Exploring the cost-effectiveness of including boys in HPV vaccination in South Africa

By Nuvika Pillay

Supervised by: Andrew Donaldson

of the School of Economics, UCT

December 2020

Topic provided by CANSA

UCT KNOWLEDGE CO-OP

The research for this Long research paper was conducted for the Honours Degree in Economics based on a request for such research by CANSA.

The UCT Knowledge Co-op facilitated this collaborative project between CANSA and UCT.

See http://www.knowledgeco-op.uct.ac.za or
Contact us at know-op@uct.ac.za / 021 – 650 4415

Abstract

The Human Papillomavirus (HPV) is responsible for nearly all cases of cervical cancer. While South Africa has implemented a girls-only HPV vaccination programme to reduce the prevalence of cervical cancer, recent research demonstrates an increasing burden of other HPV-related cancers, which affect both sexes. This study uses a dynamic Markov Model to estimate the cost-effectiveness of including boys in the existing vaccination programme. To the author's knowledge, it is the first study to investigate a universal vaccine in South Africa and to account for the effects of herd-immunity within its analysis. The analysis of a two-dose, universal vaccination programme that reaches 60% of the population, yields an incremental cost-effectiveness ratio of ZAR 196 868 per quality-adjusted life year (QALY) gained, which falls within the WHO's cost-effectiveness threshold. The results also find a single dose programme, reaching 80% of the population, to have a lower price (ZAR 185 412) per QALY, making this programme more desirable.

1. Introduction

The Human Papillomavirus (HPV) is the most common sexually transmitted infection and a well-established cause of almost all cases of cervical cancer (World Health Organisation, 2017). To combat South Africa's high burden of cervical cancer, the National Department of Health introduced the HPV Vaccination program in 2014. The school-based vaccination programme is administered to female Grade 4 learners who receive two doses of the vaccine, six months apart. The programme has been hailed as a success, reaching approximately 65% of targeted female age-cohort in 2014 (Delany-Moretlwe et al., 2018).

Recently, there has been interest in the feasibility of universal HPV vaccination programmes from policymakers worldwide. Further research has provided evidence of HPV also being responsible for an important fraction of other anogenital, head, neck and throat cancers (Bruni et al., 2019). Thus, universal vaccination could prevent other HPV-related cancers that affect both men and women. While there is evidence that a female-only vaccination program indirectly protects males through 'herd-immunity', it has been argued that extended national HPV vaccination programmes provide males with greater protection. In 2014, Australia launched the first national universal HPV vaccination program with the United Kingdom following suit in 2019 (Prue, Grimes, Baker, & Lawler, 2018).

This paper preliminarily explores the cost-effectiveness of adding boys to the South African HPV vaccination programme. It does so in a three-pronged approach. First, the study reviews relevant research in the field of HPV and associated cancers, both domestically and internationally. Following that, the paper proposes and describes a Markov Model used to estimate the cost-effectiveness of a universal vaccine. The next section describes the results obtained from the crude model designed in this study, considering varying levels of coverage and scenarios. Lastly, the

paper considers the limitations of this initial study and describes future areas of development for future studies.

2. Literature Review

Despite it being a preventable disease, cervical cancer remains the leading cause of cancer mortality for women in southern Africa, (Delany-Moretlwe, Chikandiwa, & Gibbs, 2013). Bruni et al. (2019) found there were 20.2 million women at risk for cervical cancer in South Africa. Annually, the country diagnoses 12,983 new cases of cervical cancer and the disease leads to an estimated 5,595 deaths (Bruni et al., 2019). In South Africa, more than half of women diagnosed with cervical cancer will die of the disease (Richter, 2015). Research has shown that HPV types 16 and 18 are responsible for roughly 70% of cervical cancer cases worldwide (Bruni et al., 2019). This points to HPV vaccination as a vital intervention in preventing cervical cancer. Consequently, the World Health Organization (WHO) (2017) recommends vaccinating young girls against HPV before they are sexually active, as the most cost-effective public health measure against cervical cancer in high-prevalence environments like South Africa (World Health Organisation, 2017).

Based on the WHO's recommendation, the Department of Health implemented a school-based, girls-only HPV-vaccination programme in April 2014 (Delany-Moretlwe et al., 2018). The programme vaccinated over 350 000 grade 4 girls and reached 16 000 public schools in its first year (Delany-Moretlwe et al., 2018). This represents 65% of the targeted cohort. A school-administered programme was chosen as primary school attendance is compulsory and 'virtually universal' in South Africa (Delany-Moretlwe et al., 2018). However, private schools were excluded from the intervention (Richter, 2015). Up-take on HPV vaccines in the private-health sphere also remains low, possibly a result of the high price of the vaccine (Richter, 2015). This suggests a significant proportion of the total female cohort has not been vaccinated (Richter, 2015). Richter

(2015) estimates the total coverage of the vaccine amongst all children born in 2004 (including all boys and girls in private schools) to be approximately 39%. Thus, there is scope to increase vaccine coverage within the population despite the success of the government's HPV vaccination programme.

However, there has been growing evidence to suggest men also face a significant burden of HPV infection and suffer from its associated diseases (Kotsopoulos, Connolly, & Remy, 2015). Men infected with HPV are at greater risk of various forms of anogenital (most commonly anal and penile), head and neck cancers (Delany-Moretlwe et al., 2013). Research has shown an increasing prevalence of HPV-related anal and penile cancers in high-income countries but similar prevalence information for sub-Saharan Africa is limited (Prue, Grimes, et al., 2018). That said, one recent study, analysed the prevalence of other HPV-related cancers (defined as all HPV-cancers besides cervical cancer) in South Africa (Chikandiwa, Pisa, Sengayi, Singh, & Delany-Moretlwe, 2019). This study relied on information from the South African National Cancer Registry and mortality reports from Statistics South Africa in order to investigate developing trends in these cancers from 1994 to 2013, taking into account changes in lifestyle and other factors. Importantly, Chikandiwa et al. (2019) showed an increased incidence and mortality rate for anogenital cancers for both men and women in this period. Thus, there is scope to reduce anogenital cancer infections and mortality in South Africa by extending HPV protection to both sexes.

Of particular relevance in South Africa, the literature emphasizes that the incidence of HPV-related cancers is higher in HIV positive populations (Chikandiwa et al., 2019; Kotsopoulos et al., 2015; Palefsky, 2010). HPV vaccination programmes are particularly pertinent in South Africa due to the country's combined burden of diseases, which leads to higher risk for both men and women (Williamson, 2015). Chikandiwa et al. (2019) propose that the increased HPV-related burden of disease is due to South Africa's rising HIV prevalence in recent periods. HIV is associated with an

increased risk of HPV infection, persistence and progression to cancer (Chikandiwa et al., 2019). The HIV-positive population is more likely to develop pre-cancerous lesions such as anal intraepithelial neoplasia and cervical intraepithelial neoplasia, which if untreated, develop into cancer (Williamson, 2015).

Importantly, Palefsky (2010) shows that the incidence of HPV-related cervical and anal cancers in the HIV-positive population does not decline with the introduction of antiretrovirals (ARVs). Instead, prolonged life-span enabled by ARVs has resulted in an increased number of cases being reported, as there is more time for the precancerous lesions to accumulate genetic changes (Palefsky, 2010). This is compounded by the lack of clear screening guidelines for cancer in South Africa which give the infection more time to develop undetected (Palefsky, 2010). Chikandiwa et al. (2019) argue that there exists a complex, reciprocal relationship between the diseases, as men and women who are infected with multiple HPV types are at greater risk of HIV-infection. It is therefore possible that increased protection against HPV could also result in decreasing HIV-levels, though this effect needs to be studied more closely to establish the relationship more precisely. Overall, it appears that rising HIV levels has resulted in an increased incidence and mortality rate for anal cancer among both sexes and increased prevalence for vulvar cancers amongst younger women (Chikandiwa et al., 2019). This indicates that there are substantial benefits associated with HPV preventions measures in South Africa's population.

