines are delivered intra-muscularly with high antigen dose, and there is rapid and direct access to lymph nodes and spleen where adaptive immune responses are initiated.[32]

2.10. Efficacy of HPV vaccines

The surrogate endpoint used in the Cervarix® (bivalent vaccine) registration clinical trials was the absence/presence of cervical intraepithelial neoplasia grade two or greater (CIN2+). The Total Vaccinated Group (TVC) consisted of women who received at least one vaccine dose and the TVC-naïve group consisted of women with no evidence of oncogenic HPV infection at baseline. Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92.9% (96·1% CI, 79.9% to 98.3%) in the primary analysis.[33] The vaccine efficacy against CIN3+ (immediate precursor to invasive cervical cancer) in the four year end of study analysis was 100% in women in the TVC-naïve group and 45.7% in the TVC group. The vaccine efficacy against adenocarcinoma in situ (AIS) was 100% in the TVC-naïve group and 76.9% in the TVC group.[34]

Transudation of anti-HPV IgG antibodies from the serum to the cervical mucosa is thought to be the primary mechanism of protection against persistent oncogenic HPV infection, the necessary cause of cervical cancer. In clinical trials Cervarix® adjuvanted with Adjuvant System 04 (AS04) compared to the same antigens adjuvanted with aluminium hydroxide alone showed:

- At least two fold higher antibody titres at all time-points analysed up to four years after the first dose.

- Higher functional antibody titres analysed up to four years after the first dose.
- Approximately two fold higher B cell memory frequency, at all time-points analysed up to two years after the first dose.[35]

The primary composite end point used in the Gardasil® (quadrivalent vaccine) registration trial, was CIN2 or CIN3, AIS, or invasive carcinoma of the cervix due to HPV16 or HPV18 or both. Vaccine efficacy for the prevention of the primary composite end point was 98% (95.89% confidence interval [CI], 86 to 100) in the per-protocol susceptible population and 44% (95% CI, 26 to 58) in an intention-to-treat population of all women who had undergone randomization (those with or without previous infection).[36]

A review article of clinical trials of HPV prophylactic vaccines indicated that both vaccines exhibited excellent safety and immunogenicity profiles, high and similar efficacy against vaccine-targeted types in women naïve to the corresponding vaccine type at the time of vaccination.[37] The quadrivalent vaccine may have an advantage, due to protection against anogenital warts, over the bivalent vaccine in reducing healthcare costs and QALYs lost. The bivalent vaccine may have an advantage in preventing death due to cancer. However, considerable uncertainty remains about the differential benefit of the two vaccines.[38]

***Table 2.7: Key findings from clinical trials of HPV Vaccines*.[37]**

Study group	Outcome	Gardasil®	Cervarix®
Young women	HPV Infection efficacy	Proven	Proven
	CIN2+ efficacy	Proven	Proven
	CIN3 efficacy	Proven	Proven
	VIN/VaIN 2/3 efficacy	Proven	Proven
	Genital warts efficacy	Proven	Not a target
	Anal infection efficacy	Not proven	Proven
	Partial cross-protection infection	Proven	Proven
	Partial cross-protection CIN2+	Proven	Proven
	Therapeutic efficacy	None	None
	Safety	No concerns	No concerns
Mid-adult women	Infection efficacy	Proven	Proven
	CIN2+ efficacy	Proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns
Young men	Infection efficacy	Proven	Not proven
	Genital wart efficacy	Proven	Not a target
	Anal infection	Proven	Not proven
	AIN2+ efficacy	Proven	Not proven
	Safety	No concerns	No concerns
Children	Infection efficacy	Not proven	Not proven
	Disease efficacy	Not proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns

A review of clinical trials of HPV vaccines found that there is evidence that both HPV vaccines are immunogenic and safe to use in children (see Table 2.7).

2.11. Vaccine schedule: Fewer than three doses

Immunological bridging studies with data from young women aged 15 to 25 years showed that three doses of the bivalent vaccine in girls aged 10 to 14 years induced geometric mean antibody titers (GMTs) two fold higher than in women aged 15-25 years. The immunogenicity, logistical issues on completion of a three-dose vaccine

schedule, potential cost savings prompted evaluation of a two-dose HPV vaccine schedule.[39]

A randomised study by Romanowski et al. found that HPV-16/18 vaccine on a two-dose schedule (month 0 and month 6) is immunogenic and generally well tolerated in girls aged nine to 14 years.[39]

A Cost Rica Vaccine Trial (CVT) evaluated the vaccine efficacy of fewer than three doses of the HPV16/18 vaccine Cervarix. Vaccine efficacy was 80.9% for three doses of the HPV vaccine (95% CI = 71.1% to 87.7%; 25 and 133 events in the HPV and control arms, respectively), 84.1% for two doses (95% CI = 50.2% to 96.3%; 3 and 17 events), and 100% for one dose (95% CI = 66.5% to 100%; 0 and 10 events). The non-randomized analysis four years after vaccination, of women who appeared to be uninfected, suggests that two doses of the HPV16/18 vaccine, and maybe even one dose, are as protective as three-doses.[40]

A follow up to CVT explored the likelihood that efficacy will persist longer term, measured the HPV16 and HPV18 specific antibodies by VLP-ELISA using serum from enrolment, vaccination, and annual visits through four years in four vaccinated groups; one-dose (n=78), two-doses separated by one month (n=140), two doses separated by six months (n=52), and three scheduled doses (n=120, randomly selected). Compared with the natural infection group, HPV16/18 geometric mean titres (GMTs) were, respectively, at least 24 and 14 times higher among the two-dose and nine and five times higher among one-dose vaccines. Antibody levels following one-dose remained stable from month six through month 48. Results raise the possibility that even a single dose of HPV VLPs will induce long-term protection.[41]

A study by Dobson et al. measuring mean antibody levels to HPV-16 and HPV-18 showed that girls aged nine to 13 years old, receiving two-doses (at 0 and 6

months) had non inferior antibody levels to girls receiving three-doses (at 0, 2, and 6 months) and durability of non-inferiority to 36 months.[42]

Both Gardasil® and Cervarix® vaccines have received favourable opinion in some countries for a two-dose schedule. Jit et al.[43] reported that the two-dose HPV schedules have been adopted in Quebec, Switzerland, the Netherlands and Mexico. In South Africa, the two-dose schedule has been accepted (personally correspondence with National Department of Health on 22 October 2014).

WHO's Strategic Advisory Group of Experts (SAGE) on Immunization have received recommendations based on the evidence of the effect of a two-dose HPV vaccine schedule compared with the licensed three-dose schedule on immunological and clinical outcomes in preadolescent and adolescent girls.[44] Recommendations for SAGE's consideration include, programmatic advantages to reducing the number of doses (e.g. reduced delivery costs), and flexible intervals between doses (e.g. annual doses easier for school-based delivery) might also lead to increase in vaccination coverage.[44]

2.12. Safety of HPV vaccines

Both the bivalent and quadrivalent vaccines exhibited excellent safety profiles in the clinical trials. The most common adverse events in both vaccines were mild to moderate injection-site symptoms, headache and fatigue. Both vaccines also had similar rates of serious adverse events (SAEs) in the vaccine and control groups. The numbers of SAEs judged to be possibly related to vaccine injection was low for both vaccines and similar to the numbers in the control groups.[37]

Block et al. summarized up to three years of post-licence surveillance of the HPV-6/11/16/18 vaccine using updated clinical trial data (median follow-up time of 3.6 years) HPV-6/11/16/18 vaccination was associated with more injection-site pain than placebo but had similar incidences of systemic and serious AEs and new medical conditions, potentially consistent with autoimmune phenomena. They concluded that

the benefits of vaccination to prevent the majority of genital tract precancers and cancers continue to far outweigh its risks.[45]

A pooled analysis of the safety of HPV-16/18 vaccine was performed in a cohort of almost 30,000 girls and women aged 10 years and older, 16,142 who received at least one-dose of the HPV-16/18 vaccine and 13,811 who received one of three control vaccines. Analysis of this large database shows the HPV-16/18 vaccine to have a favourable safety profile in women of all ages.[46]

More than 175 million doses of HPV vaccine have been distributed worldwide through national immunisation programmes, The Global Advisory Committee on Vaccine Safety (GACVS), continued to be reassured by the safety profile. Serious adverse events reported as potential signals have been investigated and were not confirmed, including Guillain-Barre syndrome, seizures, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries has not detected any adverse outcomes above expected rates.[47]

The GACVS noted the importance of continued surveillance and epidemiological investigation of any adverse events which may occur following vaccination and cautious that allegations of harm due to vaccination based on incomplete information may lead to unnecessary harm when effective vaccines are not used.[47]

2.13. Safety and Immunogenicity of HPV vaccine in HIV-positive women

A study in South Africa evaluated the safety and immunogenicity of the HPV-16/18 vaccine in asymptomatic HIV-positive women aged 18 to 25 years. Anti-HPV-16/18 antibody and CD4+T-cell responses, CD4+T-cell count, HIV viral load, HIV clinical stage and safety were evaluated for 12 months. The safety and reactogenicity profile of the HPV-16/18 vaccine was comparable in HIV-positive and HIV-negative women. Irrespective of baseline HPV status, all HIV-positive and HIV-negative women who

received the HPV-16/18 vaccine were seropositive for both HPV-16 and HPV-18 after the second vaccine dose (month two) and remained seropositive for both antigens at month 12. Anti-HPV-16/18 antibody titres at month 12 remained substantially above levels associated with natural infection. The HPV-16/18 vaccine induced sustained anti-HPV-16/18 CD4+T-cell responses in both HIV-positive and HIV-negative women. No impact of baseline CD4+T-cell count or HIV viral load was observed on the magnitude of the immune response in HIV-positive women. In HIV-positive women, CD4+T-cell count, HIV viral load and HIV clinical stage were unaffected by HPV-16/18 vaccine administration. The study concluded that the HPV-16/18 vaccine appears immunogenic and well-tolerated in women with HIV infection.[48]

The effectiveness of HPV vaccination might vary with the timing of vaccination relative to time of HIV acquisition, or other sources of immune suppression. Among children infected with HIV at the time of birth or as neonates, vaccination prior to sexual debut may prevent initial HPV-16 or 18 infection and CIN due to these types. Adolescents, who acquire HIV at, or subsequent to, sexual debut, may derive less benefit because of the higher likelihood of prior exposure to the HPV types in the vaccine.[49]

2.14. Cost-effectiveness of HPV vaccination

There are numerous health economic evaluations published on the cost-effectiveness evaluation of the HPV vaccine. An ideal clinical trial endpoint measure for prevention of cervical cancer would be incidence of cervical cancer cases or mortality due to cervical cancer. As this is not feasible with the outcomes from the current HPV vaccine efficacy trials, since cancer typically develops twenty years after HPV infection, mathematical models are used to project the impact of vaccination programs on cervical cancer rates (based on vaccine titre levels) and to determine the long-term benefits of vaccination. Some models have incorporated economic parameters to determine the most cost-effective strategy.[50]

Static Markov (also referred to cohort model) and transmission dynamic models are two types of mathematical models used to evaluate the long-term effectiveness of a vaccination program.[50] In a cohort model each individual can reside in only one health state at any point in time and transitions occur from one health state to the other at defined equal length intervals according to transition probabilities. A dynamic model tracks a changing population over time, individuals constantly enter the model as they are born and exit it as they die thus the model does not have a natural stopping point.[50]

2.15. Systematic Review of HPV Vaccination Cost Effectiveness Models

Marra et al. (2009) performed a systematic review of effectiveness and cost effectiveness of HPV vaccine studies from 1966 to 2008 and included English language articles which compared HPV vaccination with Pap test screening program.[50] Of the 22 economic models identified 10 were Static Markov models, 11 were Dynamic models and one was a Hybrid model. 13 models conducted a cost effectiveness analysis (settings were Australia, Brazil, Canada, France, Mexico United Kingdom, United States of America) and all showed that a female only vaccination program is cost effective compared with Pap test screening program.[50]

A systematic review by Seto et al. (2012), found seventeen studies from 2007 (when HPV vaccines were in use), that reported on cervical disease outcomes and twelve studies that included non-cervical disease outcomes such as genital warts, JORRP, vulvar, vaginal, penile, anal, oral and oropharyngeal cancers.[51] The model settings were generally single country based settings and included United States of America (USA), Canada, United Kingdom (UK), Netherlands, Taiwan, India, Ireland, Vietnam, Belgium, Argentina, Brazil, Chile, Mexico, Peru, South Africa, Spain, Finland, Austria, Israel, Italy, Hungary and Denmark.[51] Different model structures, input parameters and baseline assumptions were used and the consistent finding was that routine vaccination of females is cost effective compared with cervical cancer screening alone.[51]

Fesenfeld et al. (2013) performed a review of HPV cost effectiveness studies in low and middle income settings and found 25 HPV vaccine economic analyses.[7] The country settings were generally single country settings and included Kenya, Mozambique, Tanzania, Uganda, Rural China, Argentina, Brazil, Chile, Mexico, Peru, Brazil, India, Malaysia, 72 GAVI eligible countries, Asia Pacific Region, 33 countries in Latin America and the Caribbean, Vietnam, Thailand, South Africa, Poland and Lithuania. Study assumptions and results varied widely and despite the heterogeneity, most studies concluded that HPV vaccination is likely to be cost effective and possibly even cost saving, particularly in settings without organised cervical cancer screening programs.[7]

There was one study identified comparing HPV vaccination with cervical cancer screening, by Praditsitthikorn et al.; that found controlling cervical cancer by increasing the numbers of women accepting the VIA and Pap test screening as routine and by improving the performance of the existing screening programs is the most cost-effective policy option in Thailand.[52] The first (and only) HPV vaccine cost effectiveness analysis undertaken in South Africa, by Sinanovic et al. (2009), exploring the cost-effectiveness of adding the HPV vaccine to the existing cervical cancer prevention program, showed that adding the HPV vaccine to the current cervical cancer screening strategy in South Africa is cost-effective at a vaccine price of $120 US dollars per dose.

2.16. HPV vaccination programs in Middle and Low Income Countries

HPV vaccine delivery is feasible to implement in schools; however, eligibility for vaccination based on grade/class in school, rather than age, was found to be easier to implement and monitor in Uganda to ensure administration of all three doses.[53]

School based vaccine delivery programs, with girls aged between 9 and 14 years achieved coverage of 82.6% in Peru, 88.9% in Uganda in 2009, 83% in year one in Vietnam and 96.1% in year two in Vietnam. In India a combination of school and health center based delivery achieved coverage between 77.2% and 87.8%,

depending on the geographical area. The highest coverage of 98.6% was achieved in Vietnam health center based program and lowest of 52.6% in Uganda Child Days Plus program where girls were vaccinated on the basis of age.[54]

2.17. HPV vaccination in South Africa

Until 2014, HPV vaccination has been mostly occurring in the private health sector. An HPV vaccination demonstration project in the public sector in the province of Kwa-Zulu Natal, South Africa showed high uptake of vaccination with 99.7%, 97.9% and 97.8% for the first, second and third doses respectively. There were no adverse events attributed to the HPV vaccine. The project demonstrated successful HPV vaccination among nine to 12 year old learners, using the school health teams.[55]

In March 2014, the National Department of Health in South Africa launched an HPV vaccine program for grade four girls in all government schools. Two-doses of Cervarix® vaccine would be given, the first vaccination dose schedule commenced in March and April and the second dose schedule is planned for September and October 2014.[56] A newspaper article indicated that for the first HPV vaccine dose of the National HPV Vaccination Program, the provincial health departments have reported that some parents have not returned consent forms and say anti-vaccine literature posted on social media appears to be putting them off. KZN reported that of 79 657 Grade four girls targeted, 68 593 (86%) had been immunized with the first dose of HPV vaccine. The remaining eligible girls were not immunised, either because they were absent from school on the day or parental consent had not been granted. The uptake is lower in the Western Cape, where 56% of Grade four girls immunized with the first dose of HPV vaccine.[56]

Conclusion

There has been one economic evaluation of HPV vaccination done for South Africa in 2007 which requires updating due to changes in the input costs over the past six years. This study was undertaken to determine the updated cost effectiveness

analysis of introducing a school based HPV vaccination program for nine year old girls in the public sector.

3. Aims and Objectives

3.1. Aims

The aim of this research was to perform an economic evaluation of a school based HPV vaccination program in the public sector in South Africa.

3.2. Objectives

The objectives of the study were:

I. To estimate the burden of cervical cancer and determine the costs of treating each cervical cancer case in South Africa that is caused by HPV strains 16 and 18.

II. To incorporate the latest costs and prevalence data into a cost-effectiveness model (based on the original HPV model of Sinanovic et al.[58] to:
   a. Determine the number of cervical cancers cases that would be averted with an HPV vaccination program in South Africa.
   b. Determine the incremental cost effectiveness of an HPV vaccine program followed by screening and treatment versus screening and treatment of cervical cancer patients in South Africa.

III. Determine the annual cost of a school based HPV vaccination program in South Africa.

4. Methodology

4.1. Introduction

Pharmacological interventions are intended to improve the morbidity/mortality of a disease through an active pharmaceutical ingredient, which alters a biochemical process, resulting in the relief of signs and symptoms that are usually straightforward to measure. However, vaccines are intended to induce a biological response thereby affording protection to an individual against a particular organism. Trials investigating vaccine efficacy often use surrogate rather than final outcome measures due to the long time lag for the final outcome and ethical considerations. HPV vaccination is intended to prevent the development of HPV induced cervical cancer which occurs long after vaccination therefore the best tool to assess effectiveness and costs is a mathematical model.

