THE IMPACT OF DUAL HIV AND HPV VACCINE STRATEGIES AMONG ADOLESCENTS IN A RESOURCE CONSTRAINED SETTING

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DECLARATION

This thesis is submitted in the optional format, approved by the Faculty of Health Sciences, of published work with the additional chapters of an introduction and conclusion.

I, Nishila Moodley, declare that this thesis is my original work. Where there has been contribution from other people, this has been acknowledged. It is being submitted for the degree of Doctor of Philosophy in Public Health in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.

I have read and understood the sections on referencing and plagiarism in the University of the Witwatersrand Plagiarism Policy. Further, I acknowledge that plagiarism may result in suspension or permanent expulsion of students in serious cases. This body of work submitted for assessment for the above degree is my own unaided work except where I have explicitly stated otherwise. I have followed the standard, required conventions in referencing the thoughts and ideas of others. I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:

Name: Nishila Moodley

Date: 13 December 2016

DEDICATION

To Bernadette Sheldon, the greatest teacher I have ever had.

Rather than an acknowledgment of your contribution, may this message serve as the start of a very humble apology to the people I hold most dear. An apology for every moment I missed, for every hour lost with each of you when I was 'too busy' when you reached out. An apology exceeded only by the immense and humble gratitude I feel for the support you have given me during this journey.

To my long-suffering husband, Jonathan, who has unwittingly taken this emotional roller coaster alongside me, has 'emotionally' (as opposed to physically) written drafts and re-drafts and re-re-drafts, endured my mercurial change of moods and survived my protracted zombie-like states, you were right all along….I am the lucky one to have you.

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

PUBLICATIONS

- Moodley N, Gray G, Bertram M. The Price of Prevention: cost-effectiveness of biomedical HIV prevention strategies in South Africa. Clin Res HIV/AIDS. 2016; 3(1):1031-44.
- Moodley N, Gray G, Bertram M. Projected economic evaluation of the national implementation of a hypothetical HIV vaccination program among adolescents in South Africa, 2012. BMC public health. 2016;16(1):1-13.
- Moodley N, Gray G, Bertram M. The Case for Adolescent HIV Vaccination in South Africa: A Cost-Effectiveness Analysis. Medicine. 2016;95(4):0000000000002528.
- Moodley N, Gray G. Global evidence reaffirms the case for routine HPV and potential HIV adolescent vaccination in South Africa. Future Virology. 2014;9(2):207-20.

SUBMITTED PAPERS UNDER REVIEW

- Moodley N, Gray G, Bertram M. It all adds up! Cost-effectiveness analysis of dual HIV and HPV vaccine programs for school-aged girls in South Africa.
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NON-PEER REVIEWED PUBLICATIONS

- Moodley N. Is the HIV vaccine our best shot? Why the answer to HIV prevention will be found in South Africa. SACEMA Quarterly, June 2015. http://sacemaquarterly.com/hiv-prevention/is-the-hiv-vaccine-our-best-shot-why-the-answer-to-hiv-prevention-will-be-found-in-south-africa.html (accessed Jun 18, 2015).

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CONFERENCE PROCEEDINGS

- Moodley N, Gray G, Bertram M. The price of prevention: Including HIV vaccines into South African health programmes. South African AIDS Conference, International Convention Centre, Durban, South Africa. 9-12 June 2015. (Oral presentation)
- Moodley N, Bertram M. Is a HIV vaccine a viable option in South Africa and at what cost? 1st HIV Research for Prevention Conference, Cape Town, South Africa, 28-31 October 2014. (Poster presentation)
- Moodley N, Bertram M. The potential cost-effectiveness of adding a HIV vaccine to the HIV treatment and prevention programme in South Africa. 2nd Biennial Southern African HIV Clinicians Society Conference, Cape Town, South Africa, 24-27 September 2014. (Poster presentation)
- Moodley N, Bertram M. An economic evaluation of adopting HIV vaccines into the existing South African HIV public sector programmes. Faculty of Health Sciences Research Day & Postgraduate Expo, University of the Witwatersrand, Johannesburg, South Africa, 17 September 2014. (Poster presentation)
- Moodley N, Bertram M, Welte A, Gray G. The cost of adolescent sexual health. SACEMA Research Days, University of Stellenbosch, Stellenbosch, South Africa, 20 March 2014. (Oral presentation)
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AWARDS

- Awarded a scholarship to attend the HIV Research For Prevention Conference, Cape Town International Convention Centre, South Africa (28-31 October 2014)
- Awarded a scholarship to attend the 2nd Biennial Southern African Clinicians Society Conference, Cape Town International Convention Centre, South Africa (24-27 September 2014)
- Awarded the South African Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA) scholarship for PhD Studies (2012-2015)
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ABSTRACT

Introduction

With the largest epidemic in the world, the consequences of human immunodeficiency virus (HIV) in South Africa extend far beyond its disease burden. In fact, patterns of HIV-related infection and mortality in South Africa still reflect social cleavages and inequalities. Similarly, poverty-related issues such as poor education, unemployment and subsequent low socio-economic status, rural residence and inadequate access to health care are all implicated in human papillomavirus (HPV) associated cervical cancer-related mortality (of which South Africa also has the highest globally). Despite the knowledge of reproductive functions and sexuality being poor among adolescents in South Africa, the majority commence their sexual activity early with an estimated national average of 15 years for girls and 14 years for boys. Further, many South African adolescents engage in sexual risk-taking behaviours including concurrent partners and unprotected sexual acts that considerably increase their vulnerability to sexually transmitted infections including HIV and HPV. In recognising the unique health needs of adolescents in South Africa, the national government has already pin-pointed school health services as a strategic arm of primary health care re-engineering. The aim of this body of work is to elaborate on restructuring of adolescent health care by introducing the HIV and HPV vaccine concomitantly in South Africa via a school-based sexual and reproductive health service.

Methodology

Data from four studies were analysed and are presented in three published and two unpublished papers. The first study evaluated the synergism between HIV and HPV in the South African context and formed the basis of the literature review. The second study considered HIV vaccine implementation alone. The third study assessed dual HIV and HPV vaccine strategies among females and the final study compared the dual vaccination strategy against recognised biomedical HIV prevention interventions.

The studies evaluated the implementation of a hypothetical HIV vaccine and the bivalent HPV vaccine both individually and in combination when administered to school-going adolescents in South Africa. The health outcomes and the cost-effectiveness of these strategies were assessed. Assumptions were made regarding the hypothetical HIV vaccine (based on HIV vaccine studies conducted to date) including a coverage rate of 60% (uncertainty range: 30-70%), vaccine efficacy of 50% (uncertainty range: 30-70%) and vaccine price per dose of US$ 12 (uncertainty range: US$ 3-24). The uncertainty ranges were tested in the sensitivity analysis. Mortality statistics, disease transition parameters (for the individual diseases and the models representing joint disease) and HPV vaccine characteristics were drawn from the South African literature. The joint effectiveness of the dual vaccine strategy was considered multiplicative.

Nine year old adolescents attending South African schools in 2012 were eligible for the intervention (vaccination) that was introduced opportunistically as part of the national health initiative introducing school-based sexual and reproductive health services. The learners were targeted prior to their reported sexual debut. The HIV vaccine was considered against the comparator of HIV counselling and testing (HCT) and the national roll-out of antiretroviral therapy (ART) that constituted the standard of care in South Africa. The HPV vaccine was modelled as prevention against HPV-related cervical cancer and pre-cancerous HPV-related cervical states. The health service provider (provider) perspective was adopted and the cohort was modelled through a lifetime horizon of 70 years with annual cycles. The economic costs and health outcomes were discounted at 3% with an uncertainty range between 0% and 6% assessed. Cost valuations were for 2012 and costs were adjusted to this common year.

The quality-adjusted life year (QALY) was used as the outcome measure of health related quality of life and was used to calculate the incremental cost-effectiveness ratio (ICER) of the comparator against the vaccination interventions. The core model was a semi-Markov simulation with annual cycles. The study population entered the model HIV and HPV disease free and were exposed to the risk of acquiring each disease annually. The model structure was parameterised drawing from South African data available in the literature. One-way sensitivity analyses evaluated the impact of single assumptions on cost and outcomes. Probabilistic sensitivity analysis (PSA) with a bootstrapping technique explored the uncertainty in the model and evaluated the robustness of the results. The PSA data generated determined if the intervention fell below the willingness-to-pay (WTP) threshold. As South Africa does not have a pre-defined WTP threshold, the Gross Domestic Product (GDP) per capita (for 2012) was used as a proxy in accordance with the World Health Organization's Guide to Cost-Effective Analysis. Additionally, benchmark interventions were used in the final comparison study as a measure of cost-effectiveness. Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Findings

The second study explored the implementation of the HIV vaccine on an individual and national, programmatic level. The simultaneous implementation of HIV vaccination services with current HIV management programmes would be cost-effective, even at relatively higher vaccine cost. At base vaccine cost of US$ 12, the ICER was US$ 43 per QALY gained, with improved ICER values yielded at lower vaccine costs. The ICER was sensitive to the duration of vaccine-mediated protection and to variations in the vaccine efficacy. Data from this work demonstrate that vaccines offering longer duration of protection and at lower cost would result in improved ICER values.

Assessing this HIV vaccine model on a national programmatic level, yielded an ICER of US$ 5 per life-year gained (LYG) (95% CI US$ 3-12) compared with the comparator. This fell considerably below the national WTP threshold of cost-effectiveness. This also translated to an 11% increase in per capita costs from US$ 80 to US$ 89. National implementation of this intervention could potentially result in an estimated cumulative gain of 24 million years of life (95% CI 8–34 million years) among those adolescents aged between 10-19 years that were vaccinated. The 10 year absolute risk reduction projected by HIV vaccine implementation was 0.42% for HIV incidence and 0.41% for HIV mortality. The ICER was sensitive to the HIV vaccine efficacy, coverage and vaccine pricing in the sensitivity analysis.

The third study assessed the impact of dual HIV and HPV implementation strategies. Programmes that involved the dual vaccine strategy were assessed as cost-saving. ICER values were sensitive to the HIV vaccine cost. The dual vaccine strategy resulted in 10 year absolute risk reductions in HIV incidence (5.24%), dual mortality (1.21%) and a reduction in HPV incidence (0.39%) compared with no vaccination. Importantly, the reduction in HIV incidence rate and dual mortality rate in the dual vaccine strategy exceeded the reductions noted with the use of the HIV vaccine alone. All scenarios assessed with the dual vaccine strategy were cost-effective. Lower vaccine prices and reduced discount rates were associated with improved ICER outcomes. The final study compared the biomedical interventions of oral pre-exposure prophylaxis (PrEP), voluntary medical male circumcision (VMMC) and the scaling-up of ART coverage against the vaccine strategies. When compared with other biomedical HIV prevention interventions, the dual vaccination intervention was the most cost-effective strategy (US$ 7 per QALY gained) and averted 29% of new HIV infections. VMMC (US$ 30 per QALY gained) proved more cost-effective than HIV vaccination alone (US$ 93 per QALY gained), though VMMC averted 6% more new infections than the HIV vaccine. PrEP interventions were the least cost-effective. Combined dual vaccination and VMMC strategies represent the only dominant intervention. Strategies involving oral PrEP were the least cost-effective.

Conclusion

The findings of this thesis have implications for school-based adolescent health care and HIV- and HPV-related disease prevention among adolescents, a highly susceptible population. The cost-effectiveness of the dual HIV and HPV vaccine strategy was demonstrated, and the improved health outcomes associated with the interventions quantified. Proposals were suggested regarding possible combinations of HIV prevention interventions that could yield the favourable health outcomes with the most efficient use of financial resources. Several important areas for future research were identified to shed light on improving adolescent health care and for optimising HIV prevention strategies. These include integrating HIV and HPV services as part of the re-engineering of primary health care in South Africa, and then formulating economic evaluations of HIV/HPV prevention strategies targeting adolescents specifically. Further, more effective methods of collecting data on socially marginalised populations such as young people need to be explored.

Another vital research area is the discussion and implementation of existing school health documents with the ideals embodied in the school health programme envisaged under the National Health Insurance restructuring. Once these are integrated, the cost implication of the combined programmes need to be assessed.

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LIST OF ABBREVIATIONS

AMC	Advanced market commitment
ANA	Annual National Assessments
ARR	Absolute risk reduction
ART	Antiretroviral therapy
AIDS	Acquired immunodeficiency syndrome
bNAbs	Broadly neutralizing HIV-1 antibodies
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHH	Child-headed households
CIN	Cervical intraepithelial neoplasia
CPI	Consumer Price Index
CROI	Conference on Retroviruses and Opportunistic Infections
CVT	Costa Rica HPV Vaccine Trial
DALY	Disability-adjusted life years
DES	Discrete event simulations
DTP	Diphtheria, tetanus and pertussis
EPI	Expanded Programme of Immunisation
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FRESH	Focus Resources on Effective School Health
FTC	Emtricitabine
GAVI	Global Alliance for Vaccines and Immunisation
GDP	Gross domestic product
HCC	Half-cycle correction
HCT	HIV counselling and testing
HIV	Human immunodeficiency virus
HPV	Human papillomavirus

HRQOL	Health-related quality of life
HSIL	High-grade squamous intraepithelial lesion
HVTN	HIV Vaccine Trial Network
IAVI	International AIDS Vaccine Initiative
ICER	Incremental cost-effectiveness ratio
IPV	Intimate partner violence
ISHP	Integrated School Health Programme
LMIC	Low- and middle- income countries
LSIL	Low-grade squamous intraepithelial lesion
LYG	Life-year gained
MSM	Men who have sex with men
NCD	Non-communicable disease
NHI	National Health Insurance
NHLS	National Health Laboratory Services
NMB	Net monetary benefit
NSHP	National School Health Policy
NW	North-west
P5	Pox-Protein Public-Private Partnership
Pap smear	Papanicolaou smear
PATH	Program for Appropriate Technology in Health
PATRICIA	Papilloma Trial against Cancer In young Adults
PHC	Primary health care
PMTCT	Prevention of Mother to Child Transmission
PrEP	Pre-exposure prophylaxis
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
RR	Relative risk
SE	South-East
SG	Standard gamble
SRH	Sexual and reproductive health

SSA	Sub-Saharan Africa
STI	Sexually transmitted infection
TasP	Treatment as prevention (antiretroviral)
TDF	Tenofovir disoproxil fumarate (Tenofovir)
TTO	Time trade-off
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNESCO	United Nations Educational, Scientific, and Cultural Organization
UNICEF	United Nations Children's Fund
UPFS	Uniform Patient Fee Schedule
US$	United States Dollar
USA	United States of America
VAS	Visual analogue score
VIA	Visual inspection with acetic acid
VLP	Virus-like particle
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
WHO-CHOICE	World Health Organization Choosing Interventions that are Cost-Effective
WTP	Willingness-to-pay
YPLL	Years of potential life lost
ZAR	South African Rand

GLOSSARY OF TERMS

Adolescent: The period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19 [as defined by the United Nations Population Fund (UNFPA) along with the World Health Organization (WHO) and United Nations Children's Fund (UNICEF)]. It represents a critical transition period that has been marked in recent times by earlier onset of puberty, later age of marriage, urbanization, global communication, and changing sexual attitudes and behaviours. The UNFPA breaks this age category down further by classifying early adolescence for the ages 10-14 years and late adolescence for the ages 15-19.

Bootstrapping: Bootstrapping is a re-sampling procedure that employs raw computing power to estimate an empirical sampling distribution for the statistic of interest. The bootstrap method randomly selects samples from the original data set with replacements. The process is repeated a large number of times and can generate a confidence interval for cost-effectiveness analyses.

Child-headed households: This is usually defined as a household where all members are younger than 18 years of age. The phenomenon has grown rapidly in sub-Saharan Africa, particularly in countries afflicted by HIV/AIDS.

Consequences: Represent the changes occurring in an individuals' health (positive or negative) and includes all the effects of the health programme not accounted for by the resources.

Consumption: The final purchase for use of goods or services by individuals (consumers).

Cost-effective: When an intervention is effective or productive in relation to its cost.

Cost-effectiveness analysis: A type of economic analysis in which the incremental costs of an intervention are compared to the incremental outcomes of the intervention expressed in physical units such as diseases averted, lives saved or quality-adjusted life years gained.

Consumer price index: Measures changes in the price level of a market basket of consumer goods and services purchased by households.

Decision analysis: Refers to a systematic, quantitative and interactive approach to addressing and evaluating important choices confronted by organisations in the private and public sector.

Disability-adjusted life year: The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.

Discounting: Discounting is a method used to account for individuals' time preference. Most individuals have a positive rate of time preference whereby benefits are preferred sooner rather than later and costs incurred later rather than sooner.

Dominant intervention: An intervention is assumed to 'dominate' the comparator if it is cheaper and more effective than the comparator.

Economic evaluation: This is the process of systematic identification, measurement and valuation of the inputs and outcomes of two alternative activities, and the subsequent comparative analysis of these assessing both the costs and consequences. The purpose of economic evaluation is to identify the best course of action, based on the evidence available.

Externality: Cost or benefit that does not fall on the person producing or consuming a good.

Gross domestic product per capita: Refers to the gross domestic product (GDP) divided by midyear population. The GDP is the sum of the gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products.

GDP deflator: A measure of price inflation/deflation with respect to a specific base year; the GDP deflator of the base year itself is equal to 100.

Health care costs: Refer to the tangible resources of the health care system including staffing, equipment and buildings and consumables like drugs.

Health economics: The study of how scarce resources are allocated among alternative uses for the care of sickness and the promotion, maintenance, and improvement of health, including the study of how health care and health-related services, their costs and benefits, and health itself are distributed among individuals and groups in society.

Heterogeneity: The variability between patients that can be attributed to characteristics of those patients (e.g. difference in mortality rates between males and females).

High-grade squamous intraepithelial lesion: Indicates moderate or severe cervical intraepithelial neoplasia or carcinoma in situ. The lesions may lead to invasive cervical cancer, if not managed appropriately.

HPV treatment: In the context of this thesis, HPV treatment refers to the health care administered to either prevent (screening via PAP smear) or treat HPV-associated lesions (including cancerous lesions) that may occur in the cervix.

- Screening costs include the Pap smear costs as well as the clinic related costs (e.g. human resources and laboratory costing).
- Patients with low grade lesions do not receive any treatment unless the lesion persists at a Month 12 visit.
- Costs for high-grade lesions consist of colposcopy and biopsy costs as well as the clinic related costs (e.g. human resources and laboratory costs).
- Cancer treatment costs included the cost of surgery and chemo-radiation.
- All costs were inflation adjusted for the year 2012.

Incremental cost-effectiveness ratio: The ratio is a statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is obtained by dividing the difference between the costs of the two interventions by the difference in the outcomes, i.e. the extra cost per extra unit of effect.

Life-table: A table of statistics relating to life expectancy and mortality for a given category of people.

Life expectancy: The average period that a person may expect to live.

Low-grade squamous intraepithelial lesion: Indicates possible cervical dysplasia. It usually indicates mild dysplasia, more than likely caused by a human papillomavirus infection.

Markov assumption: Refers to the 'memoryless' feature of the Markov model. Once a patient moves from one state to another, the Markov model has 'no memory' regarding where the patient has come from or the timing of that transition.

Markov chain: (Markov model) A stochastic model describing a sequence of possible events in which the probability of each event depends only on the state attained in the previous event.

Microbicides: These are compounds formulated as gels, films, or suppositories that can kill or neutralize viruses and bacteria. Researchers are studying both vaginal and rectal microbicides to determine if they are able to prevent the sexual transmission of HIV, thus preventing new infections.

National Health Insurance: This is a legally enforced scheme of health insurance that insures a national population against the costs of health care. Commonly referred to as NHI, the system will ensure equal access to appropriate, efficient and quality health services. In South Africa, it will be phased-in over a period of 14 years and will entail major changes in the service delivery structures, administrative and management systems.

Pap smear: A Papanicolaou (Pap) smear is a microscopic examination of cells taken from the uterine cervix. A Pap smear can detect certain viral infections such as human papillomavirus, which is known to cause cervical cancer.

Primary health care: Refers to essential health care and is the first level of contact individuals, families and communities have with the health care system. It is a basic level of health care that includes programmes directed at the promotion of health, early diagnosis of disease or disability, and prevention of disease.

Pre-exposure Prophylaxis: This is a method of HIV prevention where people who are HIV-negative (but are at high risk of acquiring the disease) take a pill every day to prevent acquiring HIV infection.

Quality-adjusted life year: A measure of health outcome that assigns to each health state a weight ranging from 0 (equivalent to death) to 1 (perfect health) corresponding to the health-related quality-of-life of that health state. These values are then aggregated across all the relevant health states.

Quintile: A system of ranking and funding schools which takes into account the socio-economic circumstances of learners. The intended objective is to ensure that public funding is skewed in favour of the poorest learners.

Relative risk: Measures the magnitude of an association between an exposed and non-exposed group. It describes the likelihood of developing disease in an exposed group compared to a non-exposed group.

Semi-Markov process: A semi-Markov model involves the adding of tunnel states into a Markov model as a means of implementing time-dependency, and therefore adding memory.

Sensitivity-analysis: A process through which the robustness of an economic model is assessed by examining the changes in results of the analysis when key variables are varied over a specified range. It represents a means of representing uncertainty in the results of economic evaluations. The four main types of sensitivity analysis are: one-way simple sensitivity analysis, multiway simple sensitivity analysis, threshold sensitivity analysis and probabilistic sensitivity analysis.

Social rate of time preference: The rate at which society values present over future consumption.

Time-tradeoff: Method of eliciting the value that individuals place on a health state by asking them their preference between a shorter time spent in perfect health, and a longer time spent in a health state.

Treatment as prevention: HIV prevention methods that use antiretroviral treatment to decrease the risk of HIV transmission. The antiretroviral treatment reduces the HIV viral load in the blood, semen, vaginal fluid and rectal fluid to very low levels (‘undetectable’), reducing an individual’s risk of onwards HIV transmission.

Uncertainty: *Parameter uncertainty*: The uncertainty in estimation of the parameter of interest. *Structural uncertainty*: The assumptions inherent in the decision model.

Utility: A measure of the 'satisfaction' (benefit) obtained from consuming goods and services.

Variability: Random variability in outcomes between identical patients. Also referred to as first-order uncertainty.

Willingness-to-pay: The process in which individuals are asked the maximum they are willing to pay, in monetary terms, to achieve a given benefit of an intervention/service.

CHAPTER 1

INTRODUCTION

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1. INTRODUCTION

'*The roots of a dysfunctional health system and the collision of the epidemics of communicable and non-communicable diseases in South Africa can be found in policies from periods of the country's history, from colonial subjugation, apartheid dispossession, to the post-apartheid period. Racial and gender discrimination, the migrant labour system, the destruction of family life, vast income inequalities, and extreme violence have all formed part of South Africa's troubled past, and all have inexorably affected health and health services'* (1).

When Apartheid ended in 1994, the South African plan for an integrated and comprehensive health system was undone by the two-tiered system of public and private health care (based largely on social class) that replaced it - a system that perpetuated the health inequalities of the past (2). The National Health Insurance (NHI) policy represents a bold, ambitious plan that seeks to transform health care provision and delivery in South Africa through the improved management and administration of a comprehensive package of services entrenched in the principles of primary health care (PHC) (3).

While the NHI aims to address the inequalities of the past through widespread social reform, South African society still remains marked by gross inequities spanning class, gender and racial lines (4). These social and political factors intricately weave with behavioural patterns to determine the course of disease in the country.

2. THE DIMENSIONS OF DISEASE

2.1 HIV AND POVERTY

South Africa currently faces a quadruple burden of disease in the form of communicable diseases (human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and tuberculosis in particular); as well as maternal and child mortality, non-communicable diseases (NCD) and violent injuries (5). Most governments tend to justify their constrained health resources by the apparent endless demands placed on it; demands that they believe would likely never be satisfied (6).

With the largest epidemic in the world, the consequences of HIV in South Africa extend far beyond its disease burden. It is widely acknowledged that poverty in Africa is a critical factor implicated in HIV/AIDS transmission and in doing so worsens the toll of the poverty (7). In fact, patterns of AIDS-related infection and mortality in South Africa still reflect social cleavages and inequalities (4), but the role of poverty remains poorly understood (8). There is an empirical link between higher HIV rates among the poor and the poverty-related characteristics of low education and low knowledge levels of methods of avoiding HIV infection. Tladi (2006) suggests the situation among the poor and less educated is exacerbated by the inability to negotiate condom use either due to personal financial dependence on a partner or as a result of the household they belong to experiencing hunger (and thus household dependence on their partner) (8). Mufune (2015) argues that there are several dimensions in which poverty is manifested in South Africa describing it as a '*complex, multi-dimensional concept that relates to inequalities, material deprivation, and exclusion*'; all of which must be accounted for in relation to HIV/AIDS (7). In the South African context, factors such as labour migration, religion and the country's historical legacy are still relevant considerations (9). The relationship between HIV/AIDS and poverty can be described as both synergistic and symmetrical when considering the impact on household functioning. Adults chronically ill with HIV/AIDS can exert untenable pressure on households already struggling to survive. It is often the poorer households that are the most drastically compromised and vulnerable to the long-term impact of HIV/AIDS (10). South African studies suggest that AIDS-associated illness may be more prevalent in rural rather than urban populations; often attributed to the great distances to clinics and health care service provision and poor public transport systems (9).

Further studies in South African highlight the disproportionate burden of HIV disease and HIV fear among the poor and vulnerable South Africans; who are further disadvantaged by poor access to HIV information and HIV/AIDS services (11). Even with HIV prevention information, education, and counselling initiatives reaching the poor, the stark reality of their lives makes this messaging intangible (12). Often circumstances dictate that recommended behaviours are not adopted simply because there are no resources or incentives to do so (12). The emergence of HIV in South Africa reflects that of the developing countries of sub-Saharan Africa (SSA). The pattern emerging is of a heterosexual epidemic, characterised by high rates of infection in the general population with women particularly susceptible to infection (4). Of concern is the fact that it is young women in particular that become infected (4), both underpinning their predicament and highlighting the need to prioritize them for prevention efforts

2.2 CERVICAL CANCER AND POVERTY

Similarly, poverty-related issues such as poor education, unemployment and subsequent low socio-economic status, rural residence and inadequate access to health care are all implicated in cervical cancer-related mortality (13-15). Where cervical screening practices are available, it is frequently marred by poor infrastructure and inadequately trained staff such that estimates suggest that approximately five percent of women in developing countries have been screened for cervical dysplasia in the preceding five years; compared with 40% to 50% of women in developed countries (16, 17).

In developing countries, most women attending clinic for services such as family planning and sexually transmitted infection (STI) treatment tend to be younger which is important as this places them at high risk for developing cervical cancer (18). Women often acquire the human papillomavirus (HPV) infection in their teenage years or in their twenties, followed by a period of dormancy of up to 20 years before the HPV infection manifests (19). The majority of HPV infections are transient in nature and are cleared spontaneously by the immune system. The persistence of infection is a risk factor for the development of pre-invasive lesions and invasive cervical carcinoma (20). Women with cancer face an entirely different social dimension to their disease. Their need to access treatment for their personal health crisis is exceeded by the primary responsibilities they have to attend to their families (21). A similar situation prevails when a mother dies from HIV/AIDS; particularly in SSA where many households are headed by women (22). In countries with extreme poverty, the death of a mother has catastrophic consequences for her children (21).

It thus becomes imperative to understand that the factors that allow the cervical cancer disease burden to grow are not purely biological.

Several studies have consistently demonstrated that misinformation and poor knowledge of cervical cancer and screening practices remain significant hurdles to adherence to screening practices (23-29). Women struggle to differentiate between screening and diagnostic tests and often believe that Papanicolaou (Pap) smears are performed to investigate reproductive health problems like vaginal bleeding (23, 26). Often women reporting low adherence to screening are not consulted by health care providers that speak their first language, hence the breakdown in communication regarding the need for the cervical screening procedure (23, 25, 30). Cultural beliefs and practices present another barrier to cervical screening, as it impacts on decision-making (23, 31, 32). The decision to access treatment may require the input of the whole family, and if the decision is made that the treatment does not comply with her cultural practices, she may be prevented from accessing any further treatment (33). Women have also reported the attitudes of health care providers as insensitive and discourteous as an additional deterrent to being screened for cervical disease (24, 28, 30). In fact, their interaction in general with their service providers has been shown to influence their adherence to screening (24, 26, 28, 30). Not surprisingly, the fear and anxiety surrounding the potential pain and fear of a cancer diagnosis prevents women from screening (23-25, 27, 30, 34-36). Loss of privacy and embarrassment at having to expose their genitalia is also frequently cited as a barrier to screening (30, 34, 35). The last reason cited resonates universally with access to health care, particularly in South Africa. Knowing that the clinics present long waiting periods, lengthy travelling (often at great cost) and inconvenient operating hours present an additional deterrent to screening (23, 25, 30).

3. DECIPHERING THE LINK BETWEEN HIV AND HPV

3.1 THE MEDICAL LINK

What is the relevance of considering these diseases together? HIV and HPV disease are known to share risk factors (37). Although the risk of acquiring HIV and HPV infection differ slightly (only HPV can be transmitted by non-penetrative sex), both are transmitted via sexual contact (including vaginal, anal, and oral penetrative sex), while HPV may also be transmitted via non penetrative sex (38). HIV transmission and acquisition is enhanced in the presence of HPV (39, 40) suggesting a potential reduction in HIV risk should an effective HPV preventive strategy be implemented (37). The prevalence of HPV has been found to be higher among HIV-positive populations rather than their HIV-negative counterparts (41) with data from Brazil (42) and Zambia (43) establishing higher HPV co-infection rates among HIV-positive women at 60.6% and 80% respectively. Additionally, it has been shown that women previously infected with HPV may have an increased likelihood of becoming infected with HIV (44). Conversely, HIV-positive individuals are at substantial risk of being infected with HPV (often with multiple strains) attributable to their weakened immune status (45, 46). This translates to a subsequent increased risk of cervical cancer in women and penile and anal cancers in males. HIV-positive females are at higher risk of persistent HPV infections should their HIV infection progress to significant immune suppression (47, 48) are more likely to experience treatment failures related to their HPV pre-cancers (49), have more reported disease recurrences (50) and progress more frequently and quickly from the early stages of infection to precancerous stages of disease (51-53) than HIV-negative females. Invasive cervical cancer has been regarded as an AIDS defining condition since 1993 (54, 55).

Studies linking HIV/AIDS and cancer registries Data on 499 230 individuals diagnosed with AIDS from 1980 till 2004 were linked with cancer registries in 15 USA regions and demonstrate a considerable increase in the incidence of invasive cervical cancer among HIV-positive females compared with those that are HIV-negative (53). Further, lower CD4 counts have been correlated with more aggressive forms of HPV disease (56, 57), and while CD4 counts for most individuals on ART tend to rebound to normal levels, ART does not appear to limit the progression or severity of HPV-related cervical, anal, or oral cancers (58, 59). Studies from sub-Saharan Africa demonstrate that HR-HPV occurs commonly among HIV infected heterosexual men (60). The presence of HIV infection enhances HR-HPV acquisition and reduces clearance of the virus (61, 62). Among males, circumcision has been conclusively shown to reduce the incidence of HIV in men, and indirectly in women (63-65). Additionally, the circumcision of HIV-negative men reduces their risk of acquiring HPV (66), reduces the incidence of penile cancer (67), and limits HPV transmission to female partners (68). Importantly, the circumcision of HIV-positive men does not appear to reduce HPV transmission (69).

It thus becomes imperative that outreach programmes targeting the prevention of HIV and HPV should reach young men prior to their sexual debut (70, 71). The World Health Organization (WHO) is currently revising its recommendations for cervical cancer screening and treatment among HIV-positive women or women of unknown status, and emphasizing the importance of offering HIV testing and counselling for women coming to a clinic for cervical cancer screening and vice versa. Thus the provision of a sexual and reproductive health (SRH) platform with the integration of HIV and HPV disease prevention education represents a logical continuum of care (41).

HPV currently has limited treatments available; thus greater priority is given to vaccine introduction among populations noted for their higher prevalence of HIV; notably SSA. Most studies account for the impact of HIV disease on HPV prevalence and cancer incidence in developed countries with low HIV prevalence. It becomes important that models in developing countries account for higher HIV prevalence rates and the fact that HIV-positive women are more vulnerable to developing of cervical cancer (61). Modelling data dating as far back as 1996 have demonstrated the potential reduction in endemic HIV prevalence attributable to low efficacy HIV vaccines, although these were estimated at high coverage rates (72). With that in mind, a partially efficacious HIV vaccine administered at high coverage rates in combination with a highly immunogenic HPV vaccine could herald significant reductions in both disease burdens.

3.2 INTEGRATING SERVICES

Efforts to strengthen health systems to addressing the global burden of HPV-related cancers with prevention (affordable vaccines and appropriate diagnostic screening tests) and treatment (particularly among those living with HIV) in resource limited settings (73) will likely benefit from the strides made in universal access to HIV prevention, treatment, and care services, and conversely. The argument that HPV screening, pre-cancer treatment, and advanced cancer therapies are prohibitively expensive in LMICs is negated by the global improved access achieved in HIV prevention and treatment (74, 75). A systematic literature review was undertaken to identify formal and informal evaluations of HPV vaccine use in low- and middle-income countries paying specific attention to the demonstration projects conducted in India, Peru, Uganda, and Vietnam. The key lessons of intensive planning and coordination of services across all sectors while being sensitive to the need for information and communication channels among youth, parents, and communities underscored the findings and held huge potential for adapting these services to provide accelerated adolescent HIV services (76). Parents, young adolescents, community members and key informants interviewed in the North West and Gauteng Provinces were in favour of integrated adolescent health care provision and showed particular preference for detailed information about the HPV vaccine, general health information and specific sexual and reproductive health information.

HPV-related cancers are preventable. Apart from prevention strategies (vaccination), behaviour change strategies reducing the risk of viral exposure is required. As with HIV prevention, effective HPV prevention raises concerns regarding adolescent sexuality causing parental queries and anxiety (77). Steps assessing existing HIV-related stigma, stigma related to dual HIV and other sexually transmitted infections, or even stigma related to cancer will go a long way to improving the quality of life, access to screening and testing services, and vaccine implementation (78). Apart from HIV-related stigma, the condemnation of pre-marital and adolescent sex (especially for girls) by many cultures tends to steer girls away from accessing such health services. Given the predilection for disease HIV and HPV share, evidence-based screening and treatment guidelines become imperative (79). Thus women seeking HIV testing should be advised to test for HIV and reciprocally, a woman seeking cervical cancer screening, she should be advised on HIV testing and counselling, especially if she resides in a country with a high documented HIV prevalence (80).

Evidence from developed countries points to the HPV vaccine platform being a useful springboard to deliver other needed adolescent health care services, particularly through school-based vaccination programmes (81). Evidence from these countries also suggests that adolescents use scheduled HPV vaccination visits to address their other health care requirements (82, 83). Challenges in reaching adolescents through traditional health care services and high levels of school enrolment suggest that school-based HPV vaccination would potentially be the most effective delivery strategy (84).