In light of the rising burden of HPV-related anogenital diseases, consideration must be given to men's risk of HPV-infection. First, international literature points to a substantive burden of HPV-related disease amongst men who have sex with men (MSM) (Brewer & Calo, 2015). Zou et al. (2015) investigated the incidence of HPV amongst 200 Australian adolescent MSM (aged 16-20 years old). Within this cohort, incidence rate per 100 person-years for anal HPV infection was 57 and the 12 for penile HPV infection (Zou et al., 2015). These estimations illustrate a high burden of HPV-related diseases within the MSM population. This disproportionate burden has created

policy debate on the need for a HPV vaccination programme that targets the MSM population (Seto, Marra, Raymakers, & Marra, 2012). These programmes are attractive because they target young MSM who are at higher risk and are likely to receive more benefit from the vaccine (Brewer & Calo, 2015). However, this type of intervention is likely to be unsuccessful as many young MSM might not identify as MSM until after sexual-initiation (Brewer & Calo, 2015). Thus, Brewer and Calo (2015) argue that *universal* vaccination programmes are the most effective way to reduce the high-burden of HPV-disease in MSM.

Secondly, the incomplete level of female coverage puts men at risk of contracting HPV in heterosexual relationships. High female coverage is thought to provide males with 'herd-immunity', stopping the spread of infection (Williamson, 2015). However, if female coverage is incomplete then both men and women would benefit from the vaccination of males. Brisson, van de Velde, Franco, Drolet, and Boily (2011) explain that if all girls in the population are vaccinated, then the number of boys vaccinated is not relevant as there will always be one party protected in heterosexual relationships. Brisson et al. (2011) found, when female-coverage is high (above 70%), including boys in the programme (and achieving 70% coverage) would reduce population-level prevalence by a maximum of 24%. This research indicates that increasing coverage within the female-population may be more cost-effective in country with an already high-coverage (Brisson et al., 2011). Conversely, in a low-coverage setting, the benefit of including men is more tangible and potentially cost-effective (Brisson et al., 2011; Prue, Grimes, et al.). Thus, the protective effect of extending vaccination coverage to boys, and thereby approaching herd-immunity, depends on the level of female coverage.

Yet, the exact level of female coverage achieved by the current HPV vaccination programme is uncertain. In 2014, Delany-Moretlwe et al. (2018) found that the first dose of the vaccine programme achieved a relatively high female coverage (86.6%) amongst grade 4 public schoolgirls.

Their results also exhibit some districts where first-dose HPV vaccination coverage was only approximately 40% (Delany-Moretlwe et al., 2018). The subsequent performance of the programme has been reported as numbers of vaccinated learners that have not been converted to population coverage estimates (Ngcobo, Burnett, Cooper, & Wiysonge, 2019). However, the reported numbers do show a substantial decrease in the number of vaccinated girls between the first and second dose of the vaccine. There was a 21,4% decrease in the number of vaccinated girls between the first and second dose in 2014 and a 26.0% decrease in 2016 (Ngcobo et al., 2019). Overall, the national coverage level for both doses of the *Cervarix* vaccine is approximated at 60% (van Schalkwyk, Moodley, Welte, & Johnson, 2019). These estimates demonstrate the institutional difficulties involved in consistently achieving the high-levels of female-coverage required to provide males with herd-immunity in a single-sex vaccination programme.

As the current national programme offers vaccines to all grade-4 girls in public sector schools for free, it is necessary to understand the drivers of the current low-levels of coverage in order to successfully implement an intensive-girls only programme. Ngcobo et al. (2019) attribute the low levels of coverage in specific-regions to supply-related constraints such as the costs and availability of the vaccine, access to healthcare, the availability of the vaccine and capacity of the health and education systems to administer it as well as a significant degree of vaccine-hesitancy within communities. Importantly, the suboptimal coverage is predominantly attributed to lack of consent by parents in the school-based programme (Ngcobo et al., 2019). The relationship between HPV and cervical cancer (and other anogenital cancers) is not well-understood amongst parents who express concern regarding the safety and side-effects of the vaccination (Ngcobo et al., 2019). Moreover, Ngcobo et al. (2019) describe that the belief that HPV-vaccination encourages risky sexual adolescent behaviour or lowers the age of sexual debut is commonly held. Thus, to the achieve the high levels of coverage required by the intensive-girls only programme, further research is needed to investigate the extent and causes of vaccine hesitancy amongst parents and the reasons

for the high drop-out levels between the first and second doses of the schools-only vaccine (Ngcobo et al., 2019).

In light of the difficulties experienced by the two-dose vaccine schedule, it is important to consider the possibility of a single-dose vaccination programme. The South African girls-only programme uses the bivalent HPV vaccine, *Cervarix,* administering two-doses of the vaccine six months apart (Delany-Moretlwe et al., 2018). Recently, Kreimer et al. (2020) found evidence that women who had received only a single dose of *Cervarix*, continued to be protected from HPV16 and 18, after nearly a decade. The vaccine efficacy[1] against HPV16 and 18 infection was estimated as 80,2%, 83,8% and 82,1% for the three-dose, two dose and single dose schedule, respectively (Kreimer et al., 2020). These results show little variation in efficacy amongst doses, indicating that a single-dose schedule would be at the least, *as effective* as the current two-dose schedule. The findings could also imply that female coverage is higher than previously supposed. Since 86% of the female population received the first dose of the vaccine, female-coverage could be higher than previously estimated. A single-dose vaccination programme would not only be less expensive, but would be less logistically complex to administer (National Cancer Institute, 2020). Multiple doses require administrative infrastructure to track when each person received their first dose, which poses a challenge to widespread vaccination programmes (National Cancer Institute, 2020). Therefore, a single dose HPV vaccine schedule would result in a universal vaccination programme becoming more economically and logistically feasible, without compromising on its effectiveness.

[1] Vaccine efficacy is the percentage reduction of disease amongst the vaccinated population in comparison to an unvaccinated group (Kreimer et al., 2020).

After establishing the potential need for a universal HPV-vaccination programme, it is necessary to review previous literature of the cost-effectiveness of HPV vaccination. The following section will consider previous cost-effectiveness analyses of girls-only and universal programmes in South Africa and internationally.

The cost-effectiveness of the current female-only vaccination programme was first determined by Sinanovic et al. (2009). Sinanovic et al. (2009) developed a static Markov Model on *TreeAge* software to estimate the life-time costs and life expectancy of a hypothetical cohort of women in South Africa. To determine the cost, they examined: provider costs, management costs, transport costs and patient costs, adjusted by the consumer price index (CPI) and compared these to the effectiveness of the programme, measured in life years saved and quality-adjusted years (QALYs) gained (Sinanovic et al., 2009). They estimated the incremental cost per life-year saved as US $4995 and the cost per QALY gained as US $1078 (Sinanovic et al., 2009). As South Africa does not have a willingness to pay threshold per QALY gained, they compared the incremental cost effectiveness per QALY ratio to the gross domestic product (GDP) per capita that year (US $5724) (Sinanovic et al., 2009). As the incremental ratio is less than the GDP per capita, the programme was considered to be 'very cost-effective'.

Following this study, South Africa implemented the girls-only programme in 2014. However, in determining the cost of vaccination and potential cost of expanding it, it is important to remember South Africa is not eligible for Gavi[2] funding to support its vaccination policies (Médecins Sans Frontières, 2015). As such the Department of Health must directly negotiate the price of the

[2] GAVI, is officially called 'Gavi, the Vaccine Alliance'. It is a public-private global health organisation that facilitates the partnerships between developing countries and donor organisations (governments, the World Health Organization, the World Bank, the Bill and Melinda Gates Foundation, amongst others) to increase access to immunisation in developing countries.

vaccine with pharmaceutical companies. In 2014, the Department of Health directly negotiated a price of R157 per dose of the HPV vaccine *Cervarix,* with its producer GlaxoSmithKline (Médecins Sans Frontières, 2015). This price is on par with the lowest prices paid for the vaccine by other middle-income countries (Médecins Sans Frontières, 2015). Even so, this price is approximately three-times higher than the price paid by Gavi-countries (Médecins Sans Frontières, 2015). Thus, the relatively high price of the vaccine could pose a significant challenge to expanding the vaccination programme.

It is commonly argued that a *universal* HPV vaccination programme is not cost-effective. As universal programmes have not been investigated domestically, it is necessary to consider international literature. Seto et al. (2012) conducted a qualitative systematic review of 29 cost-effectiveness studies on HPV vaccinations. Their results showed that universal vaccination programmes are often not considered cost-effective as is they do not fall within the widely accepted cost-effectiveness threshold of $US50,000 per QALY (Seto et al., 2012). A more recent study conducted in New Zealand by Pearson et al. (2014) modeled the incremental health gains and costs of a universal vaccination programme. Here, universal HPV vaccination was not cost-effective, as the country's girls-only programme had achieved high coverage (Pearson et al., 2014).