4.2. Justification for the methodology of Mathematical models for HPV Vaccination

Due to the absence of data on long-term effectiveness of HPV vaccination, a number of mathematical models have been developed to provide insight to policy makers of the projected long-term epidemiologic and economic consequences of vaccination to enable them to evaluate alternate vaccination policies. The three types of HPV models reported in the literature are cohort, population dynamic and hybrid models.[57] The cohort and hybrid models have evaluated the cost effectiveness of vaccination strategies for cervical cancer. The dynamic model accounts for both direct and indirect (herd immunity) effects of HPV vaccination.[57]

4.3. Research Procedures for the Mathematical Model

Cost, utilities and probability data was obtained from published literature and where no published literature was available personnel correspondence was used to obtain values and inputs to populate the Markov model parameters for probabilities (effects), costs and utilities. South Africa data was used were possible (e.g. Vaccine cost, cost of Pap test, cost of school vaccination program).

Subjects for this study were a hypothetical cohort of nine year old school girls, prior to sexual debut receiving both HPV vaccine followed by screening and treatment or receiving screening and treatment alone. A cost effectiveness analysis was performed and ICER reported. The base case model assumptions are detailed in section 4.5.

A one way sensitivity analysis was performed on a range of parameters to assess which model parameters were most sensitivity to change to highlight areas of uncertainty (see Table 5.4). Individual model parameter values were varied and ICERs obtained where compared to the base case model ICER and results presented as a reduction or increase to the base case ICER.

The average probability (per age group) of a health state, generated by the Markov model for each arm (No HPV vaccine and HPV vaccine), was used to calculate the number of females in 2013 in each health state, and the number of cases that would be averted due to HPV vaccination.

4.4. Mathematical model used in this study

A static cohort model, based on a previous model for South Africa by Sinanovic et al.[58] was developed to simulate the natural history of HPV 16 and 18 infections, cervical cancer screening and management of precancerous and cancerous lesions. A Markov static, deterministic, aggregate closed model was chosen as the aim of this study was to estimate the cost effectiveness of routine vaccination of girls aged nine years old with no inclusion of catch up vaccination or male vaccination.[59] The static model is relatively straightforward to develop and is transparent.

The main features of the model include; the extent of infection changes as a function of age, changes are pre-specified, the population is closed (the model does not allow new individuals to enter the model over time), the population's behavior is simulated using values which are population averages (aggregate) and the model is

deterministic as all events occur in a pre-specified way based on the parameter values and initial conditions of the model.[60]

The disadvantages of a static model is that it cannot capture indirect benefits due to herd immunity, random nature of events, and the number of health states required to capture heterogeneity can make the model cumbersome and inefficient.[60]

A model was based on a public sector health care perspective, with costs of providing a school based vaccination program, screening, diagnosis and treatment of cervical cancer. The costs and outcomes were both discounted at an annual rate of 5% as proposed by the South African Department of Health Pharmacoeconomic Guidelines.[61]

The natural history of the health states and possible transitions between states is shown in Table 4.1.

Table 4.1: Health states and possible transitions between health states.[58]

Base Health State	Possible health state transitions
Well	Well, HPV, dead (from other causes)
HPV	Well, HPV, LSIL, HSIL, dead
LSIL	Well, HPV, LSIL, HSIL, dead
HSIL	Well, HPV, LSIL, HSIL, unknown cancer stage I, dead
Unknown cancer stage I	Unknown cancer stage I, detected cancer stage I, unknown cancer stage II, dead
Unknown cancer stage II	Unknown cancer stage II, detected cancer stage II, unknown cancer stage III, dead
Unknown cancer stage III	Unknown cancer stage III, detected cancer stage III, unknown cancer stage IV, dead
Unknown cancer stage IV	Unknown cancer stage IV, detected cancer stage IV, dead
Detected cancer stage I (year 1 to 5 where each year is a transition state)	Detected cancer stage I (year 1 to 5), cancer survivor, dead
Detected cancer stage II (year 1 to 5 where each year is a transition state)	Detected cancer stage II (year 1 to 5), cancer survivor, dead
Detected cancer stage III (year 1 to 5 where each year is a transition state)	Detected cancer stage III (year 1 to 5), cancer survivor, dead
Detected cancer stage IV (year 1 to 5 where each year is a transition state)	Detected cancer stage IV (year 1 to 5), cancer survivor, dead
Cancer survivor (one state per stage of cancer)	Cancer survivor, dead
Dead	Absorbing state (i.e. patients remain in this state for the reminder of the simulation)

The decision tree comprises of two arms, No HPV Vaccine Arm and a HPV Vaccine arm. Each arm consisted of the same base case health states and transition health states. The difference between the two arms of the model are different transition probabilities of acquiring HPV infection (due to HPV vaccination or no HPV vaccination) and the HPV arm has additional cost for HPV vaccine and administration of the vaccine.

The model time horizon was a women's lifetime and divided in to one year intervals each representing a Markov cycle. For each cycle a women has a time dependent risk of transitioning health states if she acquires and HPV infection i.e. she could either have persistent HPV, progress to a low-grade squamous intraepithelial lesion (LSIL) or a high-grade squamous intraepithelial lesion (HSIL) or HPV infection could resolve.

The model starts with nine year old girls with no exposure to HPV infection and each year they could transition to a different health state based on age-dependent probabilities of acquiring HPV infection.

The model is populated with data (see Tables 4.2, 4.3, 4.4, 4.7 and 4.8) on probabilities, utilities and costs to diagnose and treat the various health states as per Table 4.1. South Africa all-cause mortality rates were obtained from the Actuarial Society of South Africa ASSA) 2008 AIDS and Demographic model.[62] Local experts were consulted on assumptions regarding the natural history of HPV infection, disease and treatment and resulting model predictions.

The Figure 4.1 below shows the different health states and transitions to subsequent health states for the "No HPV Vaccine Arm" of the decision tree. The HPV vaccine arm in decision tree has the same structure as No HPV Vaccine Arm.

Figure 4.1: "No HPV Vaccine" Arm of the Decision Tree

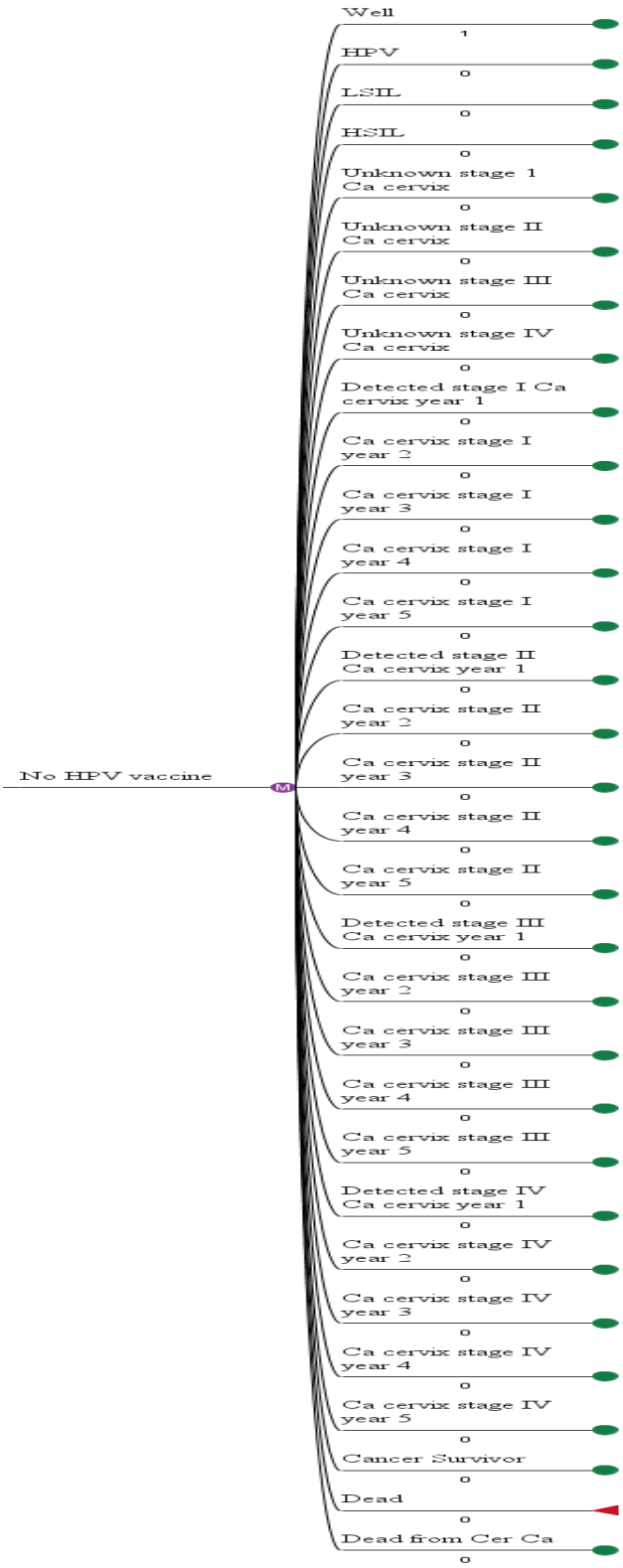
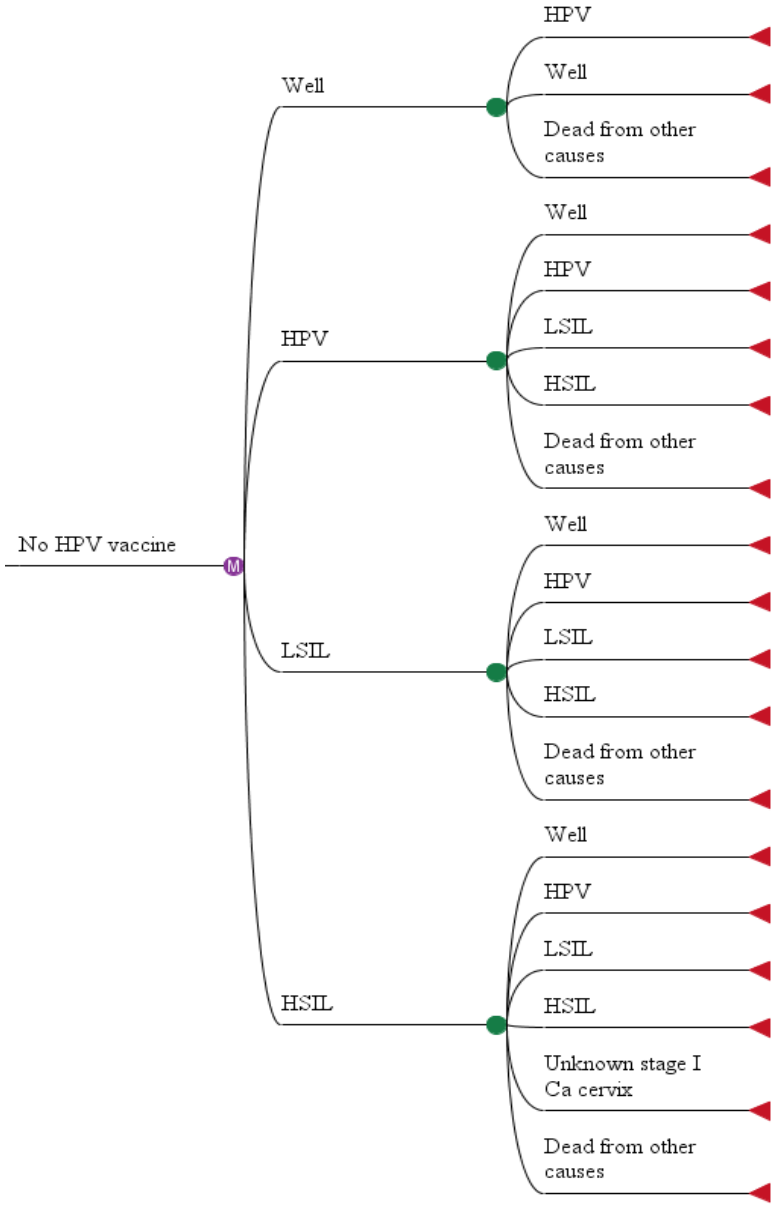


Figure 4.2 below is a more detailed outline of the base case health states for Well (i.e. No HPV infection), HPV (HPV infection present), LSIL, HSIL and their corresponding transition health states in the model. A women can either remain in a particular base case health stage, progress or regress between Well, HPV, LSIL and HSIL health states.

Figure 4.2: Base Case Health States: Well, HPV, LSIL and HSIL and transition health states



Unknown cervical cancer health states were included in the model as there are a number of cervical cancer cases in South Africa that go undetected due to a varitety of reasons, for example, lack of symptoms, lack of awareness and limited access to healthcare.[63] Figure 4.3 below outlines the four stages of unknown cervical cancer, base health states and their corresponding transition health states in the model.

Figure 4.3: Unknown cancer stage 1 to 4 and transition health states

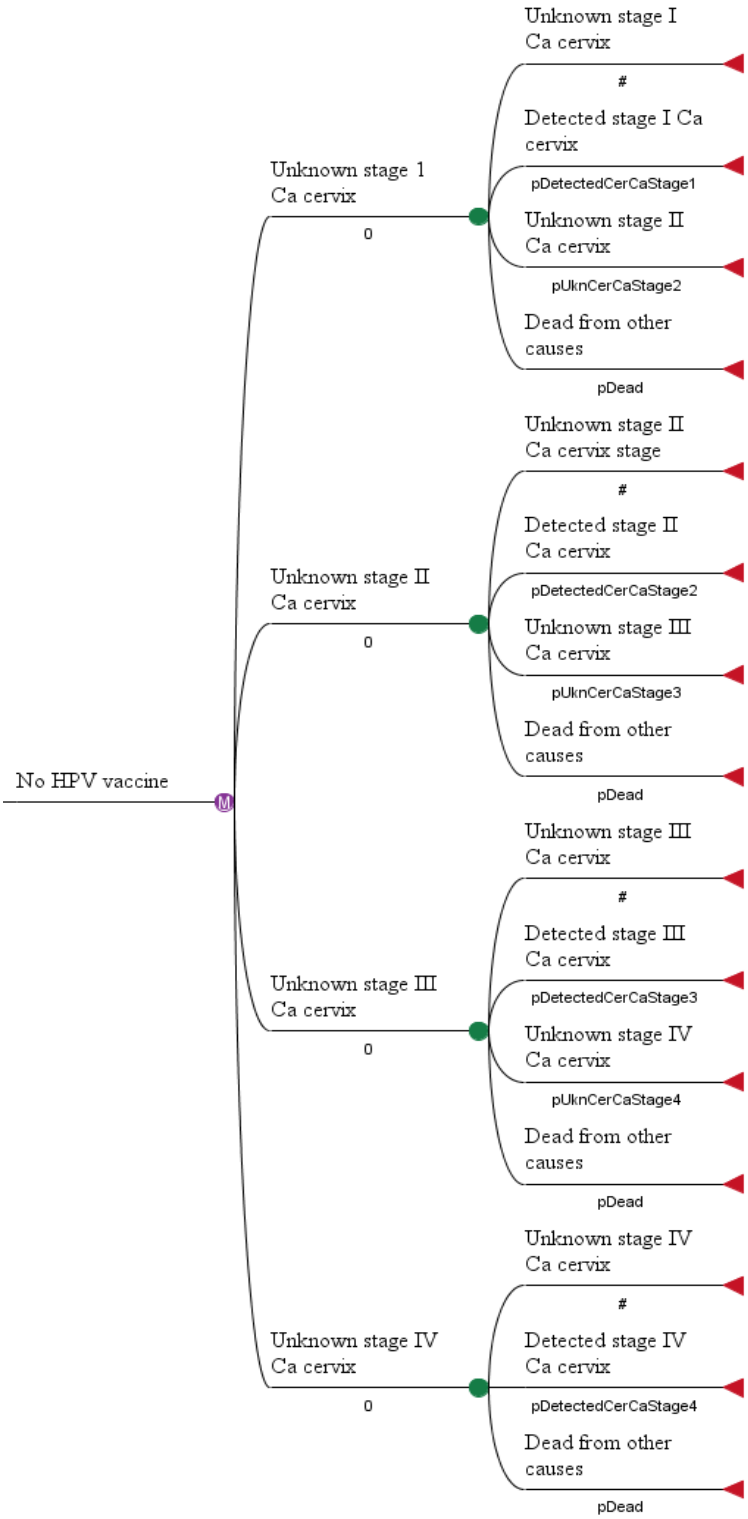
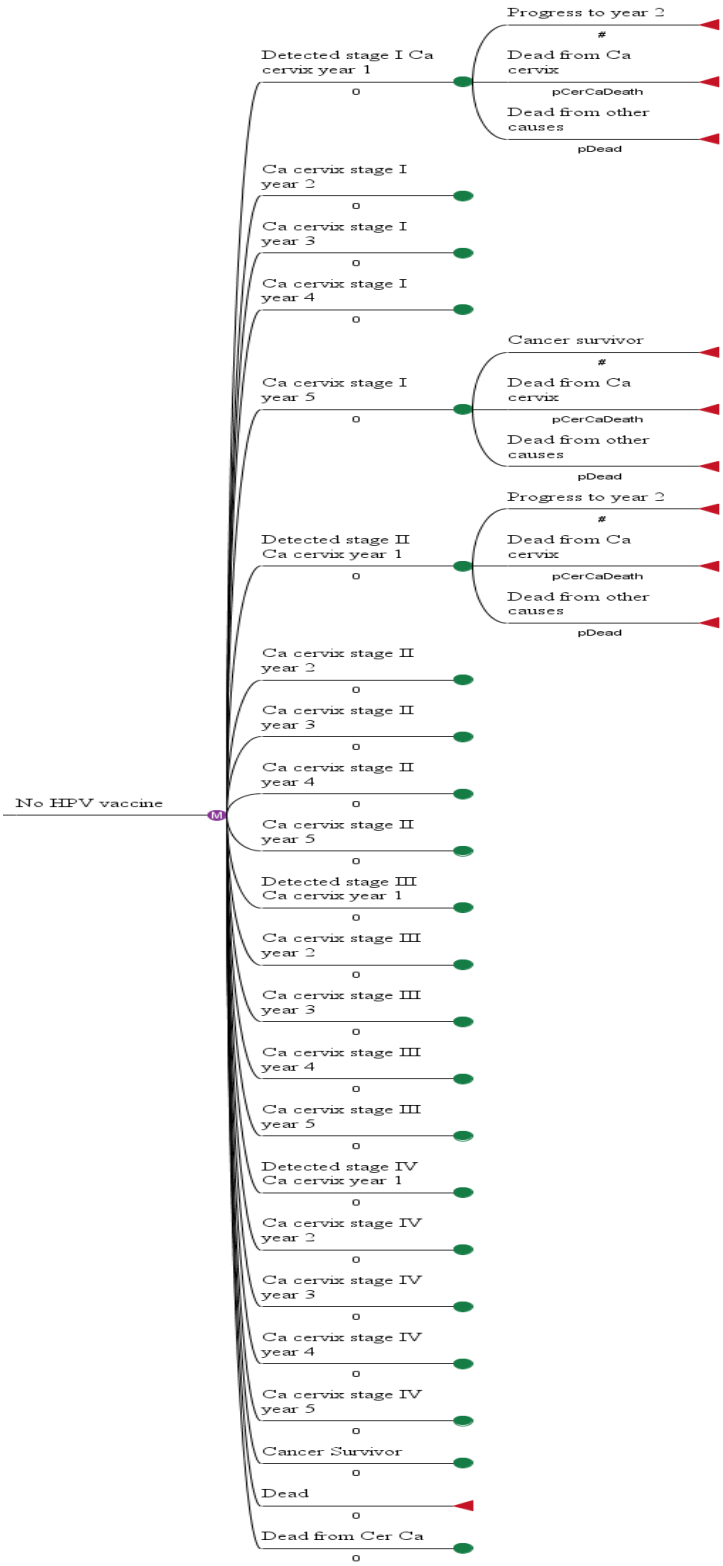