3.3 GLOBAL MODELS OF INTEGRATED SERVICES

Since the introduction of the HPV vaccines on the market, there have been several initiatives aimed at strengthening cervical cancer prevention and control programmes and linking HIV with cervical cancer screening and control. The Pink Ribbon Red Ribbon public–private global health partnership (including UNAIDS and PEPFAR) has supported the integration of HIV and cervical and breast cancer screening and treatment using HIV-delivery platforms in Zambia, Botswana, Kenya, Tanzania, and Rwanda.

Successful integration models have been developed. In West Bengal (India), the integration of SRH services with VCT has translated increased access to both services without having financially detrimental effects (85). A similar model in 2 Kenyan districts showed that integration was acceptable and feasible, that counselling on family planning showed improvement, condom promotion was deemed more effective and the incremental costs due to integration were considered affordable (86). A retrospective cross sectional data from a regional hospital in Cameroon where women accessed a voluntary screening campaign for cervical cancer found that HIV-infected women receiving HAART have a lower risk of cancer than women in the general population. While this may seem counter-intuitive, the finding was not attributable to ART alone but rather to all the health benefits derived from receiving a comprehensive HIV care (87). However, school health interventions in Tanzania have met with limited success. The programmes were delivered vertically and struggled with financial, human resource and logistic constraints which was exacerbated by limited community engagement, rumours, and lack of strategic advocacy has affected uptake of some interventions (88).

To expand access to rural populations, WHO and health systems experts increasingly advocate linking treatment with follow-up, screening for cervical cancers in primary health care (89), and strengthening primary healthcare-based health systems (90).

4. TARGETING ADOLESCENTS

In developing countries, adolescent SRH is a cause for major concern. Why is this concerning? Why are adolescents being targeted? Adolescents are engaging in an alarming amount of unprotected sex as evidenced by close to 50% of the 20 million new STIs that are reported in the United States of America (USA) annually occurring among adolescents aged 15-24 years of age (91). While STIs are for the most part treatable, it is the repercussions of them not being treated that are concerning – particularly the risk of acquiring and transmitting HIV or HPV infection, infertility or death (92-94). The HIV statistics for young people are sobering. Close to 7000 young people are infected daily, and close to 50% of those infected before age 25 will die an AIDS-related death before 35 years of age (93). The cervical cancer-related HPV statistics are no kinder with many young people acquiring infections in their youth with little or no recourse to medical care later in life. Yet despite their vulnerability, adolescents continue to encounter endless barriers when trying to access health care with concerns expressed from lack of privacy and confidentiality to judgmental staff and clinic standards of poor quality (95, 96).

The South African context mirrors that of the developing countries. In most cases, the development of other STIs occurs before the development of HIV (93). Nearly 25% of new HIV infections reported in South Africa occur among the youth (97). Data continues to show that women remain more susceptible to HIV infection than men (97, 98). Most young South Africans report an early sexual debut with 15% of girls and 26% of boys reporting their sexual debut before 14 years of age (99). It is not surprising from this that 33% of young girls aged between 15–19 years and 59% of those between 20–24 years have reported a pregnancy, most of which were unplanned and unwanted (98). The problem persists. Young people in South Africa are known to have limited knowledge regarding SRH (in particular concerning pregnancy and, STIs) (100) and tend to avoid public health services due to the reported barriers of staff attitudes, operating times of the clinic, confidentiality concerns and embarrassment and simply put, a poor understanding of their diagnosis (101).

The National Adolescent Sexual and Reproductive Health and Rights Framework Strategy (2015) acknowledges the crisis that exists among the South African youth and hopes to build on the Programme of Action of the International Conference on Population and Development (ICPD) in Cairo (1994) which called for the promotion of "*responsible and healthy reproductive and sexual behaviour among adolescents and the youth to reduce the incidence of high risk teenage pregnancies, abortion and sexually transmitted diseases, including HIV/AIDS, through the provision of life skills, sexuality and gender sensitivity education, user-friendly health service and opportunities for engaging in social and community life"*(102, 103).

The key issues raised in the framework strategy included higher levels of sexual activity amongst young male adolescents (particularly among those younger than 16 years of age), multiple concurrent sexual partners with increasing trends of intergenerational sexual relations, poor uptake of condom use resulting in high levels of HIV/AIDS and STIs and importantly; vulnerability and sexual violence arising from their social context of poverty and the disruption of the family unit (102).

The dire need for dynamic SRH services for adolescents is not being debated. The question is whether we can take the service to them?

5. MODELLING HIV AND HPV DISEASE

Infectious disease modelling has long been the domain of mathematicians. With greater emphasis being placed on implementing interventions that cost effective, health economic modelling has come to the fore. The problem is that many developing countries often lack the expertise and technical capacity to perform and interpret the results generated from the economic appraisals of interventions, including vaccines (104). Mathematical models provide a useful framework by which cost-effectiveness of new interventions may be defined. These combined models allow for data integration from various sources and can potentially predict the future impact of emerging innovations (105). There have been an impressive number of modelling exercises undertaken in the HIV and HPV field. The list is exhaustive, but a select few are highlighted to demonstrate the scope of the work conducted.

5.1 HIV MODELS

Given the magnitude of the global HIV epidemic, there has been significant increases in research and commitment to prevention strategies. It is not surprising that there are concerns emerging regarding the cost and cost-effectiveness of potential HIV cure strategies (106). By illustrating the cost-effectiveness of HIV strategies, simulation models can be vital in highlighting the value of pursuing specific research strategies and informing trial design (105, 107). Considering HIV vaccines specifically, Hankins et al. concluded that while mathematical models were able to estimate the population-level impact of partially efficacious vaccination strategies on HIV incidence in different settings, they can produce conflicting outcomes when the methods, assumptions and parameters varied (108). Understandably, mathematical models cannot be parameterized to every potential scenario nor applied to every conceivable HIV prevention programme but can be used to refine and validate simpler decision-making tools (109, 110). Regarding the HIV vaccine, the consistent findings suggest that a modestly efficacious vaccine applied in a population at low risk of heterosexual HIV exposure could have tangible population-wide benefits (108).

Several theoretical mathematical models were independently developed to elucidate the role that the HIV vaccine would play in the epidemic. Examples of these include Massad et al. who considered the implementation of an imperfect vaccine and the impact behavioural disinhibition would have on health outcomes (111), Nowak and Maclean explored the antigenic drift and the immunogenicity of a potential HIV vaccine (112) and Blower et al. presented a mathematical model for an imperfect pre-exposure vaccine with therapeutic effects (113).

The Futures Institute and IAVI have developed a HIV vaccine computer simulation module as part of the Spectrum Policy Modeling System to explore the impact and costs of other HIV prevention and treatment interventions (114). The model, easily accessed by national governments, was intended to explore the potential impact of HIV vaccines on their specific country epidemic by applying relevant demographic, epidemiological, and vaccine uptake data (115). This has allowed for global tracking of the intervention as well as in specific countries such as Brazil (116), Kenya (117) and Uganda (118). The strength of the Spectrum HIV vaccine model lies in the fact that it assesses three anticipated modes of vaccine actions, and most of the necessary data inputs can be ascertained from epidemiological surveillance data, national surveys, and behavioural surveillance surveys. A further strength of the model is that the future projections can be tailored to incorporate scenarios that explore the impact of vaccines alongside expanded prevention programmes, increased ART use models and technologies such as PrEP and microbicides. The model is limited by limited mixing between risk groups and the limited movement of people in and out of risk group over the course of their lifetime (119).

In South Africa, the ASSA 2002 vaccine model was developed by adapting the ASSA 2002 AIDS and demographic model to allow for the effect of vaccination. Vaccination scenarios with full protection, partial protection and no protection were considered and vaccines were administered in 3 doses providing 10 year of protection. The model was limited by its inability to account for revaccination and by the simplistic assumptions underlying it: the vaccine was free, it would be delivered through the current system with no scale-up of services and the utilisation of health facilities remained the same. Concerns regarding behavioural disinhibition were raised. Unsurprisingly, deaths averted and numbers of infections averted increased with increasing vaccine efficacy. The model described a short term benefit in vaccinating individuals in adolescence rather than in childhood. Further, the model demonstrated that a vaccine reducing susceptibility by 95% was still unlikely to reduce the total number of new infections by more than 50%; mostly because of those unwilling to be vaccinated or those who failed to complete the vaccine course (120). More recently, Smith et al. used a deterministic compartmental model of heterosexual HIV transmission in South Africa to determine the costs and effects of scale-up of existing interventions but also the introduction of new interventions such as a vaccine (121).

5.2 HPV MODELS

HPV infection has attracted a wide array of mathematical and economic modelling. Several mathematical models of HPV transmission have been published. Elbasha et al. assessed the epidemiologic consequences and cost-effectiveness of alternative strategies of administering a prophylactic quadrivalent HPV vaccine as part of screening practices in the USA using a dynamic transmission model. Their work showed that vaccinating girls before the age of 12 years would prove cost-effective and would reduce the incidence of genital warts (83%) and cervical cancer (78%) (122). Barnabas et al. developed a transmission model of HPV estimating the transmission probability of the virus, changes in patterns of sexual behaviour and smoking on age-specific trends in cancer incidence, and to determine the impact of HPV vaccination in the Finnish population. Their findings showed that changes in sexual behaviour and smoking accounted, in part, for the increase seen in cervical cancer incidence in women between 35 to 39 years old. Further, they found that high vaccine coverage of women alone, sustained over many decades, with a long duration of vaccine-conferred protection would have the greatest impact on type-specific cancer incidence (123). A similar study in Finland showed that vaccinating 12 year olds delays the predicted decrease in cervical cancer, compared to vaccinating older adolescents or young adults (124). Dynamic models of HPV transmission were developed to describe the infection spread and development of cervical neoplasia, cervical cancer (squamous cell and adenocarcinoma) and anogenital warts in the United Kingdom. Results suggest that vaccinating 12-year-old girls at 80% coverage will translate to a 38–82% reduction in cervical cancer incidence and 44–100% reduction in anogenital warts incidence if the vaccine programme were to endure for 60 years with vaccine protection lasting 20 years on average (125).

However model development is based on assumptions and degrees of uncertainty. Van de Velde developed a cohort model of HPV vaccination designed to measure parameter uncertainty. This work showed that vaccinating 12 year old girls would reduce their lifetime risk of HPV infection, CIN 1, CIN 2/3 and squamous cell carcinoma by 21%, 24%, 49% and 61% respectively. The uncertainty around these predictions widen as the vaccine efficacy is reduced or as the vaccine protection wanes (126).

Much research has been conducted in HPV vaccine economic evaluation. Jit and Demarteau compared six HPV vaccination models representative of low-income and middle-income countries viz. (i) the Harvard model (127), (ii) the WHO-CHOICE ('CHOosing Interventions that are Cost Effective') model (128), (iii) the Thai model (129), (iv) the South African model (130), (v) the Merck model (122) and (vi) the GlaxoSmithKline (GSK) model (131). The analysis was intended to compare model predictions before and after vaccination of adolescent girls in terms of HPV prevalence and cervical cancer incidence, as was the incremental cost-effectiveness ratio of vaccination under different scenarios. The comparison demonstrated large decreases in type 16/18 HPV prevalence and cervical cancer incidence, likely due to vaccination. Cost-effectiveness was greatly influenced by the discount rate, duration of vaccine protection, vaccine price and HPV prevalence. The work emphasized the usefulness of considering results from several models (104).

Natunen et al. conducted a systematic review specifically assessing HPV vaccine cost-effectiveness in low-and middle income countries (132). Sixteen studies were identified from 25 countries from Europe, Africa, Latin America, and Asia. The review concluded that HPV vaccination alone or in combination with screening strategies was cost-effective in countries with high cervical cancer incidence and moderate to low GDP per capita (132). The affordability of the vaccination programme was a crucial element in determining the success of cervical cancer prevention by country. Most models considered the natural history of HPV infection and efficacy of HPV vaccination strategies and included parameters of basic cost, screening assumptions and some sensitivity analyses (133-136).

5.3 DUAL DISEASE MODELS

Modelling of dual infections has remained the domain of the mathematicians. Much work has been concentrated on diseases that are known to occur together commonly. HIV and malaria is particularly relevant. Mukandavire et al. used a deterministic model to demonstrate the co-interaction of HIV and malaria in a community. Their work demonstrated that the reduction in sexual activity of individuals with malaria symptoms decreases the number of new cases of HIV and the mixed HIV-malaria infection but increased the number of malaria cases. Additionally, HIV-induced increase in susceptibility to malaria infection showed a marked increase in the number of dual HIV-malaria infection (137). Barley et al. explored another perspective of HIV-Malaria co-infection suggesting that biological differences could alter the effect of co-infection. Their model used a system of differential equations linking the host-vector system of malaria with co-infection with HIV and showed very high mortality associated with co-infection. The simulations also showed that the HIV-induced increase in susceptibility to malaria infection increases the number of new cases of the dual HIV-malaria infection (138). Nyabadza et al. developed a mathematical model of 13 interlinked equations that examined the role of malaria and/or HIV treatment in altering populations' dynamics. Reproductive numbers were then evaluated from the sub-models developed. Finally, sensitivity analyses were conducted to determine the impact of selected parameters on the dynamics of malaria (139).

Malaria was also considered in the context of typhoid fever and lymphatic filariasis. With lymphatic filariasis, Slater mathematically emphasized the perils of targeting one infection (and ignoring co-epidemics) when designing control programmes. The study additionally highlighted the need for better data on how co-infection impacts hosts and vectors for better predictions on co-transmission dynamics. The modelling framework developed explored key immunological interactions in co-infected hosts (140). Malaria and typhoid remain a major public health problem in developing tropical countries. The Mutua et al. mathematical model represents a novel approach to describing the malaria-typhoid co-infection dynamics. Using illustrative data from Kenya, the model was applied to demonstrate that the con-infection basic reproduction number can be reduced to below one, thus eradicating both diseases through prevention programmes targeting the co-epidemics (141).

Another prominent co-infection epidemic is HIV-TB. Mathematical modelling of joint dynamics is formidable as the diseases are distinct, there is considerable overlap in the populations at risk of either infection and the magnitude of the proportion of individuals at risk for both diseases is unquantified. Using a highly simplified deterministic model, Roeger et al. demonstrated that the increased progression rate from latent to active TB among those co-infected played a significant role in the rising prevalence of TB (142). Silva et al. proposed a co-infection model that additionally considered ART for HIV infection and treatments for latent and active tuberculosis. The HIV-only and TB-only sub-models were analysed separately, and then as a joint full model. The models computed basic reproduction numbers, and equilibria and stability were assessed (143). Mathematical models by Shah et al. applied differential equations to understand the dynamics of disease spread till steady state conditions were derived (144). Similar to the Shah model, Bolarin et al. studied co-infection models that demonstrated stable disease free equilibrium states and stable endemic equilibrium (145). HIV models were also considered in light of other diseases including Hepatitis C (146).

Modelling HIV in conjunction with HPV is a relatively new endeavour. There are a few studies in the literature but they are limited in their application. Xiao et al. developed one of the few models assessing HIV and HPV disease. Their study evaluated the cost-effectiveness of a 2-dose schedule HPV vaccination programme of HPV of HIV-negative and HIV- positive 12-year-old girls independently in two separate models in South Africa. A previously developed Markov cohort model was used and showed the HPV vaccination to be dominant over screening alone. Targeting the HIV-positive sub-population alone remained cost-effective but at a higher incremental cost-effectiveness ratio (147). While the model assessment was novel, it assessed the HIV-negative and HIV-positive populations in silos and didn't allow for meaningful comparisons in a population where both HIV statuses co-exist. The only other HIV-HPV con-infection model identified was at molecular level. In unpublished work, Erwin sought to address the effect of HIV on HPV pathogenesis using a mathematical model that captured the known interactions such as decreased HPV-specific cytotoxic T cells and increased HPV viral production. The model aimed to predict the biological conditions under which coinfected individuals can clear HPV and addressed the clinical implications of ART use in co-infected individuals compared with previous clinical observations (148).

From the above discussion, it is clear that despite the endemicity of HIV-HPV in certain regions and the synergism described between HIB and HPV, there is a dearth of modelling work encompassing both diseases in the literature. The model developed for the purposes of this thesis is thus considered novel and will not only lay the foundation for future research and modelling initiatives, but will also contribute to health planning and decision-making in South Africa.

6. PROBLEM STATEMENT

It is acknowledged that people younger than 25 years of age constitute half the world's population and their differing health needs from adults' warrants specific attention (149). The SRH concerns among adolescents have emerged as an area of global concern resulting in a paradigm shift in the provision of health care to adolescents. Despite the knowledge of reproductive functions and sexuality being poor among adolescents in South Africa, the majority commence their sexual activity early in their mid-teens with an estimated national average of 15 years for girls and 14 years for boys (150). It is further documented that many South African adolescents engage in sexual risk-taking behaviours including early sexual debut, concurrent partners and unprotected sexual acts that considerably increase their vulnerability to STIs such an HIV and HPV (92, 151, 152). The provision of school-based health services by national government was announced in 2010, and progress has been slow (153). Another significant shortcoming of the programme is that it targets quintiles one and two only, and thus leaves a large sector of the adolescent population uncovered (153). Public clinic services remain largely inaccessible to adolescents for reasons ranging from operating hours, overlapping school times to unfriendly, judgemental staff that limit open discussion about sexual matters (95, 151). In summary, adolescents are acknowledged to have early sexual debut, poor understanding of reproductive health and safe sexual practices, report high incidence of HIV and HPV disease and have poor access to health care; particularly since the school health services remain largely underdeveloped.

7. JUSTIFICATION OF THE RESEARCH

South Africa has the highest reported rate of HPV-related cervical cancer incidence and mortality globally, and much of the disease burden is acquired in adolescence (92). To exacerbate the situation, young women aged 15-24 years of age comprise approximately 25% of the annual HIV incidence reported nationally (152). It is in understanding the widely acknowledged synergy between these two diseases that adolescent health care requires specialised services.

In recognising the unique health needs of adolescents in South Africa, the national government has already pin-pointed school health services as a strategic arm of PHC re-engineering (154). The aim of this body of work is to elaborate on restructuring of adolescent health care by introducing the HIV and HPV vaccine concomitantly in South Africa via the school-based SRH services. The major contribution of this PhD is to evaluate the cost and cost-effectiveness of introducing the HIV vaccine alone and then in combination with the HPV vaccine. By specifically targeting a group acknowledged to be highly susceptible to these infections, we are able to ascertain what impact the intervention could have on disease burden and financially compared to the current strategies that are employed.

The HPV vaccine is currently available on government tender and is being rolled-out at quintile one and two schools. This PhD work models the HPV vaccine being delivered to all eligible candidates and thus may more accurately predict the long-term impact of a national roll-out programme. The HIV vaccine is being clinically evaluated in Phase I clinical trials in six clinical trial sites in South Africa and the vaccine is earmarked for critical Phase IIb/III trials in South Africa in 2016 in a study designated HIV Vaccine Trial Network 702 (HVTN 702). Once the HIV vaccine becomes commercially available, it would be important to identify a point of entry into the health system. The premise of the PhD is that both vaccines would be delivered via the Expanded Programme of Immunisation (EPI) which has been established in South Africa since 1995. The EPI, introduced by the World Health Organization (WHO) in 1974, aimed at vaccinating all children below the age of one year against six killer diseases (155). The South African EPI has evolved with scientific advancement, most recently with the addition of the rotavirus and pneumococcal vaccines (156). The current programme reaches children till the age of 12 years when the fourth (school-going) dose of tetanus toxoid is administered (155).

During the research and development of the PhD, significant gaps in the literature became apparent. Most of this information pertained to HIV treatment allocations and patterns of testing for HPV disease. This information is considered fundamental to health service planning and budget projections going forward. This PhD assessed proxy values for these parameters (obtained from the literature) into the models developed. The work undertaken by this PhD sought to tie in these various concepts by evaluating the administration of both vaccines to adolescents as part of school health services.

8. CONCEPTUAL FRAMEWORK: THE PUBLIC HEALTH PERSPECTIVE

The development of this conceptual framework (Figure 1) and the integration of the factors associated with adolescent SRH were influenced by two major reports from the WHO viz. the World Health Report 2000 (Health Systems: Improving Performance) (157) and the WHO health system's framework (158).

Health sector reform (Addressing issues of equity)*

Cassels defined health sector reform as 'sustained, purposeful changes to improve the efficiency, equity, and effectiveness of the health sector' (159). The model begins at national level where health sector reform is introduced to improve the architecture of South African health care by proposing equitable access to health care through re-engineering and re-establishing PHC as the bedrock principle of the health care system (3, 160). By adopting the PHC approach, the government adopted the underpinning values of universal access, equity, participation and intersectoral collaboration (158). The WHO then divided the national health system into discrete building blocks that serve distinct functions (158). While the issue of a health workforce and human resources in general remains a crucial component of health care nationally and internationally, it was not considered unique to adolescent health care and was not discussed further.

Governance (Youth access to health services)*

Ensuring effective governance has become a public heath priority that is crucial to the success of broader health objectives (161). Engaging civil society in policy development demonstrates the strength of society as a partner to government and also highlights the ability of the government to address the concerns of society (162). In this context, the Departments of Basic Education and Health have endeavoured to strengthen health services at schools through the Integrated School Health Programme (ISHP). The policy focuses on addressing the immediate health concerns of learners (particularly those that constitute a barrier to learning) in addition to the implementation of interventions that promote the health and well-being of learners during childhood and into adulthood (153).

Financing

Access to essential health care and financial protection remain a priority of low- and middle-income countries (LMICs) (163). Access to health care in these settings may be subject to cultural and language barriers and transport costs, making the prospect of universal coverage difficult (164, 165). It is in situations such as these that issues such as policy development; and financial and economic evaluation of interventions become crucial.

Health information (Generation of health data)*

Health information systems are vital to understanding the linkage between the health reforms and the health system. However, the timeliness, accuracy and indeed availability of data in LMIC remains challenging mostly due to inadequately trained staff and poor infrastructure (166). A key feature of this work is to identify gaps present in the South African literature that impact effective health planning.

Medicine and technologies

'A well-functioning health system ensures equitable access to essential medical products, vaccines, and technologies of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use' emphasizes the need for effective supply chain management (158). As the demand grows for improved drugs, vaccines and diagnostics, the procurement capacity of the government has to be responsive (163). Supplying an intervention like a vaccine to the entire population may be considered altruistic but is largely financially prohibitive. The priority then becomes to identify the populations that would benefit most from these interventions. Once identified, it is the imperative of the government to ensure the availability, distribution and continued access to the intervention.

Health service delivery (School health services to adolescents)*

The purpose of any health system is to provide accessible, equitable and responsive health service delivery (158). The delivery of health services hinges on the availability of health facilities, health care workers, adequate diagnostics, appropriate pharmaceuticals and a responsive community. Strengthening health systems impacts positively on access and uptake of services (167) which in turn improves equity in health service access (168). The delivery of quality health services remains an important outcome measure of health reforms and health systems (163).

Health outcomes (Impact on HIV/HPV disease burden)*

The logical translation of health sector reform and strengthening and ongoing evaluation of health service delivery is the improvement in health outcomes. This is assessed as comparative improvements in disease burden and reduction in disease-associated mortality.

*The headings marked within parentheses represent the key areas of discussion and are extensively elaborated on in Chapter 9.

9. AIM & OBJECTIVES

9.1 AIM

The aim of this PhD is to estimate the impact of HPV and HIV dual vaccination preventive strategies on the HIV and HPV disease burden when administered to school-going adolescents as part of the school health programme envisaged under the PHC re-engineering model.

9.2 OBJECTIVES

The objective of this body of work was to quantitatively:

Objective 1: Explore the cost-effectiveness and long-term health outcomes of HIV vaccination on HIV-associated infection and disease mortality.

Objective 2: Explore the cost-effectiveness and long-term health outcomes of dual HIV and HPV vaccination on HIV- and HPV-associated infection and combined disease mortality.

Objective 3: Evaluate the health impact of the dual vaccine strategy compared with other biomedical HIV prevention strategies in terms of infection and disease-associated mortality.

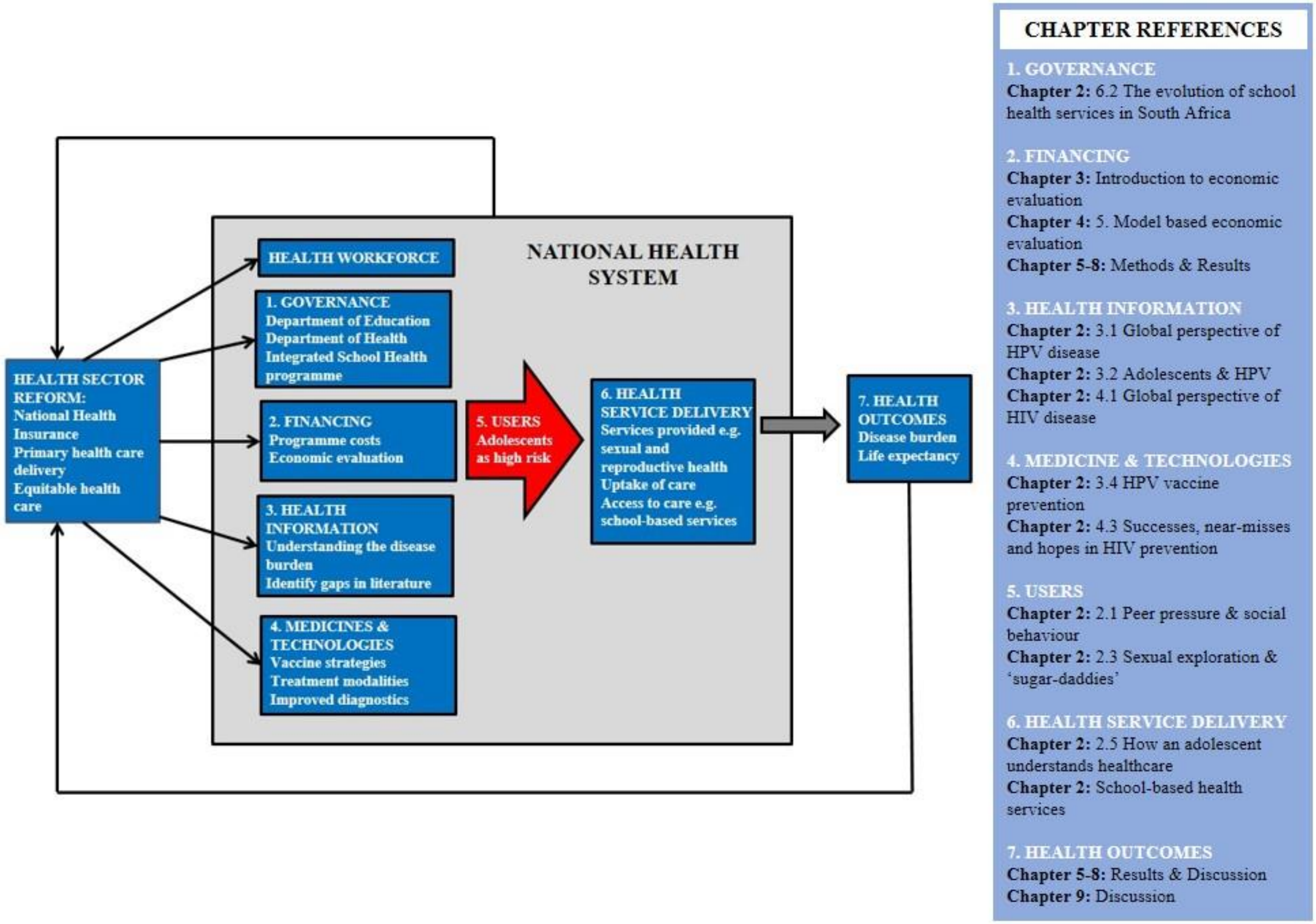

Figure 1. Conceptual framework adapted to adolescent health care

The figure shows the interaction between the health sector reforms envisioned and the country's health system and highlights the concepts discussed in the literature review.

10. OVERVIEW OF THE THESIS

Chapter 1 has defined the four important targets of this PhD (viz. adolescents, their health care, their predilection for HIV and HPV disease and the potential impact of the vaccines). The justification for this body of work is presented and the components of the PhD detailed. The conceptual framework within which this PhD can be understood is explained.

Chapter 2 presents the epidemiology of HIV and HPV disease in South Africa. It outlines the programmes and the prevention strategies that are in place. The chapter draws on the literature to explain why adolescents are a key population to prioritise in disease prevention attempts going forward. Several concepts from Chapter 2 have been published as a review in Future Virology (2014) (169).

Chapter 3 provides a background to health economics and economic evaluation, contextualising the work that follows. It provides the theory and rationale of the concepts adopted in the methodology of the study.

Chapter 4 describes the methodology of the papers. It details the procedures of the cost-effectiveness analysis (CEA), model life-table analysis and the cost and disease reduction consequences between the intervention and comparator models. My role is described in the project management section.

The results of the thesis are embodied in four journal articles and each article is presented as a separate chapter.

Chapters 5 and 6 explored HIV vaccination of adolescents at school. Chapter 5 looked at the cost-effectiveness and the sensitivity analysis of the vaccine characteristics using Markov models. Chapter 5 has been published in Medicine (2016) (170). Chapter 6 assessed the national programmatic projections of the vaccine intervention looking at the financial implications, changes in life expectancy and cost and disease consequences of the programme using life-table analysis. Chapter 6 has been published in BMC Public Health (2016) (171).

Chapter 7 examines the dual implementation of the HIV and HPV vaccine to school-going girls. The study assessed the health impact, cost and cost-effectiveness of three separate scenarios on both HIV and HPV disease: (1) HIV vaccination; (2) HPV vaccination and (3) dual HIV and HPV vaccination. Chapter 7 is currently under review at Cost-Effectiveness and Resource Allocation.

Chapter 8 compares the dual HIV and HPV vaccine strategy to the biomedical HIV prevention strategies of voluntary medical male circumcision (VMMC) and pre-exposure prophylaxis (PrEP). Subsequently, these results are compared to the scaling-up of antiretroviral therapy (ART). Chapter 8 is currently under review at PLoS ONE.

Chapter 9 discusses the findings of this PhD in relation to the aims and objectives. The gaps in the literature are identified. Strategies regarding adolescent HIV/HPV care are explored and future areas of research suggested.

CHAPTER 2

LITERATURE REVIEW

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1. INTRODUCTION

This chapter provides the background for the PhD and presents an overview of how the factors discussed are intrinsically linked. The focus of this PhD is the South African adolescent and an understanding of their environment is crucial to understanding the motivations for their decisions. The disease burdens of HIV and HPV are explained biologically; and then by their social paradigm. Current treatment and prevention strategies adopted in South Africa are described, and the significance of vaccination in society explored. The chapter ends with a discussion on the global experiences of school-based health care and its potential application in the South African context.

2. BEING AN ADOLESCENT IN POST-APARTHEID SOUTH AFRICA

Adolescents constitute close to 25% of the world's population with most residing in LMIC (84). The decisions made; and behaviours and interventions adopted during this period have ramifications for their morbidity and mortality that extend into their adulthood (172).

Adolescents encounter specific health risks particularly regarding SRH (173). They constitute 11% of births and 14% of maternal deaths globally (95% of which occurs in developing countries), are vulnerable to unwanted pregnancies and subsequently unsafe abortions (174, 175) and are prone to HIV infection with limited access to SRH services. Approximately 68% of adolescents have unmet contraception needs (97, 174). Young southern African adolescents disproportionately contribute close to 30% of all new HIV infections and females seroconvert five to seven years earlier than their male counterparts. This age-sex disparity in HIV acquisition maintains the unprecedented high incidence rates documented. The key to the incidence can be ascribed to adolescent engagement in age-disparate and often transactional relationships, limited schooling and gender-based violence that increases the chances of disease acquisition (176). It is thus vitally important to teach HIV prevention to these young women especially when they are unable to negotiate monogamy or condom use (176). It is in these circumstances that the development of a SRH platform becomes a public health imperative.

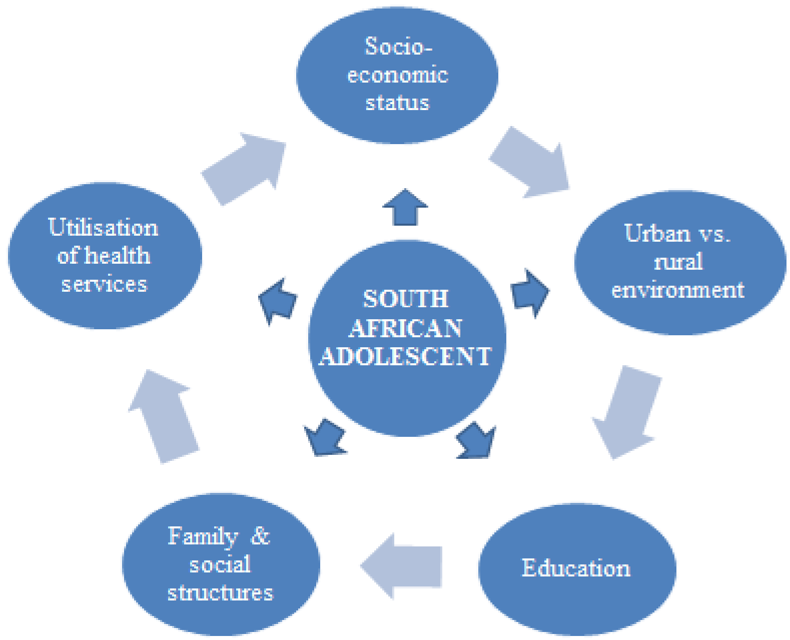


Figure 2. Determinants of adolescent behaviour

There are complex interactions of the factors influencing the social, sexual and health behaviours of adolescents.

The basic needs of the South African adolescent extend far beyond the complexities of SRH (Figure 2). Household food insecurity is rife with more than a fifth of households in Kwa-Zulu Natal reporting being food insecure in the last month (177). The persistently high prevalence of poverty in South Africa perpetuates the cycle of hunger, malnutrition and food insecurity that children must face (178). The physical effects of poor nutrition are far-reaching, potentially resulting in impaired motor and cognitive development and impacting learning abilities and thus educational achievement in the long-term (179). Poverty is inextricably linked to health and wellbeing and limits access to education, nutrition, health care services and safe environments (178). Despite government initiatives targeting hunger, malnutrition and food insecurity, 16% of children live in households where child hunger was reported (180). Adolescents residing in these vulnerable environments report significantly higher risks of depression, traumatic stress, and suicide (181). In South Africa, black adolescents have significantly greater stressors regarding school performance, school attendance, financial pressure and emerging adult responsibility than adolescents operating from different environments (182-184). Educational prospects are limited in many southern African countries. School retention and completion is hampered by limited educational facilities, poor school infrastructure, unfair re-entry policy for teenage girls who have dropped out of school due to pregnancy, poverty, absenteeism due to illness, gender-based violence and sexual harassment by educators, or other learners. Drop-out rates are high as learners face a multitude of problems ranging from the cost of schooling, unplanned pregnancies, loss of parents and lack of safety when traveling to school, to children being withdrawn from attending school to save on school costs that can be redirected to care for sick family or to supplement household incomes (185).