The United Kingdom has also undertaken several universal HPV cost-effectiveness analyses in light of the country's high burden of cancers. One study (Datta et al., 2019) reiterated the herd-immunity claims of Brisson et al. (2011). Datta et al. (2019) explain that adding boys to the vaccination programme becomes increasingly more cost-effective for lower levels of coverage amongst the female population. Interestingly, the study showed that the impact on prevalence of a universal vaccination campaign that reached 60% of the population was comparable to the current impact of the girls-only programme that reaches 85% of the female population (Datta et al., 2019). This is necessary to note given the difficulties South Africa faces in reaching high levels

of coverage. Another study (Prue, Grimes, et al., 2018) explains that female-coverage in United Kingdom varies substantially by region. This variation reduces the protection offered to men through herd-immunity. Prue, Baker, et al. (2018) estimate that the annual cost of male-vaccination (£20-22 million) is considerably lower than the costs of treating men for HPV-related diseases (£ 86.5 million). Overall, these studies demonstrated the need for a universal vaccination programme in the United Kingdom, which was implemented in 2019.

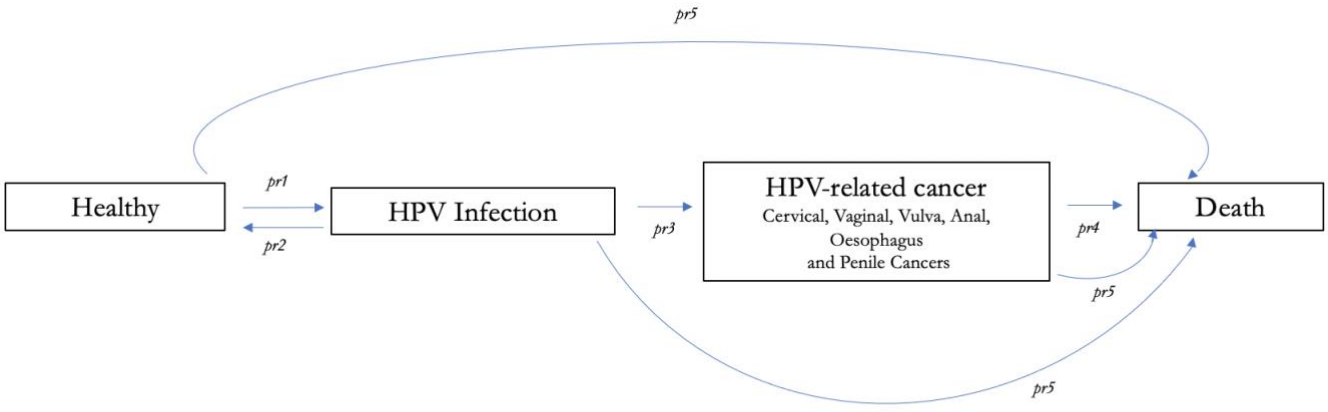
Moreover, Kotsopoulos et al. (2015) combined methodologies from generational accounting, health economics and human capital to estimate the broader economic consequences of a universal vaccination in Germany. Their findings suggest preventing the long-term mortality and morbidity of HPV infections is expected to bring about substantial economic benefits in the form of: medical cost-saving; improved productivity; increased earnings and tax revenue; and a prolonged number of years within the workforce (Kotsopoulos et al., 2015). This was reiterated by Prue, Grimes, et al. (2018) who argue that cost-effectiveness evaluations of universal HPV vaccination programmes must be "expanded to encompass the broader economic consequences and benefits to society" to be more accurate.

After considering the available evidence on the performance of the girls-only vaccination programme; increasing burden of anogenital HPV-related cancers; the negative impact of HIV; effects of varying levels of herd-immunity and previous empirical literature on the cost-effectiveness of vaccination both locally and aboard, there appears to be merit in exploring the possibility of extending the HPV vaccine to boys in South Africa. The next section describes the methodology used in this study to provide a preliminarily evaluation of the cost-effectiveness of a universal vaccine in South Africa.

3. Methodology

This paper adopts a Markov model to perform a cost-benefit analysis of the inclusion of males in the South African HPV vaccination programme. The Markov Model has been frequently used in economic evaluations of healthcare interventions (Komorowski & Raffa, 2016). It uses 'disease states' to model how individuals move ('transition') between disease states over time. These states are mutually exclusive and exhaustive; meaning a representative individual may only be in one state at any given time (Komorowski & Raffa, 2016). Time is measured in discrete time periods referred to as 'cycles. 'Transition probabilities' are calculated and represent the probability of moving from one disease state to another, in successive cycles. A cost-benefit analysis measures the costs (in monetary terms) and benefits (the utility-gained) associated with spending a cycle in a specific disease state (Komorowski & Raffa, 2016). These are then aggregated over successive cycles for the whole cohort. The method allows for comparison between scenarios where no HPV vaccination programme has been implemented, compared to girls-only or universal programmes.

Figure 1: Stylized Markov Model for the progression of HPV-related diseases



There are four-transition states in the above model. The transition probabilities are given by *pr1*, *pr2*, *pr3*, *pr4* and *pr5*. The probability of contracting and recovering from HPV is shown by *pr1* and *pr2*, respectively. *Pr3* represents the weighted probability of developing an HPV-related cancer. *Pr4* represents the HPV-related cancer mortality rate and *p5*, the all-cause mortality rate. The transition probabilities have been calculated using data from the National Cancer Registry Report (2016) and number of deaths in 2017 obtained directly from Statistics South Africa. *Please refer to Table 2 & 3 in the Appendix.*

The model above was built on Microsoft Excel©. Within it, a cohort of 100 individuals, 50% female and 50% male, enter the model at age 15 and are followed over their lifetimes. The model has used year-long cycles. There are four disease states: *'Healthy, HPV-Infection, HPV-related cancer* and *Death'*. The transition probabilities for movement between states are represented by *pr1, pr2, pr3, pr4* and *pr5*. It is necessary to note that pre-cancerous lesions have been omitted in the model of HPV-related diseases above. This is due to the lack of information available on the prevalence of these lesions in South Africa. Though HPV infections are often not detected, the model has included an *HPV-infection* state in order to model the progression of HPV-related illnesses. The model assumes that a proportion of the population acquires HPV each year, moving from *Healthy* to *HPV-infected*. As HPV is a sexually transmitted disease, the paper takes age 15, the average age of puberty, as the base year.

3.1 Transition Probabilities

Cancer Incidence Rate & Mortality Risks

The probability of developing HPV cancer in the model has been calculated using data provided by the National Cancer Registry's 2016 Report. The report provides age-specific incidence rates per 100 000 individuals for various forms of cancer. Females have been modelled to be vulnerable to cervical, anal, vulva, vaginal and oesophagus cancers. Males are modelled as susceptible to anal, penile and oesophagus cancers. These forms of cancers have been weighted according to their proportion of all HPV-cancer cases *(see Table 1 in Appendix)*. Using the incidence rates provided, the model has created a weighted, age-specific probability of developing an HPV-related cancer (*pr3*) for females and males. These are displayed in **Table 2 and 3** *(see Appendix)*.

The probability of death due an HPV-related cancer *(pr4)* and the all-cause mortality rate (*pr5)* have been calculated based on the reported number of deaths from each type of HPV-cancer and all-cause death numbers. This information has been provided from Statistics South Africa directly.

Using the number and causes of deaths; the weights of each type of cancer previously used; and total population estimations for each age bracket, the paper has estimated the age-specific HPV-cancer and all-cause mortality probabilities *(see **Table 2 and 3** in the Appendix).*

The study models the incremental effect of vaccinating boys, conditional on the continuation of the girls' vaccination programme. Thus, it is necessary to consider the impact of the existing girl's programme on the transition probabilities created. Richter (2015) describes that the maximum impact of the 2014 HPV vaccine will only be seen from 2034 onwards, when it will prevent HPV-related cancers from developing amongst vaccinated girls. The first cohort of HPV-vaccinated Grade 4 girls will be 14 years old in 2019 (the year of study) and are unlikely to be sexually active. Therefore, it is unlikely that the current vaccination programme has impacted these transition probabilities. As such, *pr3* and *pr4* are assumed to represent the probabilities for an unvaccinated population.

Probability of contracting HPV: Accounting for Herd Immunity

While previous cost-benefit investigations (Li, Stander, Van Kriekinge, & Demarteau, 2015; Sinanovic et al., 2009) performed on the South African population have adopted a static Markov Model, this paper uses a dynamic Markov Model to account for changes in transition probabilities associated with the effects, over time, of a vaccination programme on immunity levels. Female's protection from HPV through the girls-only vaccination programme is believed to offer males herd-immunity. Thus, it is vital to account for this added protection both to girls and boys within this cost-benefit analysis.