Figure 4.4 outlines the base case health states of the four stages of detected cervical cancer and their corresponding transition health states in the model. Each year a women can transition into another year in the same cervical cancer stage (up to a maximum of five years in each stage), die due to cervical cancer or die due to other causes. A woman is counted in the cancer survivor health state if alive after five years in the applicable cervical cancer stage.

Figure 4.4: Base Case Health States: Detected Cervical Cancer, Cancer Survivor, Death due to Cervical Cancer, All-cause Mortality and Transition Health States



As HPV natural disease progression and regression between the various health states is complex, the following assumptions were made:

- Persistent HPV infection resulted in cervical cancer.
- All enter the model at age nine years and will receive two-doses of HPV vaccine in the vaccine arm followed by standard screening and treatment for cervical cancer and all those who enter the Non HPV vaccine arm receive the standard screening and treatment for cervical cancer.
- Vaccine protective effect is lifelong.
- Women who survive five years after cancer diagnosis and treatment become survivors and can die only from other causes.
- Women are exposed to HPV 16 and 18 infections only i.e. incidence, progression and regression estimates are averages for all main oncogenic viral types.
- If a transition to a health state is detected, they could either progress to the next stage, regress to previous health state (except for cervical cancer stages and death) or remain in the same health state.
- Probabilities are those for the general population, as literature did not state HIV status of female study population.
- The side effects of HPV Vaccine do not incur any costs.
- The sensitivity and specificity of Pap test is equal in both arms of the model.

4.5. Base Case Model parameters

4.5.1. Health State Transition Probabilities

The model input parameters for precancerous health states progression and regression probabilities are shown in Table 4.2.

Table 4.2: Markov model transition probabilities and incidence rates of precancerous health states after HPV infection

Parameter	**Base case estimate**	**Source**	**Base case estimate probability**	
Epidemiological parameters [a]				
Life Expectancy	61 years	64	N/A	
Age-specific incidence of HPV infection[b]				
9–14	0.05/12 months	Assumption	0.0488	
15–16	0.1/12 months	65	0.0952	
17	0.12/12 months	65	0.1131	
18	0.15/12 months	65	0.1393	
19	0.17/12 months	65	0.1563	
20	0.15/12 months	65	0.1393	
21	0.12/12 months	65	0.1131	
22–23	0.10/12 months	65	0.0952	
24–29	0.05/12 months	65	0.0488	
30–49	0.01/12 months	65	0.0100	
≥50	0.005/12 months	65	0.0050	
Age-specific regression rate(HPV to Well)[b,c]				
9–14	0.95/18 months	Assumption	0.4692	
15–24	0.7/18 months	65	0.3729	
25–29	0.5/18 months	65	0.2835	
≥30	0.15/18 months	65	0.0952	
Progression rate HPV to LSIL[c]	0.2/36 months	65	0.0645	
Proportion of infections progressing directly to HSIL	0.1	65	0.0064	
Regression rate LSIL to HPV or Well [b,c]			Well	HPV
9–14	0.9/72 months	Assumption	0.1254	0.0139
15–34	0.65/72 months	65	0.0924	0.0103

≥35	0.4/72 months	65	0.0580	0.0064
Proportion of LSIL reverting to Well[c]	0.9	65		
Progression rate LSIL to HSIL[b,c]				
9–14	0.05/72 months	Assumption		0.0083
15–34	0.1/72 months	65		0.0165
≥35	0.35/72 months			0.0567
Regression rate HSIL to LSIL or Well[c]	0.35/72 months	65	0.0567 LSIL: 0.0283	HPV: 0.0142 Well: 0.0142
Proportion of HSIL reverting to Well[c]	0.5	65		
Progression rate HSIL to stage I cancer	0.4/120 months	65	0.0392	

(a) Rates (the number of events per unit time), were converted into probabilities for the Markov model.

(b) Acquisition of HPV, LSIL and HSIL was based on age-specific incidence rates.

(c) It was assumed that women can progress and regress between various precancerous states.

The cervical cancer health state transitions probabilities and annual probability of survival after being diagnosed with cervical cancer are shown in Table 4.3. Rates were converted to probabilities.

Table 4.3: Markov model transition probabilities and estimated rates of progression of invasive cervical cancer

Parameter	**Base case estimate**	**Source**
Progression rates and probability of symptoms in unscreened patients		65
Stage I	0.9/4 years	
Progression rate (stage I to stage II)	0.15	
Annual probability of symptoms		
Stage II	0.9/3 years	
Progression rate (stage II to stage III)	0.225	
Annual probability of symptoms		
Stage III	0.9/2 years	
Progression rate (stage III to stage IV)	0.6	
Annual probability of symptoms		
Stage IV		
Annual probability of symptoms	0.9	
Annual probability of survival after diagnosis		65
Stage I		
Year 1	0.9688	
Year 2	0.9525	
Year 3	0.9544	
Year 4	0.9760	
Year 5	0.9761	
5-year survival	**0.8390**	
Stage II		
Year 1	0.9066	
Year 2	0.8760	
Year 3	0.9225	
Year 4	0.9332	
Year 5	0.9604	
5-year survival	**0.6566**	
Stage III		
Year 1	0.7064	

Year 2	0.7378	
Year 3	0.8610	
Year 4	0.9231	
Year 5	0.9142	
5-year survival	**0.3787**	
Stage IV		
Year 1	0.3986	
Year 2	0.4982	
Year 3	0.7638	
Year 4	0.8652	
Year 5	0.8592	
5-year survival	**0.1127**	

The model parameters for Pap test screening, treatment of precancerous lesions and cervical cancer; and bivalent vaccine are shown in Table 4.4.

Table 4.4: Screening, treatment of precancerous lesions and cervical cancer and HPV vaccine parameters

Parameter	Base case estimate	Source
Screening (pap test)		
Eligibility age for screening	At 30, 40 and 50 years	66
Screening coverage	100%	Assumption
Treatment		
HPV 16 and 18 infection	Asymptomatic and ~90% clear within a few years	10
Proportion of women with HSIL receiving loop electrosurgical excision (LEEP)	0.8	58
Proportion of women with HSIL receiving cold-knife conization	0.1	58
Proportion of women with HSIL receiving simple hysterectomy	0.1	58
Proportion of women with invasive cancer having surgery (hysterectomy)	0.25	58
Proportion of women with invasive cancer receiving chemo-radiation	0.75	58
Adherence to treatment for cervical pre-cancerous and cancerous lesions	100%	Assumption
HPV Bivalent Vaccine		
Age of vaccination	9 years	
Coverage of school based vaccination program	100%	Assumption
Efficacy against HPV16 and 18 (2 doses of vaccine)	0.9	67
Proportion of vaccinated girls receiving a booster dose	0%	No booster vaccine will be given in public sector (Correspondence with DOH)
Duration of vaccine efficacy	Lifetime	68
Vaccine safety	100% safe	Assumption based on key findings from clinical trials of HPV vaccines.[37]

4.5.2. Cost calculations and inputs

Cost estimates were based mainly on published literature from South Africa. All costs in foreign currency were converted to South African Rand (R) using the average currency conversion rate for the applicable year, and then inflated using the annual Consumer Price Index as published by Statistics South Africa to reach 2013 year costs.[69] Costs from the public sector service provider perspective were used. Patient costs were not included as this economic analysis focused on costs from a policy maker perspective.

The tender price per dose of HPV vaccine (Cervarix®) of R140, to the Department of Health, used in current public sector school vaccination program rollout, was obtained from Biovac Institute in South Africa (29 October 2013).

Costs for a school delivery vaccination program were estimated and included school health nurse (senior professional nurse) salary, transport, equipment, management and support; school health promoter salary and transport (see Table 4.5 below). These cost estimates were based on the information obtained (in April 2013 through personal communication) from the National Department of Health on School Health Costing Scenario.

Table 4.5: Estimation of vaccination program cost per vaccine dose administered

	Annual cost
School Nurse Salary	R350 000
School Nurse Management and Support Overhead (15%)	R52 500
School Nurse Transport Overhead (7.5%)	R26 250
School Nurse Equipment Overhead (2.5%)	R8 750
School Health Promoter Salary	R200 000
School Health Promoter Overhead (10%)	R20 000
Total Annual Salary and Overhead Cost for School Nurse and Health Promoter	**R657 500**
Number of school days	200 days /year
Hours worked per day by school nurse and health promoter	5 hours/day
Time required to explain, obtain consent, vaccinate and complete records	0.25 hour per dose
Number of HPV vaccinations given in one year	4 000
Vaccination program cost to administer two vaccine doses (excluding vaccine cost)	**R328.75 (R164.38*2)**

The following assumptions for the school vaccination program costs (see Table 4.6) were made:

- There are no additional costs for vaccine cold chain.
- Transport for delivering the vaccines to schools will be integrated into the existing Expanded Programme on Immunisation (EPI) delivery transport program and therefore will not incur any additional costs.
- Vaccine wastage is 10% and this includes the cost of waste management.
- A school nurse/health worker spends five hours a day at a school (the balance of the time assumed for transport) and works a total of 200 school days per annum.
- There are no donated HPV vaccines.
- There are no costs associated with managing HPV vaccine adverse events.

Table 4.6: Cost of school based administration of a two-dose bivalent HPV vaccination schedule

	Cost
2 doses Cervarix® (0 and 6 months)	R280.00
10% wastage	R28.00
School vaccination program cost to administer 2 doses	R328.75
Total cost per vaccinated girl (vaccine plus program cost)	**R636.75**

The costs of diagnosis and treatment of LSIL, HSIL and cervical cancer stages (see Table 4.7) were based on health service costs from the study by Sinanovic et al.[58] and inflated per year until 2013, by the annual consumer price index (CPI) published by Statistics South Africa.[69] See supplemental document for more information. The original costing studies for South Africa were performed by Goldie et al.[70]

The cost of LSIL was based on the cost of screening and two clinic visits as this is based on the standard practice in South Africa, where women diagnosed with LSIL, are not offered any treatment but are screened 12 months after the initial diagnosis. If the infection persists, they are referred for further diagnosis.[58]

HSIL costs were based on the medical care costs and included the cost of colposcopy and biopsy (100% of cases), LEEP (80% of cases), cold-knife conization (10% of cases) and simple hysterectomy (10% of cases). The percentage of cases is based on expert opinion of treatment of HSIL in South Africa.[58]

Treatment of cervical cancer costs were estimated for the four stages of cancer, including the cost of surgery and the cost of chemo-radiation.[58]

The cost of a Pap test in the public sector was calculated using 2012 Uniform Patient Fee Schedule for facility fee and general medical practitioner fee and inflated by 10% for medical inflation, to estimate 2013 cost.[71] See supplemental document

for more details. The cost of laboratory cytology testing was obtained from the National Health Laboratory Services (NHLS) state price list 2013.[72]

Table 4.7: Unit cost of vaccination, screening, diagnosis and treatment of HPV precancerous lesions and cervical cancer in 2013 South Africa Rands.

	Healthcare cost 2013 (in South African Rand) per female
Vaccination (vaccine plus program cost per fully immunized girl)	636.75
Screening: Pap test (three per lifetime)	675.81
Diagnosis and treatment of one case of low SIL	366.98
Diagnosis and treatment of one case of high SIL	6 483.31
Diagnosis and treatment of one case of cancer stage I	36 914.38
Diagnosis and treatment of one case of cancer stage II	50 445.57
Diagnosis and treatment of one case of cancer stage III	50 445.57
Diagnosis and treatment of one case of cancer stage IV	68 907.47

4.5.3. Model Effectiveness Inputs

The model was populated with quality adjusted life years (QALYs) gained, from the literature (see Table 4.8). QALYs are calculated by estimating the total life-years gained from a treatment by weighting each year with a quality of life score (from zero, representing worst health, to one, representing best health) to reflect the quality of life in that year.[57] As there was no South Africa population based published health state values or utilities for all disease states associated with cervical cancer screening, prevention and treatment, quality of life weights from existing international published studies were used in the model,[73, 74] see Table 4.8.

Table 4.8: Markov model health-related quality of life weights for health states

Parameter	Base case estimate (Utility)	Source
Well	1	75
HPV	1	Assumption
LSIL	0.91	73
HSIL	0.87	73
Cancer stage 1	0.65	74
Cancer stage 2	0.56	74
Cancer stage 3	0.56	74
Cancer stage 4	0.48	74
Cancer survivor	0.84	73
Dead due to cervical cancer	0	75
Dead	0	75

4.5.4. Discount Rate

A discount rate of 5% was applied to both costs and benefits as recommended by the Department of Health in the Guidelines for Pharmacoeconomic Submissions.[61]

4.6. Exploratory Markov Model: HPV vaccination of HIV positive nine year old girls

The input model parameters for two variables were changed to assess the impact of a HIV positive status of a nine year old girl, on the cost effectiveness of HPV vaccination:

- Increased cervical cancer screening costs due to the increase in frequency of Pap tests. The eligibility age for screening (start age for screening would be earlier). Assumed the start age of cervical cancer screening is 20 years old with a Pap test every six months for one year, and every two years thereafter until the age of 40 years and then every five years until age of 50 years. A total of 14 Pap tests would be required.

- Increase by a factor of 2.35 times in the age specific probability of HPV infection due to HIV co-infection. Transition probabilities and incidence rates of HPV prevalence in HIV positive women are assumed to be 2.35 times greater than in HIV negative women. This value was estimated from the median of ratios for HPV-DNA prevalence in HIV-positive and HIV-negative women, obtained from various studies in Africa including South Africa as reported by De Vuyst et al.[76]

The following assumptions were made for the model:

- Patients are on HAART as per standard treatment guidelines. Ahdieh et al. reported that the probability of 16 and 18 HPV infection is two times greater if a patient is on HAART and five times greater if not on HAART.[19]
- Unit costs of vaccination, diagnosis and treatment of HPV precancerous and cervical cancer in HIV positive women is same as for HIV negative women.
- Health state transition probabilities (other than HPV infection) and utilities are the same for HIV positive and HIV negative women.
- Annual cervical cancer survival probability does not change if HIV positive.[77] This is based on patient receiving HAART

4.7. Ethical considerations

No patient datum was obtained for this research. All data were obtained from published literature.

Ethics Committee approval was received from the University of Pretoria, Faculty of Health Science Research Ethics Committee.

5. Analysis of Data, Results and Findings

5.1. Introduction

The model outputs were analysed and key findings are included below. The findings were then validated against South African data (where available) and compared to other similar economic analyses.

5.2. Results for each research question

5.2.1. Cost effectiveness analysis

A Markov model cost effectiveness analysis was performed and the following scenarios were modelled using TreeAge Pro Healthcare 2014 Suite software (Release 1.0).

- The impact of HPV vaccination of nine year old school girls who are not HPV positive.
- The impact of no HPV vaccination on nine year old school girls.
- Exploratory model for HIV positive nine year old school girls.

The incremental cost per life year saved, and incremental Cost/QALY gained by comparing addition of HPV vaccination to the existing standard of care (cervical cancer screening, diagnosis and treatment program) was calculated.