Many South African youth are exposed to multiple forms of violence and trauma, particularly young males (186). Domestic victimization has emerged as the strongest predictor of internalizing and externalizing difficulties, where the cumulative exposure often manifested as conduct disorders and aggression (186). The repeated witnessing of trauma further culminated in the development of post-traumatic stress disorder, mood and anxiety disorders and substance abuse (187). Finally, is it widely acknowledged that the youth face significant barriers in attempting to access care with low coverage levels attributed to stigma and discrimination fashioned at health system and policy level (188). What the adolescent population needs is a comprehensive, integrated service that focusses on the specific concerns of adolescent health, education and social needs.

2.1 PEER PRESSURE AND SOCIAL BEHAVIOUR

Adolescence has often been described as a period of ‘stress and storm’ characterised by physical maturation, the desire for independence and prominent peer and social pressures that are reflected in their patterns of behaviour (189).

Data from rural schools in South Africa have confirmed the high level of sexual activity among adolescents with 48% reporting having had sex before the age of 15 and 42% reporting penetrative sex with more than one partner in their lifetime. The peer influence of boys is widely recognised in promulgating risky sexual behaviours among adolescents (190). Pregnancy is thus common among adolescents in South Africa. In fact the belief that the adolescent female and her male partner considered each other their main partners increased the chances of either an unplanned or unwanted pregnancy, despite the fact few young women reported having a close relationship with their partners postpartum (191, 192). Higher socio-economic status was protective against unplanned, unwanted pregnancies (192). Physical abuse and experiences of physical violence enhanced the potential for having unwanted pregnancies (192). Among girls, more so than boys, previously identified instances of sexual abuse, baseline school drop-out, and physical assault instigated in the community strongly predicted sexual abuse (193). Adolescent pregnancy is fraught with human capital deficits. Adolescent mothers are forced to drop-out of school and hence fall behind in schooling relative to other girls their age. Additionally, they are at high risk for HIV infection and mortality due to lower reported use of condoms and sexual partners significantly older than themselves (194, 195).

Alcohol use and abuse remains a significant public health challenge globally, with South Africa being no exception. Apart from robbing adolescents of their normal development, alcohol is strongly associated with crime, unintentional accidents and violence. Alcohol use among adolescents is driven by age, gender, parental alcohol use and peer pressure (196). Alcohol consumption also adversely impacts on behaviours resulting in a disinhibiting effect increasing the likelihood of sexual risk-taking and disease transmission (197). Research conducted in Cape Town and Port Elizabeth assessing the relationship between sexual risk behaviour and hazardous alcohol use found a statistically significant association between excessive alcohol use and multiple concurrent partners, two or more partners and age-disparate sex in the last year (198). To compound the problem, adolescents are implicated in the increased use of popular substances such as like crystal methamphetamine (called 'tik' locally) and diacetyl morphine (heroin) (199), cannabis and in fact, substances in general (200). These substances have a demonstrated comorbid psychopathology component associated with its use (201).

The complexity of these inter-related factors culminate into especially high attempted and completed suicide attempts among adolescents nationally and internationally. Almost 20% of South African adolescents have attempted suicide, with forced sexual encounters, poor social support networks and previous attempts strongly implicated in suicidal ideation or attempts (202).

2.2 EDUCATION AND EMPLOYMENT

Despite large spending on education and free compulsory primary school education for children aged seven to fifteen (15) years, South Africa reports much worse educational performance than many other countries in the region (203). The education of adolescents serves as an important indicator of employment and thus future economic development in a country (204). In the face of high levels of poverty in South Africa, a quality education is often compromised by the realities of life. On reaching adolescence, many children are expected to actively contribute in caring for their younger siblings and ill parents, share in household chores and generate an income (204).

The school education of children is often characterized by poor attendance, absent or poorly qualified teachers, pregnancy and school-related violence and abuse (204). Classrooms are overcrowded and ill-equipped, teachers are poorly qualified (if at all), literacy and numeracy levels are low and despite large budgetary injections by the national government, the quality of education remains sub-standard particularly in townships schools (205). One method that the Department of Basic Education has devised to produce credible data on learner achievements has been the Annual National Assessments (ANA) targeting the literacy and numeracy development among grades one till six. The ANA has since been inconsistently implemented. In many cases, the South African government has failed its duties by its inability to provide library and laboratory facilities but also more crucial elements such as textbooks (206). The problems at schools are multi-faceted. Studies show that close to a fifth of teachers were absent on Mondays and Fridays, and almost a third were absent at the end of the month (207). The plight of education continues to fall on the underserved black schools where lack of discipline and focus by the teachers were largely to blame for poor scholastic outcomes (206). Sexual involvement of teachers with students is another shockingly regular occurrence especially when considering the already high rates of HIV disease reported among adolescents. Understandably, all sectors including parents and educators are concerned about providing a safe physical and emotional environment for male and female learners. Parents have a fundamental responsibility to guide their children through school - a phenomenal task considering that many parents themselves have no formal schooling. Often parents work long hours and are unable to ensure the proper completion or supervision of work. Studies show that parents investing time in their children's education correlated with better educational achievement among the children. Nonetheless, parents found to contribute to their child's schooling through advocacy, involvement in fundraising and oversight roles made for better learner achievements (206).

Violence in schools is another alarming issue. Sexual abuse, pregnancy and poverty are all implicated in the high drop-out rates reported in secondary schools (208). Gender-based violence threatens to undermine international and national efforts to ensure girls remain in school long enough to acquire the skills needed to succeed in life (209). Boys and girls are equally implicated as HIV infection, teenage pregnancy, substance abuse and other risky behaviours have a negative impact on the education of both genders. The Girls Education Movement was first introduced in Uganda in 2001, followed closely by South Africa in 2002 where the programme was run by peer leaders supported by the Department of Basic Education and the school management. The Girls and Boys Education Movement provided young people a platform to access skills and information, space for open discussion and a portal for community engagement to address the rights of boys and girls (210).

2.3 SEXUAL EXPLORATION AND 'SUGAR DADDIES'

Sexual exploration by adolescents in South Africa remains complicated by early sexual debut, multiple sexual partners, inconsistent or no condom use and poor sexual decision-making (often influenced by alcohol use) that sadly translates into unwanted pregnancies, high rates of STIs and HIV acquisition (211-213). In eThekwini (Kwa-Zulu Natal), the high prevalence and spread of HIV among the youth are exacerbated by the regular occurrence of *inkwari* (A Zulu word for raves or weekend-long parties). Inkwari are characterized by limited adult supervision, easily accessible drugs and alcohol and interactions with peers and potential sexual partners (214). Sexual behaviour among adolescents in South Africa is characterised by early sexual interaction, though the nature of the sexual exposure varies. Early sexual debut, voluntary or coerced, increases the risks of SRH problems. Median ages of voluntary consent averaged 16 years for females and 15 years for males while reported coerced sexual debut included children younger than 11 years of age (215). Data emanating from a cohort of Eastern Cape adolescents confirmed the high risk of STIs and HIV acquisition and associated it with the practices of intimate partner violence (IPV) and concurrency (216). There are high reported rates of IPV among adolescents (217). Those struggling financially are particularly vulnerable. Almost 37% of ever partnered adolescents in Johannesburg reported episodes of IPV in the last year and instances of IPV were associated with substance abuse, poor mental health and poor SRH (218). Another perspective is that a young man's perpetration of IPV is a significant predictor of subsequently fathering a pregnancy. 'South African hegemonic masculinity' rationalises the display of virility by men as they exert control over women and their subsequent reproductive rights (219). Forced sexual practices are emerging as a major concern as it is not only being perpetrated by adults. Dating violence is another cause for concern given its strong link to risky sexual behaviours. Males were associated with high levels of dating violence victimisation and perpetration, targeting particularly females from lower socio-economic backgrounds (220). Young males also held positive views about forced sex as they believed it corresponded to a sign of love and considered it an appropriate way to satisfy sexual urges particularly if the girl was financially dependent on them. They had poor understanding of the legal repercussions of their actions (221).

Transactional sex is acknowledged as a noteworthy contributor to the HIV epidemic among young South African women. Despite the severe health implications associated with transactional sex, most youth recognized it as a common phenomenon in their communities even though they understood the risks it entailed (222, 223). High risk sexual behaviour may take the form of age-disparate intergenerational relationships, concurrency and unsafe sexual practices – all of which is rooted in South Africa's daunting political past as well as matters of globalization and economics. Data from the townships in the Western Cape suggest that transactional sex affords poor, young women to the opportunity to access material items valued by young people the world over: trendy clothes and social inclusion (224). The context of the transactional sexual encounter is often associated with high risk sexual encounters, a laid back attitude towards HIV, and male domination (224). Often, the young women involved in these relationships do not perceive themselves as victims however. While many choose this age-incongruent relationships to meet their subsistence needs of school fees and food, many young women who are better off financially adopt these relationships to secure luxuries like expensive handbags and glamorous lifestyles (225).

2.4 SOCIO-ECONOMIC STATUS AND CHILD-HEADED HOUSEHOLDS

The phenomenon of child-headed households (CHH) is complex. Commonly defined as a household where all members are younger than 18 years of age, the phenomenon of CHH has grown rapidly in SSA particularly in countries afflicted by HIV/AIDS (226). In South Africa, the situation is not created by HIV/AIDS alone as emergent infections like drug-resistant tuberculosis, violence; motor vehicles accidents and migrant labour purport the same consequences (227). The South African Children's Act suggests that CHH be supported by an adult mentor that acts in their best interests, a practice that has been shown to add no value to the lives of these children (226). On the contrary, these children are placed at greater risk due to poor access to services, poverty and compromised finances compounded by feelings of unresolved grief and poor self-worth (228). CHH are unlikely to reside in formal dwellings and generally have poor access to water and sanitation, as they are disproportionately based in rural areas (229). The challenges that CHH have to endure have far-reaching consequences including limited academic opportunities as a result of poverty, risk of sexual abuse perpetrated by relatives or neighbours; child prostitution and child labour; difficulties in obtaining birth registration which is vital for accessing health care and social security benefits and experiencing further loss should families or the communities take their land (230, 231).

In fact, many of these children are left destitute by caring for their terminally ill HIV/AIDS affected parents who drain the family resources prior to death through hospitalisation and medication costs (227). Often the trauma and distress experienced by these children are so overwhelming that they adopt destructive behaviour to self and others such as substance abuse, lacking morality and being poorly disciplined (227). Ayieko describes how this constant exposure to financial hardships draws them into a world that increases their vulnerability to HIV, substance abuse, delinquency and child labour (232).

Poor housing is rife with shared bedrooms, inadequate space and unstable building structures (227). The head-child is often described as trying to sustain educational activities among the other children as he/she is unable to attend school due to household duties and responsibilities. Inability to pay school fees translates to no qualifications, skill or trade which further translates to poor employability, thus perpetuating the cycle of poverty.

2.5 HOW THE ADOLESCENT UNDERSTANDS HEALTH CARE

Several studies from Soweto have highlighted the sexual and reproductive plight of adolescents including high rates of unintended pregnancies, the need for medical abortions, antenatal care, and STI treatment (including HIV/AIDS) (233). All factors identified by the National Youth Policy as significant challenges (234). The poor health outcomes observed in this group is borne out of barriers encountered when trying to access health services, including contraceptive services that are legislated (235, 236). Recognised barriers include complaints of sub-optimal quality of health care, judgemental and critical staff, lack of confidentiality, inconvenient clinic operating hours (151, 233) and the absence of properly implemented school health promotion and health service activities that further limit access to care. It is known that adolescents prefer health services delivered separately from adult health services (237). While youth-friendly services have been envisioned in South Africa, the implementation has been slow. Although having services and space dedicated wholly and solely to adolescent health care may not be feasible, the provision of adolescent friendly services may prove more practicable in terms of staff training, attitudes and actions (238).

3. HUMAN PAPPILOMAVIRUS ASSOCIATED DISEASE

3.1 THE GLOBAL PERSPECTIVE OF HPV DISEASE

As the most common STI globally, HPV will be acquired by most sexually active individuals at some point, irrespective of gender, living standards or levels of health care (239). HPV prevalence and age share an inversely proportional relationship with the highest rates documented among young women. Globally, cervical cancer ranks as the third most common malignancy, with markedly increased prevalence and mortality in developing countries (239, 240). Women from SSA have much higher HPV infection rates (24%) than global estimates (11-12%), as a repercussion of multiple partners rather than as a consequence of disease progression. Though HPV prevalence has been shown to increase markedly with severity of cervical pathology (approximately 90% of women with cervical intraepithelial neoplasia 3 (CIN 3) and invasive cancer are HPV-positive) (239). South Africa carries a substantial burden of cervical cancer globally (age standardized incidence rate of ~30.2 per 100 000) (92). However, HPV infection prevalence among young adult females from industrialised countries approximates 40-80% indicating that industrialized countries are not exempt from disease (61).

From as early as 2006, the Program for Appropriate Technology in Health (PATH) introduced HPV demonstration projects in varying geographic areas including India, Peru and Uganda with donations from the vaccine manufacturers ensuring continued vaccine circulation in Rwanda and Bhutan (241). Innovative public–private partnerships such as the Pink Ribbon Red Ribbon initiative have built on established relief-based platforms in Africa and Latin America endeavouring to accelerate national implementation strategies thereby reducing cervical cancer mortality by 25% from 2012–2016 among women accessing the programme (242). Primary HPV prevention strategies in developing countries are subject to the challenges of competing health demands, poverty, poor educational structures, cultural influences, weakened health systems and financial resources (243). Studies in Ghana and Botswana have identified the role of educational programmes in addressing these barriers, potentially improving HPV vaccine uptake (244, 245).

The South African National Guideline for Cervical Cancer Screening Programme proposed three Pap smears from age 30 at ten year intervals predicting a 64% reduction in cumulative incidence provided widespread coverage (approximately 70%) is achieved (246). HIV-infected women have cervical cytology performed at HIV diagnosis and annually thereafter (247). However, South Africa's fragmented health system has struggled to deliver a sustainable cervical screening programme (17). Kawonga and Fonn summarized the challenges faced in developing countries as a dire need for reliable screening methods; mechanisms to educate and attract women for screening; validated cytology laboratories; trained personnel to perform screening tests, read and interpret smears; improved communication between service sites and laboratories; systems of follow-up and up-referral in the case of women with precursor lesions or invasive disease; facilities for diagnosis and treatment of pre-cancer and invasive cancer; mechanisms to recall women according to national screening schedules; and continuous monitoring and evaluation systems (17). Cervical cytology remains the gold standard of cervical cancer prevention in many countries with abnormal cytology being referred for colposcopy and treatment (248). Visual inspection with acetic acid (VIA) and HPV DNA testing have been considered in combination with cytology or as an adjunct to cytology. Although VIA has low reported sensitivity, it has been considered as a reasonable alternative to cytology in low-resource settings with poor infrastructure for laboratory-based testing (249). HPV DNA sampling tested superior to VIA, but the cost remains prohibitive (248). Whichever methodology is eventually adopted remains moot, as the screening rates among South African women remain extremely low, and the follow-up post screening and access to treatment even lower (92, 250).

3.2 ADOLESCENTS AND HPV

Cervical cancer dominates the global burden of HPV-related disease (61). Available data for children aged nine to fourteen (14) years alludes to limited or no access to health care despite a high untreated disease burden (251). Adolescents and HPV remains a complicated situation – involving them in trials is perplexing considering the extended follow-up periods required to reach disease endpoints and the fact that they have to be vaccinated prior to sexual activity for a disease that potentially manifests mostly in women older than 45 years of age (252). Understanding this complexity of the HPV pathogenicity represents the foundation for constructing models of vaccine testing strategies, immunisation policy and conceptualizing the health economic models for HPV control (61). Understandably, the best evidence would be gauged from adults vaccinated in adolescence though the immunogenicity profiles documented in adolescents have been encouraging to date (252). Based on this, the next step would be to develop cost–effectiveness and impact models evaluating the implementation of the vaccine. To date, ministries have often been unable to construct these models and have relied on data generated from neighbouring countries or generic literature-based models (253).

Childhood vaccines being nearly universal make an important case for clinical trials evaluating HPV vaccination at younger ages. The scenario makes immunological sense as younger children generally develop more robust immune responses with more durable levels of protection (251). In South Africa, it may serve as a safeguard against HPV acquisition among young girls that are sexually abused (254). Adding a new vaccine to the existing immunisation schedule has infrastructural, logistical and cold chain systems implications with current systems needing to be optimized (240). Many have considered a school-based programme the optimal strategy for the HPV vaccine to reach young adolescent populations in developing and industrial worlds. The United Nations Children's Fund (UNICEF) reports that 84% of children in developed countries attend primary school (84, 240). With 90% of South African children currently being primary school enrolled, the school-based health services is reinforced as a practicable option considering the challenges experienced by adolescents in accessing traditional health care (84, 240). In fact, HPV vaccination introduction studies in Rwandan schools boasted vaccine coverage of 96% among 11 year old school girls (84). Cooperation between the education and health departments is pivotal to such success. The South African reintroduction of the ISHP, based on WHO guidelines, makes provision for on-site services focusing on SRH from grades four till twelve (12) (84, 153). The principle would be to provide comprehensive counselling encompassing diverse adolescent concerns from alcohol and drug use, smoking, diet, emotional issues as well as health concerns such as immunisation (240).

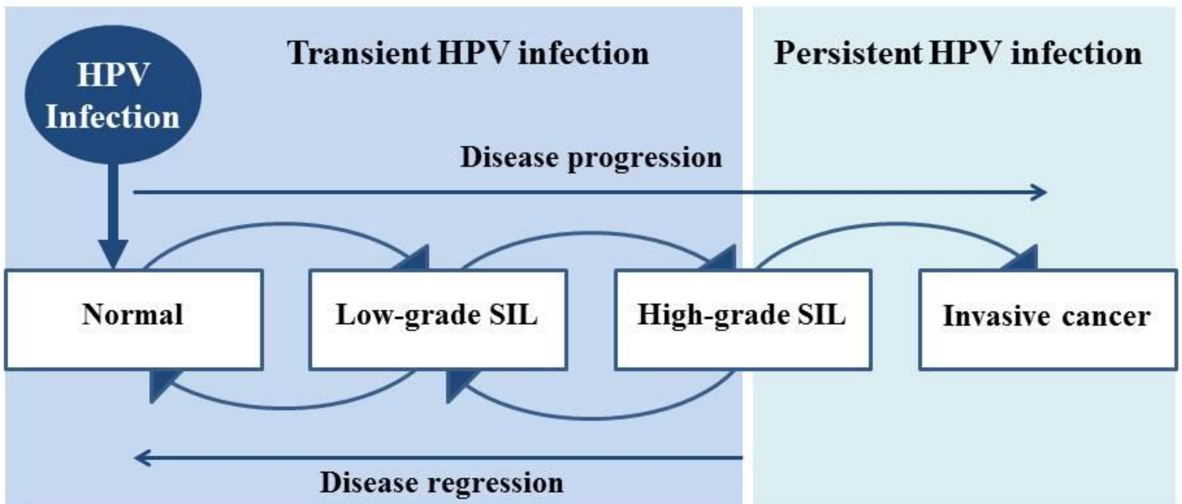
Vaccine discovery leads to discussions on costing prevention and medical care within the confines of limited financial and human resources, implementing what should be theoretically plausible and societal norms regarding reproductive health (251). A prime focus of future modelling would be developing countries and effects of vaccination on screening programmes (253). Randomised controlled trials (RCTs) have clearly demonstrated the high public health value of HPV vaccine interventions. The focus now shifts to ensuring cost-efficient delivery to those most likely to benefit (252).

3.3 RELEVANT CLINICAL ASPECTS OF HPV DISEASE

HPV is a necessary (but not solely sufficient) cause of cervical cancer (255). HPV is well adapted to infecting epithelia and is highly prevalent. It is primarily latent, subclinical and opportunistic for sporadic reproduction and transmission. HPV is generally in quasi-equilibrium with the host (251). Studies identify wide variation on transmission rates between heterosexual couples. Cervix to anus and anus to cervix autoinoculation among women occurs commonly – whether this serves as a long-term reservoir is unknown. Steady prevalence rates across all ages suggest that in men, unlike women, protection against reinfection does not occur. Males thus have an extremely high cumulative risk of HIV and their risk is associated with sexual behaviour (256). Factors determining infection clearance or persistence are unknown (61). Anal HPV commonly clears with few developing persistence; however HIV-positive status strongly influences the development of anal neoplasia (256). Reactivation of latent HPV infection has been reported among sexually inactive HIV-positive women (257, 258). The protracted lag between peak HPV infection and cancer incidence (between 20–40 years) makes cervical cancer an appropriate target for screening and early detection. Cervical cancer is the end stage of unresolved HPV infection, the persistent presence of HPV DNA in repeated testing of cervical specimens (61).

New infections appear at any age and are benign unless they persist. CIN 1 is a diagnosis based on histology that often spontaneously regresses and is associated with benign viral replication (259-261). Studies in adolescents and young women show regression rates exceeding 90% (259-262). The biologic behaviour of CIN 2 is more controversial as it is considered pre-cancerous, and is commonly treated (263). The regression rates of CIN 2 in adult women range from 15-23% with more than 50% regressing within four to six years (261, 264, 265). CIN 3 is considered a true pre-cancer and has the potential to progress to invasive cancer at the rate of 0.2-4% within 12 months (266). Among adolescents, CIN 1 and CIN 2 lesions are more likely to regress (263). However, HIV-infected women are more likely to have persistent infections, and have a reduced likelihood of regression of HPV-related cervical lesions (267-269).

The HPV-associated cervical disease stages applied in the model (Figure 3) are based on previous work conducted by Goldie in South Africa and on the 2001 Bethesda System used for reporting results of cervical cytology (270, 271). Most HPV infections are transient (263).



Applied Bethesda System

- *Normal:* negative for intraepithelial lesion or malignancy
- *Low-grade intraepithelial lesion (LSIL):* HPV, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1
- *High-grade intraepithelial lesion (HSIL):* moderate or severe dysplasia, carcinoma in situ, CIN 2, CIN 3
- *Invasive cancer*

Figure 3. Health states of HPV disease incorporated into the model

Most low-grade lesions regress spontaneously. When HPV infection persists, there is a greater chance of disease progression. Model adapted from Goldie, 2001 (271) and Wright, 2003 (272)

3.4 HPV VACCINE PREVENTION

Two vaccines were licensed for prevention of cervical cancer in 2006: a quadrivalent (Gardasil®; Merck & Co, USA) and a bivalent (Cervarix®; GlaxoSmithKline, UK). Cervarix and Gardasil are both non-infectious subunit vaccines composed primarily of virus-like particles (VLP) that are completely non-infectious and non-oncogenic as they lack the viral DNA genome required for this activity (252). The vaccines are considered safe and immunogenic (with efficacy exceeding 90% in the prevention of infections caused by oncogenic strains HPV 16 and HPV 18, which are postulated to cause 70% of cancer globally) (84, 252, 273). The quadrivalent provides additional protection against non-oncogenic strains HPV 6 and HPV 11 implicated in genital wart disease (61, 84). Data from the FUTURE I and FUTURE II placebo-controlled RCTs in women aged 16–26 years demonstrated a per-protocol vaccine efficacy of 96% for CIN 1 and 99% for genital warts after an average of 42 months of follow-up (37). The vaccines displayed increased immunogenicity, extended duration of protection (approximately 8.4 years to date) and every indication is that there is a strong ability to induce memory (251, 252). Subsequent work published from the PApilloma TRIal against Cancer In young Adults (PATRICIA) showed vaccine efficacy against CIN 3 associated with HPV 16/18, as well as against adenocarcinoma in situ (274). The reduction in HPV 16/18 disease burden may not be apparent for decades (275), but promising data emanating from the USA and Australia have already demonstrated significant reductions in high-grade cervical lesions (276, 277). Trial results demonstrate little geographic variation implying the global validity of the vaccines (61, 278). The reduction in genital wart incidence may be more noticeable as Gardasil offers protection exceeding 99% in both males and females (6, 30). The Australian programme has already demonstrated a significant decline in number of cases of anogenital warts, attributed in part to herd immunity (275).

Going forward, the Global Alliance for Vaccines and Immunization (GAVI) has pledged support for HPV vaccine implementation in 56 of the poorest countries. UNICEF is instrumental in procuring and delivering the vaccines in most GAVI eligible countries through technical partnerships with national ministries. South Africa, a middle-income country ineligible for GAVI assistance, has made huge strides in negotiating vaccine pricing with the manufacturers (240).

3.5 THE ETHICAL HEALTH PERSPECTIVE OF HPV VACCINATION

The major concern by parents that, given the sexual transmission of HPV, the vaccine would be misconstrued as an endorsement of premarital sex was dismissed as conjecture and invalidated by studies conducted in Peru, Uganda and Vietnam (240). Progress in societies hinges on the fact that HPV prevention and care does not unleash promiscuity but on the contrary, enhances the worth of life and health. This however poses a dilemma for political leaders who appear to be challenging the autonomy of parents by advocating for sexual health interventions among adolescents and pre-adolescents (251). The grave disjuncture between media and pop culture that glamorizes sexuality and the need for candid, open discussion about sexual health and impact of STIs needs to be explored further (251). Parents in the developing world displayed poor knowledge regarding HPV causing cancer, though they were aware of cervical cancer given its high prevalence. Studies show that parents knowledgeable about HPV were more likely to be accepting of the vaccine and thus allow for the immunisation of their girls. Conservative cultures remain reluctant to vaccinate adolescents, opting for vaccination prior to marriage. Research however shows that parents still believe their children engage in sexual activities which favour the need for early vaccination (240). Concerns raised by parents include effect on fertility, safety, effectiveness and accessibility (240).

Global health economic evidence calls for female-only immunisation in the developing world (240). Males, however, have a distinctly higher probability of HPV infection acquisition than females through increased sexual activity, decreasing ages of first sexual encounter and infrequent condom use (279). HPV-infected males serve as an important HPV reservoir contributing to higher transmission rates and maintenance of infection among females (280). Massey and Durrheim have argued that the extension of HPV vaccine services to boys may not be the most sensible use of public resources (281). Economic evaluation of the HPV programme does not support the addition of males as cost-effective in Australia or the USA (282, 283). Apart from the costs incurred, there have been limited gains in herd immunity from vaccinating males in populations with high coverage rates achieved among the female population (284). In the South African context, it may be more feasible and cost-effective to concentrate efforts on the female population where the reported incidence and mortality rates associated with cervical cancer are exceedingly high (92).

4. HUMAN IMMUNODEFICIENCY VIRUS ASSOCIATED DISEASE

4.1 THE GLOBAL PERSPECTIVE OF HIV DISEASE

There has been an almost 20% reduction in HIV incidence reported globally, except among key populations in Eastern Europe and Central Asia (intravenous drug users) and Asia, America and

Africa (men having sex with men [MSM]) and persistent sexually transmitted epidemics among young women and girls in SSA (285). Youths in SSA aged 15-24 years face the highest risk of HIV acquisition with 0.8% of the 34 million people living with HIV globally belonging to this reproductive age group (286). This disproportionate concentration of the worldwide epidemic remains seated in Africa with female predominance (at least eight times higher than males) and highest rates reported among young women and adolescents (285, 286).

The South African HIV epidemic is well documented, generalized, driven by heterosexual transmission and estimated to account for 18% of the global HIV prevalence with adolescents particularly vulnerable to infection (287, 288). HIV prevalence among 15-19 year olds has steadily risen from 2% (1990s) to 14% currently with 21% of females and 5% of males acquiring HIV by 24 years of age (285, 289). The course of the epidemic can only be changed by breaking the transmission cycle in females through exigent prevention strategies (285). Adolescent women in this setting are susceptible HIV acquisition, unplanned pregnancies and development of STIs (290). The implication of adult prevention measures applied to the youth remains unclear as they are behaviourally and socially different (291). There is much value to be added from early interventions as they serve to establish safer sexual practices these formative years. The stigmatization reported among South African youth accessing health care makes a school-based setting more relevant (289). In fact the decision to provide HIV counselling and testing (HCT) in secondary schools is a huge stride in improving access (292).

The South African government had endeavoured to halve HIV incidence by 2014, with little success (293, 294) and has since expanded interventions to subdue the epidemic. The national HCT campaign launched in 2010 saw a 15% increase in numbers of people having HIV tests between 2008-2012 (295). Data from modelling studies estimate that the universal implementation of HCT among South Africans from the age of 15 years could result in a 1% HIV prevalence reduction over a 50 year period (296). Since 2010, prevention of mother to child transmission (PMTCT) of HIV services could be accessed from 98% of public health facilities and has triggered a decline in annual new infections from 56 500 (2009) to 29 100 (2011) (297). Further to this, South Africa also has the most established condom distribution programme globally in the world with 495 million condoms (male) distributed in 2010 alone (298). HIV and AIDS education has become a core component of primary and high school curriculums through a Life Skills Education Programme. The dynamic programme was developed to support those children already living with HIV in addition to preventing new infections through education. Lastly, South Africa is home to the most expansive ART treatment programme in the world boasting a 75% increase in HIV treatment services between 2009 and 2011 (97, 299). The reality remains though that 58% of South Africans eligible for ART treatment still cannot access it (300). Despite these massive initiatives made by government to ease the HIV burden, South Africa accounted for 16% of the global HIV incidence rates reported in 2013 suggesting the need for an alternate strategy (300). Increasing the investment to scale-up ART delivery will prove challenging (301). These exorbitant, escalating costs underpin the potency of a HIV vaccine as a primary preventative strategy. Already, there have been noteworthy applications of HIV vaccines in those aged 15-29 years using mathematical modelling studies to assess feasibility, cost–effectiveness and overall impact on disease burden (296, 302-305).

4.2 RELEVANT CLINICAL ASPECTS OF HIV DISEASE

Primary HIV infection is characterized by transient symptomatic illness in 40-90% of individuals, associated with high levels of viral replication. HIV-specific immune response lacks efficacy during early stages of HIV spreading during primary infection (306). There is widespread dissemination of virus and a marked decrease in the numbers of CD4 T-cells in the peripheral blood during the early period following primary infection. The body mounts an immune response to the HIV, which causes a reduction in the viraemia, followed by a period of clinical latency (307). Antibodies are produced by the B-lymphocytes of the immune system. Receptors found on the surface of each circulating B-cell are unique, enabling an immune response to any foreign structure. B-cells meet an antigen (foreign entity) that matches its receptors and is stimulated to proliferate and secrete antibodies against the structure. B-cell genes frequently undergo somatic mutation (non-germline) to increase the affinity of the antibodies they produce. HIV antibodies are unusual in that they are highly somatically mutated which means they are different to those evaded by B-cells initially responding to infection (308). Infected individuals present with non-specific symptoms of fever, fatigue, rash and lymphadenopathy. The symptomatic phase lasts two to four weeks in individuals with normal rate of disease progression, whereas severe and prolonged symptoms are associated with rapid disease progression. Once chronic disease has been established, the course is determined by substantial influence of host (genetic and immunological) or virological factors. HIV-specific antibodies appear to have limited efficacy in control of virus replication during chronic infection (306). Some patients infected with HIV (10-30%) develop broadly neutralizing antibodies (bNAbs) late in natural infection (~two to four years post-infection) (308, 309). The CD4 T-cell counts decreases in the years that follow, till it reaches a critical level below which the risk of opportunistic infections remains high (307). The disease stages used in this PhD apply the clinical conditions or symptoms used in the WHO Clinical Staging of HIV/AIDS for Adults and Adolescents (Figure 4) (310).

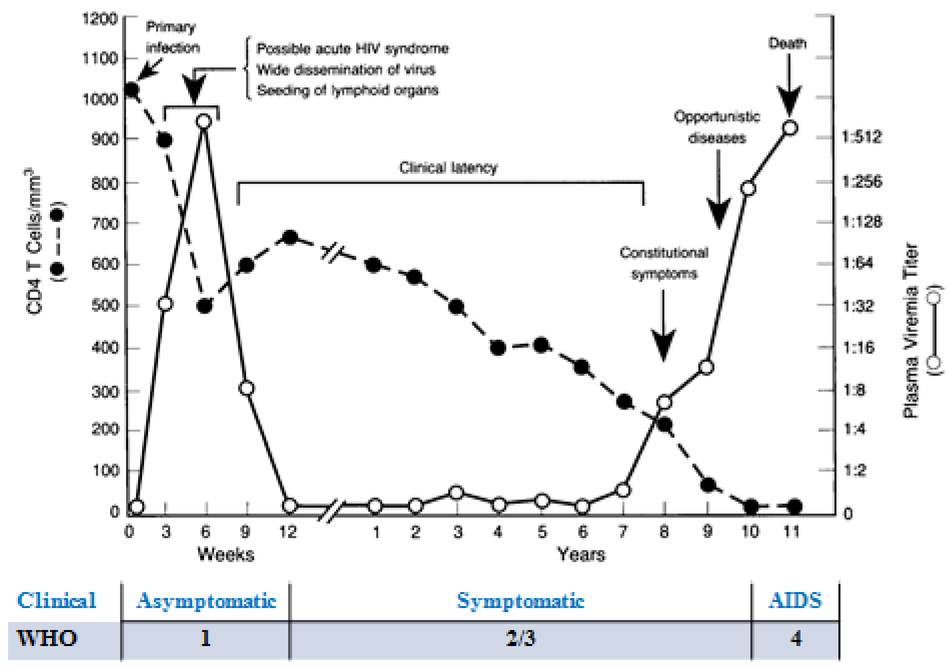


Figure 4. The course of HIV infection correlated with the WHO staging

A generic representation of the relationship between HIV viral load and CD4 counts over the average of untreated HIV infection [Source: Pantaleo (307)]. The breakdown of the immune response is described as the HIV infection becomes more established. The relationship is correlated to the WHO clinical staging of HIV/AIDS [Source: Weinberg (310)].

4.3 SUCCESSES, NEAR-MISSES AND HOPES IN HIV PREVENTION

Evidence-based HIV prevention strategies research has received global attention, and much has been achieved (Figure 5).