The paper relies on the Dynamic Bayesian Markov Model proposed by Haeussler, van den Hout, and Baio (2018) to account for this effect. Haeussler et al. (2018) propose a method by which to adapt the transition probabilities in a Markov Model to depend on the population dynamics and

prevalence within the cohort. This creates a dynamic 'force of infection' or interaction effect, that is calculated separately within each cycle. It is a function of the time-dependent HPV prevalence (ψ_t); the probability of transmission per contact (β); and the rate of contact between susceptible and infectious members (ω).

According to Haeussler et al. (2018), time-dependent HPV prevalence is calculated as:

$$\psi_t = \frac{I_t}{N_t}$$

where I_t is the number of people who have HPV and N_t is the number of people alive at time t.

Then, the force of infection (λ_t) can be recalculated at each Markov cycle as:

$$\lambda_t = \beta\omega\psi_t$$

Based on the assumption that the force of infection (λ_t) remains constant for the year-long Markov cycle, the time-dependent transition probability of moving from the disease state *Healthy* to *HPV-related cancer* at time t is:

$$\pi_{1,2,t} = 1 - e^{-\lambda_t}$$

This paper relies on HPV prevalence simulations provided by van Schalkwyk et al. (2019) to estimate the time-dependent HPV prevalence (ψ_t) in **cycle one**. In subsequent cycles, van Schalkwyk et al.'s (2019) prevalence rates are compared to the time-dependent HPV prevalence rates predicted by the model. This ensures the model plausibly predicts the level of infection amongst individuals.

To estimate the rate of contact (ω) between *HPV-infected* and *Healthy* members of the population, the paper must attempt to model the sexual behaviour of individuals. This is a function of the

number of sexual encounters and number of sexual partners an individual has per year. Individuals might have more than one sexual partner at a time which suggests that sexual encounters rather than sexual partners must be modelled[3]. A number of simulations were used with varying numbers of sexual encounters for different ages periods to develop a crude rate of sexual encounters metric[4]. These rough estimates for the rate of sexual contact were chosen as they best recreated the predicted prevalence levels of HPV estimated by van Schalkwyk et al. (2019). For simplicity, the number of sexual encounters per year was assumed to be the same for each of the individuals in the model. This is a strong assumption that is unlikely to provide an accurate approximation of societal behaviour. Further research should include a probability distribution of sexual behaviour to improve the model's usefulness. This is beyond the scope of the preliminary analysis conducted herein.

Next, it is necessary to estimate the probability of transmission of HPV per contact between individuals (β). A previous study (van Schalkwyk et al., 2019) found that individuals contract HPV from a sexual encounter with an HPV-infected person with an approximate probability of 0.6. This was figure was assumed to be constant at all ages and was used throughout the model.

Lastly, as HPV infections are not permanent, the model must also calculate *pr2,* the probability of recovering from HPV. Li et al. (2015) assume that the annual probability of recovering from HPV

[3] Even if an individual has only one sexual partner, it is possible that their partner might have more than one sexual partner. As such, it is possible for the individual to contract HPV at every sexual encounter, even if the encounters are with one person consistently.

[4] A rate of sexual contact in this model is interpreted as the number of sexual encounters over the period of time observed. Individuals are modelled as having one sexual encounter between the ages of 15 to 19; ten encounters between ages 20-35; seven encounters between the ages 36-50; five encounters between 51-65 and two encounters between 66 and 85. These crude estimates are necessary to ensure that level of HPV prevalence is highest between the ages of 25-50, the ages when the highest number of cancer cases are reported.

is between 0.293 and 0.553. The model randomly assigns a probability of recovery within this range to every cycle.

3.2 Measuring Costs & Benefits

Cancer & Vaccination Costs

All costs and benefits are stated in 2019 constant price Rands. The estimated costs used in this paper are shown in **Table 4** *(refer to the Appendix)* and have been extrapolated from previous literature (Datta et al., 2019; Moodley, Tathiah, & Sartorius, 2016; Sinanovic et al., 2009). The costs for the treatment of cervical cancer were taken from a previous study modelling the cost-effectiveness of the girls-only vaccination programme (Sinanovic et al., 2009). The costs were converted into rand values (ZAR) using the 2007 US $ exchange rate and then adjusted for inflation to be in 2019 prices. Due to the lack of information regarding the costs of other anogenital and head and neck cancers in the South African context, the paper has used a previous study conducted in the United Kingdom to estimate these costs (Datta et al., 2019). These costs have been combined to form a weighted average *HPV-related cancer* cost for each sex. The paper acknowledges that this poses a severe limitation to the paper's ability to accurately measure the costs of cancer treatment in South Africa and recommends that further research is conducted to rectify this in future studies.

The cost of vaccination depends on two factors: the price of the drug and the indirect costs involved in its administration. The national tender price for the drug is substantially due to the state's increased bargaining power (Li et al., 2015). In 2014, the government negotiated a price of R157 per dose of *Cervarix* (Médecins Sans Frontières, 2015). Assuming this negotiated price holds, the cost per dose is R201 in 2019 constant price Rands. The indirect costs are adapted from (Moodley et al., 2016).

Benefits of Vaccination

The model has used quality-adjusted life years (QALYs) to measure the benefits of vaccination. Health is a function of longevity and quality of life (Prieto & Sacristán, 2003). The QALY metric was developed to combine these aspects of health into a single index number (Prieto & Sacristán, 2003). It is calculated as the change in utility induced by the health intervention, multiplied by the duration of the treatment effect (Prieto & Sacristán, 2003). The utility of a health state is ranges from 0 to 1, where 0 represents the 'utility' of the 'death' state and 1 the utility of a 'perfect health' state (Komorowski & Raffa, 2016). A year of life lived in perfect health is worth 1 QALY *(1 Year of Life x 1 Utility = 1 QALY)* (Prieto & Sacristán, 2003). A year of life lived in less than perfect health is worth less than 1.

In the model, the perfect health QALY of 1 is reduced by the disutility value of being in the HPV-related cancer health state and multiplied by the years spent in the HPV-related cancer state (Komorowski & Raffa, 2016). The utility values of the health states are reported in **Table 5** *(see Appendix)*. These values were extrapolated from a previous study conducted by Li et al. (2015). Disutility values for other anogenital cancers have been extrapolated from Datta et al. (2019) due to lack of data in the South African context. The values from the various cancers have been averaged and weighted, to form one utility for *HPV-related Cance*r for each sex. As HPV can go undetected for years and has no immediate effect on quality of life, there is no disutility value attached to infection. Within each scenario, the number of QALYs are compared. This demonstrates how vaccination, which prevents cancer, can improve longevity and quality of life for individuals.

However, while QALYs are widely used in cost-effectiveness analyses, they have been "criticised on ethical, conceptual and operational grounds" (Prieto & Sacristán, 2003). First, QALYs assign a utility value to a health state. Yet whose preferences determine this quality-of-life weight varies

across methodologies. Some analyses use patients' preferences as they are most affected by the disease and can best judge the quality of life (Neumann & Cohen, 2018). Other analyses aggregate the preferences of the general population, as they are taxpayers and should have power in determining health resource allocations that will potentially affect them (Neumann & Cohen, 2018). This inconsistency in methodology undermines QALYs ability to objectively measure health benefits. Next, QALYs have been ethically challenged for attaching a 'value' to a life, which is argued to be dehumanizing (Neumann & Cohen, 2018). Conceptually, QALYS are flawed as they do not distinguish between a short period of time in a severe health state and a long period of time in a moderately diminished health state (Neumann & Cohen, 2018). This undermines their ability to accurately measure the benefits of an intervention. Although these critiques are valid, Neumann and Cohen (2018, p. 2474) describe that "no single number can ever capture the complexity of preferences for health". Instead, QALYs offer a flawed and necessary metric to measure and compare the benefits of health interventions (Neumann & Cohen, 2018).

3.3 Model Specifications

The study explores multiple scenarios such as the impact of the existing girls-only programme, the introduction of a universal vaccine; and the possibility of a single-dose vaccination programme.