Table 5.1: Base case cost-effectiveness of adding a two-dose HPV vaccination to the existing screening program in South Africa

Model Scenario	Strategy	Lifetime Cost (per patient)	Incremental Cost (per patient)	Effect (per patient)	Incremental Effect (QALY) (per patient)	Incremental Cost Effectiveness Ratio (R/QALY)	
2 Dose Vaccine (90% efficacious and 5% discount rate) Life expectancy 61 years	HPV vaccine	R2 033.93	-R4 383.98	45.03 QALYs	0.41 QALY	-R10 567.79	Undominated
	No HPV vaccine	R6 417.90		44.62 QALYs			absolute dominated

The HPV vaccine scenario had absolute dominance (see Table 5.1) over the No HPV vaccine scenario for both costs and effects. An option is said to be dominated if it both costs more and is less effective than the comparator.

Table 5.2: Base Case Cost-effectiveness of adding a three-dose HPV vaccination to the existing screening program in South Africa

Model Scenario	Strategy	Lifetime Cost (per patient)	Incremental Cost (per patient)	Effect (per patient)	Incremental Effect (QALY) per patient	Incremental Cost Effectiveness Ratio (R/QALY)	
3 Dose Vaccine (90% efficacious and 5% discount rate) Life expectancy 61 years	HPV vaccine	R2 328.11	-R4 089.79	45.03 QALYs	0.41QALY	-R9 858.64	Undominated
	No HPV vaccine	R6 417.9		44.62 QALYs			absolute dominated

For a three-dose HPV vaccine schedule, the base case ICER is less dominant (less cost saving), reduced by 7% (R709.15) compared to the two-dose vaccine schedule (see Table 5.2).

Table 5.3: Cost-effectiveness of HPV vaccination of HIV positive nine year old girls in South Africa

	Strategy	Lifetime Cost (per patient)	Incremental Cost (per patient)	Effect (per patient)	Incremental Effect (QALY) (per patient)	Incremental Cost Effectiveness Ratio (R/QALY)	
2 Dose Vaccine (90% efficacious and 5% discount rate) Life expectancy 61 years*	HPV vaccine	R10 636.88	-R1 756.21	44.95 QALYs	0.74 QALY	-R2 375.62	Undominated
	No HPV vaccine	R12 393.09		44.21 QALYs			absolute dominated

The exploratory Markov model of HIV positive girls included increased costs due to increased frequency of cervical cancer screening and increased HPV infection probability by a factor of 2.35. The HPV vaccine was a dominant strategy (see Table 5.3).

5.2.1.1. Handling uncertainty in the base case model

One way sensitivity analysis was performed, to study the effects of changing a single model input on the following parameters (ranges are given in brackets):

(1) Vaccine (two-dose schedule) efficacy (70% and 95%)

(2) Vaccine duration of protection (10 years as opposed to lifelong in model)

(3) Vaccine dose schedule: one-dose and three-dose schedule (vaccine efficacy of 90%)

(4) Discount rate for both costs and benefits (0% and 10%).[61]

(5) Vaccination program costs (no program costs and 25% increase in program costs)

(6) Female life expectancy of 56 and 66 years

(7) Health related utilities for HPV infection, LSIL, HSIL, cervical cancer and cancer survivor (10% decrease/increase).

(8) Costs of treating LSIL, HSIL and cervical cancer (10% decrease/increase)

(9) Probability of age specific incidence of HPV infection (50% decrease/increase)

(10) Probability of stage 1 and 2 cervical cancer (10% decrease/increase)

(11) Probability of stage 3 and 4 cervical cancer (10% decrease/5% increase for total branch probability ≤ 1)

(12) Probability of cervical cancer death (10% decrease/increase)

The above input parameters were selected based on other reported cost effectiveness analysis studies.[58, 7] Fesenfeld et al. reported (based on a systematic review of cost effectiveness of HPV vaccination in LMICs) that vaccine price was the key influential parameter explored in sensitivity analysis in all studies. Other parameters tested in sensitivity analysis were discount rate, vaccine and screening coverage, duration of vaccine protection, vaccine efficacy, target age, natural history parameters, cervical cancer incidence and mortality, screening test performance as well as warts treatment costs.[7]

5.2.1.2. Results of one way sensitivity analysis

Table 5.4: Results of one way sensitivity analysis (Costs in South African Rands)

Variable (Low, High values)	Low Value			High Value			Dominant strategy
	Incremental Cost (Rands)	Incremental Effect (QALY)	Incremental Cost Effectiveness Ratio(R/QALY)	Incremental Cost (Rands)	Incremental Effect (QALY)	Incremental Cost Effectiveness Ratio(R/QALY)	
Vaccine efficacy (70%, 95%)	-2 708.51	0.29	-9 228.20	-4 832.04	0.45	-10 804.49	HPV vaccine
Vaccine protective effective (10 years)	171.83	0.12	1 429.33	Not applicable			N/A
Vaccine dose schedule (1, 3)	-4 678.15	0.41	-11 276.92	-4 089.79	-0.41	-9 858.64	HPV vaccine
Discount rate (0%, 10%)	-5 409.67	0.41	-13 040.27	-4 207.34	-0.41	-10 142.01	HPV vaccine
Program	-4 687.74	0.41	-11 300.04	-4 118.17	0.41	-9 927.06	HPV

costs (Nil, increased by 25%)							vaccine
Life expectancy (56 years, 66 years)	-3 820.00	0.36	-10 631.22	-5 001.41	0.47	-10 616.61	HPV vaccine
HPV utility (0.8, 0.9)	-4 383.98	1.21	-3 628.90	-4 383.98	0.84	-5 198.50	HPV vaccine
LSIL utility (0.82, 0.99)	-4 383.98	-1.42	3 097.03	-4 383.98	-2.18	2 008.22	No dominance
HSIL utility (0.78, 0.96)	4 383.98	1.45	3 019.66	4 383.98	2.00	2 197.20	No dominance
Cervical cancer stage 1 utility (0.59, 0.72)	-4 383.98	0.41	-10 740.45	-4 383.98	0.41	-10 821.18	HPV vaccine
Cervical cancer stage 2 utility (0.50, 0.62)	-4 383.98	0.41	-10 573.31	-4 383.98	0.41	-10 606.28	HPV vaccine
Cervical cancer stage 3 utility (0.50, 0.62)	-4 383.98	0.41	-10 618.24	-4 383.98	0.41	-10 634.76	HPV vaccine
Cervical cancer stage 4 utility (0.43, 0.53)	-4 383.98	0.41	-10 572.38	-4 383.98	0.41	-10 579.06	HPV vaccine
Cancer survivor utility (0.76, 0.92)	-4 383.98	0.41	-10 725.88	-4 383.98	0.38	-11 481.76	HPV vaccine
Cost of LSIL (330.28, 403.68)	-5 120.29	0.41	-12 342.72	-5 451.66	0.41	-13 141.49	HPV vaccine
Cost of HSIL (5834.98,	-18 361.93	0.41	-44 262.32	-22 276.74	0.41	-53 699.18	HPV vaccine

7131.64)							
Cost of Stage 1 cervical cancer (33222.94, 40605.82)	-4 756.06	0.41	-11 464.71	-4 928.99	0.41	-11 881.58	HPV vaccine
Cost of Stage 2 cervical cancer (45401.01, 55490.13)	-4 516.29	0.41	-10 886.75	-4 590.75	-0.41	-11 066.22	HPV vaccine
Cost of Stage 3 cervical cancer (45401.01, 55490.13)	-4 410.86	0.41	-10 632.59	-4 430.89	0.41	-10 680.87	HPV vaccine
Cost of Stage 4 cervical cancer (62016.72, 75798.22)	-4 398.37	0.41	-10 602.48	-4 431.75	0.41	-10 682.96	HPV vaccine
Probability HPV infection (50%, 150%)	-2 047.45	0.23	-8 739.73	-6 224.31	0.56	-11 163.2	HPV vaccine
Probability Stage 1 cervical cancer (0.181, 0.222)	-4 383.34	0.42	-10 517.70	-4 384.49	0.41	-10 613.53	HPV vaccine
Probability Stage 2 cervical cancer (0.233, 0.285)	-4 382.76	0.42	-10 541.99	-4 385.05	0.41	-10 590.97	HPV vaccine
Probability Stage 3 cervical cancer	-4 383.98	0.41	-10 567.79	-4 383.52	0.41	-10 569.68	HPV vaccine

(0.326, 0.381)							
Probability Stage 4 cervical cancer (0.810, 0.945)	-4 382.97	0.41	-10 564.59	-4 384.41	0.41	-10 569.16	HPV vaccine
Probability of cervical cancer death (90% and 110%)	-4 383.98	0.41	-10 689.23	-4 383.98	0.42	-10 454.98	HPV vaccine

The results of the one way sensitivity analysis (see Table 5.4) indicates that the HPV vaccine is the dominant strategy, for the majority of the variables tested and result in cost saving ICERs, except for LSIL and HSIL outcomes. Varying the LSIL and HSIL base case utility values by 10%, results in non-dominance of HPV vaccination strategy. For LSIL outcome, it will cost an additional R3 097.03 or R 2 008.22, to get an additional QALY when the LSIL utility is at the low value of 0.82 or high value of 0.99 respectively. For HSIL outcome, it will cost an additional R3 019.66 or R2 197.20, to get an additional QALY when the HSIL utility is at the low value of 0.78 or high value of 0.96 respectively.

The Table 5.5 below is a reflection of the variance in the base-case ICER based on the ranges used in the sensitivity analysis above.

Table 5.5: Sensitivity analysis effect on base case ICER (two-dose vaccine schedule)

Variable	Base Case Value	Change in Value	ICER	Effect on base case ICER
Vaccine efficacy	90%	70%	-9 228.2	Reduced by 13%
Vaccine efficacy	90%	95%	-10 804.49	Increased by 2%
Duration of vaccine protective effect	Lifelong	10 years	1 429.33	Reduced by 114%
Vaccine dose schedule	2 doses	1 dose	-11 276.92	Increased by 7%
Vaccine dose schedule	2 doses	3 doses	-9 858.64	Reduced by 7%
Discount rate	5%	0%	-13 040.27	Increased by 23%
Discount rate	5%	10%	-10 142.01	Reduced by 4%
Program costs	R328.76 for 2 doses	NIL	-11 300.04	Increased by 7%
Program costs	R328.76 for 2 doses	125%	-9 927.06	Reduced by 6%
Life expectancy	61 years	56 years	-10 631.22	Increased by 1%
Life expectancy	61 years	66 years	-10 616.61	No change
HPV utility	1	0.8	-3 628.9	Reduced by 66%
HPV utility	1	0.9	-5 198.5	Reduced by 51%
LSIL utility	0.91	0.82	3 097.03	Reduced by 129%
LSIL utility	0.91	0.99	2 008.22	Reduced by 119%
HSIL utility	0.87	0.78	3 019.66	Reduced by 129%
HSIL utility	0.87	0.96	2 197.2	Reduced by 121%
Cervical cancer stage 1 utility	0.65	0.59	-10 740.45	Increased by 2%
Cervical cancer stage 1 utility	0.65	0.72	-10 821.18	Increased by 2%
Cervical cancer stage 2 utility	0.56	0.50	-10 573.31	No change
Cervical cancer stage 2 utility	0.56	0.62	-10 606.28	No change
Cervical cancer stage 3 utility	0.56	0.50	-10 618.24	No change
Cervical cancer stage 3 utility	0.56	0.62	-10 634.76	Increased by 1%
Cervical cancer stage 4 utility	0.48	0.43	-10 572.38	No change
Cervical cancer stage 4 utility	0.48	0.53	-10 579.06	No change
Cancer survivor utility	0.84	0.76	-10 725.88	Increased by 1%
Cancer survivor utility	0.84	0.92	-11 481.76	Increased by 9%
Cost of LSIL	R366.98	R330.28	-12 342.72	Increased by 17%
Cost of LSIL	R366.98	R403.68	-13 141.49	Increased by 24%
Cost of HSIL	R6 483.3	R5 834.98	-44 262.32	Increased by 419%
Cost of HSIL	R6 483.3	R7 131.64	-53 699.18	Increased by 508%
Cost of Stage 1 cervical cancer	R3 6914	R33 222.94	-11 464.71	Increased by 8%
Cost of Stage 1 cervical cancer	R3 6914	R40 605.82	-11 881.58	Increased by 12%
Cost of Stage 2 cervical cancer	R50 446	R45 401.01	-10 886.75	Increased by 3%
Cost of Stage 2 cervical cancer	R50 446	R55 490.13	-11 066.22	Increased by 5%
Cost of Stage 3 cervical cancer	R50 446	R45 401.01	-10 632.59	Increased by 1%
Cost of Stage 3 cervical cancer	R50 446	R55 490.13	-10 680.87	Increased by 1%
Cost of Stage 4 cervical cancer	R68 907	R62 016.72	-10 602.48	No change

Cost of Stage 4 cervical cancer	R68 907	R75 798.22	-10 682.96	Increased by 1%
Probability of HPV infection	Age specific incidence 100%	Age specific incidence 50%	-8 739.73	Reduced by 13%
Probability of HPV infection	Age specific incidence 100%	Age specific incidence 150%	-11 163.15	Increased by 6%
Probability of Stage 1 Cervical Cancer	0.2015	0.181	-10 517.70	No change
Probability of Stage 1 Cervical Cancer	0.2015	0.222	-10 613.53	No change
Probability of Stage 2 Cervical Cancer	0.2592	0.233	-10 541.99	No change
Probability of Stage 2 Cervical Cancer	0.2592	0.285	-10 590.97	No change
Probability of Stage 3 Cervical Cancer	0.3624	0.326	-10 567.79	No change
Probability of Stage 3 Cervical Cancer	0.3624	0.381	-10 569.68	No change
Probability of Stage 4 Cervical Cancer	0.9	0.81	-10 564.59	No change
Probability of Stage 4 Cervical Cancer	0.9	0.9450	-10 569.16	No change
Probability of cervical cancer death	Varies per cancer stage and year	10% decrease in probability	-10 689.23	Increased by 1%
Probability of cervical cancer death	Varies per cancer stage and year	10% increase in probability	-10 454.98	Reduced by 1%

Of the 25 variables tested in one way sensitivity analysis (see Table 5.5), 11 variables resulted in 0% to 1% change to the base case ICER and 15 variables had between 2% and 508% change to the base case ICER.

Figure 5.1: One way sensitivity analysis results of most sensitive variables

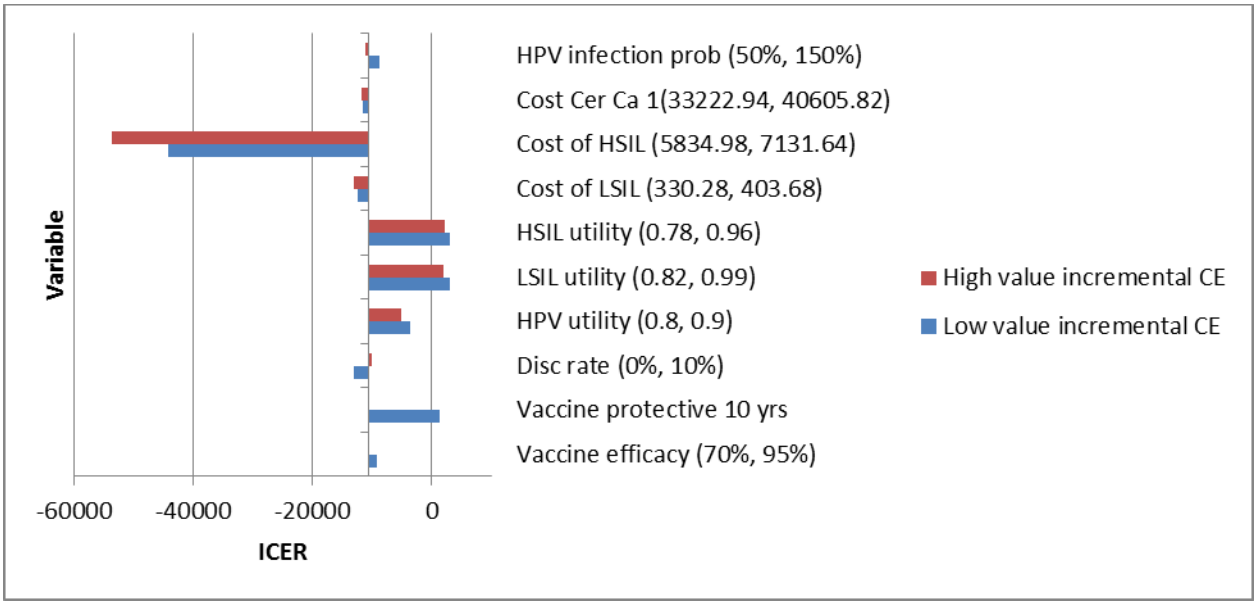
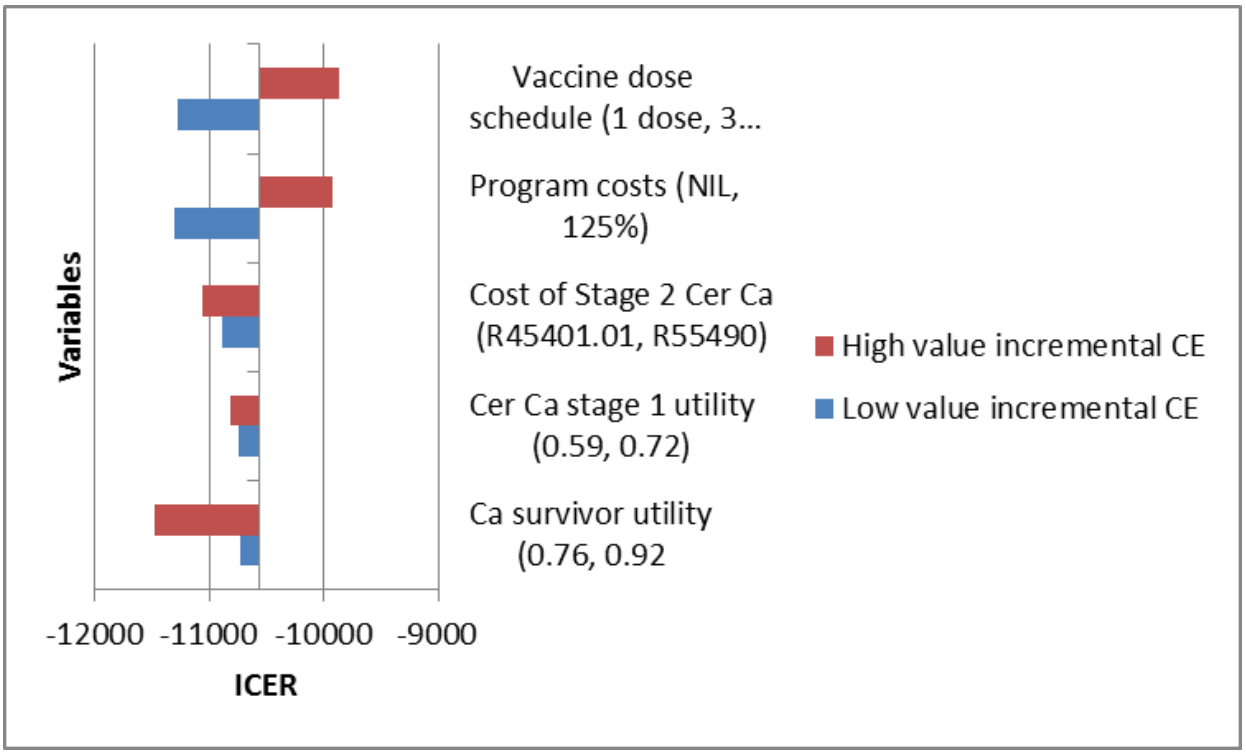