Prior	At transmission	Treatment	REFERENCES			
Behavioural			1987	Hopkins, D.	Public Health Report	
	Condoms (M)		1996	Brody, S.	NEJM	
	Condoms (F)		2001	Felblum, P.	AIDS	
PMTCT*	PMTCT*		1994	Connor, EM.	NEJM	(PACTG 076)
			1999	Guay, LA.	Lancet	(HIVNET 012)
			2002	Petra Study Team	Lancet	(PETRA)
STI treatment			2000	Grosskurth, H.	Lancet	
HCT			2000	Coates, T.	Lancet	
		PEP*	2002	Schekter, M.		
VMMC			2005	Auvert, B.	PLoS MED	(ANRS 1265)
			2007	Gray, R.	Lancet	
			2007	Bailey, R.	Lancet	
Vaccines			2009	Rerks-Ngarm	NEJM	(RV144)
PrEP*			2010	Grant, R.	NEJM	(iPrEX)
			2011	Baeten, J.	NEJM	(Partners PrEP)
			2011	Thigpen, MC.	NEJM	(TDF2)
			2013	Choopanya, K.	Lancet	(Bangkok TDF study group)
Microbicides*	Microbicides*		2010	Abdool-Karrim, Q.	Science	(CAPRISA 004)
Treatment as prevention*			2010	Donnell, D.	Lancet	(Partners in Prevention)
			2011	Cohen, M.	NEJM	(HPTN 052)

*ART based intervention

Figure 5. Summary of HIV prevention strategies by implementation stage

PMTCT – Prevention of mother to child transmission, STI – sexually transmitted infection, HCT – HIV counselling and testing, PEP – post exposure prophylaxis, VMMC – voluntary medical male circumcision, PrEP – pre-exposure prophylaxis

4.3.1 Antiretroviral prophylaxis

Microbicides for women

Microbicides are developed for vaginal or rectal use and hold great potential for HIV prevention, especially when among women experience difficulty negotiating condom use (311). Following several years of disappointing trial results (in clinical trials spanning the last 20 years, six candidate products have failed to show any effectiveness), the Centre for the AIDS Programme of Research in South Africa (CAPRISA) study 004 (CAPRISA 004) was able to provide the first proof of concept for microbicides (312). Assessing the safety and efficacy of a one percent vaginal gel formulation of Tenofovir (TDF), administered pericoitally in a Phase IIb proof of concept study, the study showed an approximately 39% reduction in HIV acquisition overall, and a 54% reduction among those women with high adherence (313). Adherence to the gel, however, became a contentious issue. Unfortunately, the results of MTN-003/VOICE, which investigated daily application of TDF gel and oral PrEP, further highlighted the role of adherence when all three VOICE arms were stopped prematurely for showing no effect (314). The TDF gel arm was stopped when it became evident that daily gel use was safe but not effective (315). Similar results were obtained in the remaining two study arms testing daily doses of TDF and TDF/FTC respectively (FTC is a drug called emtricitabine, and the combination of TDF/FTC is a drug called Truvada®) (315). While the CAPRISA 004 study provided the initial evidence for pericoital vaginal application of TDF, confirmatory data was required to strengthen the application for licensure (314). The findings of the FACTS 001 study announced at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2015 found the gel to be ineffective in preventing HIV acquisition, with adherence once again implicated (316).

Oral pre-exposure prophylaxis

PrEP is the use of a pharmacological agent to prevent infection prior to a potential HIV exposure (317). In 2010, the landmark iPrEx study demonstrated an encouraging 44% reduction in HIV incidence among MSM using daily doses of TDF. Data from this work forms the basis for the MSM ART chemoprophylaxis standard of care in South Africa (318). Baeten showed similar results in Kenya and Uganda (Partners PrEP study) working with serodiscordant heterosexual in 2012 (319). Thigpen et al. validated the use of chemoprophylaxis for heterosexual transmission among males and females in a study conducted in Botswana (TDF2 study) (320). The Bangkok Tenofovir Study Group demonstrated comparable findings among injection drug users in Thailand (321). However, PrEP efficacy remains limited by poor adherence (similar to microbicides). Futility as a result of poor adherence was also quoted as the reason for halting the FemPrEP study and the two arms of the VOICE trial. However, protection reaching 90% was conferred among those participants with high adherence (314, 322). A concern in the PrEP trials was that the poor adherence stemmed from the female participants who were younger and at high risk of HIV acquisition - the group mostly likely to be considered for the intervention (323). Several additional concerns, apart from adherence, have been raised including the accessibility and acceptability by those populations that are hardest to reach and at most risk and concerns around negative perceptions and stigmatization by both peers and health care providers (324). The bottom line is that PrEP can confer protection reaching 99%, the cost-effectiveness of which has to be weighed up against ART scale-up.

Treatment for prevention

Treatment as prevention (TasP) or combination ART stunts HIV replication and thus the infected partner's use of ART serves to reduce HIV blood concentrations and genital secretions of HIV resulting in a reduced risk of sexual transmission of HIV to the uninfected partner (325). The Partners in Prevention HSV/HIV Transmission Study (which was conducted at 14 sites in seven African countries including South Africa) demonstrated 92% reduction in HIV-1 transmission risk following ART initiation among heterosexual couples, likely attributed to markedly reduced plasma HIV-1 levels (326). HPTN 052, a pivotal study conducted in 2011, was associated with a 96% reduction in HIV transmission to the HIV-negative partner when ART was initiated early (in people with a CD4 T-cell count between 350-550 cells/mm^3) in the HIV-positive partner of a serodiscordant couple (325). Based on the HPTN 052 findings, the WHO widely endorsed ART to all serodiscordant couples to reduce HIV transmission (327). The concern remains issues of risk compensation due to decreased condom use and adherence with South African data indicating that only 64% of those initiated on ART between 2002-2007 were still on treatment three years later (328). The greater challenge in the South African HIV health care planning is justifying curtailing funds earmarked for scaling-up ART access in lieu HIV prevention efforts. This scenario seems rather unlikely in a country with the highest global burden of HIV disease where 58% of those eligible for treatment are still unable to access it (300).

4.3.2 Voluntary medical males circumcision

Landmark studies in Rakai, Uganda and Orange Farm, South Africa have definitively proven that VMMC can reduce female to male sexual transmission of HIV by 60% (63, 65). These findings informed the WHO decision to launch the exceptional public health initiative in 2009 proposing 80% coverage of voluntary, safe, culturally appropriate and affordable VMMC by 2016 (63). South Africa conducted 150 000 VMMCs by April 2011, averting one infection for every five procedures done in an attempt of observing the call from the WHO (329). However, the services in South Africa have been limited as initially, the procedures could only be performed by doctors and the procedures were marred by inadequate health facilities and poor surgical care (330). The introduction of PrePex (an elastic ring device requiring no local anaesthetic that can be placed and removed by a mid-level health care worker) in South Africa since has proved promising and may hold the key to increasing the amount of VMMCs performed without impacting on the limited numbers of health care workers available (331). The value of VMMC is limited among key populations (i.e. MSM, injection drug users and commercial sex workers) but is marked in countries like South Africa that have high HIV prevalence rates, primarily as a result of sexual transmission. VMMC is considered a highly cost-effective intervention (332). It represents a once-off procedure that can carry potentially lifelong health benefits, apart from the fact that there is convincing evidence supporting its role in preventing the acquisition of new HIV infections (333).

4.3.3 HIV vaccine development

The development of a HIV vaccine presents a unique set of challenges to scientists. Recovery in humans has never been documented so there is no natural immune mechanism to attempt to mimic nor have any comparable successful animal models been developed. To compound the problem, HIV destroys the immune system – the actual system of cells required to mount a response to infection. Following an individual acquires HIV infection, the virus is assimilated into the human genome, relatively ‘protected’ from discovery. The tremendous genetic diversity of global circulating strains of HIV-1 has long been the bane of vaccine-mediated protection. To date only five efficacy studies have evaluated four vaccine concepts, with only one showing promise (Table 1).

Table 1. Summary of HIV vaccine efficacy studies to date

TRIAL	CONCEPT	POPULATION	COUNTRY	OUTCOME	REF
VAX003	Bivalent Env (gp120) protein	Injection drug users	Thailand	No efficacy	(334)
VAX004	Bivalent Env (gp120) protein	MSM and high-risk women	N. America Netherlands	No efficacy	(335)
STEP (HVTN 502)	Ad5 gag/ pol/ nef	High-risk men and women including MSM having unprotected anal sex and high-risk heterosexuals	Americas, Caribbean, Australia	Non-efficacy in reaching end-points. Stopped in 2007	(336)
Phambili (HVTN 503)	Ad5 gag/ pol/ nef		South Africa		(337)
HVTN 505	DNA/Ad5 with multi-clade inserts ENV	Men and transgender women who have sex with men	USA	No efficacy	(338)
RV 144	ALVAC/ protein/ alum prime-boost	Low risk men and women	Thailand	Estimated efficacy of 31.2%	(339)

The STEP (Americas, Caribbean and Australia) and Phambili studies (South Africa) evaluated Merck's Trivalent Ad5-HIV-1 gag/pol/nef vaccine in high-risk MSM and heterosexual men and women in Australia and South Africa (340, 341). The STEP study was terminated prematurely in 2007 on the grounds of futility: the vaccine failed to prevent infection or impact on early viraemia (337, 342). The Ad5 vaccine vector has since been under scrutiny due to a non-significant trend for higher HIV-1 infections among vaccinees with pre-existing Ad5 specific neutralizing antibodies (336). To add to the HIV vaccine woes of the STEP study termination, Phambili was then suspended (340). *Post hoc* multivariate analyses of STEP participants showed an increased incidence of HIV among vaccinees that was largely accounted for by uncircumcised males and/or pre-existing Ad5-specific humoral immunity (337). The Phambili study did not prevent HIV-1 infection (341), but alarmingly both STEP and Phambili may have increased the acquisition of HIV among vaccinees (343). The HVTN 505 study vaccinations were discontinued based on interim analysis indicating the regimen to neither be efficacious nor effective in reducing the set-point viral load after infection (338).

The Thai Trial/RV144 evaluated four priming injections of recombinant canarypox vector vaccine (ALVAC–HIV[vCP$_{1521}$]) plus two booster injections of recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E) (339). Canarypox prime-boost regimens induced humoral and cell-mediated immunity, thus establishing the prime-boost concept as a candidate for further testing (339). The Thai Trial/RV144 offered 31% protection against HIV-1 acquisition showing antibody response and protection in a human trial, thereby revitalizing the quest for an antibody-based HIV vaccine (308, 339). The protection was moderate and transient and the decline in vaccine efficacy from 60% (year 1) to 31% (year 3.5) raised the question of boosters (339). The Thai vaccine was then evaluated in South Africa to determine if the immune response profile differed from the Thai study. The study, designated HVTN 097, found the response rates and magnitudes of Env-specific CD4 T-cells in South Africans induced by the same vaccine regimen to be comparable, if not better, than those induced in Thai Trial/RV144 (344).

Apart from changes to the protein and adjuvant, the HIV vaccine regimen was additionally modified to Clade C before entering South African clinical trials (Phase 1) at six key sites under the umbrella of the HVTN 100 study (345). The regimen used the ALVAC prime ALVAC/gp120 boost of the RV144/Thai trial but an additional ALVAC/gp120 boost at month 12 was introduced. The booster dose at month 12 was included to enhance the immune response given the waning immunity described after 12 months in the Thai trial. Should the vaccine induce adequate immunogenicity, it will be entered into landmark Phase IIb/III HIV vaccine efficacy studies (provisionally scheduled for South Africa in 2016) called the HVTN 702 study.

It seems unlikely that South Africa could treat its way out of the HIV epidemic it faces. The huge financial implications of ART scale-up and expansion forms only part of the reason for why the HIV vaccine is imperative. In the South African landscape, the issue of adherence becomes controversial if booster vaccines are needed to maintain protection. The value of the vaccine is that it would be administered independent of behaviour change (especially abstinence) and would not need to involve partner negotiation as with condoms. Children could be targeted prior to sexual debut at schools and this could allow for the development of herd immunity if critical coverage levels are achieved. The HIV vaccines would not be considered as an isolated intervention though, but would rather complement the evidence-based strategies currently being offered in the public sector (i.e. HCT, condoms, PrEP, STI treatment and TasP) together with behavioural and structural interventions developed around sexual health education, outreach and support services.

4.4 ADOLESCENTS IN VACCINE TRIALS

The susceptibility of adolescents to HIV, STI and HPV disease is well established (346, 347). Adolescent behaviours predisposing them to HIV transmission and acquisition and the critical biological and socio-epidemiological information they hold for vaccine development and eventual roll-out makes their role in HIV vaccine research pivotal (348). Answers to these socio-behavioural questions cannot be extrapolated from adult data as adult decision-making processes differ vastly from those of the adolescent (348). Yet despite this, there still remains a reluctance to involve adolescent participants, particularly young women, in clinical research (349).

There has been no documented adolescent aged younger than 18 years that has participated in HIV vaccine trials to date, with a limited number involved in microbicidal trials and HPV vaccine trials despite the high concentration of disease among adolescent females (15-24 years) in SSA (346, 350, 351). Vaccine efficacy has yet to be demonstrated through RCTs in South Africa. The expedient conduct of well-organized bridging trials will hopefully counter the inherent legal and ethical complications of adolescent involvement in clinical trials (351). South African law does not explicitly prohibit adolescent clinical trial participation (352). Rather the law is circumspect in that adolescents do not have the individual capacity to participate in medical research often requiring parental consent from both parents, legal guardian or parental consent to all forms of research or parental consent with adolescent assent (352, 353). The major drawback to parental or guardian involvement in consent processes is adolescent reluctance to involve them in trials monitoring sexual behaviour and practices.

Adolescent willingness to participate in vaccine trials has been demonstrated, especially following the premature discontinuation of the HVTN 503/Phambili HIV vaccine trial (354). Various such studies have addressed barriers to enrolment in this group including HIV testing, stigmatization post-testing, mistrust of the health system and concerns around sexual disinhibition (354, 355). Theoretically, urgent adolescent inclusion in HIV vaccine preventive trials has been welcomed from all sectors (356-358). The practical application thereof requires painstaking qualification and safety is a major concern. Concerns ranged broadly from involvement of adolescents only once safety had been established among adults and parental and cultural acceptability of the vaccines, to concerns of sexual disinhibition and fears of HIV testing and disclosure (356, 357). South African legislation governing nontherapeutic research in minors is unclear. Section 71 of the National Health Act allows for research in minors as prescribed (‘prescribed’ itself is unclear), with either ministerial consent, consent from the parent, guardian or the minor (if capable of understanding) (359). The Minister may refuse consent in circumstances where the objectives could be achieved if conducted in adults; is unlikely to result in significant benefit to minors; poses significant risk to the health of the minor and where the benefit does not significantly outweigh the risk. In its entirety, the document dissuades essential research on the needs of children and serves little ethical purpose (360).

As the epicentre of the global HIV pandemic, South Africa is a convincing location to launch a primary HIV vaccine roll-out and these important considerations have to be borne in mind. Despite the large and immediate HIV prevention need of adolescent girls and young women, there is a dearth of evidence-based interventions to reduce their risk. The exclusion of adolescents in biomedical research presents a huge barrier. School and community-based education programmes are commonplace in many settings, yet few have been evaluated and none have demonstrated efficacy in preventing HIV infection (176).

4.5 RISK FACTORS ASSOCIATED WITH DISEASE

Drawing from the discussions thus far, the risk factors associated with HIV and HPV disease independently and in combination are illustrated in Figure 6. Rather than being repetitive, this brief section was intended to highlight the complex interplay of risk factors implicated in disease acquisition and progression.

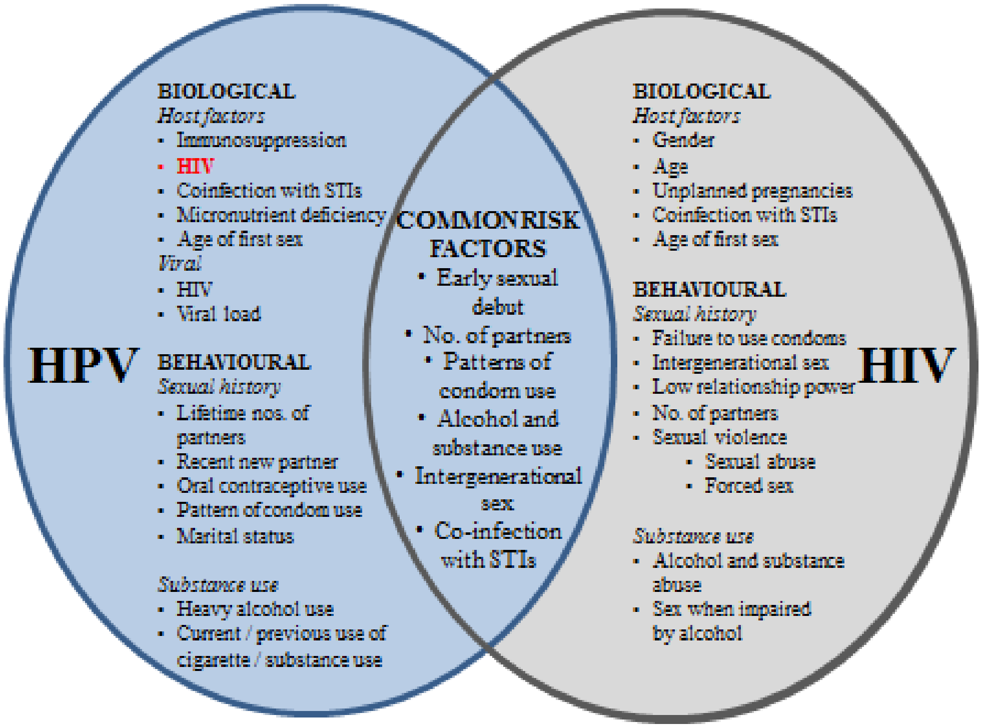


Figure 6. Exploring the risk factors associated with HIV and HPV disease

The risk factors for disease are represented individually and independently. The shared risk factors are highlighted [Sources: Dempsey (361), Dietrich (213)]

5. VALUING VACCINES

The prevention of disease and death through vaccination is commonly regarded as one of the greatest public health achievements of the 20th century (362, 363). Yet many young people in Africa succumb to vaccine-preventable diseases due to lack of vaccination. The knowledge, attitude and practices of parents, adolescents and teachers are vital in understanding the implementation of adolescent vaccination policies, and their subsequent uptake of services (364).

Vaccination has led to remarkable health gains over the last century. While large coverage gaps still remain globally, more than 100 million children are vaccinated annually against diseases such as diphtheria, tetanus, pertussis, tuberculosis, polio, measles, and hepatitis B averting an estimated 2.5 million deaths annually (365). In fact, the eradication of smallpox prevented 350 million new smallpox victims and approximately 40 million deaths from the disease (366). More recently, global efforts directed at polio eradication have seen a 99% reduction in the number of cases reported to the WHO since 1988 (366, 367). Often, the economic benefit of vaccination is restricted to its links with health care, underestimating the broader social context such as productivity gains from the protection afforded and reductions in the productive time lost in seeking care for affected children or household members (365, 368). The rationale for investing in immunisation programmes in developing countries is clear. The investment is low risk, highly cost-effective, has shown proven returns and can be financially sustainable in developing countries (366, 369).

5.1 PROCUREMENT

The affordability of a vaccine versus it cost-effectiveness are two completely distinct considerations. In a world of constrained budgets and competing demands, cost-effectiveness explores the most beneficial use of scarce resources by comparing the net cost against the net benefits of a vaccine initiative, as has been conducted with the HPV vaccine (370). A potential HIV vaccine could have a substantial impact on the pandemic provided it is made accessible and is quickly implemented. It is here that long-term strategic demand forecasts present an invaluable decision-making tool than can guide policy to achieve these goals (370). Global, and indeed national, HIV vaccine demand forecasting has to address issues concerning the effect on demand of vaccine characteristics, price and vaccination strategies. The International AIDS Vaccine Initiative (IAVI) reached consensus that a vaccine needed to be at least 50% effective before governments would consider implementation in the general population, with lower thresholds considered in groups that were highly susceptible to HIV infection such as commercial sex workers (371). Similar sentiments regarding vaccine efficacy were shared by the Pox-Protein Public-Private Partnership (P5) who are tasked with driving the initial Thai Trial/RV144 findings forward (372). The IAVI estimates the average global demand annually for a first generation preventive vaccine could range between 28-142 million courses over a 30 year period. While South Africa (as a middle-income country) is not eligible for GAVI support, the 47 poorest countries that are GAVI eligible could potentially account for between 19-42% of the total global demand by volume but only contribute between four to nine percent of anticipated revenues (371).

Advanced market commitment (AMC) may be considered as an alternate financing strategy for vaccines. The aim of AMCs is to speed up the processing of a new vaccine while ensuring affordable pricing mechanisms in developing countries. The AMC concept is that donors subsidize the purchase of a new vaccine when it is developed to certain standards and is demanded by developing countries The AMC subsidy of the bulk of the price, secures a more reasonable co-payment by the countries wishing to access the vaccine. The donor commitment serves to incentivize private sector investment and production scale-up (373). While it is appreciated that HIV vaccine development may take years, if not decades, it is important to start considering the policy issues regarding access and demand. This PhD explored the interplay of the drivers of demand for new vaccines based on the IAVI model (Figure 7).

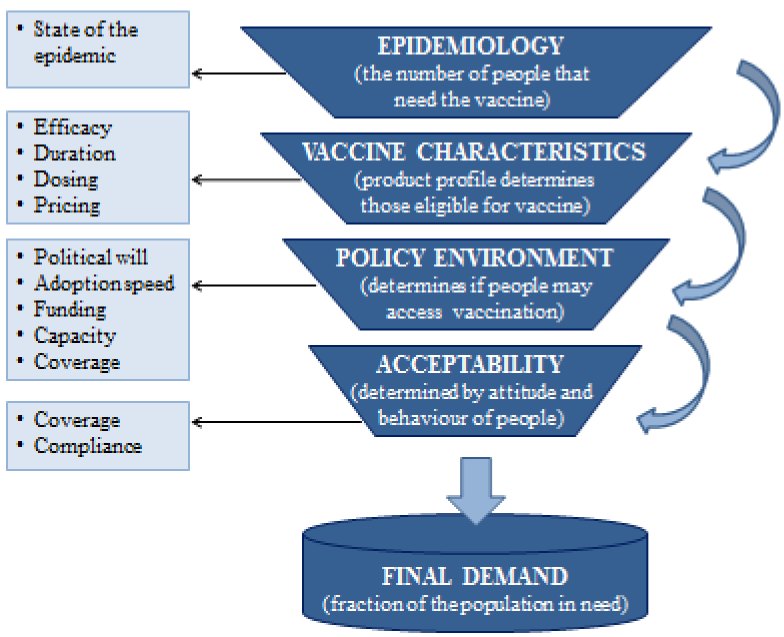


Figure 7. Characterizing the demand framework from need to final demand

From Figure 7, it is important to understand that the disease burden, incidence and prevalence determine the *need* for a vaccine. The *characteristics of the vaccine* would determine the storage, transportation and administration requirements. The vaccine programme has to be driven by *political will* for the initiative and backed by the *capacity* and infrastructure to deliver the programme. *Funding* has to be secured from national government or international donors.

Probably most importantly, the *acceptability* has to be understood as it is the major determinant of predicting utilisation (371).

6. SCHOOL-BASED HEALTH SERVICES

Adolescents are a challenging population to reach with preventive health care services (374, 375). However, their health and well-being hinges on access to comprehensive sexual, reproductive, and mental health care services (376). School-based health care is considered an effective strategy for delivering comprehensive primary and preventive health care to young people, particularly those underserved by health services (377-380). It serves as an effective mechanism to offer youth-friendly health services that connects them with other services offered in the community (378). Further benefits of health care located within a school, are the potential to minimise transport costs, improve accessibility to health care and the building of links between the schools and communities (377). School-based health services that include school delivered education programmes on topics such as HIV, particularly in communities with high prevalence rates, have encouraged considerable increases in condom use (377) with females the predominant users of the services (381-383). Generally, the health services tended to be accessed by those involved in high-risk behaviours such as unprotected sexual intercourse and substance use (384-386). This, in itself, highlights the urgent need for these school-based interventions and supports the South African government initiatives that prioritize these services (377).

Comprehensive sexuality education is vital in addressing adolescent risk behaviours (387, 388). Several studies concerning youth interventions conducted in both developed and developing countries continue to promulgate school-based health services as an integral intervention that improves young people's knowledge of sexuality, reproductive health and HIV prevention – an intervention that often translates to reductions in sexual risk-taking behaviours among adolescents (387, 389-394). Such programmes conducted among young people in SSA have been shown to be effective in several systematic reviews (392, 395-401). In fact the evidence for school-based health services is so strong that its implementation is being prioritised by several governments (402-405). However, results of school-based interventions conducted in SSA found a greater impact on HIV knowledge and attitudes among adolescents rather than on the sexual behaviours reported (390).

These findings were supported by large scale trials in Tanzania (the Mema kwa Vijana Project) and in Zimbabwe (the Regai Dzive Shiri Project) that positively impacted sexual knowledge and attitudes, aspects of male sexual behaviour and self-reported pregnancy (399, 406).

The convenience of school services cannot be underestimated. Schools provide a ubiquitous venue for HIV prevention education, and several schools throughout SSA operate youth targeted services discussing HIV, STI and pregnancy prevention (407).

6.1 GLOBAL PERSPECTIVES ON SCHOOL HEALTH

Studies in the USA reported that many adolescents attending health centres for HPV vaccination used the opportunity to access preventive services (82). The WHO has suggested leveraging this relationship by using the HPV vaccination as a platform from which to deliver preventive health services and provide information, especially in LMIC (84). Research has positively shown the impact of school-based health services on delivery of preventive care interventions such as immunisations, managing chronic illness such as asthma and providing reproductive health services for adolescents (408). Importantly, school-based health offers an opportunity for preventive counselling against STIs even in the absence of other reproductive health services (409, 410). In low-income countries, the pre-existing infrastructure of the schooling system presents an attractive alternative for the delivery of simple health interventions as schools often outnumber clinics and teachers outnumber trained nursing staff (411). In LMIC, child health programmes rarely extend into adolescence and school-based HPV vaccination presents a unique and validated opportunity for extension of these services (412, 413).

Health and education are closely linked. The concept of health promoting schools has been developed under the auspices of the 'Declaration of Alma Ata' (calling for renewal of PHC) and the Ottawa Charter for Health Promotion (414). In 1995, the WHO launched the Global School Health Initiative to strengthen health promotion among scholars and their communities through the school. In April 2000, the Focus Resources on Effective School Health (FRESH) initiative was launched by the WHO, UNICEF, The World Bank and the United Nations Educational, Scientific and Cultural Organization (UNESCO) at the World Economic Forum in Dakar, Senegal to ensure child friendly learning environments covering policies such as safe water and sanitation facilities, health education and school-based nutritional services (411, 414). Based on the FRESH initiative, an Essential Package of services was designed (Table 2). The Essential Package was adapted in the Southern Africa regional strategy from the Sahelian Alliance model and targets ten southern African countries including Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe that share common features including unstable weather, crop failures, depleted food reserves, and the highest prevalence of HIV/AIDS (185).

Optimizing the school environment to advocating for gender-sensitive approaches will hopefully promote improved teacher-student dialogue that allows for the rehabilitation and re-integration of pregnant girls into the school system following delivery (415). In fact, promoting intergenerational (with parents, teacher and other involved adults) communication on matters of sexuality is associated with several positive outcomes and is thus vital to establish (416).

Table 2. Outline of the school-based health service endorsed by the WHO

The table outlines the Essential Package of services proposed by FRESH, and delineates the 'gender-sensitive' approach of child-friendly schools. [Source: Nederveen (417)]

'Essential Package' of services for Health Promoting Schools	Gender sensitive approach of child-friendly schools
• Support to basic education • Food for education, which includes on-site school meals and take-home rations • Promotion of girls' education • Potable water and sanitary latrines • Health, nutrition and hygiene education • Systematic deworming • Micronutrient supplementation • HIV and AIDS education and life-skills training; • Psycho-social support • Malaria prevention • School gardens • Improved stoves.	• Gender specific issues • Promotes gender equality in enrolment and achievement; • Eliminates gender stereotypes; • Guarantees facilities, curricula, textbooks and teaching and learning processes that are friendly to girls; • Socializes girls and boys in a non-violent environment; and • Encourages respect for others' rights, dignity and equality.

6.2 THE EVOLUTION OF SCHOOL HEALTH SERVICES IN SOUTH AFRICA

In 1995 South Africa ratified the United Nations Convention on the Rights of the Child which effectively confirmed South Africa's intention to implement sexuality education, focusing on issues including sexuality and HIV/AIDS (418). In 1996, sexual education became compulsory in all South African government schools, and was included in the Life Orientation learning frame. The curriculum was structured to cover basic HIV/AIDS information and to understand that sexual responsibility was based on self-esteem and self-knowledge and not just information about the disease (418). By 2003, the South African National School Health Policy (NSHP) was introduced to deliver equitable and focused health services to school-going children in order to safeguard their right to optimal health and development. The NSHP was implemented in a phased manner, with disadvantaged areas being prioritized. Many issues challenged the policy implementation including poverty, staff shortages, no dedicated funding for the school health services and poor prioritization of the project by senior departmental managers (419).

The challenges in adolescents accessing existing clinic services persisted. Coupled with high school enrolments, school-based services were considered an effective delivery strategy (84). The South African government then reintroduced the ISHP based on the WHO recommendations for School Health Programmes (153). The new draft of the ISHP was jointly formulated by the Departments of Health, Basic Education and Social Development and was built on the foundations of PHC (153). The policy sought to shift from the current costly model of unsustainable hospicentric care to one of preventive care by addressing health barriers to learning, facilitating the access to services and to support the school community in creating a safe and secure environment for teaching and learning (153). With the HPV vaccine featuring highly on the SRH agenda of most countries, the WHO suggested that HPV vaccine implementation in South Africa be combined with a package of adolescent SRH services called the HPV Plus Package (Table 3). Looking more broadly however, the ISHP covers a broader spectrum of services and extends beyond adolescent care. The draft policy suggests the minimum starting point for the package on interventions making provisions for health education, health screening and provision of onsite services; with a particular emphasis on SRH (Table 4) (153).

Table 3. Suggested package of adolescent sexual and reproductive health services

The potential health services offered to adolescents, derived from the HPV Plus Package [Source: WHO (420)] and from the Adolescent Plus Package [Source: MacPhail (84)].

Intervention category	Definition	Menu of complimentary interventions
• Screening	• Testing or screening for illnesses, diseases or disabilities	• Vision screening • Anaemia screening
• Provision of information	• Providing information-based interventions	• HPV and cervical cancer • Reproductive and sexual health • Nutrition • Tobacco and alcohol
• Services	• Providing referrals	• Referrals for reproductive health services or iron replacement (if not undertaken at school)
• Commodity delivery	• Supplementation, direct provision of commodities or increasing access to commodities	• Anti-helminthic (soil transmitted) • Anti-helminthic (schistosomiasis) • Vitamin A/iron
• Vaccines	• Vaccines that are currently recommended for this age group	• Tetanus/diphtheria booster • Hepatitis B

Table 4. Summary of the School Health Package

Health screening	On-site service	Health education
Foundation phase (Grade R – Grade 3)		
• Oral health • Vision • Hearing Speech • Nutritional assessment • Physical assessment (Gross and fine motor) • Mental health • Tuberculosis • Chronic illnesses • Psychosocial support	• Parasite control. Deworming and bilharzia control (where required) • Immunisation • Oral health • Minor ailments	• Hand washing • Personal & environmental hygiene • Nutrition • Tuberculosis • Road safety • Poisoning • Know your body • Abuse (sexual, physical and emotional)
Intermediate phase (Grade 4 – Grade 6)		
• Oral health • Vision • Hearing Speech • Nutritional assessment • Physical assessment (Gross and fine motor) • Mental health • Tuberculosis • Chronic illnesses • Psychosocial support	• Deworming • Minor ailments • Counselling regarding SRH (if indicated) and provision and referral for services as needed	• Personal & environmental hygiene • Nutrition • Tuberculosis • MMC & traditional • Abuse (sexual, physical and emotional) • Puberty (e.g. physical and emotional changes, menstruation & teenage pregnancy) • Drug and substance abuse
Senior phase (Grade 7 – Grade 9)		
• Oral health • Vision • Hearing Speech • Nutritional assessment • Physical assessment incl. anaemia • Mental health • Tuberculosis • Chronic illnesses • Psychosocial support	• Minor ailments • Counselling regarding SRH (if indicated) and provision and referral for services as needed	• Personal & environmental hygiene • Nutrition • Tuberculosis • Abuse (sexual, physical and emotional) • Sexual and reproductive health • Menstruation • Contraception • STIs and HIV • MMC & Traditional • Teenage pregnancy, CTOP & PMTCT • HCT & stigma mitigation • Drugs & substance abuse • Suicide
Further education and Training (FET) (Grade 10 – Grade 12)		
• Oral health • Vision • Hearing Speech • Nutritional assessment • Physical assessment incl. anaemia • Mental health • Tuberculosis • Chronic illnesses • Psychosocial support	• Minor ailments • Counselling regarding SRH (if indicated) and provision and referral for services as needed	• Personal & environmental hygiene • Nutrition • Tuberculosis • Abuse (sexual, physical and emotional) • Sexual and reproductive health • Menstruation • Contraception • STIs and HIV • MMC & Traditional • Teenage pregnancy, CTOP & PMTCT • HCT & stigma mitigation • Drugs & substance abuse • Suicide
All schools		
	• Environmental assessment • First aid kit • Water and sanitation • Physical safety • Ventilation (airborne infections) • Waste disposal • Food gardens • Recycling	

6.3 THE CURRENT STATUS OF SOUTH AFRICAN SCHOOL HEALTH PROGRAMMES

School-based SRH is considered an important strategy in reducing risky sexual behaviour among adolescents (421). The school-based approach plays an important role in promoting comprehensive sexual health among young people (422). Numerous systematic reviews and meta-analyses have highlighted the value of school-based health services. Data from high income countries suggests that school-based health services remains popular among young people and provides vital mental and SRH services but also address health disparities in clinic attendance (377). A systematic review of eight cluster-RCTs enrolling more than 500000 participants in five trials were conducted in SSA (Malawi, South Africa, Tanzania, Zimbabwe, and Kenya), Latin America (Chile), and in Europe (England and Scotland). The studies evaluated the impact that school-based programme had on the prevalence of HIV and other STIs. The review concluded that schools remained an appropriate place to provide health education that included contraceptive choices and condoms (421). Sani et al. reviewed 21634 relevant citations evaluating school-based SRH education. From the 51 papers finally reviewed, the authors concluded that school-based health care had the potential to promote condom use among young people in SSA (422).

Adolescents need access to effective SRH interventions, but face barriers accessing them through traditional health systems. Data from rural Kwa-Zulu Natal found overwhelming community support for school-based SRH clinic services particularly in areas with high reported HIV prevalence and teenage pregnancy rates among adolescents (423). A series of after-school SRH education programmes and school health services was conducted in 18 schools and among 1576 participants in the Western Cape Province. Low rates of attendance were reported with lower rates described among those who had been victim of IPV or sexual violence, or had perpetrated IPV. Those attending were motivated by wanting to access information, and the life coaching offered but those unable to attend were hampered by the lack of available safe transport and by domestic responsibilities. There is an obvious need to reduce these structural barriers to attendance (424). Scaling-up the provision and access to HCT is a priority as the South African youth are at particular risk of acquiring HIV. Focus group discussions conducted in rural schools in the Vulindlela sub-district of uMgungundlovu in KwaZulu-Natal found that the stigma and discrimination associated with HIV testing, exacerbated by concerns of a potential positive result remained the most significant obstacles to uptake of voluntary HIV testing services. Their fears were compounded by the perceived backlash of peers, partners, family and the community (425). Systematic review of the evidence base for HIV prevention strategies among the youth yielded the key recommendations of addressing HIV social risk factors (such as gender, poverty and alcohol); targeting the structural and institutional context of their understanding; working towards changing social norms and normalising the HIV testing; and engaging schools in new ways that promote participatory learning (399). Although HIV prevalence has declined among young people in many high-burden countries, 20 countries in SSA accounted for nearly 70% of the world's new HIV infections among young people in 2009 (426).