Vaccination Assumptions

The vaccine used in this model is *Cervarix,* which protects individuals against HPV-16 and 18 (Moodley et al., 2016). Notably, Kreimer et al.'s (2020) findings indicate that a single dose of this vaccine could be as effective as the current two-dose schedule. As a result, the model considers both the cost-effectiveness of the WHO-approved two-dose schedule as well as a single-dose schedule, which could be implemented pending further research. Based on Kreimer et al.'s (2020) findings, the vaccine efficacy of the two-dose and single-dose schedule is assumed to be 84% and

82%, respectively. The model assumes lifetime vaccine efficacy, in line with the assumptions made by Sinanovic et al. (2009) in a previous cost-effectiveness analysis.

Level of Existing Coverage

Furthermore, to demonstrate the incremental impact of adding boys to the current vaccination programme, the model must make some assumptions regarding the current levels of coverage achieved. Approximately, 60% of the targeted group of girls have received two-doses of the HPV vaccine (van Schalkwyk et al., 2019). However, 86% of the targeted female-cohort received the first dose of the vaccine (Delany-Moretlwe et al., 2018). Considering Kreimer et al.'s (2020) findings on the effectiveness of a single-dose of the vaccine, this could suggest that female coverage is higher than supposed. Thus, the model contemplates both coverage assumptions.

Additionally, the model takes note of the impact of unvaccinated individuals within private schools on the population-level coverage achieved by the HPV-vaccination programme. Richter (2015) describes that individuals attending private-schools are excluded within the current government programme. These individuals are unlikely to seek the vaccine due to a lack of awareness and the high private vaccine prices (Richter, 2015). As such, the model assumes that 10% (5% boys and 5% girls) of the individuals within the cohort attend private primary schools are unvaccinated, both privately and through the girls-only or universal vaccination programme.

Modelled relationship between HPV and Cancer

Importantly, the model assumes that people can only develop an HPV-related cancer after HPV-infection. The state *HPV*-Infection is modelled as any form of HPV. This assumption implies that HPV causes all cases of HPV-related cancer within the model. In reality, the proportion of each type of cancer caused by HPV-infection varies. HPV DNA (defined as any strand of HPV) is found in 100% of cervical cancer case, 88% of anal cancer cases, 70% of vaginal cancers cases,

50% of penile cancer cases, 40% of vulvar cancer cases and an unknown proportion of oesophagus cancers (Bruni et al., 2019). Thus, the assumption that HPV causes all cases of cancer is likely valid for cervical, anal and vaginal cancers, but is unlikely to hold for other types. The implication of this assumption is to over-estimate the impact of vaccination on reducing anogenital cancers. This is partially offset by the effects of cross-protection[5] that are not accounted for within the model. Lastly, *Cervarix* only protects the recipient from HPV16 & 18, as these strands are the most common causes of HPV-related cancers in South Africa (Bruni et al., 2019). The varying proportions of cancers caused by HPV16 & 18 are reported in **Table 5** *(see Appendix)*. As these strands are only responsible for a portion of total HPV-related cancers, the model only reduces the after-vaccination HPV-prevalence estimation by the decreased prevalence of HPV strands 16 and 18[6].

Discounting

'Discounting' is common practice in cost-benefit analysis or in any evaluation that requires present and future valuations to be aggregated. It amounts to adjusting the future costs and benefits of the interventions to the 'present value' (Severens & Milne, 2004). This practice is pertinent as the costs of vaccination are incurred in the present while the health benefits occur in the future. Practically, the calculation is simple. The cost or benefit is multiplied by the expression:

$$\frac{1}{(1+d)^n}$$

where d is the discount rate and n is the cycle number.

[5] Cross-protection refers the reduction in non-targeted strands of HPV through a vaccine. The HPV16/18 vaccine has been seen to reduce level of other strands of HPV, despite the drug not directly targeting them (National Cancer Institute, 2020).

[6] The prevalence data supplied by Van Schalkwyk et al. (2019) differentiates between the prevalence of multiple different HPV strands. It has been assumed that other strands of HPV are not affected by the vaccine.

The model uses a uniform discount rate for both costs and benefits over time. This type of discounting is commonly used and recommended as it is based on the premise that the impact of time is independent on whether the future event is a cost or benefit (Severens & Milne, 2004). A real discount rate of 5% is recommended for health-evaluations in Africa's Pharmacoeconomic Guidelines (Medicines and Related Substances Act 101 of 1965, 1965). A real discount rate of 3% is also considered in following previous cost-effectiveness analyses (Datta et al., 2019; Pearson et al., 2014; Sinanovic et al., 2009).

Having discussed the methodology, data and the assumptions used to create the Markov Model specified above, the next section of the paper summarizes the preliminary costs and benefits estimated for the existing girls-only programme as well as the incremental impact of including boys to the vaccination programme. These are investigated for a two-dose and single-dose vaccination schedule.

4. Results & Discussion

The incremental cost-effectiveness ratio (ICER) informs decision-makers on the cost of the intervention in comparison to the health benefits generated (Komorowski & Raffa, 2016). The ICER of an intervention is calculated as follows:

$$\frac{Cost_{original} - Cost_{intervention}}{QALY_{original} - QALY_{intervention}}$$

The ICER is interpreted as the price per additional QALY gained through the health intervention (Neumann & Cohen, 2018). To determine cost-effectiveness, the ICER is compared to some cost-effectiveness threshold. Several thresholds have been proposed. The WHO proposes that an intervention with an ICER that is below three-times the country's GDP per capita, can be

considered to be cost-effective (Li et al., 2015). If the ICER of the intervention is below the GDP per capita, it is then considered to be 'highly' cost-effective (Li et al., 2015). South Africa's 2019 GDP per capita was R88 525 (South African Reserve Bank, 2019). Applying the benchmark testing of the WHO (3 x GDP/per capita) the cost-effectiveness threshold in this perspective is ZAR 265 575. Alternatively, the United States of America, suggests an intervention is cost-effective if its ICER is below $50 000 (Neumann & Cohen, 2018). Using the December 2019 US $ exchange rate (USD 1 = ZAR 15.14), this benchmark amounts to ZAR 757 000. Therefore, there is a stark contrast in cost-effectiveness thresholds which illustrates the subject nature of this type of analysis.

Similarly, the ICER can be used to compare the value of different interventions. By using the same cost-per-QALY metric, the 'price' of various interventions can be compared to determine which are more efficient. However, this cost-per-QALY metric has the potential to disproportionately favour younger and healthier populations, who have more QALYs to gain from treatments (Neumann & Cohen, 2018). This can lead to discriminatory health-resource allocations. Thus, cost-effectiveness analyses provide "only one input into what are invariably multifaceted decisions" (Neumann & Cohen, 2018).

Table 7 shows the costs and benefits of HPV vaccination **per 100 individuals**. First, the results demonstrate the impact of the 2014 girls-only vaccination programme in reducing female and male cancer cases. Assuming 57% of the girls within the cohort[7] (approximately 28.5 girls) are vaccinated, and that the vaccine is 84% effective, the intervention decreased female cancer costs by 15,3% and male cancer costs by 6,23% within the model, using a 5% discount rate. The ICER of the girls-only programme is ZAR165 357, under the 5% discount rate, which is interpreted as

[7] 57% of the girls within the cohort are vaccinated because the model assumes 5% of girls within the model attend private-schools and are thereby unaffected by the government-run HPV vaccination programme.

Table 7

Cost-effectiveness of adding the boys to the HPV in 2019 ZAR under the two-dose schedule

Outcomes	**No Vaccine**	**Girls-Only**	**Girls & Boys**	**Incremental Value** *girls-only compared to universal*	**ICER (**ZAR/QALY) *girls-only compared to universal*
Two-dose Scenario					
discounted at 5%					
Initial Vaccine Costs	0	R15 618	R31 236	+ 100%	
Female Cancer Costs	R29 591 700	R25 035 389	R24 250 851	- 3,13%	
Male Cancer Costs	R2 760 374	R2 588 378	R 2 410 362	- 6,88%	R196 868
QALYS	1 795,55	1 824,05	1 828, 86	+0,26%	***cost-effective***
discounted at 3%					
Initial Vaccine Costs		R15 618	R31 236	+ 100%	
Female Cancer Costs	R55 831 956	R51 341 521	R50 127 687	- 2,36%	
Male Cancer Costs	R6 673 539	R6 403 514	R6 045 378	- 5,59%	R 330 436
QALYS	2 501,37	2 528,79	2 533,55	+ 0,19%	***not cost-effective***

Values are ***per 100 individuals***. QALYs stands for quality-adjusted life years. The incremental value reflects the percentage change in costs or benefits of adding boys to the existing girls-only programme. ICER indicates incremental cost effectiveness ratio of a universal vaccine compared to the girls-only programme. The WHO cost-effectiveness ratio of (3 x GDP/capita = ZAR 265 575) has been used to determine cost-effectiveness within the table. The girls-only vaccination programme is modelled to have reached 60% of girls attending public schools. The universal vaccine is assumed to reach 60% of boys attending public schools.