Figure 5.1 shows the most sensitivity variables with a greater than 10% change to the base case ICER) were the cost of HSIL, LSIL utility, HSIL utility, duration of HPV protective effect, HPV utility, cost of LSIL, discount rate, vaccine efficacy, age specific incidence of HPV and cost of stage 1 cervical cancer. Of these variables varying the cost of HSIL alone has the largest impact on the base case ICER. The variables with the second largest change to ICER were HSIL and LSIL outcomes and reducing the duration of the vaccine's protective effect from lifelong to 10 years.

Figure 5.2: One way sensitivity analysis results of moderately sensitive variables



The variables which had moderate changes to base case ICERs (between 2% and 10%) were cancer survivor utility, vaccine dose schedule, program costs, cost of stage 2 cervical cancer and cervical cancer stage 1 utility, see Figure 5.2.

The healthcare provider cost to vaccinate nine year old girls in 2013 is reduced by 52% to R156 178 484, if no program costs are incurred, that is due to an existing school vaccination program infrastructure in place. The one way sensitivity analysis on vaccination program costs resulted in an increased ICER value to 7%, if there are no program costs, indicating no program costs makes HPV vaccination more cost saving. The ICER value is reduced by 6% (becomes less cost saving), if the base case program costs are increased by 25%.

The least sensitive variables, to the base case ICER, were life expectancy, cervical cancer stages 2, 3 and 4 utilities, cost of treatment of stage 4 cervical cancer, probabilities of all four stages of cervical cancer and probability of cervical cancer death, which resulted in either no change to ICER or 1% change to ICER.

5.2.2. Precancerous lesions and cervical cancer burden

Table 5.6: Number Needed to Vaccinate and Number of HPV infections, LSIL, HSIL, Cervical Cancer, Deaths due to Cervical Cancer averted by HPV vaccination for total vaccinated cohort of 507 073 girls

Health State	Total Number of Cases in No HPV Vaccine Arm	Total Number of Cases in HPV Vaccine Arm	Total Number of Cases Averted due to Vaccination	Number Needed to Vaccinate to Avert one case
HPV Infection	501 432	205 453	295 979	2
LSIL	460 533	118 648	341 885	2
HSIL	246 858	48 597	198 261	3
Cervical Cancer Stage 1	6 558	1 020	5 538	92
Cervical Cancer Stage 2	2 409	377	2 032	250
Cervical Cancer Stage 3	754	118	635	798
Cervical Cancer Stage 4	1 186	187	998	508
Deaths due to Cervical Cancer	3 096	490	2 606	195

HPV vaccination protective effect is against acquiring HPV infection. Table 5.6 illustrates the total number of cases averted by HPV vaccination for a cohort of 507 073 girls.

The most significant reduction, in number of cases of HPV infection, LSIL and HSIL, which are precursors to cervical cancer, occurs before the age of 35 years old.

The number of HPV infection, LSIL and HSIL cases averted by vaccination in the total vaccinated female population (from nine years to 61 years old) is 295 979, 341 885 and 198 261 respectively. This corresponds to a lifetime risk reduction of 58%, 67% and 39% respectively. This figure would vary depending on the extent of HPV vaccine cross protection with other HPV types as the model does not differentiate among the HPV types other than HPV 16 and 18. The number of HSIL and LSIL cases, appear high for this cohort and this may be due to the rates of

progression and regression per cycle within the cohort whereas for all stages of cervical cancer and cervical cancer deaths there are no regression probabilities.

The number needed to vaccinate to avert one case of HPV infection or LSIL or HSIL is very low. This is due to the high degree of protection against HPV-16/18 infection and associated cervical lesions, that is, the HPV vaccine is highly efficacious in eliciting antibody responses against HPV infection as demonstrated in clinical trials[77]. Further the static model does not take into account changes in sexual behaviour that could alter the subsequent risk for repeated HPV infections.

The absolute risk reduction (ARR) for cervical cancer stages and deaths due to cervical cancer was lower and therefore the number needed to vaccinate is higher. The ARR for cervical cancer stage 1 to 4 was 1.09%, 0.40%, 0.02% and 0.20% respectively and 0.51% for deaths due to cervical cancer.

The peak incidence of stage 1 cervical cancer in a non-vaccinated cohort of 507 073 girls occurs at about 56 years old, where the largest number, of cervical cancer cases is averted (see Table S4). There is an earlier and lower peak incidence at 37 years old. There is an 84% reduction in the number of stage 1 cervical cancer cases in this age group. The least effect occurs in age group with the lowest incidence of stage 1 cervical cancer, that is, 10 to 19 years old.

The total number of cervical cancer stage 1 cases averted due to HPV vaccination, in this female cohort, is 5 538 (Table S4).

The maximum number of stage 2 cervical cancer case averted occurred in age group 58 to 60 years old (see Table S5). The least effect occurs in age group with the lowest incidence of stage 2 cervical cancer, that is, 10 to 24 years old. The total number of cervical cancer stage 2 cases averted due to HPV vaccination is 2 032.

The maximum number of stage 3 cervical cancer case averted occurs in age group 58 to 61 years old (see Table S6). The least effect occurs in age group with the lowest incidence of stage 3 cervical cancer, that is, 10 to 28 years old. The total number of cervical cancer stage 3 cases averted due to HPV vaccination is 635.

The maximum number of stage 4 cervical cancer case averted occurred in age group 59 to 61 years old (Table S7). The least effect occurs in age group with the lowest incidence of stage 4 cervical cancer, that is, 10 to 26 years old. The total number of cervical cancer stage 4 cases averted due to HPV vaccination is 998.

The peak incidence of cervical cancer deaths in the non-vaccinated cohort occurred after age 55 years old (Table S8). The least effect occurs in age groups with the lowest incidence of stage 1 cervical cancer, that is, 10 to 22 years old. The total number of cervical cancer deaths averted due to HPV vaccination is 2 606.

5.2.3. Costs and outcomes due to HPV vaccination

5.2.3.1. School based vaccination program

The healthcare cost per vaccinated girl was R636.76 (Table 4.6). The cost to vaccinate all nine year old girls (using 2013 population estimate of 507 073 girls) is approximately R322 878 732.75 for a two-dose vaccine schedule. If no program costs are incurred, that is, if existing infrastructure prior to HPV vaccination roll out is adequate, then cost to vaccinate all nine year old girls in 2013 decreases to R156 178 484. The current HPV vaccination program in South Africa did not specify catch up vaccination plan for girls older than 10 years old.

Table 5.7: Costs averted due to HPV vaccination of total vaccinated cohort of 507 073 girls

	Number of cases averted (attributable to HPV 16 and 18)	**Cost to treat one case**	**Costs averted (undiscounted)**
HPV	295 979	No treatment cost	Not applicable, as no costs incurred
LSIL	341 885	R366.98	R125 464 957.30
HSIL	198 261	R6 483.31	R1 285 387 523.91
Cervical cancer stage 1	5 538	R36 914.38	R204 431 836.44
Cervical cancer stage 2	2 032	R50 445.57	R102 505 398.24
Cervical cancer stage 3	635	R50 445.57	R32 032 936.95
Cervical cancer stage 4	998	R68 907.47	R68 769 655.06
Total			**R1 818 592 307.90**

The cost of diagnosis and treatment of HSIL is almost 18 times more than for LSIL. The cost of diagnosis and treatment of cervical cancer stage 4 is almost two times more than for stage 1. The cost savings (cost year 2013), for the healthcare provider, as a result of the number of precancerous lesions and cervical cancer cases averted due to HPV vaccination is R1 818 592 307.90 (see Table 5.7). If societal costs are considered this value would be significantly higher. In order for all HPV 16 and 18 precancerous lesions and cervical cancer to be averted a larger population of girls will need to be vaccinated. The cost in 2013, to vaccinate nine year old school girls, is R322 878 732.75. If we assume all 10 to 12 year old girls (total of 1 519 520 girls) will also benefit from receiving the HPV vaccine an additional vaccination cost in 2013 will be R967 554 360.00, bringing the total cost of vaccination to R1 290 433 093.00. Extending vaccination to three age groups adds to the cost but also to the benefits from the healthcare service provider perspective.

Associated health costs due to increased longevity was not considered in this study and is a possible limitation of this study.

5.2.3.2. Numbers needed to be vaccinated and associated cost

If all stage 1 cervical cancers are due to HPV 16 and 18 the absolute risk reduction (ARR) will be 1.0922% and the number needed to be vaccinated to avert one case is 92.

- Absolute risk reduction = Risk in HPV vaccine arm – Risk in No HPV vaccine arm = 1.2933% - 0.2012%= 1.0922%
- Number needed to be vaccinated to avert one case of cervical cancer = 100/ARR = 100/1.0922 = 92

The HPV vaccination cost to avert one case of cervical cancer stage 1 case is R58 581.92

If all cervical cancer deaths are attributed to HPV 16 and 18 the absolute risk reduction (ARR) will be 0.5159% and the number needed to be vaccinated is 13089.

- Absolute risk reduction = Risk in HPV vaccine arm – Risk in No HPV vaccine arm = 0.6105% - 0.0967% = 0.5139%
- Number needed to be vaccinated to avert one case of cervical cancer = 100/ARR = 100/0.5139 = 195.

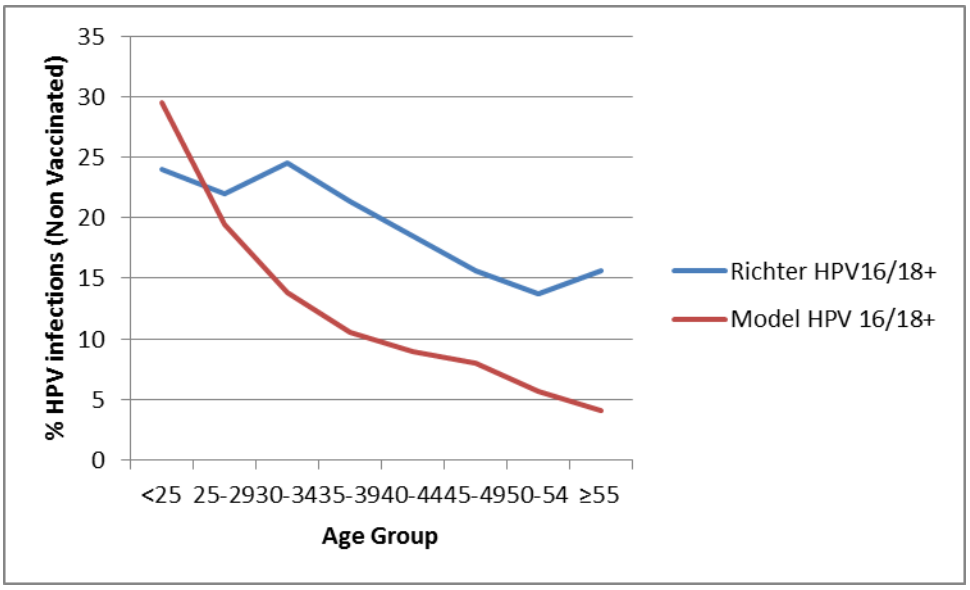
The total number of cervical cancer deaths averted due to HPV vaccination is 2 606 (see Table 5.6). The HPV vaccination cost to avert one cervical cancer death is R124 168.20

5.3. Validation of results predicted by Markov Model

The outputs from this model were compared to local data were possible to compare model results prediction with existing data.

A study reporting on age-specific prevalence of cervical HPV infection and cytological abnormalities in women in Gauteng Province[78] provides some data to compare model predicted HPV incidence.

Figure 5.3: HPV 16 and 18 incidence by age: South African data versus model prediction for unvaccinated girls (see Table S9 in supplemental information)



The HPV incidence curves in Figure 5.3 indicate some correlation however; it is difficult to draw conclusions. The province based study sample size (blue curve) was small and age group <25 years made up 7% of the sample, whereas this study (red curve) considered a cohort of 507 073 girls in South Africa.

Figure 5.4: Comparison of number of cervical cancer stage 1 cases from model to the South Africa data (2005). (See Table S10 in supplemental information)

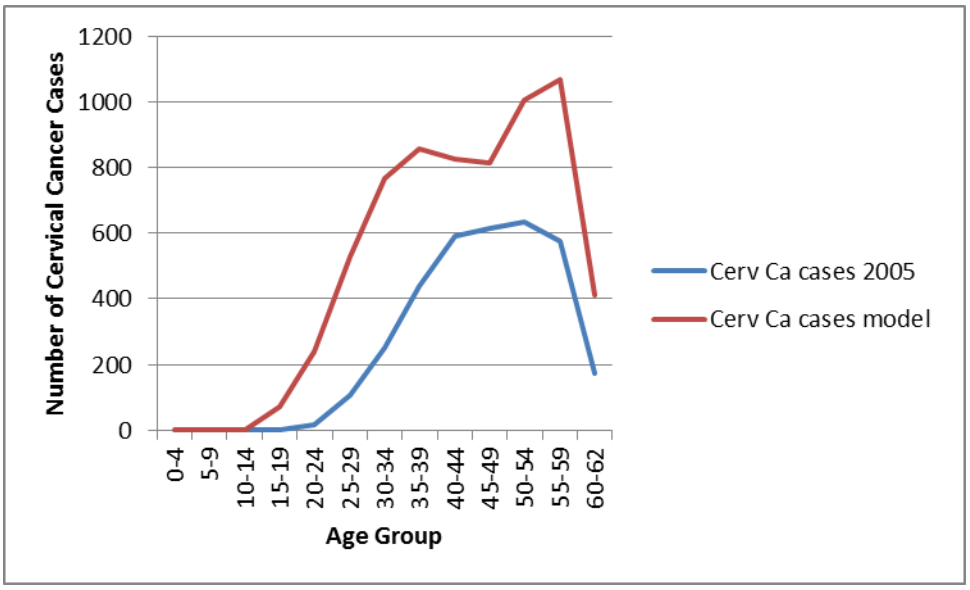


Figure 5.4 compares the Markov model prediction of cervical cancer cases to that of the South African cancer registry (2005 data). The model predicts a later peak age incidence for cervical cancer, of 55 to59 years old, compared to 50 to 54 years old from the South African cancer registry 2005 data. This shift in peak age maybe due to differences in actual country specific rates of progression and regression of precancerous lesions or it could reflect a shift that we may see in the future as women gain greater access to healthcare. The number of cervical cancer cases predicted by the model, may be higher in reality, due to the number of undetected cervical cancer cases in South Africa.[63] The SA Cancer Registry data is old and most recent data is 2005. The registry may contain inaccurate data because not all cases were necessarily reported.

Current age specific incidence, rate of progression and regression of HPV infection, precancerous and cervical cancer is required, to accurately predict the peak age of cervical cancer incidence of nine year old girls receiving HPV vaccination. This information will assist in decision making of future interventions to further reduce cervical cancer incidence and mortality.