Adolescents encounter difficulties dealing with their sexuality and the impacts of peer pressure such that they have a high propensity for engaging in early and risky sexual practices making them susceptible to early infection with diseases such as HIV (427, 428). Young people need to be empowered to make constructive decisions about their SRH and need to make informed decisions about engaging in sexual relationships once they feel emotionally and sexually mature (429, 430). However, the broader context of the adolescent in South Africa has to be taken into consideration. Many adolescent children face the daily reality of dysfunctional homes, poor role models, inadequate life-skills, violence, crime, poverty and hunger (431). Despite efforts at 'normalizing' the disease, discussions around sex and sexual behaviour often remains taboo between parents and children resulting in adolescents developing many misconceptions about sexual health and risk, increasing the probability of them acquiring STIs (432). Apart from high rates of HIV and unwanted pregnancy, poor sexuality education reinforces the environment for gender-based violence to occur, thereby harming young people in general but particularly the educational attainment of women (430, 433).

There are have been several more positive perspectives approached in school-based health care specifically in South Africa. Lawrence et al. evaluated a mobile school-based HCT service based on the WHO youth-friendly health service model that operated in two secondary schools in Cape Town. They concluded that HCT in this setting made the service more accessible but stressed an acceptable and equitable distribution of services (434). Data from HCT testing conducted in rural KwaZulu-Natal confirmed the high prevalence of HIV among female learners and further underlies the vital need for school-based HIV testing services as an entry point for HIV prevention and treatment services (435). In Cape Town, the ‘Listen Up’ programme was introduced as a structured, curriculum-based, peer-led educational system to learners entering high school on topics varying from HIV knowledge transmission to sexual attitudes. The study findings reinforced the role of peer-education in facilitating adolescents' self-efficacy in sexual relations and in improving HIV transmission knowledge, thus potentially contributing to reduced HIV transmission among adolescents (436). PREPARE, a multi-dimensional school-based programme was introduced as part of a RCT in 42 South African high schools, targeting IPV in particular. Those among the intervention arm reported lower rates of victimisation, suggesting safer relationships with a potential decreased risk of HIV acquisition (437). Exploring a strategy as diverse as VMMC in a school-based programme enjoyed a level of success. Studies that engaged learners on VMMC in 42 schools in Vulindlela found the programme was embraced as feasible, acceptable and safe in the school-based setting (333). Drawing from the outcomes of 70 consultative meetings held with the community and key-stakeholders in rural Kwa-Zulu Natal, the SRH service provision pilot was deemed acceptable and feasible for scale-up. Their additional comment was that school-based services needed to be tailored to suit the health needs of the adolescents (423).

There remains a desperate need for a comprehensive approach towards sexual health interventions and programmes that are culturally and socially sensitive and relevant. It may be the case that the educator may be unfamiliar with the cultural backgrounds of the learners. Hence the need for a working relationship between the family/community and the school to facilitate the development of a curriculum that is responsive to the needs of the child (438). From the evidence presented globally and in South Africa, school-based health services appear to be an acceptable, accessible and safe option for delivery of health care to adolescents. The school environment appears to be conducive to peer led and curriculum based learning that embraces the participation of the learners as opposed to the more traditional delivery mechanisms of health service at PHC facilities.

6.4 NEGATING CHALLENGES AND MOVING FORWARD

Communication between parents and adolescents regarding sexual matters has long been shown to be beneficial in reducing the risk of HIV transmission (439). Adolescents have also expressed a preference for mentorship around SRH communication rather than pedantic abstinence-only and peer-led in-school interventions (400, 407).

Adolescents live and interact within families, sexual and social networks and communities, and are greatly influenced by society, policies and broader environments and epidemic settings (440). Those interventions demonstrating the greatest successes adopt a combination of context-specific session programmes, HIV prevention and SRH curricula. The suggested programmes broadly address more general skills and knowledge development, and are delivered by trained facilitators (407). HCT forms the foundation of all SRH curricula; school-based or otherwise (441). Based on the outcomes of the HCT, interventions should then guide HIV-positive adolescents towards the ultimate goal of viral suppression and safer sexual practices. HIV-negative adolescents should be encouraged to maintain their status through structured biomedical and behavioural interventions that are delivered via an adolescent rights framework (442, 443). Several high burden countries including Côte d'Ivoire, Ethiopia, Kenya, Malawi, Namibia, South Africa, Tanzania, Zambia and Zimbabwe have managed to achieve a significant decline of HIV prevalence among young people (444). These declines have been critical in attempts to curb the AIDS epidemic in SSA, but much work remains to be done (445).

Apartheid South Africa saw school health services characterized by inequity cutting across racial, socio-economic and equity lines with fragmented delivery structures (1, 446). The school programme operated as a 'vertical' programme, with little interaction with other relevant child health services (447). These vast and iniquitous deficiencies resulted in several reforms that culminated in the NSHP in 2003, followed by the ISHP in 2012. Both these programmes highlighted the dire need for infrastructural and human resource development going forward. The 2003 NSHP was marred by poor coverage, inadequate nursing ratios such that some schools would be visited every five years and absence of effective referral pathways (447). The 2012 ISHP experienced its own challenges in the form of inadequate referral capacity and poor quality of health care (447).

Shung-King describes the success of the school health service hinging on three key priority areas:

(i) Identifying and prioritising the interventions that can make the greatest difference to the health and well-being of children within the confines of existing resource constraints, and with consideration given to the role and responsibilities of each sector involved;

(ii) Appropriately capacitating the key role players to perform their required duties and responsibilities; and

(iii) Facilitating processes that ensure sustainable collaborations between these key role players.

School health services should be optimized to ensure that healthy school-going children are able access their full potential by addressing the health barriers that hinder them. The South African school health service is an important health promotion and disease preventive tool that should be universally applied to any child attending formal schooling. Adolescent health care bridges the gap between the early childhood years and adulthood, and provides a catch-up strategy for those having missed childhood health services. By the school programme endorsing and promoting healthy lifestyles, it serves to prepare children for healthier adulthoods (447).

6.5 IN SUMMARY OF SCHOOL HEALTH SERVICES

Mathematical models have suggested that, over the long-term, it is more efficient to promote HIV prevention programmes among adolescents than in any other age groups (448, 449). This makes practical sense considering that adolescents are deemed a high risk group with increased vulnerability to HIV acquisition (93, 97, 98, 294, 300, 450-452). Additionally, in the absence of tailored health services, adolescents tend to have restricted access to health services, often preferring not to attend (453). Most importantly, adolescent-focused interventions are required to address the existing inequities in access to disease prevention services, as the younger they acquire a STI (or HIV), the more likely they are to transmit it to others (454). There is strong evidence to support the value of education in improving knowledge and attitudes concerning HIV and the uptake of HIV testing among adolescents both nationally and in SSA (387, 390, 392, 395-401, 455, 456).

7. CONCLUSION

South Africa is at the forefront of the HIV/AIDS pandemic, with adolescents largely implicated (300). HPV is another major contributor to the STI disease burden in South Africa, with approximately 20% of women harbouring cervical HPV infection at any given time (44, 457-460). HPV infection is frequently observed in HIV-infected individuals (44). Coupled with HIV/AIDS, cervical cancer is responsible for significant morbidity and mortality. HIV has been implicated in increasing the risk of acquiring HPV infection, increasing its persistence and with greater severity of associated cervical lesions (461). Conversely, research findings suggest that HPV infection may increase the risk of incident HIV infection in both women and men (462). If the association between HIV and HPV holds true, the use of the HPV vaccine may well reduce the incidence of HIV incidence in high HPV prevalence populations, in addition to preventing cervical cancer (463). Public sector vaccine delivery is limited by cost and delivery challenges in the resource-constrained environments of developing countries (84). However, HPV vaccine successes and potential HIV vaccine advancements are predicted to encourage even the most underdeveloped countries to scrutinize modalities to reach adolescents and pre-adolescents with vaccine initiatives (412). Organized public health programmes are needed to reach the adolescent population, as well as organization of systems of quality control and vaccine coverage monitoring to ensure long-term follow-up for vaccine effectiveness and safety evaluation (61). Discussing the vaccine policy has driven efforts to develop national comprehensive cervical cancer strategies that include vaccination, screening, treatment and palliation in areas such as Malaysia, Mexico, Peru, Rwanda, Tanzania and Uganda (61).

School-based health clinics for reproductive and mental health outcomes have been shown to provide access to health care for at risk adolescents are cost-effective in reducing health care costs due to hospitalisation and have the possibility of addressing health inequities. They are also essential to help adolescents make informed decisions about vital sexuality and relationship issues (Figure 8) (377, 378). The programmes have proven most effective when ‘adolescent-friendly facility-based approaches’ are combined with community acceptance. It is also imperative for the needs of the learners to be taken into consideration when implementing the sexuality education programme in school (173). To ensure that school-based sexuality education programmes are effectively delivered, teachers must feel comfortable about teaching about sexuality and comfortable answering adolescents' questions about sexuality issues. Thus, investing time and effort in teacher training is crucial (464). Parents play an equally important role in a success of a programme and should thus be included in the process, perhaps to review content and raise pertinent questions (465).

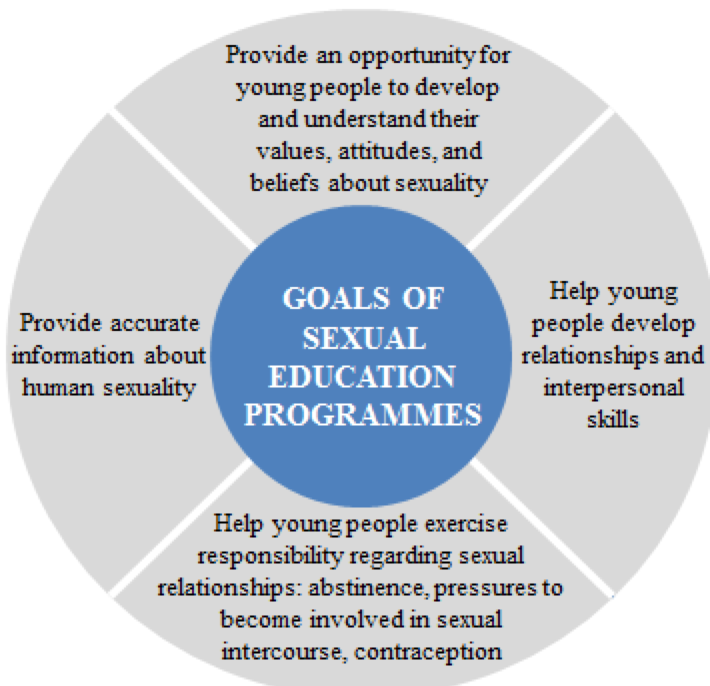


Figure 8. Comprehensive goals underlining school-based sexual and reproductive health programmes

The model addresses the key concepts that a SRH should cover to ensure adolescents develop comprehensive knowledge and sound relationship skills. [Source: Naidoo (418)].

There remain structural barriers in providing a comprehensive school-based SRH programme but special attention is required to reach vulnerable adolescents by offering different delivery modalities, making the school environment more conducive, and providing ongoing support for adolescents with identified health problems (424). Vaccines remain the one of the most cost-effective public health measures available, despite being undervalued and under-utilised globally. Society and future generations will draw the benefit from protecting populations from vaccine-preventable diseases now (366).

CHAPTER 3

AN INTRODUCTION TO ECONOMIC EVALUATION

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1. INTRODUCTION

In 1963, Kenneth Arrow contended that the "special economic problems of medical care can be explained as adaptations to the existence of uncertainty in the incidence of disease and in the efficacy of treatment" (466). More than 50 years later, Arrow's seminal article and his understanding of the health service sector remain relevant. The situation is such that health service spending has increased dramatically in most high- and middle-income countries raising concerns about cost-containment, quality and responsiveness. This is compounded in developing countries given that the renewed aspirations for improved health care often outstrips the local resources available to meet them (467). Health economics is a sub-discipline of economics that is linked to public health. It seeks to establish a connection between health and the resources required to promote it. Resources, such as human resources and time, are finite but the need for it may be indefinite. Options need to be prioritized in light of limited resources. Health economics clarifies these choices by appraising health policies, thereby providing a framework to contextualise the effects of different interventions (468). By doing so, areas lacking evidence are identified, and potential sources of empirical data sought (468). With several new vaccines of significant public health importance (including HPV) becoming increasingly available to national immunisation programmes, it becomes imperative for decision-makers to choose between vaccination strategies and alternative preventive interventions based on cost-effectiveness and value for money.

2. UNDERSTANDING ECONOMIC EVALUATION

"The ever-present need to allocate finite resources between numerous competing interventions and programmes means that economic evaluation are also used, to a greater or lesser degree, at 'lower levels' within many health care systems" (469).

Economic evaluation has become a vital tool to inform decisions made by health care systems regarding the health care interventions they should invest in (470). Economic evaluation in health care can be defined as the comparison of alternative options in terms of their costs and consequences (105). 'Health care costs' refer to the tangible resources of the health care system including staffing, equipment and buildings and consumables like drugs (470). 'Consequences' represent the changes occurring in an individuals' health (positive or negative) and includes all the effects of the health programme not accounted for by the resources (470). It is generally accepted that there are four main forms of economic evaluation. While each form compares cost, they differ in their handling of the consequences of health programmes (Table 5).

Generally some form of CEA predominates in terms of applied health research. The CEA is typically characterised by a health centred objective constrained by a health care budget – *constrained optimisation* (470). While the CEA is based on a single, generic measure of health, the quality-adjusted life year (QALY) has become the more frequently adopted measure for this purpose; as it incorporates the parameters of an individuals' length of life with health-related quality of life into a single measure (471). When a QALY is used as the measure of effect in a CEA, the analysis is termed a cost utility analysis (105). Once a measure of effect has been determined, the standard cost-effectiveness decision rules relate the differences between cost and benefits of the two interventions under comparison (472).

Table 5. Types of economic evaluation

The four main forms of economic evaluation are differentiated by measures of cost and consequence [Source: Drummond, 2005 (105)].

Type of study	Measurement / valuation of costs in both alternatives	Identification of consequences	Measurement / valuation of consequences
Cost analysis	Monetary units	None	None
Cost-effectiveness analysis	Monetary units	Single effect of interest, common to both alternatives, but achieved to different degrees	Natural units (e.g. life-years gained, disability-days saved, points of blood pressure reduction etc.)
Cost-utility analysis	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Healthy years (typically measured as quality-adjusted life-years)
Cost-benefit analysis	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Monetary units

A *dominant* intervention (yielding greater health benefits at lower costs than the comparator) would be considered unequivocally cost-effective (473). In the scenario where greater health benefits are obtained at greater cost, the decision to fund the new intervention rests on the opportunity costs falling on the health system – i.e. the QALYs that are forgone by funding the new intervention (470). In other words, the decision to implement a new intervention over an existing intervention has to take into consideration the benefits gained from the existing intervention that could be potentially lost (forgone). It is often the case that a new intervention would replace the existing intervention, as it would be financially prohibitive to run both interventions simultaneously. On this premise, the simplified decision rules have been focussed on calculating the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per extra unit of effect (e.g. QALY) from the more effective treatment (470). By comparing the ICER value to those of the other interventions; or to a hypothetical threshold value which decision-makers are seemingly willing to pay for the additional unit of effect, the preferred option from those being compared can be established (472).

3. THE PRACTICAL APPLICATION OF ECONOMIC EVALUATION

Economic evaluation, particularly cost-effectiveness analysis, has established itself as a vital determinant of overall health financing policy (474). Economic evaluations can inform decisions from the efficiency and allocation of resources to the implementation of strategies specifically designed to inform health care providers and patients alike about evidence based medicine that potentially enhances their practice (475). Economic considerations additionally impact on the planning, management and evaluation of health systems; from considering alternate methods of reimbursing providers to improved access to care by households, to defining essential packages of services for insurance and informing decisions on the inclusion of new medications in hospital, state or national formularies (476-479).

While these analyses are clearly valuable, the actual systematic impact of economic evaluation data on decision making still remains limited (480). Data from the EUROMET study examining the use of economic evaluation in Europe found that few decision makers actually made use of economic evidence (469). Similarly, there was a lack of evidence reported in an European study of evaluations of health care interventions, though some *ad hoc* evidence of impact was observed (481).

Morris, Devlin and Parkin (2007) provides the rationale for the use of economic evaluation in health care decision making as (482):

- Maximising the benefits from health care spending.
- Overcoming regional variations in access.
- Containing costs and manage demand.
- Providing bargaining power with suppliers of health care products.

Several health-care settings such as Australia, England, Wales, and Sweden have formally adopted the economic evaluation approach (469, 483). Since 1993, it has become mandatory in Australia for industry to submit economic evidence to the Pharmaceutical Benefit Advisory Committee (PBAC) for their products to be included in the Pharmaceutical Benefit Scheme, which is subsidized by the government (483, 484). Similar approaches have been adopted in Canada, England, Finland, The Netherlands and Portugal where systems have been introduced to formally link cost effectiveness to reimbursement decisions for new pharmaceuticals and, in some cases, other clinical technologies (485). The National Institute for Health and Clinical Excellence (NICE) in Wales and England consider economic evaluation to be a significant parameter in developing practice guidelines intended to influence health service delivery throughout the country (486). Sweden also adopts clinical practice guidelines based on decisions made by a central formulary committee that considers relevant economic evidence (487).

Thousands of completed economic evaluations have identified potential areas for improved efficiency. Examples of such studies are reflected in Table 6, which demonstrates clinical results varying from inefficient use of resources, yield life-years or QALYs at additional cost, or even suggesting cost-saving mechanisms. The table was adapted from Hooman and Severens (2014) (488). The wide variation in outcomes is not unexpected given the vast contrast in information input parameters used in cost-effectiveness studies (488). However, the adoption of a uniform methodology will increase the study transparency by allowing the reader to precisely critique the methodology adopted by the analysts and determine its appropriateness in the context of the study (489, 490).

Table 6. Examples of economic evaluations

AUTHOR	COMPARISON	INTERVENTION	OUTCOME	DECISION	REF
Gillespie et al. (2014)	Structured patient education with group follow-up versus individual follow-up	Self-management in type 1 diabetes versus conventional care	19,300 per QALY (cost-saving)	Not cost-effective	(491)
Mortimer et al. (2013)	Multifaceted strategy targeting primary care physicians, including interactive workshops, versus guideline dissemination alone	Evidence-based care for acute low back pain versus convention	AU$108 per x-ray referral avoided (cost-saving)	Cost-effective	(492)
Choudry et al. (2011)	No co-payments for patients versus co-payments	Preventive Medication after myocardial infarction versus no preventive medication	$54 per nonfatal vascular event or vascularization averted (cost-saving)	Cost-effective	(493)
Hooman et al. (2009)	Audit and feedback to primary care physicians versus usual care	Intensive control of blood glucose in patients with type 2 diabetes versus conventional control	25,640 per QALY	Cost-effective	(475)
Walker et al. (2009)	Financial incentives to primary care practices versus usual care	Use of ACE inhibitor and other quality indicators versus conventional care	5,623 per QALY	Cost-effective	(494)
Scheeres et al. (2008)	Multifaceted strategy, including health professional and patient education and instruction, versus usual care	Cognitive behaviour therapy of chronic fatigue syndrome versus regular counselling	5,320 per recovered patient	Cost-effective	(495)
Mason et al. (2005)	Specialist-nurse led clinics versus usual care	Lipid control in patients with diabetes versus no lipid control	$19,950 per QALY	Cost-effective	(496)

4. THE ROLE OF DECISION ANALYTICAL MODELS

Decision analytical models are becoming an integral part of the economic evaluation of health care interventions with the primary purpose of generating valuable information to assist health policy decision-makers in the efficient allocation of scarce health care resources (497). The model seeks to systematically evaluate the impact of health care interventions on costs and other outcomes; thereby accounting for uncertainty, explicating assumptions and allowing for the systematic evaluation of the trade-offs and uncertainty (498-500). The model achieves this by drawing data from several sources (RCTs, observational studies, epidemiologic data, expert opinion, etc.) to estimate the clinical and economic consequences of alternative therapeutic interventions, translating the complexity of the real world into a simplified, comprehensive decision tool that could potentially guide the decision-making process through the use of mathematical techniques and computer software (501, 502). Decision analysis tools complement CEA in informing clinical decision-making at population and individual levels. Decision modelling allows for variability and uncertainty in the model inputs by mathematically defining a series of possible consequences that could result from the alternative options being evaluated. Decision analysis enhances the validity of decision-making based on economic evaluation by: (i) providing a framework for synthesis of data sourced from different studies; (ii) effectively allowing for comparison between interventions by bringing together data from different clinical studies using statistical synthesis methods; (iii) allowing for sufficiently lengthy time horizons of comparison to reflect the key differences in cost and effects; and (iv) comprehensively accounting for the inherent uncertainty in the model using probabilistic modelling (470). While many different decision analytical models have been applied in economic evaluations, the decision tree and the Markov models remain the most notable (503, 504).

5. THE KEY STEPS IN DECISION ANALYTICAL MODELLING

Once the research question has been determined, the model structure is developed; and health outcomes and cost data incorporated into the structure. The model calculates both costs and health outcomes, explores the robustness of the initial results generated and then examines the implications thereof (503). The common steps involved in decision analysis modelling are summarized in Figure 9.

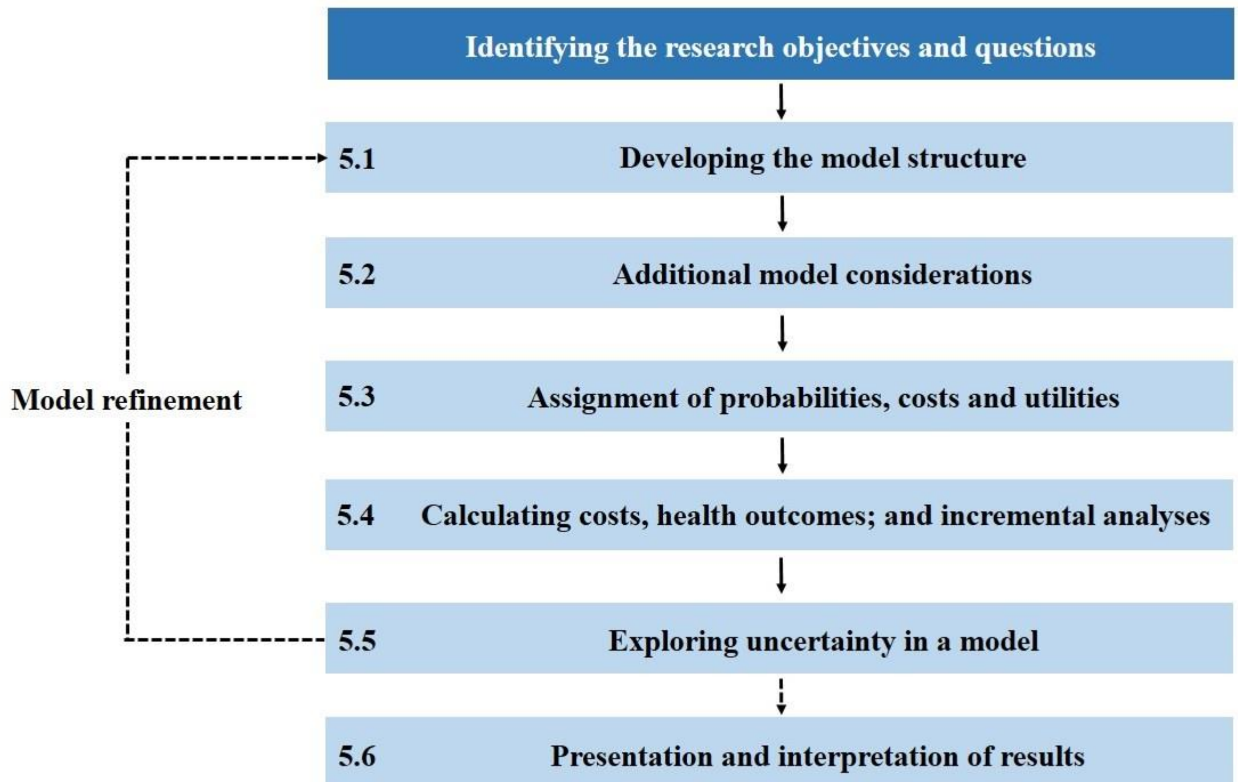


Figure 9. Steps involved in developing a decision analytical model

5.1 DEVELOPING THE MODEL STRUCTURE

There is no clear guidance on the best structure of an economic model but rather, evidence suggests how the components of a modelling problem influences the most appropriate modelling approach which further directs the development of public health interventions (505-508). Models can be constructed allowing simulations to occur at cohort or aggregate level, or to allow the behaviour of individuals to be followed independently. Cohort-level models (e.g. Cohort Markov models) allocate individuals to compartments that dictate that individuals within a compartment are homogenous. Such compartment models are simpler and less resource-intensive to construct than individual-level models, but understandably have several drawbacks. For instance, the homogeneity assumption is not satisfied if future model states are determined by an individuals' history and cohort models tend to be rather complex once several comorbidities are captured (502). Most modelling exercises tend to adopt a simple approach, with the notable exception of certain infectious disease modelling studies (508, 509). The modelling approach used depends on various factors, including the decision-maker's requirements and the disease process being considered (507, 510, 511).

5.1.1 Decision tree modelling

Decision trees are a simple, commonly used decision modelling technique that is effective for uncomplicated scenarios being evaluated (503, 512). The interventions are displayed graphically with a series of pathways or branches (Figure 10). Terminal nodes indicate the end points of each pathway using triangular symbols; to which values or pay-offs, such as costs, life years or QALYs, are assigned (512). Once the transition probabilities and pay-offs have been incorporated into the tree, the tree is averaged out to determine the calculation of the expected values of each option (513). While decision trees remain a simplistic and transparent technique of evaluation, they are limited by their lack of explicit time variable and their inability to handle recursion or looping within the tree such that chronic diseases marked by recurring events dramatically increase the complexity of the analysis (105, 502).

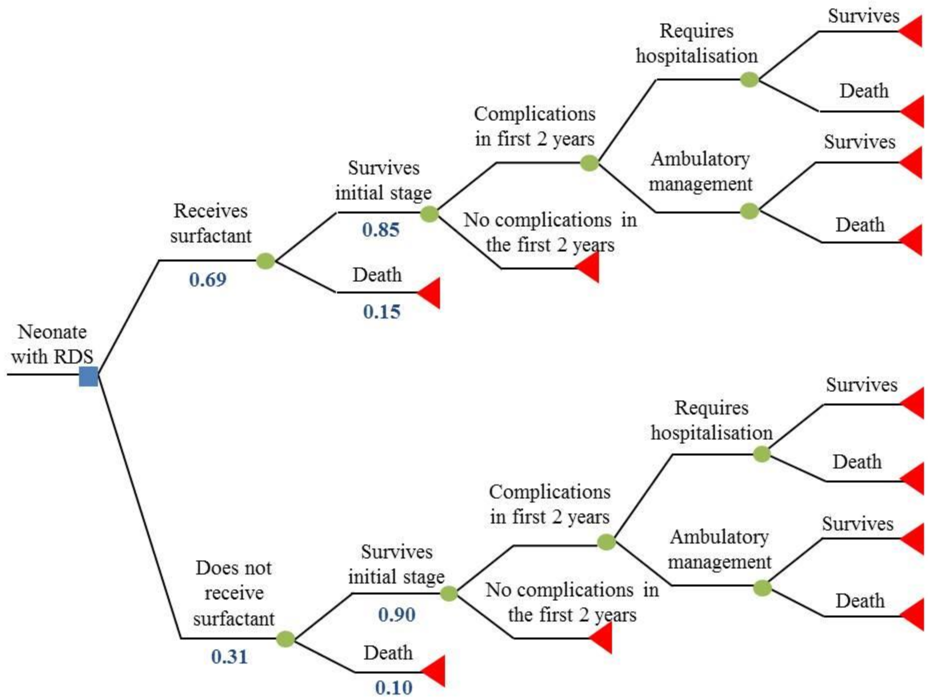


Figure 10. Illustrative example of a decision tree model

The model was adapted from Salinas-Escudero et al. (514), and does represent the actual findings. A decision tree comprises modes, branches and outcomes. Decision node (□) - describes the problem, Chance node (○) – represents the point at which several possible events can occur, terminal node (Δ) – represents the end of a tree with a pay-off attached. Branches from a chance node represent possible events patients may experience at that point in the tree. Branch probabilities represent the likelihood of each event. The sequence of chance nodes from left to right usually follows the sequence of events. The events stemming from a chance node must be mutually exclusive and probabilities should sum to 1.

RDS - Respiratory Distress Syndrome

5.1.2 Markov models

Markov models are more adaptable than decision tree modelling and have been widely used to determine the costs and health outcomes of health related interventions, particularly recursive, complex or chronic disease (471, 515-517). In a Markov model, the disease being studied is categorized into distinct states, described by the transition of disease in nature, within a stochastic framework, over a specified period of time (referred to as the *Markov cycle*) (105, 470). Each potential health condition in the model is referred to as a *Markov state*. The Markov states are intended to represent important clinical and economic events that occur to patients over time, achieved by the allocation of costs and utilities allocated to each health state (105, 503, 518). The model then simulates the transition of a hypothetical cohort of individuals through the Markov model over time, allowing the analyst to estimate the costs and outcomes (517). In each cycle, this is achieved by summing costs and outcomes across health states that are weighted by the proportion of the cohort expected to be in each state, and then finally summing across cycles (470). A time horizon of one year or more requires the application of discounting to generate the present values of expected costs and outcomes (502). The probability of remaining in a specified state or moving to another one in each cycle is governed by defined transition probabilities (502).

Defining the health states; and determining the number of health states needed and duration of the cycles are dictated by the nature of the health problem (e.g. gastro-oesophageal reflux disease may require monthly cycles, whereas cervical cancer may need annual cycles) (519, 520). To end a Markov process, termination conditions need to be set. This could be specified as a particular number of cycles, the proportion passing through or accumulating in a particular state, or the defined population reaching a state that cannot be left (e.g. death) that is referred to as an *absorbing state* (502).

Cohort simulation represents the most simplistic application of the Markov process. The simulation commences with a proposed cohort of participants (e.g. 1000 individuals) that are initially assigned to different states and then transition from between states during each cycle, thereby establishing a redistribution of the initial cohort during each cycle (503). During the cycle, the data on how many patients have remained in different states are captured and the processes are repeated for several cycles to obtain summary results on patients' spending in different states (503).

Limitations to the Markov model

Similar to any model, Markov models have limitations that must be overcome as models become more complex. An important limitation of the Markov model is what is referred to as the *Markov assumption* or the 'memoryless' feature of the Markov model where the transition probabilities depend on only the current health state, independent of historical experience (502, 521).

Additionally, the Markov model may apply two useful but infrequently used states viz. the tunnel and temporary. Temporary states are used when events have short, significant effects where participants remain in that state for at least a single cycle. Temporary states allows for the assigning of state specific transition probabilities and further allows for adjusted utilities and costs (503, 521, 522). A tunnel state, where patients transition in a pre-determined sequence, is likened to the passage through a tunnel, and is generally applied when the temporary state persists for more than a single cycle (503). In the situation where a life-threatening disease is being modelled, future events would depend on past events, which is often lost in the 'memoryless' nature of the Markov model (470). The 'tunnel state' serves to circumvent this issue by enabling the integration of health experiences from the previous cycles, thus implementing a degree of time-dependency into the model (523).

The half-cycle correction

The use of decision analytic software to implement discrete Markov models requires that transitions occur between simulated health states either at the beginning or at the end of each cycle (524). However, the usual assumption is that, on average, people will often transit between health states halfway through the cycle implying a systematic overestimation at the beginning of the cycle or a systematic underestimation when measured at the end (524-527). The half-cycle correction (HCC), a method used to deal with the inaccuracy caused by inadequate cycle length in Markov models, appears to be the gold standard correction to address this situation (524, 525, 528, 529). The benefits (and futility) of HCCs have been widely published in the international literature (525, 528). Although widely accepted, data shows that very few models actually incorporate the HCC (528). It was often the case that the ICER has changed by less than one percent when the HCC was employed and has had minimal effect on the net health benefit under certain circumstances, compared with the base-case scenario (524, 528). Additionally, standardizing the approach to the HCC remains problematic. Discounting presents a difficult prospect as the population distributions across the states becomes difficult to determine with larger populations in the first cycle and lower membership in all the others (524, 525). The result is that the discounted stream of populations within a state will always be too high (525)). Naimark et al. considers the best alternative to the HCC as no correction at all. Failing which, the adoption of a life-table approach or a correction based on Simpson's rule (an arithmetical rule and method for numerical integration based on estimating the area under a curve) (524). Barendregt considers the HCC correction to be “inelegant and baffling” in most circumstances and postulates the use of the life-table method as superior and easier to explain (525).

5.1.3 Alternative approaches to the discussed cohort models

Although Markov models, alone or in combination with decision trees, are widely applied in economic evaluations, several other approaches exist.

Patient level simulation (or microsimulation)

As the name suggests, patient level simulations track the progression of individuals rather than hypothetical cohorts within a model (502). In these models, the progression of potentially heterogeneous individuals and the accumulated history of each individual is used to determine the transitions, costs, and health outcomes (470, 507). Patient levels simulations are able to simulate the time to next event, rather than prescribing to equal cycle lengths, and additionally, are able to simulate multiple events occurring in parallel (507).

Discrete event simulations

Discrete event simulations (DES) describes the analyses of the disease progression of individuals through a resource constrained health care system with the aim of improving the organization of delivered services (530). The characteristics and outcomes are described over unrestricted time periods (507). The DES are not limited by the Markovian assumption (507). Unlike patient level simulation models, DES allows for individuals to interact with each other (e.g. in a transplant situation where organs are considered scarce, the transplant decisions and outcomes for any individual affects every individual in the queue) (510). The DES is limited by its computational complexity (often resulting in attempts to gain insights translating into futile, ambiguous models), the integration of intense randomness into the simulation making it difficult to distinguish whether an observation is attributed to system interrelationships or merely randomness and lastly, the models can be time consuming and expensive (531).

Dynamic transmission models

Dynamic transmission models (abbreviated to *dynamic models*) are able to reproduce the evolving direct and indirect effects (e.g. herd immunity) associated with communicable disease control programmes (532). The model allows for the internal feedback loops and time delays that impact the behaviour of the entire health system or population associated with the communicable disease process (533). They differ from largely static models that assume a constant risk of infection, thus changing the likelihood of infection over time and more effectively representing the progression of disease in reality (534).