Table 8

Cost-effectiveness of adding the boys to the HPV in 2019 ZAR under a single-dose schedule

Outcomes	**Girls-Only**	**Girls & Boys**	**Incremental Value** *girls-only compared to universal*	**ICER (**ZAR/QALY) *girls-only compared to universal*
Single-dose Scenario				
discounted at 5%				
Initial Vaccine Costs	R10 412	R20 824	+ 100%	
Female Cancer Costs	R24 653 270	R23 578 352	- 4,36%	
Male Cancer Costs	R 2 459 437	R2 283 534	- 7,42%	R185 412
QALYS	1 825, 52	1 831, 21	+ 0,31%	***cost-effective***
discounted at 3%				
Initial Vaccine Costs	R10 412	R20 824	+100%	
Female Cancer Costs	R51 019 852	R49 713 114	- 2,56%	
Male Cancer Costs	R6 456 478	R6 156 253	- 4, 65%	R246 762
QALYS	2528,79	2535,26	+ 0,26%	***cost-effective***

Values are per 100 individuals. QALYs stands for quality-adjusted life years. The incremental value reflects the percentage change in costs or benefits of adding boys to the existing girls-only programme. ICER indicates incremental cost effectiveness ratio of a universal vaccine compared to the girls-only programme. The WHO cost-effectiveness ratio of (3 x GDP/capita = ZAR 265 575) has been used to determine cost-effectiveness within the table. The girls-only vaccination programme is modelled to have reached 80% of girls attending public schools. The universal vaccine is assumed to reach 80% of boys attending public schools.

the price per additional QALY in the girls-only vaccination programme. This ICER is below the WHO's cost-effectiveness threshold (ZAR 265 575), indicating that the intervention is considered cost-effective. However, the magnitude of this result contradicts Sinanovic et al. (2009), who found the introduction of the girls-only vaccination to be *'very cost-effective'* as the ICER was estimated to fall below South Africa's GDP per capita in their study. This could indicate that the model design underestimates the impact achieved by the vaccination programme. However, the discrepancy could also be attributed to several differences in the structural assumptions made in Sinanovic et al. (2009), compared to this model.

Table 7 also displays the incremental impact of adding boys to the existing two-dose HPV vaccination schedule. A universal vaccine, that is 84% effective and achieves a 60% coverage amongst public-school attending individuals, is seen to reduce female cancer costs by 3,13% and male cancer costs by 6,88%, using a 5% discount rate. This amounts to a 2,36% and 1,66% decrease female and male cancer costs respectively, under a 3% discount rate. The small magnitude of these changes is indicative of the high levels of other strands of HPV in the model even after the vaccination.

Using a 5% discount rate, the ICER of adding boys to the existing vaccination programme is ZAR 196 868. This is considered cost-effective according to the WHO's cost-effective threshold. Importantly, the price per additional QALY (ZAR 196 868) using a universal vaccine instead of the girls-only programme, is higher than the price per additional QALY (ZAR 165 357) from first introducing the girls-only programme. This finding reiterates Datta et al. (2019, p. 6) claim that *"the reduction in cases from adding boys to the vaccination program is markedly less than the initial impact of adding girls",* which suggests that there is diminishing returns to health benefits from vaccination. Interestingly, under the 3% discount rate, adding boys to the existing vaccination programme is not considered cost-effective under the WHO's cost-effectiveness threshold. However, the two-

dose universal vaccination is considered cost-effective at both discount rates, when evaluated using the American threshold of US$ 50 000 per QALY (ZAR 757 000).

Notably, the above result contradicts the findings of Pearson et al. (2014), Seto et al. (2012) and Datta et al. (2019) who found a universal vaccination to be not cost-effective. This is could be attributed to higher levels of female coverage in both New Zealand (70%) and parts of the United Kingdom (above 80%) than the coverage (60%) assumed for South Africa in this model. Another consideration is the substantially lower price of the vaccine negotiated in South Africa, compared to higher vaccine prices experienced in wealthier countries like New Zealand and the United Kingdom.

Yet even when assuming higher levels of female coverage achieved by the existing girls-only programme, the results show a universal vaccine to be cost-effective. In light of Kreimer et al.'s (2020) recent finding that a single-dose of the HPV-vaccine is 82% effective in reducing HPV prevalence, the model considers a single-dose vaccine scenario in Table 8. This scenario assumes the girls-only programme vaccinated 80% of girls attending public school[1]. A universal vaccine, that administers a single dose of the vaccine to 80% of boys attending public-schools, is considered cost-effective, using both the 5% and 3% discount rates. The price per QALY in a single dose universal vaccination programme (ZAR 185 412) is unsurprisingly lower than the price of a two-dose universal schedule (ZAR 196 868). This is the result of the lower vaccination costs; as well as the higher proportion of the population that is expected to be covered under a single-dose vaccine.

Importantly, these results rely on the assumption that the single-dose programme is approximately as effective as the two-dose schedule in reducing HPV prevalence. While there is substantial

[1] The model assumes a single dose of Cervarix is 82% effective in reducing HPV-prevalence following Kreimer et al.'s (2020) findings in Costa Rica.

evidence to support this assumption, further research, especially in the South African context which experiences a high burden of HIV, is needed to validate this. Should this assumption hold, it is likely that a single dose programme would reduce the cost of vaccination by more than estimated within this model, as it would remove the administrative burden of tracking individuals to administer a second dose of the vaccine.

After exploring the existing girl programme and incremental benefit of adding boys, the study has shown that a universal vaccination programme can be considered cost-effective using both the WHO's and American cost-effectiveness benchmarks. However, this conclusion is sensitive to the assumptions made within the model. The following section will discuss the limitations within this study and identify areas of future investigation.

1. Limitations & Areas of Future Study

The above results are highly sensitive to the discount rates used; current level of coverage; estimated costs; and disease incidence and mortality rates. As such, further sensitivity analyses are needed to investigate the robustness of these results. Specifically, investigation on the costs of HPV-related cancers in the South African health context is needed to ensure the legitimacy of these results, which are sensitive to the health costs used. Notably, poor record-keeping in South Africa could severely impact the calculated cancer and mortality probabilities. Singh et al. (2015) describes that, although the National Cancer Registry has been instrumental in reporting South Africa's overall cancer burden, their data has been impacted by the withholding of patient data from some private health-care laboratories. This has caused substantial under-reporting of cancer cases (28%) amongst private health-care facilities (Singh et al., 2015). However, as an extreme majority of South Africans rely on public health-care facilities, this has only led to a 4% decrease

in overall reporting (Singh et al., 2015). This example illustrates that the model remains sensitive to issues within its input data.

The study acknowledges that the model design used is flawed in several ways. In particular, is its use of a single *HPV-related Cancer* health state. This methodology weights and aggregates: the probabilities of developing several HPV-cancers and their respective mortality risks; the costs of treatment; and the benefits of preventing different types of cancers into a single value for all HPV-related cancers. This could severely impact the results produced, as HPV-related cancers vary substantially in their severity, treatments and rate of progression. Another flaw within this single-state design is that the model does not differentiate between stages of cancer. Earlier stages of cancer are expected to have higher utility values attached to them and a significantly lower mortality risk than later stages. This could significantly alter the results seen within this model. Thus, future studies are encouraged to differentiate between types and stages of cancer, to improve the legitimacy of their model.

Moreover, in accounting for the effects of herd-immunity, the model has made several assumptions to simulate the sexual transmission of HPV between individuals. These crude estimations must be developed, perhaps with a probability distribution, to accurate represent societal behaviors. It should also be noted that sexual behaviour is likely not stochastic as assumed within this model. The 'clustering'[2] of sexual partners would severely impact the rate of HPV transmission and has not been considered in the model above.

[2] It is possible that South African society does not interact randomly with regard to sexual partnering. 'Clusters' such as neighborhoods, religious groups, racial groups, geographical location and occupations, could play an influential role in the rate of contact and transmission of HPV in certain groups and could impact the estimated HPV prevalence used in the model.