Cervical cancer mortality predicted by the model appears low, despite the average life expectancy of 61 years use in the model. Although data on age specific cervical cancer mortality is lacking in South Africa, it is estimated at 60% mortality per year.[26] This study model predicts a lifetime risk of cervical cancer mortality of 0.61% if not vaccinated. The lifetime risk from this study could be explained by use of annual probabilities of cervical cancer survival after diagnosis (see Table 4.3), from the literature which was based in more developed countries, with probably better access to healthcare. Other parameters could also impact on the model output, like the average life expectancy of 61 years and that the static model has a fixed set of conditions, for example, the model does not capture changes in sexual activity and screening behavior.[59]

This study used an annual discount rate of 5% in the base-case analysis for both costs and benefits as recommended by the South African National Department of Health Pharmacoeconomic guidelines.[61] This differs from other models in LMICs where the majority used a discount rate of 3%. In economic evaluations of a prevention strategy with long-term effects, the initial intervention costs and the choice of discount rate have a great influence on the resulting cost-effectiveness ratios. In the context of HPV vaccination, the discount rate of 3% made the vaccination cost effective in the respective countries.[58]

It is challenging to draw conclusions from comparing ICERs across studies due to a number of variations in methodologies, model type, study assumptions, bivalent or quadrivalent vaccine, costs, screening methods, discount rate, economic analysis perspective, country specific epidemiological information etcetera. However, a systematic review of cost effectiveness of HPV vaccination in LMIC found that static models resulted in higher ICERs compared to dynamic models.[7]

A study by Jit et al.[79] assessed the health and economic effects of female HPV vaccination in 179 countries and concluded that HPV vaccination is likely to be very

cost effective in most countries. For the Global Alliance for Vaccines and Immunization (GAVI)-72 countries analysis concluded that female HPV vaccination would be very cost effective in all countries except Afghanistan and the Democratic Republic of Congo.[79] The HPV vaccine price (for three doses) was estimated at between 13 to 50 US dollars through GAVI Alliance procurement, 39 US dollars at the lowest non-GAVI public sector indicative price, and more than 300 US dollars in high-income countries.[79] In South Africa public price (at tender price) per dose is within the price range of GAVI eligible countries. Future vaccine price changes in South Africa were not considered in this model.

The HPV vaccine Cervarix® price in the private sector (Single Exit Price) in South Africa in 2014 was R630.04[5] is much higher compared to the tender price (R140). The ICER obtained in this study (based in the public sector) would be substantially less cost saving if the private sector vaccine price was used if only vaccine price was considered. The impact of cost of screening and treatment of precancerous lesions and cervical cancer, which is higher in the private sector, would also alter the ICER.

The majority (22 studies) of HPV vaccination cost-effectiveness studies based in LMICs investigated HPV vaccination of girls aged 12 years or younger and 14 studies considered a range of vaccination and screening options to find the most cost effective combination.[7] 16 of the studies in LMICs used static models for estimating the cost effectiveness of routine vaccination girls only without catch up vaccination. Some of these LMICs studies were similar to this study from the perspective of health care provider, age of vaccination, time horizon of lifetime, static model, vaccine efficacy, duration of vaccine protection, comparator arm of screening, Pap test as screening method, disease outcomes of precursors to cervical cancer and cervical cancer and not taking into account future vaccine price maturity.[7] Some studies source of epidemiological data was local data while others used a combination of literature and local data.[7] The studies in the review differed from this study in that, fewer than three doses of the vaccine was not considered,

vaccination coverage of approximately 70% -90%, and screening coverage of less than 80% was used in the majority of the studies.[7]

The only economic analysis of HPV vaccination program in South Africa by Sinanovic et al.[58] also showed that HPV vaccination is a dominant strategy compared to cervical cancer screening alone. The QALY gained in the Sinanovic et al. study was lower (0.33) compared to this study (0.41). This could be because of the different start age of vaccination and life expectancy. The Sinanovic model starts at age 12 and ends at age 85 years old whereas this study start age is nine years old and ends at the age of 61 years old. When cost and benefits are discounted, the ICER in 2007 was US $1 078 (R7 007 based on 2007 foreign exchange rate of 6.5) from the health service perspective.[58] Of the input parameters (vaccine price and efficacy, type of vaccination program, mortality tables, screening test and discount rate) tested in sensitivity analysis in Sinanovic et al. study, the ICER was most sensitive to discount rate, vaccine price and vaccine efficacy.[58]

The majority of economic studies conducted sensitivity analysis on the vaccine price, discount rate, vaccine and screening coverage, duration of protection, vaccine efficacy, target age, natural history parameters, cervical cancer incidence and mortality, screening test performance as well as warts treatment costs.[7] Fesenfeld et al. reported that the range of parameters tested in sensitive analysis in LMICs differed between the studies making it difficult to draw general conclusions.[7] In this study sensitivity analysis was performed on a wide range of parameters but excluded vaccine price, screening test performance and warts treatment costs. The vaccine tender price procured for South Africa is within the range of GAVI alliance price therefore sensitivity analysis was not considered essential. Genital warts were not considered in this study as the bivalent HPV vaccine was used and the cost to treat genital warts is assumed to be equal in both arms of the model. It was assumed that cervical cancer screening test performance would be equal in both arms of the model; hence sensitivity analysis on this parameter was not performed.

This study model did not consider herd immunity which could underestimate the indirect benefits of vaccination, and did not allow for multiple simultaneous events in one time cycle for example co-morbidities.[60] A detailed model simulating the entire natural history of cervical disease conditional to each oncogenic HPV type would provide greater insights to cervical cancer prevention strategies.

6. Conclusions and implications

6.1. Introduction

Women in South Africa have a lifetime risk of 1: 42 for acquiring cervical cancer, which is the second highest cancer burden in South Africa with 4 927 reported cases in 2007.[79] The number of cervical cancer cases may be substantially higher due to the voluntary reporting to National Cancer Registry and patients who may have died undiagnosed due to lack of access to adequate healthcare. Further, cervical cancer mortality ranks number one, with 3 498 deaths, in year 2000, for the Top 20 Cancer Deaths by Cause for South Africa.[81]

The results of this study suggests that adding the HPV vaccination program to the current cervical cancer screening policy in the public sector in South Africa is cost-effective from a public sector health provider perspective. The HPV vaccination program could potentially also be cost effective from a societal perspective as demonstrated by other studies.

HPV 16 and 18 vaccination of nine year old girls with a two-dose vaccine schedule, 100% screening and cervical cancer screening coverage, 90% vaccine efficacy with no waning of protection, results in a 84% decreased lifetime risk of stage 1 cervical cancer.

6.2. Key findings

The Markov model starts at age nine years, where all girls are considered well, and have no HPV infection, and ends at 61 years old (based on an average life expectancy of a South African female). The cost effectiveness analysis indicates that adding HPV vaccination to cervical cancer screening in South Africa is a dominant strategy, i.e. cost effective resulting in a cost saving of R10 567.79 per QALY (ICER is R10 567.79 per QALY). The discounted lifetime costs, QALYs and incremental cost-effectiveness ratios (ICERs) of adding vaccination to the existing cervical cancer screening are presented in Table 5.1.

The South African pharmacoeconomic guideline does not specify a cost effectiveness threshold. The ICER of R10 567.79, for school based HPV vaccination would be assessed as affordable, if assessed directly against the National Institute for Health and Care Excellence (NICE) cost effectiveness threshold. NICE recommends implementation of an intervention where the ICER is less than 20000 £/QALY.[82] The WHO-CHOICE (CHOosing Interventions that are Cost-Effective) project derived the three categories of cost-effectiveness based on gross domestic product (GDP), namely highly cost-effective (less than GDP per capita); cost-effective (between one and three times GDP per capita); and not cost-effective (more than three times GDP per capita).[83]

The GDP per capita in 2013 for South Africa was 12 507 international dollars[84]which is equivalent to R120 449.91 (using the average foreign exchange conversion rate for 2013. Based on this WHO-CHOICE recommendation the ICER in this study is less than GDP per capita and highly cost effective.

When costs and benefits are not discounted the ICER is increased (more cost saving) by 23% to R13 040.27, suggesting that the vaccine followed by screening strategy is more cost-effective. When cost and benefits are discounted at 10%, the ICER is reduced (becomes less cost saving) by 4% to R10 142.01.

The clinical benefit of HPV vaccination occurs 30 to 40 years after age of vaccination (i.e. nine years old); therefore the cost effectiveness of adding the vaccination to the screening program is affected by several variables. The variables (see Table 5.5), that were most sensitive (greater than 10% change to base case ICER) were cost of HSIL, LSIL utility, HSIL utility, duration of vaccine protective effect, HPV utility, cost of LSIL, discount rate, vaccine efficacy, age specific incidence of HPV and cost of stage 1 cervical cancer.

The main outcome expected due to HPV vaccination is to reduce the incidence of cervical cancer and assumes the vaccine protective effect is lifelong. This economic analysis shows a marked decrease in the number of precancerous lesions (ARR in HPV infection, LSIL, HSIL of 58%, 67% and 39% respectively) and 84% decrease in all stages of cervical cancer cases over a lifetime. If the duration of vaccine protection is not lifelong, the health benefits will be lower than predicted in this study. Marra et al.[50] reported from a review of HPV vaccine cost effectiveness studies that studies conducted after 2003 showed a reduction of up to 58% in cervical cancer cases.

The number of women who have cervical cancer in South Africa is likely much higher that reported, due to a number of undetected and unreported cases of cervical cancers. This implies that extrapolation of this model predictive numbers for benefits of HPV vaccination could be underestimated. The South African cancer registry, in 1986, reported 2 897 new cases of histologically confirmed cervical cancers. In 1992, the total number of reported new cervical cancers increased to 4 467 and 4 851 in 2005. However a significant number of women with cervical cancer die without a diagnosis being made which suggests that the reported number of cervical cancer cases is underestimated.[63]

The lifetime reduction in deaths due to cervical cancer was predicted, by this model, to be 84%. Other studies by Sanders and Taira[85] and Kulasingam et al.[86], that evaluated cervical cancer deaths, reported lower reductions of 21% and 58% respectively.

The 2013 cost to the healthcare provider in the public sector, for a school based HPV vaccination program is estimated at R322 878 732.75, for a two-dose vaccine schedule. The cost to vaccinate one girl with a two-dose schedule is R636.75. In economic analyses in developed countries, program costs are dominated by vaccine procurement costs and delivery and program costs are either not considered or have a low fixed value. In LMICs program costs can have a considerable impact if there is

a lack of existing infrastructure to support school based vaccination. Program costs in LMICs ranged very widely between studies from US$9.86 to US$90.[7]

Other countries like Canada also introduced the bivalent vaccine, but with a three-dose vaccine schedule, for girls between nine and 13 years old.[87] Most high income countries that have introduced HPV vaccination have achieved vaccination coverage less than 70%.[6] Only a few countries like Australia, Canada, Portugal and the United Kingdom have achieved coverage of greater than 70% mostly by leveraging of existing adolescent health systems like school health nurses[88]. In 2010, Dorleans et al. reported that in Europe, 11 countries did not introduce HPV vaccination into their national immunization schedule due to financial constraints. Nine of the 11 concerned countries quoted a lack of funding for the vaccination or a prohibitive vaccine cost and two countries also mentioned uncertainty on the duration of protection and insufficient anticipated epidemiological impact beyond the current screening programs contributing reasons.[88]

6.2.1. Exploratory Markov Model on HIV positive girls

The exploratory cost effectiveness analysis on HIV positive girls indicates that adding HPV vaccination to cervical cancer screening in South Africa is cost effective with an incremental cost effectiveness ratio (ICER) of R2 375.62 per QALY. This ICER value would potentially show greater cost saving, if the model is populated with increased rates of progression and decreased rates of regression between the health states (due to HIV co-infection) as reported in studies conducted in Africa.[76,19,89,90]

Female HIV prevalence 2012 data in South Africa indicate that 2.4% of girls aged zero to 14 years old are HIV positive.[21] This implies that of the estimated total of 507 073 nine year old girls in 2013, approximately 12 170 maybe HIV positive. The two-dose HPV schedule is dominant in HIV positive and HIV negative girls.

6.3. Cervical Cancer Screening

This study assumed that 100% of the cohort will have cervical cancer screening as per the policy and that the Pap test screening method is equally effective in both arms of the model.

The cervical cancer screening policy in the public sector was previously estimated to have coverage of 13.6%.[1] This coverage has increased to approximately 50% in 2014 (personal communication with the DOH). Screening coverage has been shown to be much more important than frequency of screening, and even by screening women infrequently, e.g. 10-yearly but with high coverage, a two thirds reduction in cervical cancer can be anticipated.[26]

The coverage of cervical cancer screening in South Africa is currently less than two thirds of the female population. The ICER obtained from this model would probably be an overestimation of the benefits of HPV vaccination because, only 70% of cervical cancers are due to HPV 16 and 18. The remaining 30% of cervical cancers could be reduced through early detection of precancerous lesions via an effective cervical cancer screening program. Therefore a high coveragecervical cancer screening program is essential , to ensure precursors to cervical cancers are detected and treated timeously.

Strengthening of the cervical cancer screening program is required for secondary prevention of cervical cancer, as the HPV vaccine does not eliminate, but rather reduces the risk of cervical cancer. Other approaches to cervical cancer screening, such as Visual Inspection with Acetic Acid (VIA) and HPV DNA testing need to be explored as well.[58]

In all countries that performed an economic analysis of HPV vaccination, the consistent message has been to continue to strengthen cervical cancer screening or continue with existing cervical cancer screening programs in addition to the introduction of HPV vaccination. The United States introduced HPV vaccination into their national program in 2006.[91] The U.S. Preventive Services Task Force

(USPSTF) still recommends cervical cancer screening, as there is high certainty and the net benefit is substantial for cervical cancer screening, in women aged 21 to 65 years old with cytology (Pap smear) every three years.[92] For women aged 30 to 65 years, who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing is every five years.[92]

6.3.1. Cervical cancer screening in HIV-infected women

Women diagnosed with HIV who have initiated sexual intercourse, should undergo cervical cancer screening at six month intervals until two pap tests are negative, and then annually thereafter.[93] The 2012 national estimate of HIV prevalence in women in South Africa is 14.4% with peak prevalence at age 30 to 34 years.[21] As this is a significant health burden suspicious cervical lesions in HIV positive women should be closely followed up, monitored and treated in an expedited manner.

6.4. HPV Vaccine

Long term data on vaccine efficacy and final outcomes like prevention of cervical cancer is lacking due to the time required for persistent oncogenic HPV infection to progress to cancer. HPV vaccines do not appear to alter the course of established cervical HPV infection or disease.[37]

HPV Vaccine efficacy in nine year old girls has not been directly demonstrated in randomized clinical trials. Immunogenicity bridging analysis infers efficacy in this age group. Cervarix® induced Geometric mean Titers (GMTs) in 10 to14 year old girls of 2.1 to 2.5 fold higher than those induced in 15 to 25 year old women.[37] Cervarix® delivered at zero and six months to nine to14 year old girls was non-inferior to the standard three-dose schedule. Follow up studies are required to determine the durability of the two-dose regimen compared to a three-dose regimen.[37]

Jit et al. reported[43] that the bivalent HPV vaccine has received marketing authorisation in the European Union for a two-dose schedule, while the quadrivalent vaccine has received a positive opinion from the European Medicines Agency for a

two-dose schedule pending marketing authorisation. Two-dose HPV schedules have been adopted in Quebec, Switzerland, the Netherlands and Mexico. The United Kingdom's Joint Committee on Vaccination and Immunisation recently recommended a two-dose schedule.[43]

Bonanni et al. reported that bivalent vaccine data up to 6.4 years, show persistence of antibodies to both vaccine types in >98% subjects. Clarity is required on the mechanism by which vaccination induces protection, the reason for continuing vaccine efficacy (also in subjects who lost anti-HPV over time) and the possibility to induce an anamnestic response following a viral challenge occurring through a sexual intercourse.[94] Both vaccines can have a variable level of cross protection against HPV types genetically and antigenically closely related to the vaccine types.[94]

The current data on Cervarix® vaccine sustained immunogenicity and efficacy is up to 8.4 years.[95] Almost all economic studies in LMICs, including this study, assumed lifelong vaccine protection. If this assumption is incorrect this could reduce the attractiveness of HPV vaccination.

The need for a booster vaccination dose in South Africa needs to be considered, especially if the duration of protection is found to be less than lifelong. When the current vaccinated nine year old vaccinated girls reach 19 years of age, there should be data available to indicate if the duration of the protective effect is up to 10 years and this will assist decision making if a booster dose is required.

The immunogenicity and efficacy of HPV vaccines in immunocompromised individuals has been assessed for Gardasil® in children seven to 12 years old and was found to be safe and well tolerated. Seroconversion rate were greater than 95% and antibody titers were approximately 50% of those measured in HIV-uninfected individuals of similar age.[37] The results of the vaccine efficacy study in HIV positive women in South Africa will provide local setting information on the effects of HPV

vaccination in HIV positive women.[96] The AIDS Clinical Trials Group protocol A5240, a trial of 319 HIV-infected women aged 13 to 45 years old, in the United States, Brazil and South Africa determined the immunogenicity and safety of the quadrivalent HPV vaccine in three strata based on screening CD4 count.[97] The study found that the quadrivalent HPV vaccine was highly immunogenic, but women with CD4 counts <200 cells/µL had lower seroconversion rates compared with women with higher CD4 cell counts.[97]

The vaccine safety profile was considered excellent in a review conducted on clinical trials of HPV vaccines.[37] Review articles of cost effectiveness of HPV vaccines do not state the vaccine safety profile as one of the country's model input parameters suggesting that vaccine safety is not a significant factor for the economic analysis. More long term data on HPV vaccine characteristics are required in order to provide a more accurate estimate of their actual costs and benefits.[51]

An ideal HPV vaccine would be one with low cost, a long shelf life, no cold chain required and administered orally or via a nasal spray as a single dose.[2] This would have benefits of reducing vaccination program costs, injection site reactions and could possibly improve compliance and overall vaccination coverage.