5.2 ADDITIONAL MODEL CONSIDERATIONS

5.2.1 Study perspective

The perspective of a study determines the cost inputs considered, and the type of evaluation required. The patients' perspective considers the costs borne by the patient to access health care including transport costs and the costs associated with taking time off work (e.g. loss of wages). A societal perspective assesses all medical and non-medical costs, including hospitalisation, home based care, social welfare, productivity and intangible costs (535). While the societal perspective is a more inclusive approach encompassing all costs incurred by the individual and the health care provider, it is a labour intensive one with the impact of the intervention on every individual in society difficult to quantify. The approach seeks to weigh the costs involved in delivering health care against the loss of productivity as a result of employees taking medical leave. The government/health care provider perspective (abbreviated to the *provider perspective*) includes all expenses that influence the provision of health care (535). These include costs related to human resources and the provision of medication, consumables, equipment and fixed assets. This is the perspective that informs decision-making. Implementation costs and CEA results regarding the new intervention are presented to the decision-makers and are weighed up against the opportunity cost of foregoing an alternate intervention.

5.2.2 Discounting

Discounting is the concept of reducing the future value of costs and benefits to present values reflecting the fact that individuals in general have a positive rate of time preference for consumption now over consumption in the future (536, 537). Simply stated, it is based on the belief that society would opt to receive benefits sooner rather than later and pay costs later rather than sooner (537). The premise for discounting and indeed for the social rate of time preference is threefold: (i) *myopia* or pure rate of time preference reflecting the preference of society or an individual for consumption now due to impatience; (ii) time preference characterised by the inability to consume in the future due to death or catastrophe and (iii) as a result of economic growth, increased consumption now is more valuable than in the future i.e. the marginal welfare gain from each additional unit of consumption will be lower in the future comparatively (537-539).

Estimating the present value of costs follows a discrete time formula:

$$Cost_{present\ value} = \sum_{t=0}^{T} \frac{Cost}{(1+r)^t} \qquad \text{(Eq. 1)}$$

Where *r* is the discount rate and *t* is the time period when the cost occurs.

It is common in cost-effectiveness studies that future health benefits and costs are discounted at the same rate, though this practice is contentious particularly when assessing vaccines (540, 541). The controversy lies in the fact that while vaccines prevent future disease from occurring, the costs and health benefits associated with its use fall in different time frames. Jit (2015) described this as the effects of vaccines occurring in a different generation to the one paying for them, and highlighted different time parameters for time of vaccination, infection aversion and disease aversion (542). As such, vaccination as an intervention differs considerably from other health interventions and the cost-effectiveness calculated would be particularly sensitive to discounting (541). While the topic of discounting in economic evaluations concerning vaccine interventions has been avidly debated (4-10), no formal change in the methodology has been proposed to date. The WHO recommendation of standardly discounting costs and health effects by 3% (with a 0-6% range of uncertainty) remains widely applied (537).

5.3 ASSIGNMENT OF PROBABILITIES, COSTS AND UTILITIES

5.3.1 Assigning probabilities

The source of probabilities varies. It includes the medical literature (e.g. relevant meta-analyses, clinical trials and observational studies), mathematical models, and expert opinions (503). Much of the difficulties around the assigning of transition probabilities lie in the fact that many are not available from the literature, and those that are available can't easily be extrapolated to another population due to differing patient characteristics. Bayesian analysis, multivariate logistic regression analysis and survival models are some of the methods used to derive probabilities in mathematical modeling (543). Expert opinions, elicited via Delphi or modified Delphi methods, represent another vital source of information (544, 545). There has been strong support for the use of hierarchical data emanating from the massive developments in evidence-based medicine. As such, the suggestion is that these data be prioritized as they have greater validity in assessing the effects of interventions. While RCTs generally represent the best evidence for health care intervention effects; observational studies, studies without controls, modelled probabilities and expert opinions seem to feature less prominently regarding their strength of evidence (503). Populating a model requires review of relevant evidence, and synthesizing the transition probabilities obtained appropriately into the model. The fact that probabilities are often obtained from different sources strengthens the requirement for uncertainty analysis.

5.3.2 Assigning utilities and costs

The last stage of model development is the assignment of values to the described health states. Assigning costs and health utilities are distinct processes. The utility ranges from 0 to 1 and is multiplied with a natural unit of measure (e.g. life-years gained [LYG]) to obtain a quality-adjusted life expectancy result attributed to the investigated health care intervention or product. Generally, there are three major techniques are used to measure the utility viz. the visual analogue scale (VAS), standard gamble (SG) and time trade-off (TTO) (546, 547).

Each state of the model has a specified cost attached to it. Variation in costs are ascribed to resource use and unit prices. Costs are included as weighted or as single costs. Weighted costing allows for adjustment and can thus be detailed and subsequently more transparent, but with the limitation that it requires intense documentation and calculation (503).

5.4 CALCULATING COSTS, HEALTH OUTCOMES; AND INCREMENTAL ANALYSES

The three main summary measures of effectiveness in economic appraisals are the QALY, disability-adjusted life year (DALY) and the LYG (Table 7). The LYG represents a modified mortality measure that takes remaining life expectancy into account. Greater weight is accrued to young populations as a young life saved yields a greater number of life-years than if an older person was considered. The method calculates the remaining life expectancy accrued from the instance that the death was averted. Life expectancy values are extracted from life-tables that are specific per region or standardized across larger settings. The LYG is a relatively simple method for measuring population health (548).

While QALY and the DALY stem conceptually from the same framework, these concepts are not interchangeable as their underlying assumptions and methodologies differ (549). Each measure incorporates the trade-off between duration and quality of health in a single measure (548). The DALY combines the time lived with a disability and the time lost due to premature death (550). DALYs are a health outcome metric commonly used in developing countries (551, 552) where more than 90% percent of global disease burden is concentrated (553).

Table 7. Comparative table of the three main summary measures of effectiveness

<table>
<tr><th></th><th>Life-year gained (LYG)</th><th>Quality-adjusted life year (QALY)</th><th>Disability-adjusted life year (DALY)</th></tr>
<tr><td>Definition</td><td>A modified mortality measure that takes life expectancy into account.</td><td>A generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value for money of medical interventions.</td><td>A measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.</td></tr>
<tr><td>Measures</td><td rowspan="2">Remaining life expectancy at the point that death was averted.</td><td>The QOL in health gain</td><td>Health loss in QOL</td></tr>
<tr><td>Expressed as</td><td>Either 1 or 0 where
1 = perfect health,
0 = death</td><td>Either 1 or 0 where
0 = perfect health,
1 = death</td></tr>
<tr><td>Considers</td><td>Mortality and life expectancy</td><td>Burden of death</td><td>Mortality and morbidity</td></tr>
<tr><td>Other</td><td></td><td colspan="2">- Coverage and interpretation differs
- Has validity and accuracy issues</td></tr>
</table>

While South Africa is classified as a developing country (554), a systematic review conducted by Robberstad and Olsen (2010) described the use of the EuroQol EQ-5D health outcome measurement tool as appropriate for measuring health-related quality of life (HRQOL) of HIV/AIDS in Africa, thus suggesting the use of the QALY in the South African health context (555). The tool has been assessed for feasibility and reliability; and subsequently validated for South African use in adults and children through several studies covering a variety of conditions (e.g. haemophilia) (556-559).

The number of QALYs lived by an individual in one year is denoted by Equation 2:

$$\text{QALYs lived in one year} = 1 * Q \text{ with } Q \leq 1 \qquad \text{(Eq. 2)}$$

Where Q is the health-related quality of life weight attached to the relevant year of life (549).

The computer simulation was then developed to determine the incremental cost per QALY (ICER) of the current treatment strategies with and without vaccination, and is shown in Equation 3:

$$\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \qquad \text{(Eq. 3)}$$

Where C_1 and E_1 = comparator costs and effects, and C_2 and E_2 = intervention costs and effects.

5.4.1 What is cost utility analysis?

Cost utility analysis is a method of economic evaluation where the effects of different interventions are measured using utility units (e.g. QALYs) (560). Utility measures account for both quality and quantity of life in a single measure and thus represents an improvement on the unidimensional CEA that accounts for either quantity of life or quality of life (560, 561). The development of the QALY framework addresses issues of allocative efficiency as health interventions in differing clinical areas may be effectively compared (562). The intervention found to have the lowest cost per QALY gained should be prioritised so as to maximise the number of QALYs gain from a limited health budget (560). There are however, several concerns regarding the use of the QALY as a summary measure of health gain including its inability to account for issues of equity and the limitations to the benefits it may capture (563). Despite these concerns, the methodology remains widely in use and is the preferred evaluation method of the National Institute for Health and Clinical Excellence (560).

5.5 EXPLORING UNCERTAINTY IN A MODEL

Sensitivity analysis is vital in exploring the uncertainty of economic evaluation findings. The analysis aids in assessing the reliability of the study conclusions. Sensitivity analysis examines the robustness of the results. Results sensitive to a specific variable are explored to determine the degree of the sensitivity effect and if required, the model is appropriately revised (564).

5.5.1 Handling variability, uncertainty and heterogeneity

The results generated in an analytical model are subject to the influences of variability, uncertainty, and heterogeneity, and these must be handled accordingly to ensure that decision-makers are confident about the cost-effectiveness estimates (105, 511).

Variability (1st order uncertainty) represents the random variability in outcomes between similar patients (565). This variability, occasionally referred to as *Monte Carlo uncertainty*, does not provide any information and is negated by repeatedly running the model, thereby ensuring a stable estimate of the central tendency has been generated (566). Unlike variability, heterogeneity can explain in principle, to some degree, the differences between patients (i.e. differences in mortality between males and females) and does not represent a source of uncertainty (470).

Uncertainty is distinct from variability and heterogeneity. Uncertainty is further considered as parameter or model uncertainty. Parameter uncertainty relates to the uncertainty about the true numerical values of parameters used as inputs (e.g. transition probabilities, costs and health utilities) (508). This is often referred to as *second order uncertainty* to distinguish it from variability. Standard statistical methods would be used to represent the uncertainty of any estimate, but often does not give the full picture of the effects of joint uncertainty (105). This approach recognises that the data informing the parameter estimate follows a binomial distribution and thus, the standard error of the proportion can be obtained from the binomial distribution (Equation 4):

$$se(\bar{p}) = \sqrt{\bar{p}(1-\bar{p})/n}\,. \qquad \text{(Eq. 4)}$$

Where $\bar{p}$ is the estimated proportion and n is the sample size and se is the standard error.

Model (or structural) uncertainty addresses the uncertainty occurring in the structure of the model and the assumptions that underpin it (502). The model-structure uncertainty also refers to the mathematical manner in which parameters are combined to estimate costs and/or effects. Model–process uncertainty arises from the collation of decisions applied to the model through the entire process of analysis (508). Model uncertainty is assessed with sensitivity analysis – running the model with alternative structural assumptions (105).

5.5.2 Evaluating parameter uncertainty

Briggs et al. proposed three main reasons to consider assessing uncertainty in a model:

(i) Models often combine input parameters in different ways including addition, multiplication and as power functions. This results in models that are nonlinear with regard to those parameters.

(ii) The possibility of uncertainty existing in the results of an analysis implies the possibility of making an incorrect decision, which imposes a cost in terms of benefits forgone.

(iii) Policy changes have significant cost implications, with decision reversal being difficult or not possible.

One-way (univariate) sensitivity analysis

In deterministic sensitivity analysis, parameters are varied manually to test the sensitivity of the model outcome to specific parameter changes (565). This approach examines one variable at a time. The ICER is recalculated after calculating the base-case scenario with only a justified change applied to a single parameter (Figure 11). The process may be repeated with different parameters (473). A second type of one-way analysis is the 'threshold analysis' where the input parameters are varied over a range to determine the level below or above which the conclusions of the study change i.e. the 'threshold' point where neither of the decisions are favoured over the other (567).

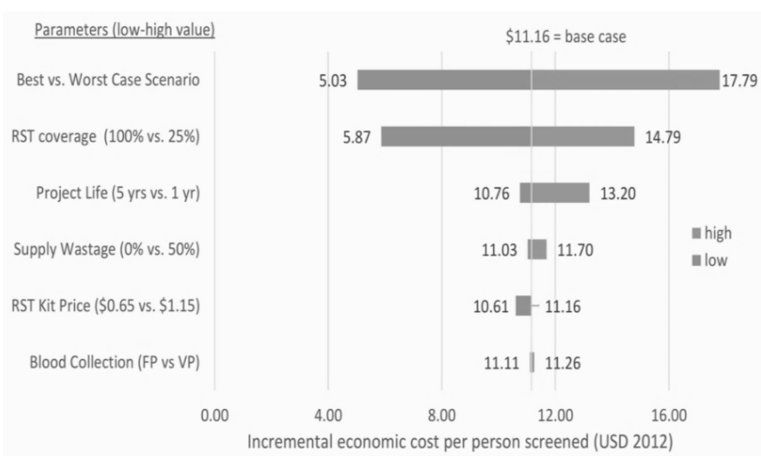


Figure 11. Illustrative one-way sensitivity analysis

The sensitivity of the ICER to different parameters is displayed. The numbers at the end of the bars reflect the range of values assessed in the sensitivity analysis [Source: Shelley, 2015 (568)].

Multi-way (multivariate) sensitivity analysis

Two-way analysis assesses two parameters that are common to the intervention being assessed simultaneously. A two-by-two matrix is developed reflecting the ICER for every potential combination for the variables; and the values that approximate a pre-determined willingness-to-pay (WTP) for a unit of effect are identified (473). The ICER is determined for a combination of three parameter estimates in a three-way analysis (473). In this technique, one of the parameters is held at a particular value and the combination of the remaining two parameters is assessed against a pre-determined WTP per unit of effect (473). The process is repeated according to the number of values that needs to be assessed for the first variable (473). This is represented graphically by Figure 12.

Multiplier Value	Protective Effect	Cost per HIA ($) in Three Unit Cost Groups		
		Unit Cost $30	Unit Cost $50	Unit Cost $100
Epidemic multiplier = 1.0	40%	350	545	1,031
	50%	234	363	688
	60%	175	271	516
	70%	140	218	413
Epidemic multiplier = 1.5	40%	234	363	688
	50%	156	242	458
	60%	117	181[a]	344
	70%	93	145	275
Epidemic multiplier = 2.0	40%	175	273	516
	50%	117	182	344
	60%	88	136	258
	70%	70	109	206

Figure 12. Illustrative example of multivariate (three-way) uncertainty analysis

The sensitivity of cost per HIV infection averted (HIA) to unit cost, protective effect and epidemic multiplier is shown per male circumcision done. This is compared to the base value of $181 per HIA [Source: Kahn, 2006 (569)].

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA), using Monte Carlo simulations, integrates the probability distribution of key variables and generate a distribution of the anticipated results (570, 571). The PSA is the preferred method of assessing parameter uncertainty as all variables are estimates of the sample mean and sampling error gauged from the best available evidence (511, 565). The PSA is executed by running the model several thousand times (iterations), with the parameter values varied across specified distributions (e.g. for costs and effects) until a distribution has been constructed and confidence intervals can be assessed (502). The information derived from the PSA can graphically represented as cost-effectiveness acceptability curves (CEAC), which demonstrate the probability that an intervention is cost-effective at an assumed maximum WTP for health gains (572). Further, in the event that a model has been derived from a single dataset, bootstrapping can be applied to the model uncertainty by repeatedly re-estimating the model outcomes using randomly drawn subsamples drawn with replacement from the full sample (502). The first two stages of the analysis involve the assigning of distributions to represent the uncertainty followed by the propagation of the uncertainty.

- **Assigning the distributions**

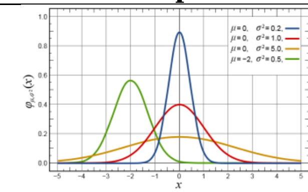
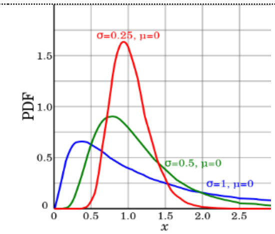
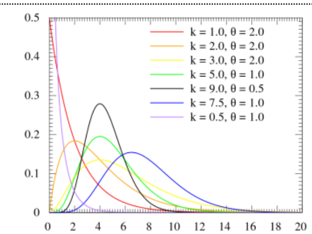
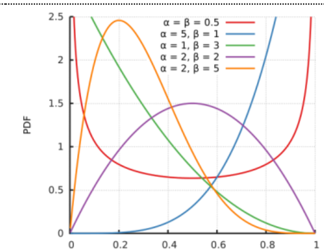
The type of parameter being considered dictates the choice and fitting distribution of the model parameters (Table 8). The idea is to match what is known about the model input with the characteristics of the distribution. Often this requires the use of the standard distributional assumptions employed to estimate confidence intervals. The selection of distributions for probability parameters are governed by two rules regarding the probabilities. The probabilities are limited to a value between zero and one and the probabilities of mutually exclusive events must sum one. However, a HIV-positive state can transition into AIDS, death or remain in the current state. The stages represent a multivariate generalization of the beta distribution with parameters equalling the number of categories in the multinomial distribution (470).

- **Propagating the uncertainty**

The parameters are assumed to be assigned specific probability distributions in a second order Monte Carlo simulation (573). When conducting sensitivity analysis, parameter values are drawn based on the distributions to calculate the estimates required (573). As a stable estimate of the mean is required, the simulation is repeated a large number of times ($\geq$ 1000) to obtain a distribution of the expected outcomes. This is normally achieved by non-parametric bootstrapping, a resampling procedure that randomly selects samples from the original data set with replacements (471). The repetition of this process a large number of times generates a vector of bootstrap replicates which represents the empirical estimate of the statistic's sampling distribution allows for the generation of a confidence interval for the analyses (573).

Table 8. Fitting parameter distributions

Distributions are assigned to match the characteristics of the parameter [Source: Briggs, 2006 (470)].

Distribution	Parameters	Values	Skewness	Uses	Information	Equations	Graphic
Normal	2 parameters mean & SD	Continuous unbound	Symmetrical Mean, median & mode are equal	Log odds ratio	Central limit theorem[1]		
Log-normal	2 parameters mean & SD	≥ 0 continuous	(+) skew; Median to the left of mean; variance dictates skewness	Resource use, relative risk	Natural log of value generates a normal distribution		
Gamma	2 parameters Shape & scale	≥ 0 continuous	Flexible Symmetrical or (+) skew	Cost parameters; mean rate of events	Mean & SD data can be converted to shape an scale	$E(\theta) = \alpha\beta = \mu$ $Var\ (\theta) = \alpha\beta^2 = s^2$	
Beta	3 parameters α, β & scale	≥ 0	Flexible Symmetrical or (+) or (-) skew	Probabilities, utility	α & β equal the successes and failures in a sample of size n = α + β[2]	$E(\theta) = \frac{\alpha}{\alpha+\beta}$ $Var(\theta) = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$	

[1]Central limit theorem: the sampling distribution of the mean will be normally distributed irrespective of the underlying distribution of the data with sufficient sample size.
[2]where α = r, and β = n-r where r is the number of events observed

5.6 PRESENTATION AND INTERPRETATION OF RESULTS

5.6.1 The problem with the ICER

The ICER is the ratio of the difference in costs between two competing interventions to the difference in their effectiveness (where *effectiveness* is considered a clinically meaningful event by a patient such as survival time, QALYs or symptom-reduced days where a larger value implies a better outcome) (574).

The ICER is a ratio statistic and as such, the estimation of a confidence interval is not clear cut (573). The problem arises with the non-negligible probability that the denominator could take a zero value (represented by red dots in Figure 13) and the ICER becomes unstable since a denominator value of zero would make the ICER infinite. The interpretation of negative ratios can also become ambiguous and the confidence interval may contain undefined values (472). The ICER also becomes difficult to interpret when the joint distribution of ΔC (incremental cost) and ΔE (incremental effect) lies in more than one quadrant. For these reasons, an alternative method of graphical representation is needed. An additional difficulty in the interpretation of the ICER is the concept of dominant vs. dominated interventions. As mentioned, dominant interventions have an ICER value higher than the next most effective intervention. Extendedly dominated interventions produce additional gains in effectiveness at higher incremental costs than those of the next most effective intervention (575). In contrast, the concept of dominance represents a completely different scenario. An intervention that is less costly and more effective is considered a case of simple dominance. However, in a situation where two or more alternatives are compared with a base scenario and both comparative alternatives have higher costs and higher outcomes gained; the alternative with the better cost-outcome ratio is preferred or dominating. In a situation where two or more new alternatives are compared with the standard and the new alternatives show higher costs but also higher outcomes gained; the alternative with the better cost-outcome ratio is considered to be dominating. The situation described is one of extended dominance (576).

5.6.2 The cost-effectiveness plane

Cost-effectiveness planes are a visual representation of incremental costs and effects and their uncertainty (577). The ΔC is plotted on the vertical (*y*) axis while the ΔE is plotted on the horizontal (*x*) axis. The advantage of the ΔE on the *x*-axis is that the slope of the line joining any point on the plane to the origin represents the ICER ratio (ICER = ΔC /ΔE) which is often the statistic of interest in cost-effectiveness analyses (578). Figure 13 further shows the plane divided into four quadrants and labelled using the points of the compass. An intervention is assumed to 'dominate' the comparator if it is cheaper and more effective than the comparator, and would thus appear in the south-east (SE) quadrant (470). When the converse applies, the comparator 'dominates' the intervention and would appear in the north-west (NW) quadrant. It appears logical to select the cheaper and more effective option when presented with these two scenarios and no further analysis is required (470). Decisions need to be made when an intervention is more effective but also more expensive than the alternative raising questions as to whether the additional health benefit is worth the added cost. If the ICER of the new treatment appears below the threshold ratio of the decision-maker, then the new treatment should be adopted. The threshold ratio is a notional amount that the decision-maker would be WTP for a unit of health gain and is denoted as λ (578). It should be borne in mind that the cost, effect and cost-effectiveness are not known with certainty but rather that the probabilistic models give a possible distribution of these values.

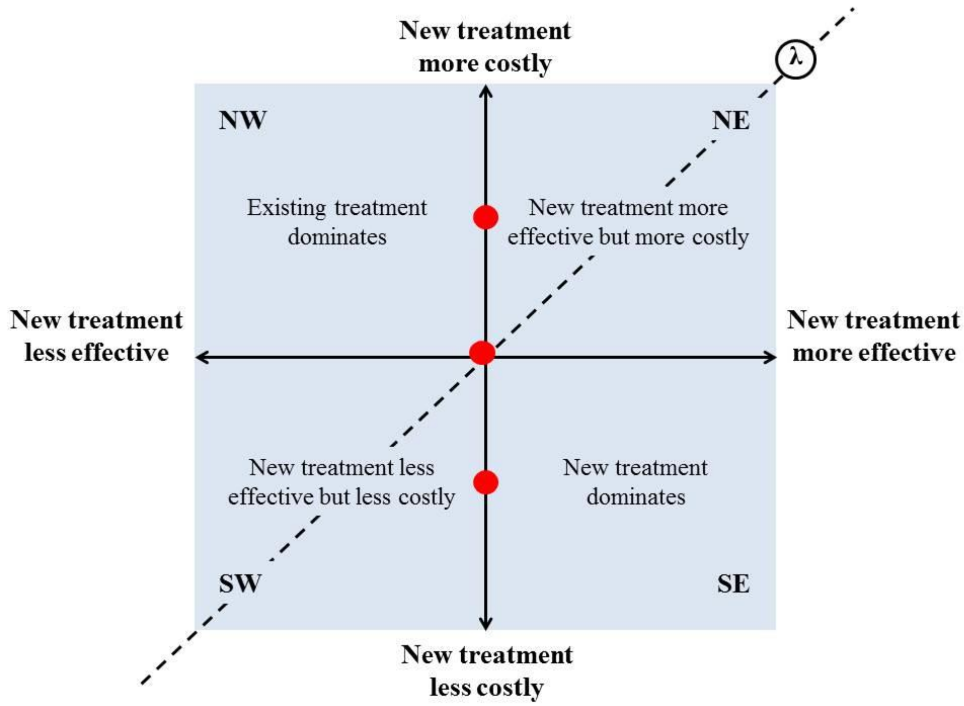


Figure 13. The incremental cost-effectiveness plane

Each dot represents a pair of incremental costs and effects. NE - northeast, NW – north-west, SE – south-east, SW - southwest, λ - maximum acceptable ICER [Source: Fenwick, 2006 (579); Briggs, 2004 (573); Hounton, 2012 (580)].

5.6.3 Cost-effectiveness acceptability curves

While the cost-effectiveness plane describes the option providing the highest level of expected benefit at differing costs, it is unable to visually display the uncertainty associated with the cost-effectiveness (581). The CEAC more effectively depicts the uncertainty around the ICER (578). It shows the probability that an intervention is deemed cost-effective compared for a range of monetary values representing the decision-makers' WTP (λ) (Figure 14) (582). The curve is constructed from the joint values of incremental cost and incremental effects usually estimated from non-parametric bootstrapping of the observed data (572). As mentioned, bootstrapping is a re-sampling procedure that generates a vector of bootstrap replicates of the parameter of interest, thereby generating the parameter's sampling distribution (573).

The net monetary benefit (NMB) was then estimated using the estimations of cost and effect for that particular cost-effectiveness threshold (Equation 5):

$$NMB = (\lambda * \Delta E) - \Delta C \qquad \text{(Eq. 5)}$$

Where λ is the WTP threshold; *ΔE* is the effectiveness and *ΔC* is the cost.

The joint pairs that are cost-effective are plotted for a range of values of the cost-effectiveness threshold, thus characterising uncertainty by estimating the probability that an option is cost-effective at differing levels of the threshold (572). The curve intersects the *x* axis at the probability that the intervention under consideration is cost-saving – the value of λ being zero implies that only cost impacts the cost-effectiveness calculation. The curve summarizes the evidence in favour of the cost-effectiveness of the intervention for every value of λ (470). Fenwick cautioned however that the option with the greatest probability of being cost-effective does not necessarily represent the option yielding the highest expected net benefit and thus the CEAC should not advise which treatment option is optimal (583).

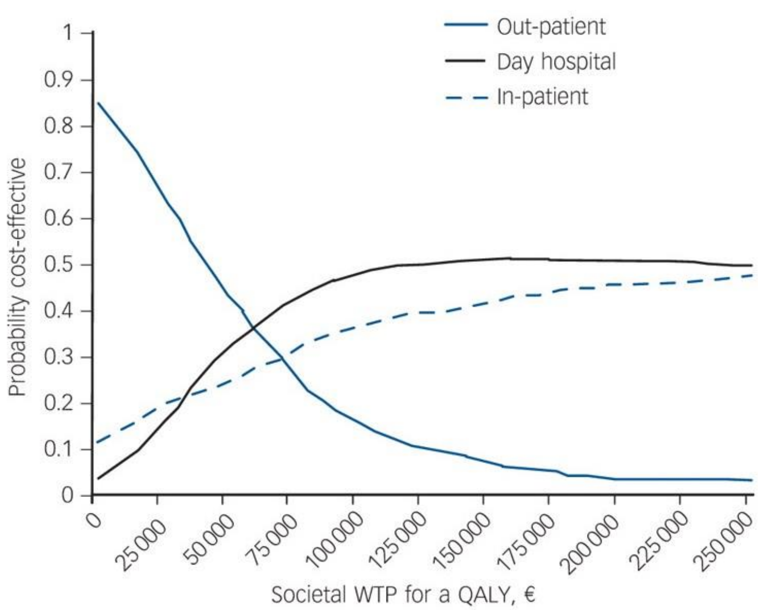


Figure 14. Illustrative example of cost-effectiveness acceptability curves

The probability of different modality being cost-effective at different values of WTP (λ) [Source: Soeteman, 2010 (584)].

5.6.4 Defining thresholds for cost-effectiveness analysis

ICERs are often used as a measure of cost-effectiveness in public health economic evaluation. Compared to what? The ICER value has little relevance to decision-makers without a reference as to what would be considered too high. There are three general approaches to this problem (585):

- Thresholds defined by per capital national incomes;
- Benchmark interventions;
- League tables

The recommendation by the Macroeconomics Commission of Health to use thresholds based on Gross Domestic product (GDP) per capita has been promoted by the WHO CHOosing Interventions that are Cost-Effective (WHO-CHOICE) project and has since been widely adopted in economic evaluations where: (586, 587).

- < 1 x GDP per capita = very cost-effective
- 1-3 x GDP per capita = cost-effective
- >3 x GDP per capita = not cost-effective

For the purposes of this thesis, the very cost-effective threshold (<1 x GDP per capita) was adopted, given the problem of easily attainability of the cost-effective (1-3 x GDP per capita) threshold (discussed below). The use of the GDP has several other significant shortcomings and alternatives have been proposed.

Thresholds

The threshold concept seeks to define the characteristics of a cost-effective and a very cost-effective intervention by relating the GDP per capita to the return on investments in health (479, 588). There are several advantages to this approach. Apart from the theoretical basis for the use of GDP, the argument for the human capital approach is strengthened by its application in many higher income countries including the UK, USA and Canada (589). The threshold also gives readers of these cost-effectiveness studies a benchmark that they may apply to judge other studies

(590). Estimating costs, health consequences and ICERs provide guidance to policy makers in three plausible ways (585):

(i) When the health-effect target is specified and the aim of the cost–effectiveness analysis would be to minimize the expenditure needed to achieve that target;

(ii) In the event of a budget constraint being specified by decisions-makers, then the aim would be to maximize the health benefits whilst keeping expenditure within the noted constraints; and

(iii) When policy-makers specify an explicit standard or threshold for what should be considered cost–effective.

All three scenarios warrant prior decisions by decision-makers on health effects or cost targets or thresholds prior to the commencement of the economic evaluation (585). Without reference to such decisions, the cost–effectiveness analysis cannot be comprehensively applied to provide decision-makers with the full range of options that may represent potential good investments (585).

However, the use of thresholds are not without question. The drawbacks to the use of GDP per include equity, affordability and neglect of the holistic approach to welfare (589). When considering equity, the use of GDP values life differently in economic terms across countries with different economic environments, thereby enforcing wide global inequities in health and wealth (589). Additionally, the GDP between the world's richest countries and poorest countries in terms of international dollars ($1; i.e. adjusted for purchasing power parity [PPP]) differs by two orders of magnitude (591). Further, exceptional prevailing conditions such as war, natural disaster and other negative economic impacts the lower average wage selectively, deepening the international inequities between affected areas and the rest of the world (589). In terms of affordability, using per capita GDP may lead to unsustainable total budgetary costs (592). This may translate to more effective but considerably more expensive interventions being suggested to replace the affordable, but inferior, option which may limit the number of people that may access the service (587, 593, 594) with much of this investment been directed towards subsidizing patient costs allaying affordability concerns for both providers and patients. Finally, Shillcut (2009) argues that a human capital approach defines a person's life according to the monetary value they produce or receive for their contribution to society (589). Defining health by income ignores the other dimensions of life that can be argued to have utility. Simply put, it suggests indifference between a life-saving intervention, and one that increases an individual's projected discounted productivity by a percentage that offsets the intervention cost (595).

Although it has been used widely, it has four major limitations (585, 596):

1. Comparisons between interventions are 'concealed'. While an intervention may be considered cost-effective in comparison to the GDP, it may not represent the best use of the national health budget and doesn't account for the trade-offs.
2. The threshold is easily attainable and far too many interventions would be deemed cost-effective making the threshold an arbitrary measure.
3. By defining the cost-effectiveness threshold based on a country's per capita GDP, the assumption is made that the country is willing to pay up to that threshold for the health benefit. There is no concrete evidence to support this assumption or indeed, the willingness-to-pay.
4. The question of affordability is not addressed and the threshold ignores the actual budget set aside by government for health programmes.

Benchmark interventions

An alternative to the GDP threshold is the use of a cost-effectiveness of a benchmark intervention already adopted in the country (585). In this approach, the cost-effectiveness is adjudged by retrospective analysis of existing practice as opposed to GDP per capita (597). Admittedly, the benchmark value does not consider affordability or the societal WTP for health benefits but does reflect an approach that has greater local relevance than thresholds based on GDP per capita (585).

League tables

League tables ignore threshold values completely and focus instead on getting the largest health impact for the budget (585). The principle is that a set of interventions would be chosen to maximise health effects, and are then ranked in a league table according to their ICER values (585). For a given budget, selection of the options begins at the top of the league table (smallest

ICER) and progresses down the list till the budget is exhausted (585). One drawback is that ICERs are sometimes not available for all interventions particularly in low-resource settings and often LMICs lack the expertise to interpret them (598). Another is the comparability of interventions evaluated in different contexts with different methodologies and different comparators. Estimating the cost-effectiveness of all relevant interventions is a labour-intensive task, even at national level and may be best considered to be conducted at a global level (e.g. WHO CHOICE) (598).

6. MODEL LIFE-TABLE ANALYSIS

6.1 INTERVENTION BENEFITS EXPLAINED BY MODEL LIFE-TABLE ANALYSIS

Life-tables have been used since 1856 to describe mortality and survival patterns in a population. Using age or age group specific mortality ratios, the life-table is able to generate information on parameters such as the number of survivors, mortality rates and life expectancy. Life-tables are able to predict how many people of a certain age will reach the next age in a certain year (599). In the context of this PhD, life-tables are able to demonstrate differences in mortality and subsequently life expectancy with and without the effects of the intervention.

6.2 ASSESSING HEALTH IMPACT USING LIFE-TABLES

The life-table aims to provide a comprehensive description of mortality in a population, by utilizing age-specific death rates by age and sex (often obtained from vital registration or census data). The use of these model have significantly contributed to understanding mortality levels and patterns over the last half century, particularly in areas with very little demographic data (600). Various institutions including research and insurance organisations, pension funds and policy makers rely on life-table data to generate human mortality estimates (601). Life-tables adopt a stratified person-years approach to compare mortality in a certain population with the mortality in the whole population. It is the conventional way of conveying information regarding age-related mortality rates (602, 603). Model life-table systems are generated from analysis of a large collection of historical mortality profiles (604). Model life-table are constructed to provide a system that gives schedules of mortality by sex and age that are defined by selected parameters. If the model is an adequate representation of reality, then the population characteristics can be surmised by the parameters of the model. This facilitates the monitoring of variation in the population over time (600).

Life-table models allow for comparisons between the population with and without the effect of an intervention. The columns in a life-table model contain the following variables: age, mortality ratio, number of survivors, number of deaths and the life expectancy. The first column invariably has the year of age, being annotated as age *(x)*. The general notations used are described in Table 9.

Table 9. Life-table notation

Explanation of the terms used in life-table analysis [Source: van der Meulen, 2012 (599)].

Notation	Explanation
${}_nq_x$ =	The mortality probability - probability of death between age (x) and the next age (x+n). this is the fundamental column of the table as other columns are derived from it (602).
I_x =	Number of survivors recorded at age (x). This column often begins with a rounded, large number of lives and is called the radix of the table.
${}_nd_x$ =	Number of people that die at age (x).
${}_nP_x$ =	Total population in age (x).
${}_nM_x$ =	Mortality rate associated with age (x).
T_x =	Cumulative years lived from age (x).
e_x =	Life expectancy at age (x) or the average number of years lived by Ix lives starting from age (x) till their death (602).

6.3 DETAILED LIFE-TABLE CALCULATIONS

6.3.1 Calculating the number of survivors and deaths in the table population

The calculation of the 'survivors' column starts with age *(x)* population size.