Lastly, the study has not accounted for several facets previously considered within HPV literature, both domestically and abroad. Firstly, Li et al. (2015) showcase the importance in accounting for increased vulnerability of the HIV-positive population, who face a higher prevalence of both diseases. This study has not accounted for the effect of HIV, likely leading to conservative cost-benefit estimates. Next, Kotsopoulos et al. (2015) & Prue et al. (2018) have shown that vaccination can have further-reaching benefits than the decreased cost of cancer treatment. These include increased productivity and years in the workforce as well as increased earnings which overall result in increased tax revenue. These potential benefits have not been considered above. Additionally, the impact of the added protection given to men who have sex with men (MSM) by vaccinating boys before sexual debut has not been measured in model above. As MSM face a disproportionately high probability of anal and penile cancers, the benefits of vaccination are likely to be substantial. The overall theoretical effect of these omitted areas of study is to indicate that the results above are conservative. Thus, further research into these omitted areas of study is recommended.

2. Conclusion

The current HPV-vaccination programme in South Africa is aimed at reducing the high levels of cervical cancer. It is therefore administered to girls only. Recent research has shown that HPV is also responsible for an important fraction of other anogenital, head, neck and throat cancers. Although males are afforded some protection from these diseases through herd-immunity, the potentially incomplete level of coverage achieved by the girls-only programme leaves the male population vulnerable.

This study has used a dynamic Markov Model to preliminarily investigate the cost-effectiveness of including boys in the South African HPV vaccination programme. The findings of this modelling

show that the inclusion of boys in the current two-dose programme at a coverage rate of 60% would fall within the WHO's three-times GDP benchmark cost-effectiveness threshold and the American US $ 50 000 per QALY threshold. The study also considers a single-dose programme that covers 80% of both the female and male population. This intervention is considered cost-effective using the same thresholds and would have a substantially lower price per QALY than the current two-dose schedule. However, further evidence to support the effectiveness of a single-dose schedule in South Africa is needed before this can be recommended.

While promising, these preliminary results remain sensitive to issues with its input data; assumptions regarding the prevalence of cancers and effectiveness of vaccines and the clustering of behaviour. These flaws must be developed and addressed to conclusively determine the impact of adding boys to the existing HPV-vaccination programme.

Reference List:

Brewer, N. T., & Calo, W. A. (2015). HPV transmission in adolescent men who have sex with men. *The Lancet. Infectious diseases, 15*(1), 8.

Brisson, M., van de Velde, N., Franco, E. L., Drolet, M., & Boily, M.-C. (2011). Incremental Impact of Adding Boys to Current Human Papillomavirus Vaccination Programs: Role of Herd Immunity. *The Journal of Infectious Diseases, 204*(3), 372-376. doi:10.1093/infdis/jir285

Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., . . . de Sanjosé, S. (2019). *Human Papillomavirus and Related Diseases in the World Summary Report*. Retrieved from

Chikandiwa, A., Pisa, P. T., Sengayi, M., Singh, E., & Delany-Moretlwe, S. (2019). Patterns and trends of HPV-related cancers other than cervix in South Africa from 1994–2013. *Cancer Epidemiology, 58*, 121-129.

Datta, S., Pink, J., Medley, G. F., Petrou, S., Staniszewska, S., Underwood, M., . . . Keeling, M. J. (2019). Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK. *BMC infectious diseases, 19*(1), 552.

Delany-Moretlwe, S., Chikandiwa, A., & Gibbs, J. (2013). Human papillomavirus infection and disease in men: Impact of HIV. *Southern African Journal of HIV Medicine, 14*(4), 183-188.

Delany-Moretlwe, S., Kelley, K. F., James, S., Scorgie, F., Subedar, H., Dlamini, N. R., . . . Rees, H. (2018). Human papillomavirus vaccine introduction in South Africa: implementation lessons from an evaluation of the national school-based vaccination campaign. *Global Health: Science and Practice, 6*(3), 425-438.

Haeussler, K., van den Hout, A., & Baio, G. (2018). A dynamic Bayesian Markov model for health economic evaluations of interventions in infectious disease. *BMC medical research methodology, 18*(1), 82.

Komorowski, M., & Raffa, J. (2016). Markov models and cost effectiveness analysis: applications in medical research. In *Secondary analysis of electronic health records* (pp. 351-367): Springer.

Kotsopoulos, N., Connolly, M. P., & Remy, V. (2015). Quantifying the broader economic consequences of quadrivalent human papillomavirus (HPV) vaccination in Germany applying a government perspective framework. *Health economics review, 5*(1), 1-8.

Kreimer, A. R., Sampson, J. N., Porras, C., Schiller, J. T., Kemp, T., Herrero, R., . . . Lowy, D. R. (2020). Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *JNCI: Journal of the National Cancer Institute, 112*(10), 1038-1046.

Li, X., Stander, M. P., Van Kriekinge, G., & Demarteau, N. (2015). Cost-effectiveness analysis of human papillomavirus vaccination in South Africa accounting for human immunodeficiency virus prevalence. *BMC infectious diseases, 15*(1), 566.

Médecins Sans Frontières. (2015). *The Right Shot: Bringing down barriers to affordable adapted vaccines*. Retrieved from https://www.msf.org.za/news-and-resources/publications/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines

Moodley, I., Tathiah, N., & Sartorius, B. (2016). The costs of delivering human papillomavirus vaccination to Grade 4 learners in KwaZulu-Natal, South Africa. *South African Medical Journal, 106*(5), 497-501.

National Cancer Institute. (2020). Single Dose of HPV Vaccine Yields Long-Term Protection from Many Cancer-Causing Types. Retrieved from https://www.cancer.gov/news-events/cancer-currents-blog/2020/hpv-vaccine-single-dose-long-term-protection

Neumann, P. J., & Cohen, J. T. (2018). QALYs in 2018—advantages and concerns. *Jama, 319*(24), 2473-2474.

Ngcobo, N., Burnett, R., Cooper, S., & Wiysonge, C. (2019). Human papillomavirus vaccination acceptance and hesitancy in South Africa: Research and policy agenda. *South African Medical Journal, 109*(1), 13-15.

Palefsky, J. M. (2010). Human papillomavirus-related disease in men: not just a women's issue. *Journal of Adolescent Health, 46*(4), S12-S19.

Pearson, A. L., Kvizhinadze, G., Wilson, N., Smith, M., Canfell, K., & Blakely, T. (2014). Is expanding HPV vaccination programs to include school-aged boys likely to be value-for-money: a cost-utility analysis in a country with an existing school-girl program. *BMC infectious diseases, 14*(1), 351.

Prieto, L., & Sacristán, J. A. (2003). Problems and solutions in calculating quality-adjusted life years (QALYs). *Health and quality of life outcomes, 1*(1), 1-8.

Prue, G., Baker, P., Graham, D., Nutting, C., Greenhouse, P., & Lawler, M. (2018). It is time for universal HPV vaccination. *The Lancet, 392*(10151), 913-914.

Prue, G., Grimes, D., Baker, P., & Lawler, M. (2018). Access to HPV vaccination for boys in the United Kingdom. *Medicine Access@ Point of Care, 2*, 2399202618799691.

Richter, K. (2015). *Implementation of HPV vaccination in South Africa*. Retrieved from https://www.phasa.org.za/wp-content/uploads/2015/02/Richter_Implementation-of-HPV_article-4.pdf

Seto, K., Marra, F., Raymakers, A., & Marra, C. A. (2012). The cost effectiveness of human papillomavirus vaccines. *Drugs, 72*(5), 715-743.

Severens, J. L., & Milne, R. J. (2004). Discounting health outcomes in economic evaluation: the ongoing debate. *Value in health, 7*(4), 397-401.

Sinanovic, E., Moodley, J., Barone, M. A., Mall, S., Cleary, S., & Harries, J. (2009). The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening programme in South Africa. *Vaccine, 27*(44), 6196-6202.

Singh, E., Underwood, J., Nuttey, C., Babb, C., Sengayi, M., & Kellett, P. (2015). South African National Cancer Registry: Effect of withheld data from private health systems on cancer incidence estimates. *South African Medical Journal, 105*(2).

South African Reserve Bank. (2019). *Full Quarterly Bulletin* (294). Retrieved from https://www.resbank.co.za/en/home/publications/publication-detail-pages/quarterly-bulletins/quarterly-bulletin-publications/2019/9632

van Schalkwyk, C., Moodley, J., Welte, A., & Johnson, L. F. (2019). Estimated impact of human papillomavirus vaccines on infection burden: The effect of structural assumptions. *Vaccine, 37*(36), 5460-5465.