6.4.1. HIV co-infection

The based case model did not take into account acquiring HIV co-infection as a girl gets older. South Africa has a high burden of HIV infection with peak prevalence occurring in women between 30 to 34 years old. HIV-infection is strongly associated with a higher prevalence, incidence, and persistence of HPV infection and correlated with prevalence, incidence, persistence, and progression of squamous intraepithelial lesions.[76]

Figure 6.1: Prevalence of HIV and Incidence of cervical cancer by age (see Table S10 and S11 in supplemental information)

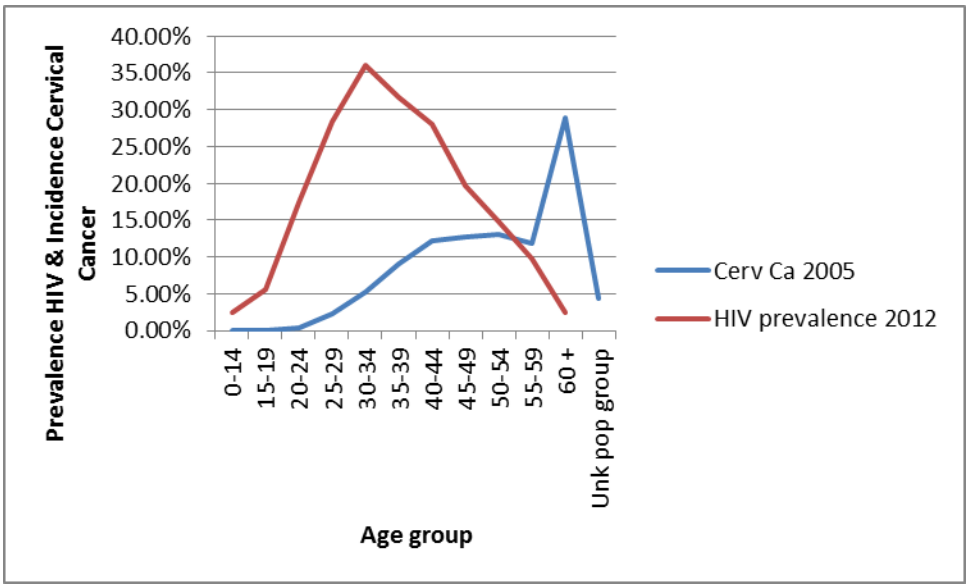


Figure 6.1 indicates the peak age of HIV prevalence (red curve) is earlier than peak age for cervical cancer cases (blue curve) in South Africa. Most cross-sectional studies show that the prevalence of cervical HPV DNA is higher in HIV-positive than in HIV-negative women, even after controlling for potential confounding factors such as age and sexual behavior.[75] The adjustment for sexual habits of the male partners was not specified in the study. The ratios of HPV prevalence between HIV-positive and HIV-negative women were In United states greater than 1 (1.4 to 2.7), 1.5 in Brazil, 3.2 in Honduras, 1.1 in Austria, 9.3 in Italy, 1.0 in Tanzania and 3.6 in Senegal.[76]

Although the roll-out of ARVs has increased in South Africa, it will take some years to obtain data to assess changes to risk in cervical cancer incidence in HIV positive women. The REACH study did not show that HAART results in immediate effects on high-risk HPV type incidence, clearance and persistence.[98] Long term studies are required to assess impact of HAART and immune restoration along with medication adherence on HPV infection.[98]

6.5. Conclusions about each research question

This study estimated the burden of cervical cancer caused by HPV strains 16 and 18 and determined the costs of treating cervical cancer in South Africa by updating a previous model by Sinanovic et al.[58] with more recent costs, prevalence data and current government roll-out of HPV vaccination. The findings are consistent with other economic evaluations of HPV vaccination in various settings in that the HPV vaccine strategy was dominant when compared to no HPV vaccination.

Mathematical modelling and economic analyses provide helpful information about the long term benefits of HPV vaccination.[50] The uncertainties identified from the model provide the basis for future research and consideration.

The percentage of cervical cancers cases (approximately 85%) averted by a HPV vaccination program in South Africa was determined at 100% vaccination coverage. The incremental cost effectiveness of a HPV vaccine program followed by screening and treatment versus screening and treatment of precancerous and cancerous health states in South Africa was determined. The cost of a school based HPV vaccination program in South Africa for the population estimate of nine year old girls in South Africa was calculated.

The results compare with other studies in low and middle income countries (LMICs) in that vaccination is likely to be cost effective and possibly cost saving as hospital based care for cervical cancer treatment is a substantial cost driver.

Cervical cancer incidence and mortality is a huge public health concern. In South Africa the female population which predominantly black (79.8%), have the highest risk for acquiring cervical cancer. This could reflect a true incidence or maybe because they present to healthcare services late due to lack of awareness, poverty and other barriers in accessing healthcare. A USA study reported that some of the disparity maybe explained by lack of screening and early detection and unknown

factors like biological disparity[99], however a much larger sample size is required to compare the natural history of HPV infection.

The cervical cancer incidence is compounded with the burden of HIV and AIDs in South Africa, which increases the risk of cervical cancer disease.[96] Interventions to prevent precursors to cervical cancer are still required in addition to high vaccination and screening coverage. Consideration should be given to provide third vaccine dose or a booster dose to known HIV positive girls due to possible decrease in antibody titres as demonstrated by a study done with Gardasil.[37] The Centres for Disease Control and Prevention recommend HPV vaccination of HIV-positive people from 11 to 26 years old regardless of CD4 count.[100] Younger women presenting with cervical cancer should be tested for HIV. Regular screening, diagnosis and prompt treatment of precancerous lesions will help to reduce the incidence of cervical cancer.

As the HPV 16 and 18 vaccine is protective against 70% of all cervical cancers, it is important to educate vaccinated women of the need for screening and the possibility of cervical cancer due to the other oncogenic HPV types (33, 35, 45) responsible for about 25% of all cervical cancers.[14]

The cost of a school based vaccination program was determined for the entire population of nine year old girls in South Africa and estimated to cost R322 878 732.75 for a two-dose vaccine schedule and no catch up vaccination. This results in a cost saving of R1 818 592 307.90 due to averting costs of diagnosis and treatment of LSIL, HSIL and cervical cancer cases, averted due to HPV 16 and 18 vaccination. If costs for vaccination of nine to 12 year old girls is factored (R1 290 433 093) then the costs of vaccination increases and the costs averted will depend on the additional number of LSIL, HSIL and cervical cancer cases averted.

This study suggests that vaccinating nine year old school girls prior to the sexual debut followed by the current screening policy to prevent cervical cancer in South

Africa is a cost-effective strategy and potentially cost saving from a public sector healthcare provider perspective.

6.6. Limitations to the study

This study was limited to vaccination of nine year old school girls receiving HPV vaccination in 2013 with no catch up vaccination for older girls. The model was populated with probabilities of events obtained from international published literature due to lack of current South Africa specific epidemiological data for the various health states.

As a static model was created, the effect of herd immunity is unknown and other co-morbidities like acquiring HIV co-infection after HPV vaccination was not evaluated. The model also did not take into account temporal effects of sexual behaviour, vaccine price maturity; and various rates of HPV vaccination uptake and cervical cancer screening coverage.

The incidence of anogenital warts, oropharyngeal, anal cancers and juvenile-onset recurrent respiratory papillomatosis (JORRP) in South Africa was also not explored since the current HPV vaccine roll-out is the bivalent vaccine which does not protect against conditions caused by HPV types 6 and 11. Low risk HPV types 6 and 11 account for 90% of anogenital warts and nearly all cases of JORRP.[101]

6.6.1. Epidemiology and local setting information

The limitations of this study include lack of current epidemiological data on incidence of HPV infections, precancerous lesions and cervical cancer; rates of progression and regression between the health states based on South African population and health-related quality of life weights for South African population. The variation in quality of life weights used in other studies makes it difficult to compare their effect on ICERs across studies.[51]

The model input data for probabilities and outcomes were obtained from the literature, which made it difficult to test the validity of the model in the local setting. A local, up to date, population-based cancer registry, with mandatory reporting of all new cervical cancer cases and cervical cancer deaths, would provide more accurate data for a robust economic analysis of HPV vaccination.

6.6.2. School based vaccination program

In South Africa grade four school girls are eligible for HPV vaccination as this is the grade when majority of girls will be nine years old. Prior to introduction of HPV vaccination, the EPI schedule did not contain any vaccinations at nine years of age; therefore this study assumed school based vaccination incurs program costs in addition to vaccine costs. The costs for school based vaccination program were based on a school health costing scenario for school nurses for audiometry assessments, from the Department of Health (personal correspondence on 9 April 2013).

The current nation HPV vaccination program targets girls in grade four. This study used the 2013 population estimate for the number of nine year old girls in 2013 and this total number of girls would differ as grade four students consist of other age groups as well.

The health intervention of HPV vaccination in South Africa coupled with an educational and surveillance program will ensure ongoing safety, monitoring and evaluation, to ensure the safety and well-being of all vaccinated school girls.

6.7. Future Research

The limitations and uncertainties raised in this study provide an opportunity for further research in economic analysis and long term follow up studies:

- The uptake of HPV vaccination in South Africa and factors contributing to success or failure of the program

- HPV vaccination with evaluation of co-morbidities, as a vaccinated girl grows older, like HIV co-infection.
- Economic analysis from a societal perspective of a two-dose vaccine schedule
- Of a two-dose schedule plus a booster vaccine for HIV positive girls
- Cost effectiveness of a two-dose quadrivalent versus bivalent vaccine
- HPV vaccination of boys in addition to girls prior to age of sexual debut
- Catch up vaccinations for girls older than nine prior to sexual debut
- Health related quality of life studies for precancerous lesion and cervical cancer health states.
- Long term studies could include the duration of immunogenicity of vaccinated nine year old girls and follow up of vaccinated girls, to study the age specific incidence of precancerous lesions and cervical cancer.

7. References

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8. Appendices

Permission letter from ethics committee

Supplemental information

Figure S1: Well State of the Decision Tree

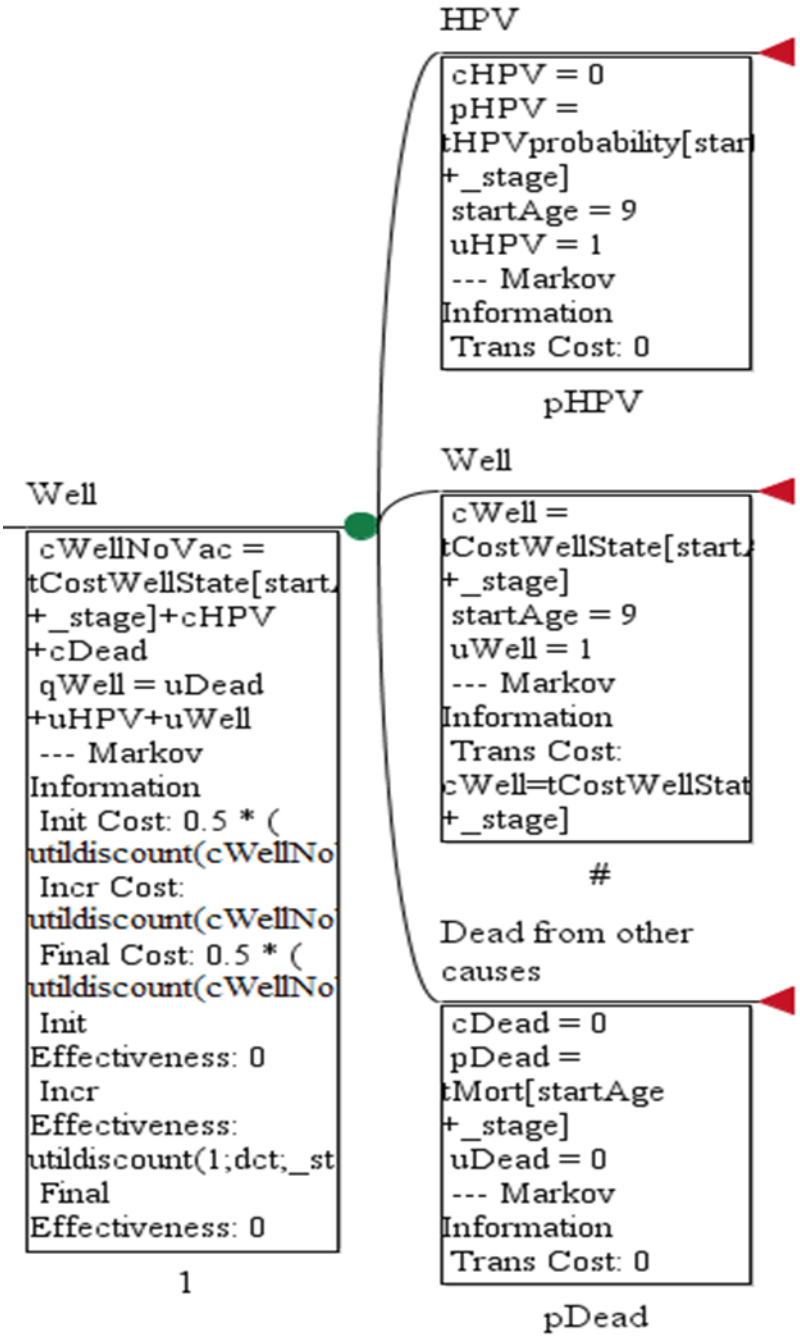


Figure S2: HPV State of the Decision Tree

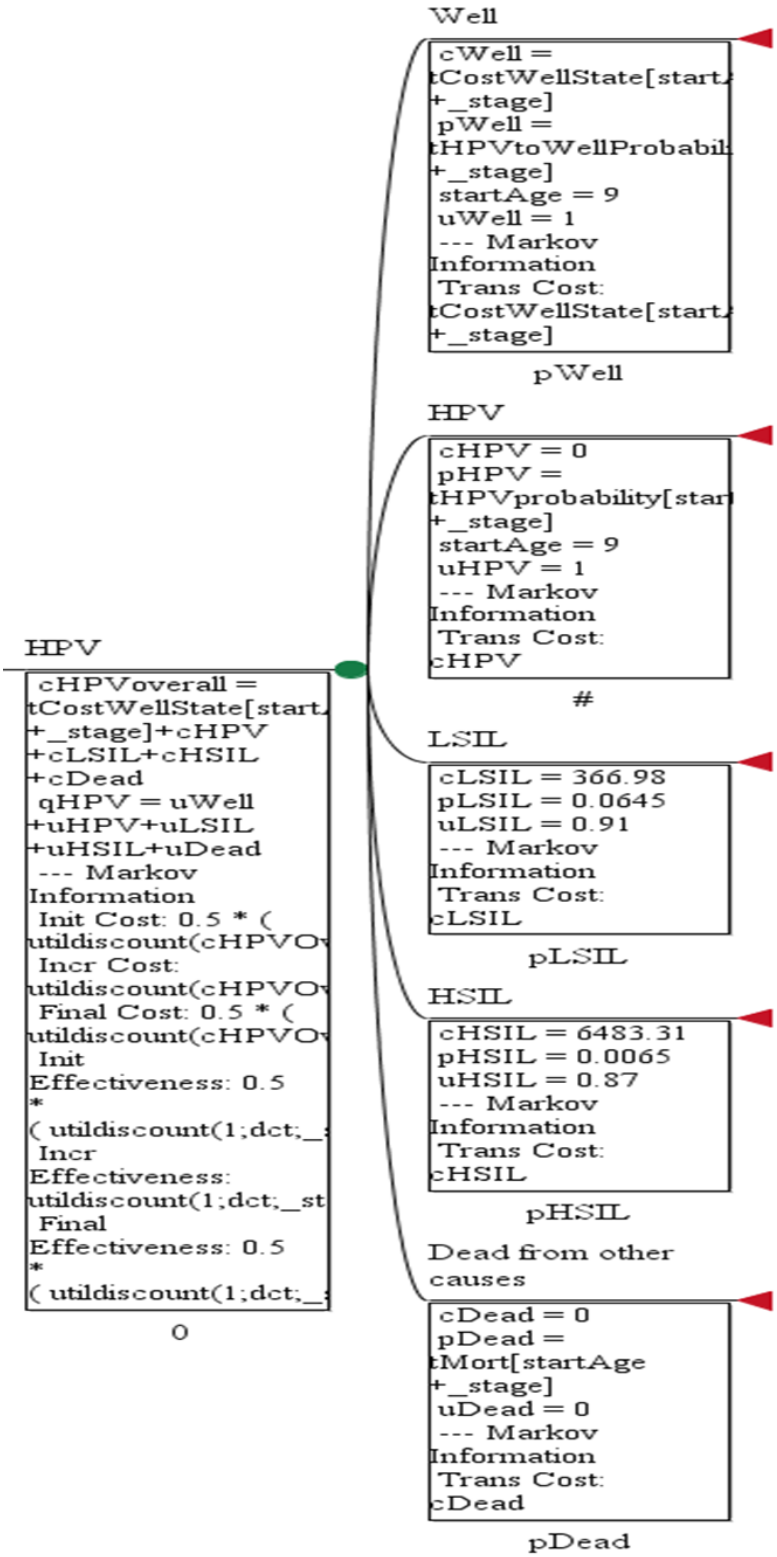
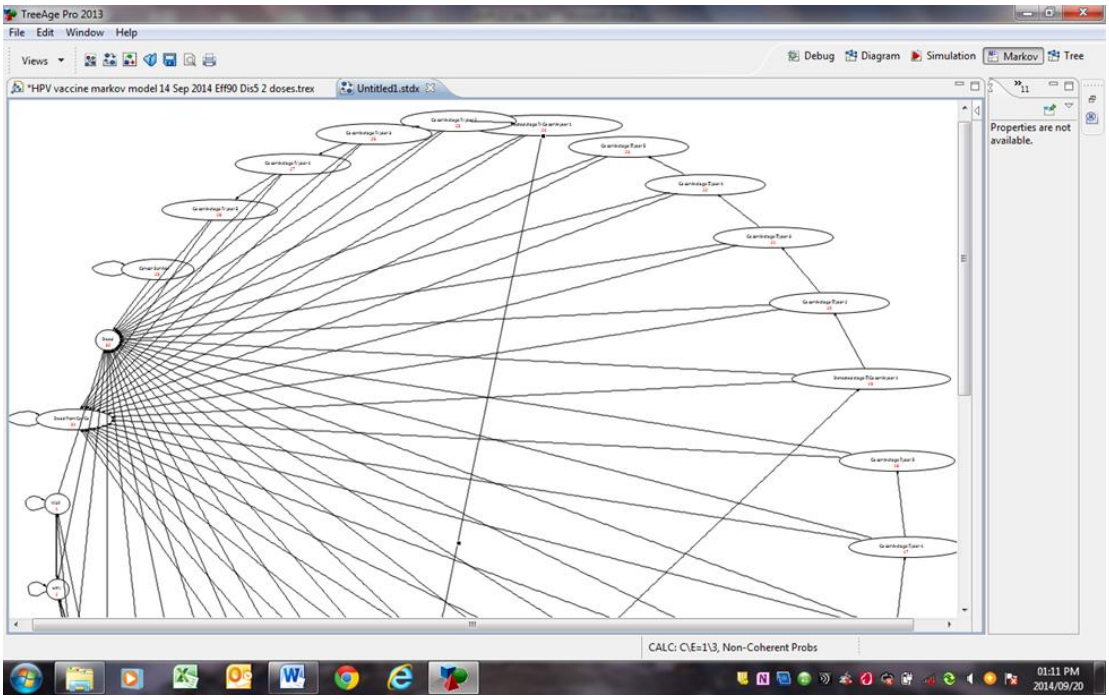