The number of people alive at age $x+n$ (I_{x+n}) in the table is calculated by subtracting the people who have died between age *(x)* and $x+n$ $({}_nd_x)$ from the number of people living at age $x(I_x)$ (Equation 6):

$$I_{x+n} = I_x - {}_nd_x \qquad \text{(Eq. 6)}$$

The number of people who have died between age *(x)* and $x+n$ in this formula $({}_nd_x)$ is obtained by multiplying the mortality probability between age (x) and $x+n$ $({}_nq_x)$ by the number of people still living at the start of the interval (I_x) (Equation 7):

$${}_nd_x = ({}_nq_x)\ X\ (I_x) \qquad \text{(Eq. 7)}$$

6.3.2 Calculating life expectancy

The life expectancy is calculated using the variables of the people living and those who have died in the previous section. The life expectancy reflects the average number of years of life remaining at a certain age. In this calculation, the cumulative number of years of life remaining from the age (x) is also determined for the table population as is termed T_x. Simple division of the cumulative years of life (T_x) by the number of people still alive at this age (I_x) results in the average number of years of life remaining or life expectancy (e_x) (Equation 8):

$$e_x = T_x / I_x \qquad \text{(Eq. 8)}$$

7. ETHICAL CONSIDERATIONS IN HEALTH ECONOMICS

Economics is intrinsically interwoven with ethics as many value judgments arise in research and policy advice. Health economic specifically deals with scarcity of resources and the maximising of health care benefits (605). With the goal of universal health care being globally striven for, the WHO describes the concept as 'all people receiving quality health services that meet their needs without being exposed to financial hardship in paying for them'(606). Voorhoeve clarifies issues of fairness arising on the path to universal care and argues that the principles of equitable coverage and service provision, benefit maximisation and fair contribution to health care costs are core (607). Norheim et al. describes fair health distribution as a combination of the weak principle of health equality and the principle of fair trade-offs (608). The weak principle of health equality suggests that health inequalities that are amenable to positive human intervention are unfair. When integrated with the principle of fair trade-offs, a more practicable understanding of health inequity is established. The principle of fair trade-offs states that weak equality of health is morally objectionable if continued reductions in weak health equality leads to unacceptable sacrifices in the overall health of the population, or results in unacceptable sacrifices of other goods considered important (e.g. education, employment and social security) (608). Daniels has determined that the health of societies is dependent on the distribution of social goods (i.e. the social determinants of health), stating further that social justice is required for population health and its fair distribution (609).

Distributive justice is pertinent to the issue of who should be the beneficiaries of an effective HIV vaccine. Whilst efficacy is evaluated in young adults, it is clear that the roll out of an HIV vaccine regimen will occur in a step wise fashion, and an investment case will be required to understand who will benefit the most from an efficacious vaccine, given limited resources in the health sector to do a mass roll out at a population level, in a setting where there are no easy venues for access to vaccination. In addition, in the early phases of scale-up, the number of doses of a vaccine will be limited, thus an efficacious vaccine will have to be rationed and choices will be made. Our choice of a school based programme targeting adolescents to be the initial beneficiaries of an efficacious vaccine, is made for two reasons: 1) ease of roll-out in an already established adolescent school-based programme to maximise success, and 2) enabling the most vulnerable and susceptible population to receive it first. Distributive justice is concerned with the socially just allocation of goods in a society (610). Distributive justice raises tensions between efficiency (maximising something subject to resource constraints) and equity (distributive fairness) (611). The focus is thus shifted from the individual (individual as a consumer) to that of the nation (individual as a citizen) (612).

Rising health care costs leads practically to the setting of priorities in health care delivery (612). It is globally acknowledged that health care institutions encounter challenges in balancing health service delivery with financial solvency (613). It cannot be morally justifiable that people be denied health care that could potentially alleviate suffering based on their inability to afford it, increasing the relevance of ethical practices. Clinicians are inadvertently accustomed to this discriminatory practice as their training differentiates between those that would benefit substantially from a treatment as opposed to those benefitting marginally; thus setting clinical priorities (605). Costs play a pivotal role here, as they represent the sacrifices made by those potential patients who are not treated (614).

Value of life is often quantified by the people's WTP to avoid risk of danger to their lives. One shortcoming of this principle is that the lives of the poor (e.g. Indian citizens) are devalued compared with the rich (e.g. American citizens) because poor people have less that they can pay (615). The situation is not that straightforward as the ethical arguments are not separated from the economic arguments easily (615). Options where the levels of co-payments and cost-effectiveness thresholds are varied in populations' runs the risk of creating a dichotomy between the rich and poor (616), distorting the distinction between fairness and fair distributions.

Moosavi et al. concluded that if health and research centres plan and act on ethical principles, the social confidence will be established and will correspondingly result in an increase in social capital (617).

8. CONCLUSIONS

Health economics is an important sub-discipline of economics that is linked to public health policy. The economic evaluation allows decision-makers to compare interventions based on cost-effectiveness and value for money. This information is translated to impact on life expectancy and health outcomes. Uncertainty is factored into the model at several levels as all decisions have an inherent level of uncertainty associated with them.

CHAPTER 4

METHODOLOGY

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1. INTRODUCTION

This PhD comprises five journal publications, the first of which was embodied in Chapter 2: Literature Review (169). This chapter describes the methodology used in the study encompassing the model development, integration of variables and interventions, data analysis and finally, the model uncertainty and limitations. The methodology was designed to address the study objectives and complied with the guidelines stipulated in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (618).

2. STUDY OVERVIEW

2.1 STUDY SETTING AND POPULATION

The global gains made in reducing the burden of HIV disease has been threatened by the critical epidemics of HIV that have been propagated among pockets of young women and girls in SSA (285). Adolescent girls in South Africa are historically socially and economically vulnerable - a vulnerability that often translates into them relinquishing control over the timing and circumstances of sex and increasing their susceptibility to HIV (619, 620). Adolescent boys are not exempt from this high risk of HIV given their predilection to the early onset of sexual activity (approx. 14 years compared to girls at 15 years) that is often associated with erratic patterns of condom use (150, 151). It is against this backdrop that the introduction of the HIV vaccination programme administered to adolescents was considered utilitarian. The premise behind the school-based vaccination concept was that the target population was not only relatively stable and accessible, but may be reached potentially prior to the onset of sexual activity. While HPV disease shares several risk factors with HIV, females were more likely to develop significant morbidity and mortality associated with HPV acquisition than males later in life (621). It would be important to consider the impact of the HIV vaccine in both male and female adolescent counterparts. However, the HPV vaccine was earmarked for administration to the adolescent female population only, where it was shown to be significantly cost-effective (622). South Africa has the highest rates of cervical cancer incidence and mortality globally (92). While the disease manifests clinically much later in life, it is the disease acquisition in early life that the HPV vaccine programme wishes to target (274). Vaccine implementation was considered individually and in combination among school-going populations in the South African PHC sector. The vaccine programme would be an important cog of the SRH platform developed at schools to re-engineer PHC within the South African borders (154).

2.2 STUDY PERSPECTIVE

The provider perspective accounts for all expenses influencing the provision of health care (535). These include costs related to human resources and the provision of medication, consumables, equipment and fixed assets. Implementation costs and CEA results regarding the new intervention are presented to the decision-makers and are weighed up against the opportunity cost of foregoing an alternate intervention. Therefore, as this is the perspective that informs decision-making and influences potential policy changes, it was the perspective adopted by this body of work.

2.3 COMPARATOR AND INTERVENTION

Despite the existing epidemiological link between HIV and HPV disease, the diseases are largely considered in isolation. The ‘current’ HPV programme is represented by the 2001 National Guideline for Cervical Cancer Screening Programme which sought to perform three lifetime Pap smears targeting 70% of women aged 30 years and older at 10 year intervals (246). The uptake of this programme has been poor, and fraught with infrastructural, human resource and accessibility issues (17). With the escalating burden of HIV disease, the guideline applied to the cervical screening of HIV-positive women was revised to an annual assessment (247) in lieu of the synergistic, pathological association of HIV and cervical cancer (463). Once cervical disease was identified by screening, patients were channelled into government sector clinics and hospitals for definitive management. Both programmes outlined are simultaneously implemented, though the 2001 national cervical screening guideline is currently undergoing revision. Unlike the cervical screening policies, the HIV portfolio is widely diversified and frequently updated; concentrating on the provision of both primary (preventive) and secondary (curative) services. The HPV and HIV vaccine strategy would serve to complement the existing standard of care described. While the school health programme does not represent the only portal of entry for these vaccines, it does target a highly susceptible adolescent population with inadequate access to health care services documented, despite the dire need for it (151). This study investigated the cost-effectiveness of the HIV vaccine strategy and then considered the dual vaccination strategy.

For the purposes of Chapters 5-7, the vaccination initiatives were compared with the current standard of ART delivery. This was defined as 29% ART coverage with access to HIV testing and care provided at all government facilities (97). Chapter 8 explored the cost-effectiveness of the vaccine strategies compared with other biomedical interventions (viz. PrEP and VMMC) tested in the South African context.

2.4 DISCOUNT RATE

Discounting involves the process of converting future values (e.g. costs and health effects) to their present value reflecting that society in general has a positive time preference (537). Discounting poses a particular challenge to economic evaluation of prevention interventions because spending is usually immediate, but the health translation of the intervention is usually seen many years later (623). Although it is widely accepted that costs and health effects should be discounted in economic evaluations, disagreement exists around the rate at which health effects should be discounted (540). While differential rates of discounting for costs and health benefits have been suggested, the WHO-CHOICE and others recommend the use of the same rate of discounting for costs and health effects (3%) with a range of 0-6% explored in the sensitivity analysis (537). They contend that applying a standard discount rate allows for greater comparability across studies (537). The analysis in this PhD applied this principle with a standard discounting rate of 3% to costs and health effects annually and undertook a sensitivity analysis of the discounting rate ranging from 0-6%.

3. OUTCOME MEASURES

3.1 CHOICE OF HEALTH OUTCOMES

As mentioned, the three main summary measures of effectiveness in economic appraisals are the QALY, DALY and the LYG. The QALY incorporates survival and HRQOL into a single summary measure of health that informs decision-making about the relative value for money of health care interventions (624). It is a standard measure of health outcome that enables comparisons across different populations and different disease areas (563). The QALY is estimated by calculating the total LYG from an intervention and then each year multiplied by a quality of life score (where 0 = worst health and 1 = best health) to reflect the quality of life in that year (130). This information formed the decision to use the QALY as the outcome measure for this PhD.

3.2 MEASUREMENT OF EFFECTIVENESS

Generally, 'intervention effectiveness' is defined as the ability of the intervention being assessed to reduce the acquisition of disease among susceptible, uninfected individuals according to the values determined by clinical trials (625). The bivalent vaccine [Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium)] contains the VLP types 16 /18 that have been implicated in 64% of cervical cancer is South Africa (92). Analyses of the two completed Phase III trials of HPV VLP vaccines in young women exhibited impressive safety and immunogenicity profiles (252). The efficacy modelled in this PhD was chosen from the PATRICIA study (274) rather than the Costa Rica HPV Vaccine Trial (CVT) (626) as the study criteria of PATRICIA more closely resembled that of this economic evaluation. Table 10 presents the differences considered between the PATRICIA and CVT study and denotes the effectiveness measures used in this modelling exercise (shaded area). While the studies were not conducted in the primary target populations of the vaccination programmes being considered in this analysis (adolescent boys and girls) for practical reasons, the immunogenicity bridging studies have demonstrated excellent safety, strong immune responses and documented durable antibody responses that have translated into protection in young adults (627-630).

Table 10. Differences in Phase III efficacy HPV bivalent vaccine studies in young women

The PATRICIA efficacy measures (shaded) were adopted in the economic evaluation as the primary end-points and study inclusion criteria more closely reflected the parameters considered in model (274, 631).

<table>
<tr><th></th><th colspan="3">PATRICIA</th><th colspan="3">CVT</th><th>Rationale for PATRICIA choice</th></tr>
<tr><td>Vaccine</td><td colspan="3">Cervarix</td><td colspan="3">Cervarix</td><td rowspan="2">Bivalent vaccine currently being implemented in SA government schools</td></tr>
<tr><td>VLP types</td><td colspan="3">16/18</td><td colspan="3">16/18</td></tr>
<tr><td>No. study sites</td><td colspan="3">135</td><td colspan="3">7</td><td rowspan="2">Findings have greater generalisability with more study sites and countries</td></tr>
<tr><td>No. countries</td><td colspan="3">14</td><td colspan="3">1</td></tr>
<tr><td>Age</td><td colspan="3">15 – 25</td><td colspan="3">18 - 25</td><td>Younger age group considered in analysis</td></tr>
<tr><td>Lifetime no. sexual partners</td><td colspan="3">≤ 6</td><td colspan="3">No restriction</td><td>Reflects the assumed sexual naivety of the adolescent group</td></tr>
<tr><td>Primary endpoints</td><td colspan="3">• Incident HPV 16/18 associated CIN2+ or greater</td><td colspan="3">• Incident 12 mo. persistent HPV 16/18 infection</td><td>Considered the long-term implications of HPV disease</td></tr>
<tr><td rowspan="7">Protection afforded</td><td colspan="3">Total Vaccine Cohort</td><td colspan="3">Intention-to-treat</td><td rowspan="7">Health states integrated into the Markov model</td></tr>
<tr><td></td><td>% Efficacy (95% CI)</td><td>Rate reduction</td><td></td><td>% Efficacy (95% CI)</td><td>Rate reduction</td></tr>
<tr><td>CIN2+</td><td>60.7 (49.6-69.5)</td><td>0.43</td><td>All</td><td>49.0 (38.1-58.1)</td><td>3.90</td></tr>
<tr><td>CIN3+</td><td>45.7 (22.9-62.2)</td><td>0.13</td><td>18-19</td><td>68.9 (53.1-79.9)</td><td>5.20</td></tr>
<tr><td>AIS</td><td>70.0 (-16.6-94.7)</td><td>0.02</td><td>20-21</td><td>42.8 (17.9-60.6)</td><td>3.60</td></tr>
<tr><td></td><td></td><td></td><td>22-23</td><td>51.5 (28.4-67.7)</td><td>4.70</td></tr>
<tr><td></td><td></td><td></td><td>24-25</td><td>21.8 (16.9-47.9)</td><td>1.60</td></tr>
</table>

The work being presented in this PhD remains contrary to this traditional definition of ‘intervention effectiveness’ in two important ways. Firstly, the hypothetical HIV vaccine being discussed is being implemented in Phase I trials currently. The characteristics of the HIV vaccine considered in the economic evaluation are in keeping the target product profile formulated by the P5, a diverse collaboration of organisations founded under the Global HIV Vaccine Enterprise to promote research based on the foundation of the RV144 trial and to draw collaboration globally to assess HIV vaccine candidates going forward (372). Secondly, the joint effectiveness of two separate interventions is rarely assessed in a clinical trial setting. Long and Stavert suggested the use of mathematical modelling to evaluate the joint effectiveness of two interventions under different assumptions in the absence of pre-existing data (625). Their initial approach is to assume the efficacy is *multiplicative* (e.g. if VMMC is 50% effective and PrEP 67%, then the combined effectiveness is calculated as in Equation 9 (625):

$$\text{Joint effectiveness} = 1 - [(1 - 50\%) * (1 - 67\%)] = 83.5\% \qquad \text{(Eq.9)}$$

A more conservative approach is adopted in the sensitivity analysis where the *maximal* effectiveness is adopted. Using the above example, the combined effectiveness is described in Equation 10 (625):

$$\text{Combined effectiveness is max } (50\%, 67\%) = 67\% \qquad \text{(Eq. 10)}$$

Wider confidence intervals are often yielded under the experimental settings of clinical trials. The purpose of the PSA remains to explore whether these efficacies of interventions would still hold in real-life settings (625).

The WTP threshold or threshold ratio (λ) represents the amount that decision-makers would be willing to pay per gain in QALY (632). The most conventionally used measure, the GDP per capita, poses several major limitations that were discussed in Chapter 3 (Section 5.6.4: Defining thresholds for cost-effectiveness analysis). In order to more accurately represent the economic evaluation of the HIV and HPV vaccine strategies, it was decided to benchmark the CEA against the cost-effectiveness of VMMC (an intervention deemed highly cost-effective in the South African setting) rather than use the GDP per capita alone (585). The biomedical HIV prevention interventions of VMMC and PrEP were compared with the current coverage of ART and against a potential scale-up of ART coverage in terms of infections averted, change in mortality and cost per QALY predicted over a ten year period. This is comprehensively discussed in Chapter 8.

3.3 MEASUREMENT AND VALUATION OF PREFERENCE BASED OUTCOMES

It is often difficult to determine which weights should be adopted into a cost-utility analysis considering the heterogeneity found in study characteristics of similar studies. Several studies have reported quality-of-life estimates for HIV infection and AIDS. Tengs and Lin conducted a meta-analysis to derive pooled utilities for HIV/AIDS that may be used for cost-utility analyses of HIV-related interventions (633). Similar pooled utility measures for HPV-related disease states do not exist in South Africa. Instead, quality of life weights from the available literature was adopted. The utility weights for both diseases appear in Table 11.

Table 11. Utility weights for HIV and HPV-related disease

The table describes the health-related quality of life weights for the different health states of both diseases.

Parameters	Estimate	Country	Published	Reference
Full health	1			
HPV disease				
LSIL	0.91	USA	2007	(122)
HSIL	0.87			
Cancer survivor	0.84			
Cancer	0.65	USA	2004	(266)
HIV disease				
Asymptomatic	0.94	Meta-analysis (25 articles published from 1985 – 2000)	2002	(633)
Symptomatic	0.82			
AIDS	0.70			

4. STUDY INPUTS

4.1 ESTIMATING RESOURCES AND COSTS

As established thus far, the economic cost of vaccination services delivered at school, as part of a school-based SRH platform, was estimated from the provider's perspective using an ingredients-based costing approach in the South African public sector.

Cost inputs regarding the HIV intervention included HIV testing, pre-and post-test counselling, the cost of the actual vaccine dose, vaccine delivery and the human resources required to deliver such services. Overhead costs were omitted in the school-based programmes. Participants found to be HIV-positive were worked up for and initiated on ART by the school nurse if indicated. Those ineligible for ART received the standard of care prescribed by the 2013 South African HIV Treatment Guideline (247). Besides the actual ART drugs, the costing included adherence counselling and the laboratory monitoring specified by the national HIV treatment guideline at each appointment (247). Those found to be HIV-negative would receive the applicable risk-reduction counselling. In the absence of the HIV vaccine, all procedures mentioned above would be adhered to without the vaccine intervention itself.

The 2001 National Guideline for Cervical Cancer Screening Programme was introduced under Chapter 4 (Section 2.3 Comparator and Intervention). As mentioned previously, the deleterious impact of HIV on cervical disease has necessitated more aggressive cervical screening practices with annual Pap smears being the current recommendation proposed by the HIV treatment guidelines (247, 463). Unlike the HIV vaccine, there would be no prior screening of adolescent girls prior to the administration of the HPV vaccine. Screening young, sexually naïve girls by Pap smear is generally not recommended as cervical cancer is extremely rare under the age of 21 years; most abnormal lesions in this age group spontaneously regress and interventions targeting abnormal cervical cytology can result in undue anxiety and potential pregnancy complications in the future (634). HPV DNA blood testing would prove financially prohibitive in a potential national roll-out of this programme (635, 636). However, the fact that young South African girls have a concerning incidence of non-consensual sexual encounters at an early age brings into question the HPV vaccines overall efficacy that is diminished in light of previous exposure to HPV types/strains (252, 254). The HPV vaccine programme would include pre-counselling and vaccine administration. Costs relating to vaccine delivery (e.g. syringes, needles, human resources) were considered. Several of these accounts overlap with the HIV vaccine service and these were accounted for in the model (e.g. one unit of pre-counselling would occur prior to both vaccines for efficiency).

While the model assumed full adherence to medication and visiting schedules when representing costs, the sensitivity analyses conducted on the cost assumptions may realistically reflect potential lower uptake of these health services as is sometimes the expected behaviour in a non-clinical trial environment (623). The development of the school-based health service was initially outlined in the ISHP in 2012 (153). It is unclear what progress or coverage the programme has achieved to date. Suffice to say, the start-up costs for a school-based programme would be considerable when considering provider education and recruitment of personnel. These costs were not considered in the cost-effectiveness models but should rather be the subject of budget impact studies (623). Key study input values are discussed below.

4.1.1 Epidemiology

HIV: The South African HIV epidemic remains the largest in the world with a national prevalence of 12% and approximately 396 000 new cases occurring in 2012 (300). A 75% increase in ART uptake was reported between 2009 and 2011 with a resultant 2 002 000 people on ART in 2012 (97, 299). Despite this, there remains a 58% shortfall in treatment access (300). HIV-related mortality remained high, with approximately 35% of deaths attributable to the disease in 2012 (637).

HPV: While the numbers affected by HPV disease appears deceptively small, the synergistic relationship between HIV and HPV should not be underestimated. South African cervical cancer incidence and mortality rates are higher than global average estimates and the disease is the highest cause of cancer-related mortality among women aged 15-44 years in South Africa (92). Approximately 64% of cervical cancer cases in South Africa are HPV 16, 18 positive (92). Table 12 described the epidemiological parameters considered.

Table 12. Relevant South African epidemiology

The table describes the relevant general, HIV-related and HPV-related parameters sourced from the literature as indicated. These 2012 estimates were drawn from the South African literature.

	Total		Male		Female		Reference
General							
Population	52 274 945	100%	25 453 074	48.7%	26 821 871	51.3%	(97)
Life expectancy	67.4	-	64.1	-	70.6	-	(637)
Mortality	1.48%	-	1.56%	-	1.42%	-	(637)
HIV-related disease							
Incidence	396 000	1.72%	145 000	1.21%	251 000	2.28%	(97)
Prevalence	6 422 000	12.20%	2 531 000	9.90%	3 873 000	14.40%	(97)
On ART	2 002 000	29.00%	651 000	25.70%	1 344 000	34.70%	(97)
Life expectancy	59.3	-	57.3	-	61.3	-	(637)
Mortality	1.69%	-	1.75%	-	1.63%	-	(637)
Related mortality	203 293	35.30%	-	-	-	-	(637)
HPV-related disease (Cervical cancer statistics)							
Women at risk of cervical cancer (≥ 15 years)					19.43 million		(92)
Crude incidence					30.2 / 100 000		(92)
Annual cases					7 735		(92)
Crude mortality					16.6 / 100 000		(92)
Annual deaths					4 248		(92)
Prevalence (%) of HPV 16 and/or 18 with cervical cancer					63.90%		(92)

*generic population epidemiological estimates are given here. Age-specific estimates were used in the calculations.

4.1.2 Economic considerations

An ingredients based costing approach was employed for most parameters while some estimates were obtained from the literature as referenced. To ensure meaningful and consistent monetary quantities, local costs were adjusted to 2012 using South African inflation indices. Costs and outcomes were adjusted at 3% p.a. (range: 0-6%) respectively in keeping the WHO-CHOICE recommendations (537). The vaccine delivery cost, including pharmaceutical, human resources and laboratory costs, was calculated at US$ 17 (the micro-costing elements of this total appears in Appendix A). Further, the base HIV vaccine cost was estimated at US$ 12 (the range of costs assessed in this evaluation [US$ 2 – 24] is shown in Annexure A). Table 13 describes the costs and economic considerations included in the evaluation.

Table 13. Parameter costs and economic considerations used in this analysis

The values in Table 13 were drawn from the South African literature for 2012.

Economics	**Value**	**Range**	**Reference**
Cost	3.0%	(0 – 6%)	(537)
Outcome	3.0%	(0 – 6%)	(537)
International comparison (ZAR: 1US$)	ZAR 8.21		(591)
HIV disease related costs	**Distribution**	**Value**	**Reference**
HIV prevention programme			
HIV vaccine*	-	12	(164)
Vaccine delivery per dose*	Gamma	17	(638-642)
Existing prevention programme (incl. HR)	Gamma	65	(639-643)
HIV counselling and testing (HCT) (per test)	Gamma	23	(639, 640)
Cost of HIV rapid testing	Gamma	1	(639, 640)
Current HIV programme (annual costs)			
Asymptomatic treatment (not on ARV)	Gamma	131	(247, 643)
Symptomatic treatment (not on ARV)	Gamma	137	(247, 643)
AIDS treatment (not on ARV)	Gamma	182	(247, 643)
Patient on ARV (average)	Gamma	424	(247, 644)
ART cost (annual)			
First-line regimen	Gamma	10	(644)
Second-line regimen	Gamma	27	(644)
Third-line regimen	Gamma	173	(644)
Laboratory costs (annual)			
First-line regimen (first year)	Gamma	17	(247, 643)
First-line regimen (subsequent years)	Gamma	46	(247, 643)
Second-line regimen	Gamma	46	(247, 643)
Third-line regimen	Gamma	92	(247, 643)
Not on ARV	Gamma	65	(643)
HPV-related disease	**Distribution**	**Value**	**Reference**
HPV prevention programme			
Cervical screening	Gamma	82	(640, 643)
HPV vaccine	-	17	(645)
Vaccine delivery per dose*	Gamma	17	(638, 640)
Treatment costs			
HSIL	Gamma	942	(130)
Cervical cancer	Gamma	7329	(130)

*Annexure A outlines the costing structures used

4.1.3 Health care

HIV: The study assumed global uptake of voluntary HCT services offered in the school programme. The uptake of ART was considered 29% (300). The programme was delivered as an out-patient service with the number of annual visits directed by the extent of disease (646).

HPV: At 13%, the uptake of cervical screening services has been poor and significantly lower than the anticipated screening target of 70% (92, 246). A sensitivity analyses was conducted at various coverage rates of vaccination achieved. Most lesions spontaneously regress, but in some, the HPV disease has a protracted latent phase (10-20 years) and disease manifestation commonly occurs several years after initial infection (647, 648). As the study adopted a lifetime horizon, the treatment costs of clinical disease were calculated with and without the HPV vaccination.

The parameters are shown in Table 14.

Table 14. Health care parameters used in the modelling process

Underlying principles adopted into the economic evaluation. The same set of parameters was applied to all models. The values in Table 14 were drawn from the South African literature for 2012.

Parameters	Value	Reference
Health care		
Cervical screening	13.60%	(92)
ARV uptake	29.00%	(300)
HPV treatment	35.30%	(250)
Reduction in disease progression with ART	46.00%	(649)

4.1.4 Vaccine characteristics

HIV: The HIV vaccine described is hypothetical. The vaccine that was assessed represents the target product profile of the P5 and embodies the minimum characteristics that would recognise the vaccine as a potential candidate for licensure. An annual booster was included in the analyses given the documented waning of vaccine protective effect documented in the RV144/Thai trial 12 months following vaccine administration (339). While it is anticipated that the booster vaccination would afford duration of protection exceeding a year, the annual booster (for the purposes of this study) represents merely an overestimation of costs than if the booster were administered less frequently.

HPV: The bivalent HPV vaccine has been used in this analysis, despite the availability of a quadrivalent vaccine (in South Africa) and the American Food and Drug Administration (FDA) approval of the use of the nonavalent (nine valent) vaccine – both of which covers additional serotypes. The bivalent vaccine has already been introduced as part of the national government programme to deliver HPV vaccines to school-going adolescents and these analyses would project the potential health outcomes of this programme (650). Further, the majority of the South African cervical cancer disease burden (64%) can be attributed to the HPV 16, 18 serotypes contained in the bivalent vaccine, thus justifying the its use (92). The analysis was intended to assess the health impacts of an extended coverage of the existing programme. The cost-effectiveness of the HPV vaccine is without question, but this cost-effectiveness has been widely limited to use in adolescent females only; and not in their male counterparts (281, 282, 284). The parameters are shown in Table 15.

Table 15. Vaccine characteristics used in the modelling process

Underlying principles adopted into the economic evaluation. The same set of parameters was applied to all models. The estimates were obtained from relevant South African literature for the year 2012.

Parameters	Value	(Range)	Reference
Vaccine characteristics			
Coverage	60%	(30 – 70)	assumption
HPV vaccine efficacy	70%	(45 – 99)	(274)
HIV vaccine efficacy	50%	(30 – 70)	assumption

4.1.5 Disease transitions

The HIV and HPV disease transitions had to be considered independently and in combination because of the well documented relationship existing between HIV and HPV (459, 463, 651, 652). The acquisition of each disease is enhanced in the presence of the other but also progresses more rapidly and aggressively (653-655). Primary data obtained from a cohort of HIV-infected adults from Soweto was analysed to quantify the degree of disease acquisition and progression when HIV-positive cohort attending a wellness clinic were routinely screened for cervical disease (51, 268). The HIV stages used in this model were guided by the WHO staging criteria and were documented as asymptomatic, symptomatic and AIDS defining (310). Every stage could potentially access ART and the treatment pool was sub-categorized into Regimens one, two and three. The transition probabilities among the HIV states and subsequently among the treatment regimens were obtained from the literature. Similarly, the HPV-related cervical disease was staged using the Bethesda Classification and annotated as normal, low-grade intraepithelial lesions (LSIL), high-grade intraepithelial lesions (HSIL) and cervical cancer (270, 656). Recurrences in HPV disease among HIV-positive individuals were known to occur and were accounted for in the modelling process. The parameters are shown in Table 16.

4.2 CURRENCY, DATE AND CONVERSION

All costs were reported for the year 2012 as this was the most recent year that a substantial amount of the costing and epidemiological data could be acquired for. The average exchange rate for the South African Rand (ZAR) to the United States dollar (US$) was applied. Costs were converted into the equivalent value for the 2012 US$ where (US$ 1 = ZAR 8.21) allowing for international comparison (Table 13: Economics) (591). The WHO CEA recommends the use of the health component of the GDP deflator to adjust costs to a common year, but also endorses the use of the consumer price index (CPI) (537). The key difference between the concepts are that the GDP Deflator reflects prices of *all goods and services currently produced within the country*, whereas the CPI reflects the prices of a *representative basket of goods (fixed) and services purchased by the consumers.* Comparatively speaking, the CPI represents an incomplete aggregate measure but does actually account for 60% of the economy's production that is purchased by most urban users (657). Costs were inflation adjusted to the year 2012 using the CPI. As South Africa has not determined a WTP threshold, the GDP value of US$ 7 508 (ZAR 61 641) per QALY gained was adopted. The use of the GDP concept, which finds its roots in the value of statistical life literature, was intended to represent the value of each additional *healthy* year accrued (587). The use of GDP per capita as the threshold value of effectiveness in Chapter 6 against the outcome measure of cost per LYG was considered justified considering there are no other definitive indications of cost-effectiveness in South Africa.

Table 16. Transition probabilities showing annual disease progression risk

Disease transition from one health state to the next is shown in Table 16. The estimates were drawn from the South African literature for 2012.

Parameter	Distribution	Estimate	Reference
HIV-related			
Change in HIV disease state			
Asymptomatic to symptomatic	Beta	0.32	(658)
Symptomatic to AIDS	Beta	0.20	(659)
AIDS to death	Beta	0.21	(658)
Change in drug regimens			
First-line to second-line	Beta	0.10	(659)
Second-line to third-line	Beta	0.01	(660)
Dual disease			
HIV-negative			
Development of LSIL	Beta	0.03	(651)
Progression of LSIL to HSIL	Beta	0.02	(651)
Progression of HSIL to cancer	Beta	0.04	(250)
Cancer mortality	Beta	0.11	(636)
HIV-positive			
HIV incidence in general population	Beta	0.02	(97)
HIV incidence in HPV disease	Beta	0.05	(651)
Development of LSIL	Beta	0.14	(51, 268)
Progression of LSIL to HSIL	Beta	0.06	(51, 268)
Progression of HSIL to cancer	Beta	0.08	(651)
Cancer mortality	Beta	0.60	(661)

5. MODEL BASED ECONOMIC EVALUATION

5.1 CHOICE OF MODEL

Markov models were used to represent the study structures. Semi-Markov models, in particular, were chosen as it allowed for the addition of tunnel states to counter the ‘memoryless’ nature of the Markov model and also allowed for recurrent disease to be modelled. The models were designed to reflect reality as closely as possible. The models were run over a 70 year time period, congruent with the current South African life expectancy. The cycle length adopted was a year.

Model 1 was used for Objective 1 and is depicted in Figure 15. The model examined the impact of HIV vaccination alone (intervention) on the South African school-going adolescent population and the outcomes were stratified by gender. The vaccine was offered voluntarily to the adolescents aged nine years or older. The model consisted of eight health states. Individuals entered the model HIV uninfected and healthy (State 1). They then transitioned into a vaccinated (State 2) or unvaccinated (State 3) state depending on the coverage rate. Individuals in either of these states could enter into the asymptomatic HIV state (State 4). This is represented by the oval shape to emphasize that this is a primary endpoint. From an asymptomatic state, the disease of individuals may develop into a symptomatic (State 5) or AIDS (State 6) state. Once individuals were HIV-infected, they could advance into the ART pool where treatment could be accessed (State 7). The treatment pool was divided into first, second and third line ART regimens, each with a possibility of progressing to death. Each previously mentioned health state could progress to death with different transition probabilities (State 8). During each cycle, an individual could remain in the current health state or progress to another. The arrows delineate the transition probabilities between the states. Costs and utility measures were then added to each health state and the model was able to predict costs and QALYs over the 70 year period for the intervention and the comparator. Event rates were considered the same for both arms of the study once the vaccine had been stopped.