Williamson, A.-L. (2015). The interaction between human immunodeficiency virus and human papillomaviruses in heterosexuals in Africa. *Journal of clinical medicine, 4*(4), 579-592.

World Health Organisation. (2017). Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. *Vaccine, 35*(43), 5753-5755.

Zou, H., Tabrizi, S. N., Grulich, A. E., Hocking, J. S., Bradshaw, C. S., Cornall, A. M., . . . Garland, S. M. (2015). Site-specific human papillomavirus infection in adolescent men who have sex with men (HYPER): an observational cohort study. *The Lancet Infectious Diseases, 15*(1), 65-73.

Appendix

Table 1
Proportions of HPV-related cancer

Type of Cancer	Proportion of all HPV-related Cancers (%)[3]
Females	
Cervical Cancer	81,96
Vulva Cancer	6,188
Vaginal Cancer	2,409
Anal Cancer	2,031
Oesophagus Cancer	9,541
Males	
Anal Cancer	10,540
Penile Cancer	15,060
Oesophagus Cancer	74,390

[3] These proportions of HPV-related cancer were calculated using the percentage of cancer cases reported in the **2016 National Cancer Registry Report.**

Table 2
Age-specific transition probabilities for **females**

Age	Probability of all-cause death[4] *(pr5)*	Probability of developing HPV-Cancer[5] *(pr3)*	Probability of death by HPV-Cancer[6] *(pr4)*
15-19	0,0014	0,0004	0,0000
20-24	0,0026	0,0008	0,0001
25-29	0,0038	0,0040	0,0008
30-34	0,0052	0,0170	0,0030
35-39	0,0064	0,0363	0,0064
40- 44	0,0081	0,0509	0,0112
45-49	0,0098	0,0527	0,0132
50-54	0,0124	0,0643	0,0177
55-59	0,0162	0,0638	0,0218
60-64	0,0220	0,0619	0,02180
65-69	0,0297	0,0692	0,0281
70-74	0,0388	0,0621	0,0300
75-79	0,0611	0,0575	0,0394
80+	0,1273	0,0559	0,0465

[4] These probabilities were calculated using the number and cause of recorded deaths in 2017 in each age-bracket. This information was provided to the author **by Statistics South Africa directly**. Using the number of deaths and the population estimates, the age-specific incidence rate and annual all-cause probabilities of death were calculated.

[5] The probability of developing HPV-related cancer was calculated using the age-specific incidence rates found in the **2016 National Cancer Registry Summary Statistics Report**. The model weights the types of cancer included (cervical, vulva, vaginal, anal, penile and oesophagus) based on their percentage of all cancers.

[6] These probabilities were calculated using the number of deaths by HPV-related cancers in 2017 in each age-bracket. This information was provided to the author **by Statistics South Africa directly**. Using the number of deaths and the population estimates, the age-specific incidence rate and annual probabilities of HPV-related cancer deaths were calculated. These were weighted by the cancer's proportion of all cancers as described above.

Table 3

Age-specific transition probabilities for **males**

Age	Probability of all-cause death[7] *(pr5)*	Probability of developing HPV-Cancer[8] *(pr3)*	Probability of death by HPV-Cancer[9] *(pr4)*
15-19	0,0014	0,0000	0,0001
20-24	0,0026	0,0000	0,0000
25-29	0,0038	0,0001	0,0001
30-34	0,0052	0,0002	0,0002
35-39	0,0064	0,0008	0,0005
40- 44	0,0081	0,0018	0,0015
45-49	0,0098	0,0047	0,0031
50-54	0,0124	0,0116	0,0087
55-59	0,0162	0,0158	0,0159
60-64	0,0220	0,0183	0,0209
65-69	0,0297	0,0218	0,0254
70-74	0,0388	0,0221	0,0276
75-79	0,0611	0,0222	0,0403
80+	0,1273	0,0239	0,0486

[7] These probabilities were calculated using the number and cause of recorded deaths in 2017 in each age-bracket. This information was provided to the author **by Statistics South Africa directly**. Using the number of deaths and the population estimates, the age-specific incidence rate and annual all-cause probabilities of death were calculated.

[8] The probability of developing HPV-related cancer was calculated using the age-specific incidence rates found in the **2016 National Cancer Registry Summary Statistics Report**. The model weights the types of cancer included (cervical, vulva, vaginal, anal, penile and oesophagus) based on their percentage of all cancers.

[9] These probabilities were calculated using the number of deaths by HPV-related cancers in 2017 in each age-bracket. This information was provided to the author **by Statistics South Africa directly**. Using the number of deaths and the population estimates, the age-specific incidence rate and annual probabilities of HPV-related cancer deaths were calculated. These were weighted by the cancer's proportion of all cancers as described above.

Table 4

Estimated health-costs used in the model

Health Service	Cost (ZAR)	Source
Cost of vaccine (per dose) [10]	201	Médecins Sans Frontières (2015)
Indirect cost of vaccination (per dose)	73	[11]Moodley et al. (2016)
Total cost per doses of vaccine	**274**	
Cervical Cancer	329 987	[12] Sinanovic et al. (2009)
Anal Cancer	256 940	[13]Datta et al. (2019)
Vulva/Vaginal Cancer	301 402	Datta et al. (2019)
Penile Cancer	269 290	Datta et al. (2019)
Oesophagus Cancer	405 171	Datta et al. (2019)
Weighted cost of cancer **for females**	340 245	*Own calculations*
Weighted cost of cancer **for males**	369 043	*Own calculations*

[10] The paper has used *Cervarix* as the HPV vaccine. This is drug is currently used in the girls-only vaccination programme.

[11] This represents the indirect costs of the vaccination as investigated by Moodley et al. (2016). These are reported as the School Health Teams, Pharmacy, Consumables, Fridge, Printing and Transport costs. Importantly, Moodley et al. (2016) conducted their investigation in Kwa-Zulu Natal, thus it has been assumed that these costs would apply nationally.

[12] The cost of cervical cancer was extrapolated from Sinanovic et al. (2009). The study was conducted in South Africa. This study used the 2007 prices in US$. The prices were converted into ZAR using the average exchange rate for 2007 (1 US $ = R7, 11) and then inflated using the consumer price index (CPI) to get its price in 2019.

[13] The costs of Anal, Vulva, Vaginal, Penile and Oesophagus cancers were taken from a previous study conducted in the United Kingdom (Datta et al., 2019). These prices were converted into ZAR using the average exchange rate for 2014 (1 £ = R17.85) as this was the year the costs were reported for. They were then inflated using the consumer price index to obtain the 2019 price.

Table 5

Utility input data

Health State	Utility Value	Source
No HPV	0	Li et al. (2015) [14]
HPV	0	Li et al. (2015)
Cervical Cancer	0,727	Li et al. (2015)
Anal Cancer	0.645	Datta et al. (2019)[15]
Vulvar /Vaginal Cancer	0.777	Datta et al. (2019)
Penile Cancer	0.798	Datta et al. (2019)
Oropharyngeal Cancer	0.826	Datta et al. (2019)
Weighted utility of cancer **for females**	0,7546	*Own calculations from above*
Weighted utility of cancer **for males**	0,8026	*Own calculations from above*

[14] Disutility Values were taken from a previous study conducted by Li et al. (2015) examining the cost-effectiveness of female-only HPV vaccinations in South Africa. It is assumed that the utility of cancer-states is the same in 2019 as it was in 2015. Importantly, by using one *HPV-related Cancer* state, the utility value attached to all stages of cancers have remained constant. This is unlikely to accurately model the utility gained in preventing severe stages of cancer.

[15] Due to the lack of similar studies in South Africa, disutility values for other anogenital and head and neck cancers were extrapolated from a study performed by Datta et al. (2019) in the United Kingdom.

Table 6

Proportion of cancer attributed to HPV 16 & 18.

Disease Type	Attributable to HPV 16 &18 (%)
Cervical Cancer	64.2
Anal Cancer	38.0[16]
Vulvar Cancer	62.2 [17]
Vaginal Cancer	36.9[18]
Penile Cancer	26.3[19]
Oropharyngeal Cancer	69.7[20]

Source Note: Data has been extrapolated from Bruni et al. (2019). The estimates have been created using 2019 data from South Africa, and where such data is unavailable, the African estimate has been used.

[16] No available data on percentage in South Africa so the estimate for Africa has been used.

[17] No available data on percentage in South Africa so the estimate for Africa has been used.

[18] No available data on percentage in South Africa so the estimate for Africa has been used.

[19] No available data on percentage in South Africa so the estimate for Africa has been used.