Figure S3: Diagrammatic representation of Transition Health States



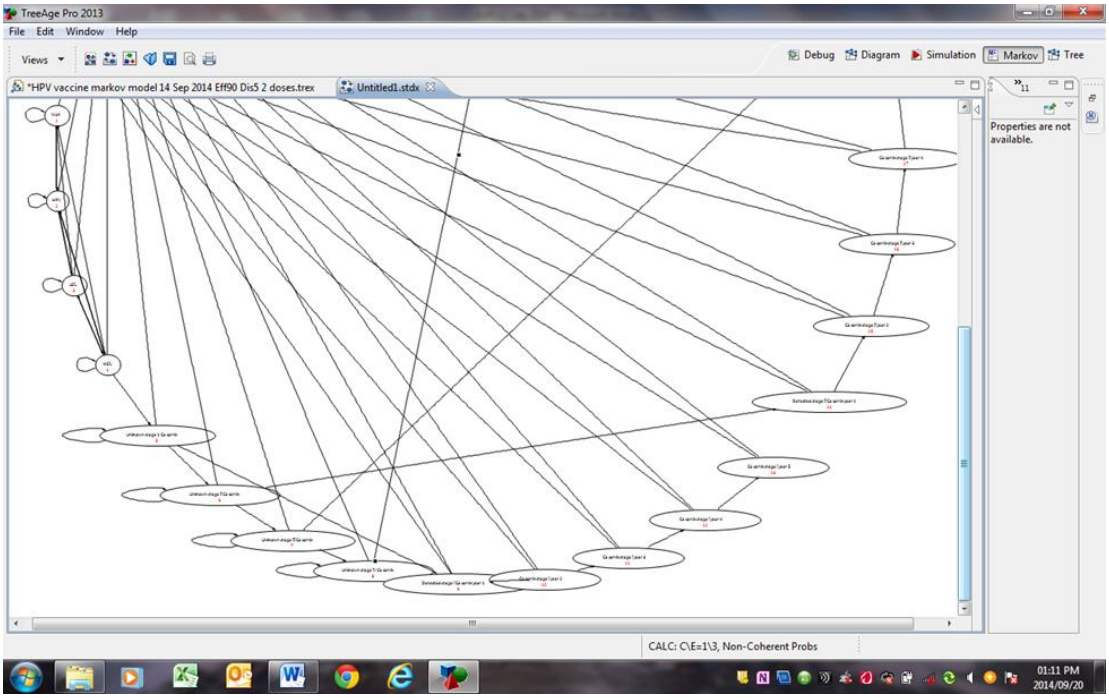


Table S1: Costs of diagnosis and treatment of precancerous lesions and cervical cancer in South African Rand

		Average currency exchange rate in 2007: 1US$=R6.50	CPI= 10.40%	CPI= 7.20%	CPI=4.30%	CPI=5.00%	CPI=5.60%	CPI=5.77%
Cost year	**Health service cost 2007 US$ (Sinanovic et al.)57**	**2007**	**2008**	**Cost year**	**Health service cost 2007 US$ (Sinanovic et al.)57**	**2007**	**2008**	**Cost year**
Diagnosis and treatment of low SIL	39	253.50	279.86	300.01	312.91	328.56	346.96	366.98
Diagnosis and treatment of high SIL	689	4 478.50	4 944.26	5 300.25	5 528.16	5 804.57	6 129.63	6 483.31
Diagnosis and treatment of cancer stage I	3 923	25 499.50	28 151.45	3 0178.35	31 476.02	33 049.82	34 900.61	3 6914.38
Diagnosis and treatment of cancer stage II	5 361	34 846.50	38 470.54	41 240.41	43 013.75	45 164.44	47 693.65	50 445.57
Diagnosis and treatment of cancer stage III	5 361	34 846.50	38 470.54	41 240.41	43 013.75	45 164.44	47 693.65	50 445.57
Diagnosis and treatment of cancer stage IV	7 323	47 599.50	52 549.85	56 333.44	58 755.77	61 693.56	65 148.40	68 907.47

The costs of diagnosis and treatment of LSIL, HSIL and cervical cancer (see table A1) was based on costs used by Sinanovic et al.[58] by converting the reported costs in US dollars back to South African currency using the average currency exchange

rate in 2007 as reported by Sinanovic et al.[58] Costs were then inflated per year by the annual consumer price index published by Statistics South Africa.[69]

Post completing this study an error was detected for the CPI inflation factor used for 2008. The correct average inflation published by Statistics South Africa was 11.50% and not 10.4%. The effect of this error is that the 2013 costs (see Table S1) is underestimated by 1%. These costs were varied in sensitivity analysis by 10% (increase and decrease) and LSIL, HSIL and cervical cancer costs were sensitive to this change (see Table 5.5).

The model was revised with corrected costs for HSIL, LSIL and Cervical cancer stages 1 to 4 as per Table S1.1 below and new ICER is shown in Table S2.

Table S1.1: Corrected costs of diagnosis and treatment of precancerous lesions and cervical cancer in South African Rand

		Average currency exchange rate in 2007: 1US$=R6.50	**CPI= 11.50%**	**CPI= 7.20%**	**CPI=4.30 %**	**CPI=5.00%**	**CPI=5.60%**	**CPI=5.77%**
Cost year	**Health service cost 2007 US$ (Sinanovic et al.)57**	**2007**	**2008**	**Cost year**	**Health service cost 2007 US$ (Sinanovic et al.)57**	**2007**	**2008**	**Cost year**
Diagnosis and treatment of low SIL	39	253.50	282.65	303.00	316.03	331.83	350.42	370.64
Diagnosis and treatment of high SIL	689	4 478.50	4 993.53	5 353.06	5 583.24	5 862.41	6 190.70	6 547.90
Diagnosis and treatment of cancer stage I	3 923	25 499.50	28 431.94	30 479.04	31 789.64	33 379.12	35 248.35	37 282.18
Diagnosis and treatment of cancer stage II	5 361	34 846.50	38 853.85	41 651.32	43 442.33	45 614.45	48 168.86	50 948.20
Diagnosis and treatment of cancer stage III	5 361	34 846.50	38 853.85	41 651.32	43 442.33	45 614.45	48 168.86	50 948.20
Diagnosis and treatment of cancer stage IV	7 323	47 599.50	53 073.44	56 894.73	59 341.20	62 308.26	65 797.53	69 594.04

Table S2: Base case cost-effectiveness of adding a two-dose HPV vaccination to the existing screening program in South Africa

Model Scenario	Strategy	Lifetime Cost (per patient)	Incremental Cost (per patient)	Effect (per patient)	Incremental Effect (per patient)	Incremental Cost Effectiveness Ratio (R/QALY)	
2 Dose Vaccine (90% efficacious and 5% discount rate) Life expectancy 61 years	HPV vaccine	R2043.18	-R4437.47	45.03 QALYs	0.41 QALY	-R10 696.74	undominated
	No HPV vaccine	R6480.65		44.62 QALYs			absolute dominated

The change to the original base case ICER is R128.95 (difference between R10 696.74 and R10 567.79 from Table 5.1).

Table S3: Cost calculation of a Pap test

Cost parameter	2012 cost per unit	2013 cost per unit (2012 cost inflated by 10%)
Facility Fee (UPFS code 1010)	R81.00	R90.00
General Medical Practitioner (UPFS 1011)	R75.00	R83.00
Exfoliative Cytology (gynae) smear (NHLS code 1370)	N/A	R52.27
Total		**R225.27**

Table S4: Number of stage 1 cervical cancer cases averted by HPV vaccination for total vaccinated cohort of 507 073 girls

Age (years)	No HPV Vaccine: Cervical Cancer Stage 1	HPV Vaccine: Cervical Cancer Stage 1	Number of Cervical Cancer Stage 1 Cases Averted
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	1	0	1
14	4	0	3
15	7	1	6
16	11	1	9
17	14	2	13
18	18	2	16
19	23	3	20
20	29	4	25
21	37	5	32
22	47	7	40
23	58	8	50
24	70	10	60
25	82	12	70
26	93	14	80
27	106	16	90
28	118	17	101
29	129	19	110
30	138	20	119
31	147	21	126
32	154	21	133
33	160	22	138
34	165	22	143
35	169	23	146
36	171	23	148
37	172	23	149
38	172	24	148
39	171	25	146
40	169	27	142
41	167	29	139
42	165	30	135
43	162	31	131
44	159	32	127
45	156	33	123
46	153	33	120
47	158	33	125
48	166	33	133
49	176	33	143
50	186	33	153
51	194	33	161
52	201	32	168
53	206	32	174
54	210	31	178

55	212	31	181
56	213	30	183
57	212	29	183
58	211	29	182
59	209	28	181
60	206	27	179
61	202	26	176
Total	6 558	1 020	5 538

Table S5: Number of stage 2 cervical cancer cases averted by HPV vaccination for total vaccinated cohort of 507 073 girls

Age (years)	No HPV Vaccine: Cervical Cancer Stage 2	HPV Vaccine: Cervical Cancer Stage 2	Number of Cervical Cancer Stage 2 Cases Averted
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	1	0	1
16	2	0	2
17	3	0	3
18	4	0	4
19	6	1	5
20	7	1	6
21	9	1	8
22	12	2	10
23	15	2	13
24	19	3	16
25	23	3	20
26	28	4	24
27	32	5	28
28	37	5	32
29	42	6	36
30	46	7	40
31	51	7	43
32	54	8	47
33	58	8	50
34	60	8	52
35	63	9	54
36	65	9	56
37	66	9	57
38	67	9	58
39	67	9	58
40	67	10	58
41	67	10	57
42	66	11	55
43	65	11	54
44	64	12	53
45	63	12	51
46	62	12	50

47	61	13	48
48	61	13	48
49	63	13	50
50	66	13	53
51	69	13	56
52	72	13	60
53	75	13	63
54	78	12	65
55	80	12	67
56	81	12	69
57	82	12	70
58	83	12	71
59	83	11	71
60	82	11	71
61	81	11	70
Total	**2 409**	**377**	**2 032**

Table S6: Number of stage 3 cervical cancer cases averted by HPV vaccination for total vaccinated cohort of 507 073 girls

Age (years)	No HPV Vaccine: Cervical Cancer Stage 3	HPV Vaccine: Cervical Cancer Stage 3	Number of Cervical Cancer Stage Cases Averted
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	1	0	1
18	1	0	1
19	1	0	1
20	2	0	2
21	2	0	2
22	3	0	3
23	4	1	3
24	5	1	4
25	6	1	5
26	8	1	6
27	9	1	8
28	11	2	9
29	12	2	10
30	14	2	12
31	15	2	13
32	16	2	14
33	18	2	15
34	19	3	16
35	20	3	17
36	20	3	18
37	21	3	18
38	21	3	19

39	22	3	19
40	22	3	19
41	22	3	19
42	22	3	18
43	21	3	18
44	21	4	17
45	21	4	17
46	20	4	17
47	20	4	16
48	20	4	16
49	20	4	16
50	20	4	16
51	21	4	17
52	22	4	18
53	23	4	19
54	24	4	20
55	25	4	21
56	26	4	22
57	26	4	22
58	27	4	23
59	27	4	23
60	27	4	23
61	27	4	23
Total	**754**	**118**	**635**

Table S7: Number of stage 4 cervical cancer cases averted by HPV vaccination for total vaccinated cohort of 507 073 girls

Age (years)	No HPV Vaccine: Cervical Cancer Stage 4	HPV Vaccine: Cervical Cancer Stage 4	Number of Cervical Cancer Stage Cases Averted
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	1	0	1
19	2	0	1
20	2	0	2
21	3	0	3
22	4	0	3
23	5	1	4
24	6	1	5
25	8	1	7
26	10	1	9
27	12	2	11
28	15	2	13
29	17	3	15
30	20	3	17

31	22	3	19
32	25	4	21
33	27	4	23
34	29	4	25
35	31	4	26
36	32	4	28
37	33	5	29
38	34	5	30
39	35	5	30
40	35	5	31
41	36	5	31
42	36	5	30
43	35	5	30
44	35	6	29
45	34	6	29
46	34	6	28
47	33	6	27
48	33	6	26
49	32	7	25
50	32	7	25
51	33	7	26
52	35	7	28
53	36	7	29
54	38	7	31
55	40	7	33
56	41	7	34
57	42	7	35
58	43	6	36
59	43	6	37
60	44	6	37
61	44	6	38
Total	**1186**	**187**	**998**

Table S8: Number of cervical cancer deaths averted due to HPV vaccination for total vaccinated cohort of 507073 girls

Age (years)	No HPV Vaccine: Cervical Cancer Deaths	HPV Vaccine: Cervical Cancer Deaths	Number of Cervical Cancer Deaths Averted
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	1	0	1
17	1	0	1
18	2	0	2
19	4	0	3
20	6	1	5
21	8	1	7
22	10	1	9

23	13	2	11
24	16	2	14
25	20	3	18
26	25	4	22
27	31	4	27
28	37	5	32
29	44	6	37
30	50	7	43
31	57	8	48
32	63	9	54
33	69	10	59
34	74	11	64
35	79	11	68
36	83	12	72
37	87	12	75
38	89	12	77
39	91	12	79
40	93	13	80
41	93	13	80
42	93	13	80
43	93	14	79
44	92	15	77
45	91	15	76
46	90	16	74
47	88	16	72
48	87	17	70
49	86	17	69
50	86	18	69
51	88	18	70
52	91	18	73
53	95	18	77
54	99	18	81
55	103	18	85
56	106	17	89
57	109	17	92
58	112	17	95
59	113	17	96
60	114	16	98
61	114	16	98
Total	**3 096**	**490**	**2 606**

Table S9: Incidence of HPV 16 and 18 from local study (Richter* et al.)[78] *versus model prediction.

Age Group (years)	Richter HPV16/18+	Model HPV 16/18+
<25	24	29
25 to 29	22	19
30 to 34	24.5	14
35 to 39	21.4	11
40 to 44	18.5	9
45 to 49	15.6	8
50 to 54	13.7	6
≥55	15.6	4

Table S10*: *Frequency of histologically diagnosed cervical cancer in South Africa in 2005 by Age and Population group versus Markov model number of Cervical Cancers Stage 1.

South Africa 2005 Data[11]		**Data derived from Markov model**	
Age Group	**Cervical Cancer cases**	**Age group**	**Cervical Cancer stage 1 cases**
0 to 4	1	0 to 8	N/A as model starts at 9 years old
5 to 9	0	9	0
10 to 14	1	10 to 14	0
15 to 19	3	15 to 19	0
20 to 24	17	20 to 24	73
25 to 29	106	25 to 29	240
30 to 34	253	30 to 34	529
35 to 39	439	35 to 39	766
40 to 44	591	40 to 44	858
45 to 49	616	45 to 49	827
50 to 54	635	50 to 54	815
55 to 59	577	55 to 59	1 004
60 to 64	433 (approximated 173 for ages 60 to 61)	60 to 61	1 069
Sub total	3 672		
65 to 69	351		
70 to 74	308		
75 to 79	178		N/A: average life expectancy of 61 years
80 to 84	81		
85+	49		
Unknown population group	212		
Total	**4 851**	**Total**	

Table S11: HIV prevalence (women) by age, South Africa 2012[21]

Age group (years)	Prevalence
0 to 14	2.40%
15 to 19	5.60%
20 to 24	17.40%
25 to 29	28.40%
30 to 34	36.00%
35 to 39	31.60%
40 to 44	28.00%
45 to 49	19.70%
50 to 54	14.80%
55 to 59	9.70%
60+	2.40%