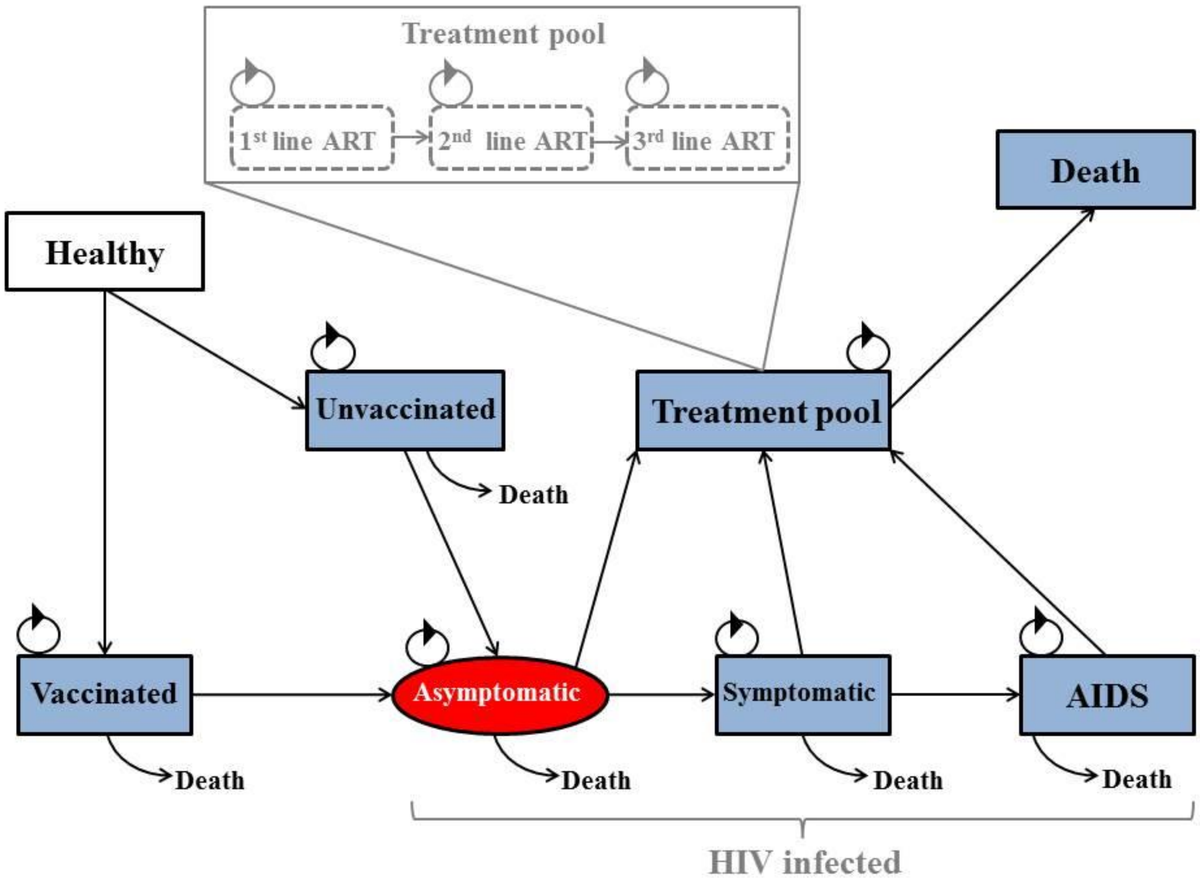

Figure 15. The semi-Markov model of the HIV vaccination strategy (Model 1)

Vaccinated and unvaccinated individuals may acquire HIV infection and transition to the HIV-positive state. Once HIV infected, individuals may transition to the accessing ART (treatment pool). Any states may transition to death but at a rate specific to that health state.

Model 2 was used for Objective 2 and is depicted in Figure 16. The model examined the impact of dual HIV and HPV vaccination among adolescent females in a school-based programme. The model accounted for the interaction of one disease in the presence of another (i.e. HIV risk was increased in the presence of HPV disease vice versa). The dual vaccination programme was offered to school-going girls aged nine on a voluntary basis. Model 2 was more complicated than Model 1 as it allowed for the interaction between the two disease states. Several health states were used to construct the model. All individuals were considered healthy and disease free at the start of the model. A proportion of these healthy individuals would be vaccinated against HIV and HPV disease, and the rest would remain unvaccinated. Each year, these healthy individuals were exposed to the risk of acquiring each disease. The two diseases could not to be acquired simultaneously in a single year due to the model construct. Healthy individuals could develop HPV disease starting from LSIL to HSIL which may then progress to cervical cancer. At each HPV-related health state, an individual may die (not represented graphically) or become HIV-infected (in which case they would progress on the lower HIV-positive spectrum). HIV-positive, HPV-infected individuals that were treated for HPV disease could potentially develop recurrent HPV disease. This state of recurrence can effectively be displayed by the semi-Markov model. The model allowed for females with HPV disease both treated and untreated to acquire HIV disease. There was a higher probability of transition to more serious HPV states among the HIV-positive vs. the HIV-negative individuals. All individuals who were HIV-positive could enter the HIV treatment pool. Every health state, including the healthy individuals without HIV or HPV disease, could progress to death at rates dependent on their current health state. These mortality transitions were excluded from Figure 16 as they rendered the model excessively 'bushy' and concealed the key message the diagram was intended to convey. The arrows represented the transition probabilities from one state to another. Costs and utility measures were then added to each health state and the model was able to predict costs and QALYs over the 70 year period for the intervention and the comparator. HPV vaccinated individuals were considered to have lower event rates than the HPV unvaccinated individuals once the HIV vaccine administration was stopped. The protection conferred by the HPV vaccine was considered lifelong (662).

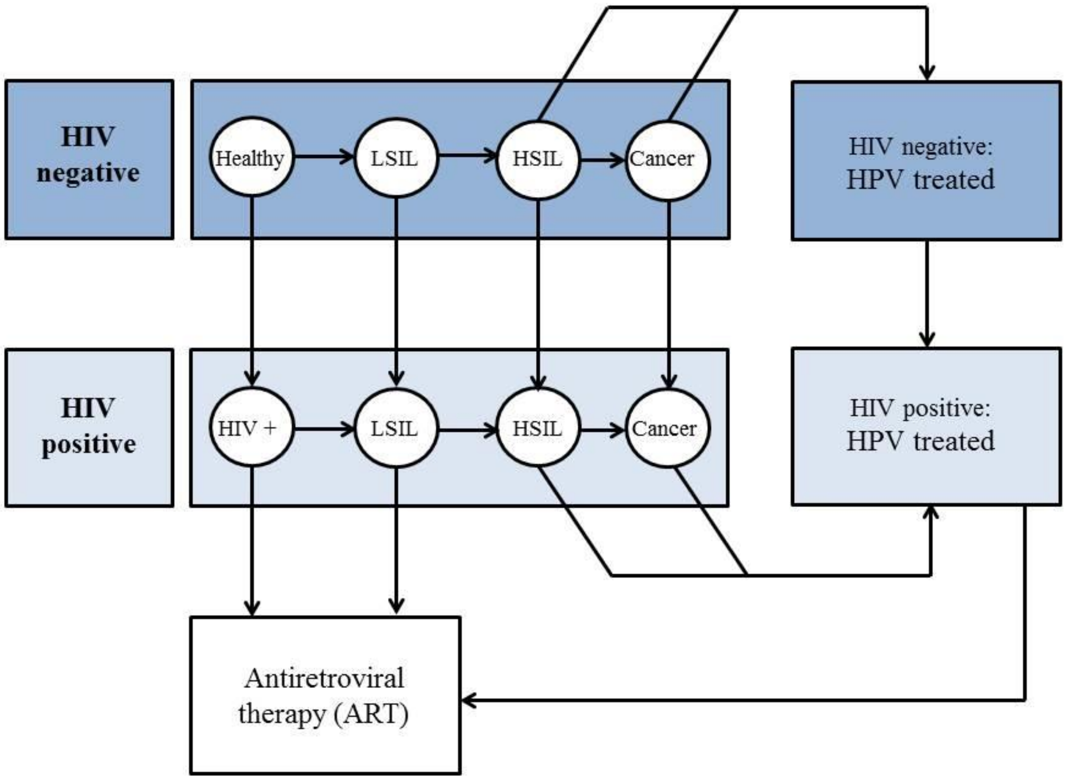

Figure 16. The semi-Markov model of the dual vaccination strategy (Model 2)

Vaccinated and unvaccinated individuals can remain uninfected or develop either HPV or HIV disease. Those developing HPV disease remain at risk of HIV disease if unvaccinated against HIV. Every state may progress to death during any cycle, though the transition probabilities differ depending on the disease state. (LSIL – low-grade intraepithelial neoplasia; HSIL – high-grade intraepithelial neoplasia)

5.2 MODEL ASSUMPTIONS

Participants were assumed to enter the model prior to their sexual debut. The rationale for this was self-explanatory in the case of the HIV vaccine, the HPV vaccine was shown to have no effect on prevalent infection or disease (252). This assumption must be considered in the light of the high incidence of non-consensual sexual acts among young children in South Africa (254). Where two HIV prevention strategies were being considered, the efficacy of the strategies were considered multiplicative (625) as there is rarely evidence available from clinical trials reporting the efficacy of two prevention interventions that were simultaneously introduced. In the case of the dual vaccine strategies, the interventions effects were implemented separately as the interventions impact in different transition probabilities. Individuals were exposed to the risk of both diseases during each cycle but could only acquire a single condition per year. Once *disease 1* was acquired, the rate of acquisition of *disease 2* was adjusted accordingly. This was to ease the computational burden of the model. The model assumed that all nine year old children that were eligible for schooling were indeed attending school, and that consent was obtained from parents and was reflected in the coverage rates. The model assumed global uptake and provision of HCT in the school environment as stipulated by the national policy (295). Despite the generally poor uptake of cervical screening services (17, 92), it was assumed that those diagnosed with LSIL would return for repeat assessments given the convenience of attending a school health service. Adolescents have long suffered poor access to health care services. Despite being issued in 2012, the ISHP has not been as widely implemented as expected, and the administration of the HPV vaccines has been limited to quintile one and two schools under the assumption that learners attending higher quintile schools would access these vaccines privately (650). The quintile refers to ‘a system of ranking and funding schools which takes into account the socio-economic circumstances of learners. The intended objective is to ensure that public funding is skewed in favour of the poorest learners’ (153). The modelling exercise assumed the national roll-out of the dual vaccination strategy under the auspices of an established school-based programme providing comprehensive health care services to all quintiles of learners. Lastly, the model assumed favourable uptake of school-based health services as the service was provided in the familiar and non-prejudicial school setting without there being any encroachment on school attendance. There has been no formal pilot studies of school-based health services conducted and thus the validation of this assumption remains speculative.

5.3 ANALYTICAL METHODS

5.3.1 Model construct

The model was constructed in Microsoft Excel (Version 2010). In the deterministic model, each health state was represented by a column. All individuals were initially considered disease free, and started in this state. The age of entry into the model was nine years. This was chosen on the premise that it preceded any sexual activity, and that the cohort was considered sexually naïve.

The vaccines considered were preventive vaccines and disease exposure prior to vaccine administration would serve to 'diminish' vaccine efficacy (252). A Markov trace was developed to map the proportions of patients that are in any health state at any given time. The number of individuals in a health state was calculated by multiplying the numbers in the health state of the previous cycle by the transition probability. Each health state was assigned to a column and the sum of all the columns in a row equalled the total cohort number. Each row represented an annual (yearly) cycle where an individual ages by one year, may potentially move between health states or remain in the current health state. The transition matrix was then developed to represent the transition probabilities of the states in the columns to the state in the rows. The entire model is populated using this transition matrix. The simple Markov model developed in this evaluation was extended by relaxing the Markov assumption. Memory was built into the model by adding additional health states, which served as a type of time-dependency by have differing costs and health-related quality-of-life estimates dependent on where in the model the patient lies. For example, the costing, HRQOL and mortality parameters would differ depending on whether an individual was on first, second or third line ART regimens as opposed to a general HIV treatment pool.

5.3.2 Building a Markov model for standard of care

The proportions of the cohort that were in any of the 'alive' states were summed per row and collated in a separate column to give the total life years accumulated in that year of life. The QALYs were then calculated by multiplying the health state quality weight by the number of people in that particular health state in each row. Additionally, the sum per row was discounted by the pre-determined discount rate. Costs were applied per health state and summed by row to estimate the cost per cycle. This was the cost per state multiplied by the number in that state. Standard discount rates were applied to all costs.

A fully probabilistic model was used to account for the inherent uncertainty in the input parameters. The effect of this uncertainty on the output measures of cost, effect and cost-effectiveness were further explored. Patient characteristics (including age and gender) and the discount rates were not subject to uncertainty and remained deterministic in the model. The model was able to switch from a deterministic to probabilistic state using the IF(…) command.

5.3.3 Parameter distribution

The lognormal distribution was used for relative risk (RR). The appropriate log mean and log standard error were calculated using the RR quoted in the literature and its corresponding 95% confidence interval. Finally, the model parameter was determined by taking a random draw from the normal distribution using the log mean and log standard error calculated. This value was then exponentiated to give the lognormally distributed RR. The disease transition probabilities were represented as beta distributions. These were applicable to bivariate decision probabilities and were fitted to the metric of number of events observed (e.g. patients on treatment) and the complement thereof (e.g. total patients – patients on treatment). The BETAINV(…) function was used to generate a random draw from this distribution. Microsoft Excel does not contain a construct for the Dirichlet distribution (multivariate probability distributions) and this function was programmed independently. The method entailed normalizing a draw from three independent single parameter gamma distributions, where a single parameter represented the number of events (α) (470). A single parameter gamma distribution has the beta value set to 1, hence gamma (α, 1). Gamma distributions were assigned to costs. As some costs were estimated by ingredients based costing and some referenced from the literature, there was little information available on variances in cost. In such cases the assumption can be made that the standard error of costs was equal to the mean (470). Using the values for the standard error of costs and mean (μ), the parameters of the gamma (α, β) are solved where:

$$\alpha = \mu\,(\alpha + \beta) \qquad \text{(Eq. 11)}$$

$$\beta = \alpha.\frac{(1-\mu)}{\mu} \qquad \text{(Eq. 12)}$$

$$\bar{\mu} = \frac{\alpha}{\alpha+\beta} \qquad \text{(Eq. 13)}$$

Using α and β values that were calculated and the GAMMAINV(…) function, a random draw is generated from the gamma distribution to populate the model.

5.3.4 Analysing and presenting simulation outputs from probabilistic models

The model analysis involved the distribution of the hypothetical cohort of adolescents into the initial health states, as regulated by the transition probabilities. With each cycle, the cohort is redistributed among the health states by the transition probabilities. Once the transitions into and out of the each health state had been finalised, the outcomes for each cycle was assigned. The outcomes were the costs and life years that were adjusted by utilities to derive QALYs. The process was repeated by the prescribed number of cycles (the lifetime horizon) and the outcomes were added to produce totals. The Markov models were then further analysed using a Monte Carlo simulation which is a multi-way sensitivity analysis in which the specified variables in the model were varied simultaneously (663). In the Monte Carlo simulation, the values for each variable was chosen randomly from the pre-defined distributions discussed. The model was run 1000 times (parametric bootstrapping), each time using a different set of values for each variable to generate a probabilistic trial. A complete picture of the probable results of the analysis was then given by the 1000 probabilistic trials drawn from the Monte Carlo simulation.

5.3.5 Exploring uncertainty

Once the 1000 probabilistic trials of the model were drawn, the incremental cost (ΔC) and effect (ΔE) for each trial of each arm (intervention and comparator) was calculated. One thousand bootstrapped effect and cost differences were then plotted on the cost-effectiveness plane. Once the probabilistic results were obtained, the confidence intervals for the ICER were calculated using the CEAC as it circumvented the problems that arose when the uncertainty estimates cover all four quadrants of the cost-effectiveness plane. The threshold ratio (λ), defined as 'the maximum acceptable WTP for a health gain' (664), was used to calculate the mean NMB in terms of the comparator, intervention and incremental costs (Equation 14):

$$\mathrm{NMB} = \lambda . \Delta \mathrm{E} - \Delta \mathrm{C} \qquad \text{(Eq. 14)}$$

Where λ is the WTP, ΔE is the effect (QALY) and ΔC represents the cost.

The most cost-effective option would have the greatest average net-benefit. Using the IF(…) function, an indicator variable was generated to determine if the comparator or intervention was the most cost-effective for each trial where 1 would indicate cost-effectiveness and 0 if it was not. A positive incremental net benefit result for the intervention indicates cost-effectiveness. The proportion of the simulation trials tallied in the intervention group represents its possibility of being cost effective given the threshold value (λ). A macro was then developed to change the threshold values (λ) and record the corresponding results relating to the intervention and comparator. These values were then plotted as the intervention and comparator curves on the CEAC. When several interventions were being compared, the CEAC was unable to determine which represented the optimal option (583). It was inevitable that the effectiveness and costs of health care programmes were subject to uncertainty. Apart from using the PSA mentioned, the CEAC was constructed to quantify and graphically represent uncertainty in this model.

5.3.6 Model life-table analysis

Model life-table analysis was used to explore Objective 1. The multi-state life-table described the differential mortality and morbidity of the model population under different interventions (600, 665). This work comprised two model life-tables: the reference population with HIV and/or HPV associated mortality of the South African adolescent population under the current treatment strategies and the second table where the adolescent population was exposed to the vaccine interventions. Disease associated deaths were drawn from the literature as described in Tables 11 and 15. National mortality data was used to determine the disease related mortality in the standard model life-table (as shown in Equation 15):

$$M_{tot} = M_{dis} + M_{other} \qquad \text{(Eq. 15)}$$

Where M_{tot} = total mortality determined in the age / sex group, M_{dis} = *mortality* attributed to the disease state and M_{other} = *mortality* attributed to all other causes.

The prevalence estimates for HIV was obtained from South African National HIV Prevalence, Incidence and Behaviour Survey, 2012 and for cervical cancer from the Human Papillomavirus And Related Diseases Report: South Africa (92, 97). The relative reduction in HIV-related mortality directly attributable to the intervention was calculated using the ratio between the comparator and the intervention (reflected in Equation 16). This reduction was used in the model life-table analysis and allowed for comparisons to be made including the life expectancy, numbers of individuals surviving and the cumulative years lived.

$$RR_m = \frac{M_i}{M_c} \qquad \text{(Eq. 16)}$$

Where RR_m = mortality risk reduction, M_i = mortality risk (intervention group) and M_c = mortality risk (comparator group).

Values entered into the model life-table determined the intervention impact on the number of life years gained and calculated the effect on life expectancy. Life tables are generally constructed to evaluate the mortality within an population and to determine the life expectancy as calculated from birth (600). The calculated life expectancy defined by the following formula (665):

$$e_x = \frac{T_x}{l_x} \qquad \text{(Eq.17)}$$

Where e_x = life expectancy at age X, T_x = cumulative person years lived after age X and l_x = individuals alive at beginning of age X.

The ICER calculation integrated the difference in cumulative years lived after 19 years of age between the intervention and comparator groups. The outcome measure of life-tables is the concept of years of potential life lost (YPLL). The YPLL estimates the average time a person would have survived had they not died prematurely. The measure serves to quantify social and economic loss attributable to premature death, particularly among specific causes of death affecting the younger age group. The YPLL combines the age of death and mathematically weights the deaths by assigning values to death at each age (666).

6. PROJECT MANAGEMENT

I conceived the study in consultation with Dr Bertram and Prof Gray. I then developed the model and sourced the parameters from the available literature. Dr Bertram provided guidance and supported the co-ordination of the study. I conducted the statistical analysis, with regular input from Dr Bertram. I was responsible for the overall drafting of the dissertation and the manuscripts. All authors contributed significantly to critically revising the content. All authors read and approved the dissertation and final manuscripts prior to submission.

7. ETHICAL CONSIDERATION

Ethics approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Annexure B).

8. CONCLUSIONS

The economic evaluation used Markov modelling and PSA to determine the cost-effectiveness of the HIV and HPV vaccine strategies implemented in a school-based programme. The model was based on South African disease and costing parameters. The model was explicitly explained. South African ART practices were compared to the HIV vaccine alone and then in combination with the HPV vaccine. The vaccine interventions were then compared to other pre-existing biomedical interventions. There is also a broad spectrum of costs associated with the interventions. While each of the interventions was likely considered efficacious, the level of cost-effectiveness varies, as does the uncertainty surrounding the input parameters. The outcomes were considered in terms of the number of new infections and deaths averted. Lastly, ethical consideration for the study was obtained from the University of the Witwatersrand.

CHAPTER 5

RESULTS: THE CASE FOR ADOLESCENT HIV VACCINATION IN SOUTH AFRICA: A COST-EFFECTIVENESS ANALYSIS

1. INTRODUCTION

South Africa remains the epicentre of the HIV pandemic with 18% of the global HIV prevalence concentrated within its borders (300). There have been worldwide reductions in HIV prevalence reported but these gains are being threatened by the sub-epidemics of HIV disease persisting among the historically vulnerable young women and adolescents of SSA (285). The South African literature clearly demonstrates the disproportionately high disease burden among women aged 15-24 years where a fourfold increase in HIV prevalence is apparent (97). Males are also at risk though. South African society is marked by early sexual debut among both males and females that has been linked to the realities of forced sex and intergenerational relationships which greatly increases the risk of HIV infection (99).

South African has countered the burgeoning HIV burden by improving HIV treatment and prevention access focussing on expanding condom distribution (298), increased coverage of VMMC (667) and by offering national HIV testing and improving the coverage of ART (299). The Joint United Nations Programme on HIV/AIDS (UNAIDS) has however reported that South Africa accounted for 16% of global HIV incidence in 2013 and still had a 58% deficit in ART delivery (294, 300). Vaccines are widely considered the most cost-effective intervention in health care (668). In Thailand (2009), Rerks-Ngarm et al. released the results of the first HIV vaccine regimen (RV144/Thai trial) to demonstrate vaccine efficacy in human subjects (339), negating several earlier setbacks experienced in HIV vaccine trials (337, 342). The study evaluated the use of two priming injections of a recombinant canarypox vector (ALVAC-HIV[vCP1521]) administered at weeks 0, 4, 12 and 24. Boosting injections of recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E) were then administered at weeks 12 and 24. The result was a conservative efficacy of 31% over 3.5 years. However, rapidly waning immunity in the first year, raised speculations about the need for subsequent booster injections (339). Apart from changes to the protein and adjuvant, the HIV vaccine regimen was additionally modified to Clade C before entering South African clinical trials (Phase 1) at six key sites under the umbrella of the HVTN 100 study (345). Introducing the HIV vaccination strategy into the EPI would have far-reaching financial implications but still present a key advocacy tool to decision-makers should this vaccine become available (669, 670). Evaluating the long-term impact and cost-effectiveness of a HIV vaccine strategy hinges on where in the health system the vaccine is introduced. The delivery of vaccines to adolescents via a SRH platform at school has strong associations with improved vaccine coverage rates (669-671). South African HIV prevention strategies have enjoyed limited successes as high HIV incidence rates still prevail (300). Future expansion of the ART programme is a viable option but requires a substantial injection of financial and human resources to ensure sustainability (672). It is based on this understanding that the national government prioritized the development of a SRH platform at school level targeting primary HIV prevention strategies among adolescents as a key stream of restructuring PHC in South Africa (154).

The study aimed to determine the cost-effectiveness of implementing school-based HIV vaccination as an HIV prevention strategy in the public sector. The analysis sought to determine how the vaccine and programme characteristics potentially impacted the cost-effectiveness by conducting sensitivity analysis.

2. METHODS

The study methods complied with the reporting guidelines of the CHEERS statement (618).

2.1 STUDY OVERVIEW

The study population was nine year old children attending South African schools in 2012; that accepted the vaccine on a voluntary basis. The introduction of the vaccine intervention were in line with the plans of the national health department to develop school-based SRH services (154). The learners were to be targeted prior to the onset of sexual activity to circumvent any potential exposure to HIV. The study population was then modelled through a 70 year life expectancy which was congruent with the current South African life expectancy (637). The vaccine strategy would be school-based, with the vaccines potentially integrated into the EPI offered in the South Africa. The study adopted the provider perspective to gain insight into health service delivery and delineate the financial implications of the new intervention being introduced into the public health care sector. Finally, the provider perspective allows us to generate health information that could potentially guide national health planning. The HIV vaccine regimen being administered in the South African studies (HVTN 100) was used as the HIV prevention intervention that would potentially impact the HIV-associated mortality and burden of disease. The vaccination intervention was considered against the current standard of care in South Africa (viz. HCT, the national ART roll-out campaign, the distribution of condoms and the treatment of STIs) (247). It is vital to remember that the intervention comprised the vaccination strategy in conjunction with all the components of the standard of care, as the vaccine strategy would never be considered as a stand-alone programme while people were still accessing ART. Economic costs and health outcomes were discounted at a rate of 3%, with an uncertainty range of 0-6% explored, in keeping with the recommendations of the WHO-CHOICE guidelines (537).

2.2 OUTCOME MEASURES

The QALY was used as the outcome measure to compare the HIV vaccine intervention with the standard of care. The QALY serves as a standardized measurement from comparative effectiveness research that incorporates a quality of life "utility score" adjustment applied to life expectancy (673). The QALY allows for mortality and morbidity estimates in a single outcome measure, allowing for comparability across studies (105). The outcomes are then used to calculate the ICER. The ICER thus calculates the difference in costs between the strategies and the difference in effects (e.g. QALYs) between alternative interventions (Equation 18). The ICER was measured in US$ per QALY gained.

$$\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \qquad \text{(Eq. 18)}$$

Where C_1 and E_1 = costs and effects of the comparator, and C_2 and E_2 = the costs and effects of the intervention.

The HIV vaccine modelled was hypothetical. The vaccine characteristics considered in this model (Table 17) were suggested by the product description defined by the P5, a diverse collaboration of organisations founded under the Global HIV Vaccine Enterprise to promote research based on the foundation of the RV144 trial and to draw collaboration globally to assess HIV vaccine candidates going forward (372). The regimen assessed used the ALVAC prime ALVAC/gp120 boost of the RV144/Thai trial with the introduction of an additional booster at month 12. The purpose of the booster was to enhance the diminishing immune response described after 12 months in the Thai trial. Should the vaccine induce adequate immunogenicity, it will be entered into landmark Phase IIb/III HIV vaccine efficacy studies (provisionally scheduled for South Africa in 2016) called the HVTN 702 study.

The estimated vaccination coverage was considered at 60% receiving the initial course, representing a guarded estimate on the 68% coverage achieved for the 3rd dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine (DTP3) (674). The DTP3 coverage has been globally adopted as a proxy for immunisation system strength (performance) as it has been available in most countries in the recent decades (675). Vaccine coverage was then explored in the sensitivity analysis. The HIV vaccine was assessed at the cost of US$ 12 per dose (base-case), had a 50% vaccine efficacy and a 10 year duration of protection (including annual booster injections). The impact of diminishing immunity demonstrated in the RV144/Thai trial (12 months following vaccine administration) prompted the inclusion of the booster vaccinations. This declining immunity was addressed in the economic evaluation by adopting a conservative approach of annual boosters. While this may not be the most practical option, in the context of an economic evaluation it merely translated into a marginal cost overestimation. The HIV vaccine priced at nearly US$ 12 roughly approximated the public sector HPV vaccine price (US$ 17). Markedly reduced vaccines prices were considered justified by the overwhelming HIV disease burden in the country and by weighing up the sensitive issues of accessibility and coverage. Additionally, the prices were deemed attainable considering the success achieved in negotiating lower priced ART and HPV vaccines in the public sector (644, 676). The pricing structures were tested in the sensitivity analysis.

The utility of HIV-related interventions was derived from a meta-analysis of the pooled utilities relating to HIV/AIDS (633). The utility weights for both diseases appear in Table 17.

Table 17. HIV characteristics and disease utility weights adopted

Parameters	Estimate	(Range)	Reference
Vaccine characteristics			
Coverage	60%	(40 – 70)	assumption
HIV vaccine efficacy	50%	(31 – 70)	assumption
Utility weights			
Full health	1		
HIV disease			
Asymptomatic	0.94		(633)
Symptomatic	0.82		(633)
AIDS	0.70		(633)

AIDS - acquired immune deficiency syndrome, HIV - human immunodeficiency virus.

2.3 STUDY INPUTS

The model was parameterised using South African epidemiological data drawn from published literature to contextualize the study (Table 18). The disease transition probabilities between HIV disease states were also obtained from the relevant South African literature (Table 19). Statistics South Africa has consistently cited mortality figures for HIV/AIDS approximating 3% annually, despite unabated increases in deaths among young adults (677, 678). Further scrutiny suggested these figures underestimated mortality as several conditions known to be HIV/AIDS-associated (e.g. TB, parasitic diseases, infectious intestinal diseases) were reported as independent causes of death (679). The 2012 HIV/AIDS-related mortality rates were revised by Statistics South Africa in 2014 based on this inconsistency (637).

Table 18. Relevant South African HIV epidemiology

The table describes the relevant general, HIV-related and HPV-related parameters sourced from the literature. The estimates were drawn from the South African literature for 2012.

	Total		Male		Female		Reference
General							
Population	52 274 945	100%	25 453 074	48.7%	26 821 871	51.3%	(97)
Life expectancy	67.4	-	64.1	-	70.6	-	(637)
Mortality	1.48%	-	1.56%	-	1.42%	-	(637)
HIV-related disease							
Incidence	396 000	1.72%	145 000	1.21%	251 000	2.28%	(97)
Prevalence	6 422 000	12.2%	2 531 000	9.90%	3 873 000	14.40%	(97)
On ART	2 002 000	31.2%	651 000	25.70%	1 344 000	34.70%	(97)
Life expectancy	59.3	-	57.3	-	61.3	-	(637)
Mortality	1.69%	-	1.75%	-	1.63%	-	(637)
Related mortality	203 293	35.30%	-	-	-	-	(637)

ART - antiretroviral therapy, HIV - human immunodeficiency virus.

*generic epidemiological population estimates are given. Age-specific estimates were used in the calculations

Table 19. Transition probabilities showing annual disease progression risk

Disease transition from one health state to the next is shown in Table 19. The estimates were drawn from the South African literature for 2012.

Parameter	Distribution	Estimate	Reference
Health care			
ART uptake	-	29.00%	(300)
Reduction in disease progression with ART	-	46.00%	(649)
Change in HIV disease state			
Asymptomatic to symptomatic	Beta	0.32	(658)
Symptomatic to AIDS	Beta	0.20	(659)
AIDS to death	Beta	0.21	(658)
Change in drug regimens			
First-line to second-line	Beta	0.10	(659)
Second-line to third-line	Beta	0.01	(660)

ART - antiretroviral therapy, AIDS - acquired immune deficiency syndrome.

Relevant HIV-related cost components were extrapolated from the 2013 South African national HIV treatment guideline (247). While 2012 was considered the reference year for this study, the 2013 guideline was considered in this model as it included fixed-dose combination therapy (FDC). The FDC was important as it impacted the costing and proposed integrated health management of SRH conditions. The PHC nurses were presumed to deliver health services at schools, and would refer complicated cases upwards to doctors or medical specialists at clinics. Costs were inflation adjusted to the year 2012 using the CPI. The average exchange rate for the South African Rand (ZAR) to the United States dollar (US$) was applied. Costs were converted into the equivalent value for the 2012 US$ where (US$ 1 = ZAR 8.21) allowing for international comparison (591). HIV vaccination costs considered human resources, counselling (pre- and post HIV testing), HIV testing, delivery costs (e.g. needles and syringes) and storage costs (Table 20). The cost of laboratory tests were obtained from the National Health Services Laboratory. Human resource cost of medical personnel [derived from the Uniform Patient Fee Schedule (UPFS)] as well as pricing of medication, consumables and additional pharmaceuticals were obtained from the National Department of Health. These parameters are detailed in Table 21.

Table 20. Comparison of costs and components of the HIV vaccination programme

Detailed costs of the intervention compared to the standard of care. The intervention includes the vaccine intervention and the comparator costs. Costs are shown in US$.

Cost category	Per capita expenditure			
	Intervention	Standard	Difference	(% change)
Laboratory	**12.73**	**13.09**	**0.35**	**(-2.78)**
HIV rapid testing	1.06	1.41		
CD4 count	4.05	4.05		
Pap smear	1.13	1.13		
Viral load	5.95	5.95		
Creatinine	0.53	0.53		
Pharmaceuticals	**39.86**	**30.21**	**9.64**	**(+31.92)**
STI treatment	1.11	0.92		
Condom distribution	1.35	1.12		
Contraception	0.77	0.63		
Anti-retroviral therapy	27.34	27.34		
Vaccine	8.94	0.00		
Vaccine delivery*	0.15	0.00		
Bactrim® prophylaxis	0.20	0.20		
Human resources	**35.94**	**36.67**	**0.63**	**(-1.76)**
PHC nurse	20.70	22.24		
Counsellor	11.03	11.81		
Enrolled nursing assistant	1.68	0.00		
Medical officer	0.46	0.46		
Medical specialist	2.07	2.07		
Transport †	**0.47**	**0.00**	**-**	**-**
Total	**89.00**	**79.87**		

*Vaccine delivery includes the needle, syringe and alcohol swab for administration

†Calculated from average car rental cost incurred in providing a school-based service

HIV - human immunodeficiency virus, CD4 - cluster of differentiation 4 (T-helper cells); PHC - primary health care

Table 21. Economic considerations of the analysis

The estimates were obtained from relevant South African literature for the year 2012. Costs are in US$.

Economics	**Value**	**Range**	**Reference**
Cost	3.0%	(0 – 6%)	(537)
Outcome	3.0%	(0 – 6%)	(537)
International comparison (ZAR: 1US$)	ZAR 8.21	-	(591)
HIV disease related costs	**Distribution**	**Value**	**Reference**
HIV prevention programme			
HIV vaccine	-	12	(372)
Vaccine delivery per dose*	Gamma	17	(638-642)
Existing prevention programme (incl. HR)	Gamma	65	(639-643)
HIV counselling and testing (HCT) (per test)	Gamma	23	(639, 640)
Cost of HIV rapid testing	Gamma	2	(639, 640)
Current HIV programme (annual costs)			
Asymptomatic treatment (not on ART)	Gamma	131	(247, 643)
Symptomatic treatment (not on ART)	Gamma	137	(247, 643)
AIDS treatment (not on ART)	Gamma	182	(247, 643)
Patient on ART (average)	Gamma	424	(247, 644)
ART cost (annual)			
First-line regimen	Gamma	10	(644)
Second-line regimen	Gamma	27	(644)
Third-line regimen	Gamma	173	(644)
Laboratory costs (annual)			
First-line regimen (first year)	Gamma	17	(247, 643)
First-line regimen (subsequent years)	Gamma	46	(247, 643)
Second-line regimen	Gamma	46	(247, 643)
Third-line regimen	Gamma	92	(247, 643)
Not on ART	Gamma	65	(643)

ART - antiretroviral therapy, HIV - human immunodeficiency virus, HCT – HIV counselling and testing

*Annexure A outlines the costing structures used

2.4 MODEL-BASED ECONOMIC EVALUATION

Data was captured and analysed using Microsoft Excel® (Version 2010) (Microsoft Corp., Redmond, WA). Ersatz version 1.2 (www.epigear.com) was used to perform the uncertainty analysis. Ersatz is a boot-strap add-in application for Excel. The disease transition probabilities and the effectiveness of the interventions dictated the movement between health states (Figure 17). The semi-Markov simulation constructed showed annual cycles. The semi-Markov model specifically allowed for the addition of tunnel states. This countered the 'memoryless' nature of the Markov model. The study population started disease-free and was exposed to an annual risk of acquiring HIV disease.

The model examined the impact of HIV vaccination alone (intervention) on the South African school-going adolescent population and the outcomes were stratified by gender. The vaccine was offered voluntarily to the adolescents aged nine years or older. The model consisted of eight health states. Individuals entered the model HIV uninfected and healthy (State 1). They then transitioned into a vaccinated (State 2) or unvaccinated (State 3) state depending on the coverage rate. Individuals in either of these states could enter into the asymptomatic HIV state (State 4). This is represented by the oval shape to emphasize that this is a primary endpoint. From an asymptomatic state, the disease of individuals may develop into a symptomatic (State 5) or AIDS (State 6) state. Once individuals were HIV-infected, they could advance into the ART pool where treatment could be accessed (State 7). The treatment pool was divided into first, second and third line ART regimens, each with a possibility of progressing to death. Each previously mentioned health state could progress to death with different transition probabilities (State 8). During each cycle, an individual could remain in the current health state or progress to another. The arrows delineate the transition probabilities between the states. Costs and utility measures were then added to each health state and the model was able to predict costs and QALYs over the 70 year period for the intervention and the comparator. Event rates were considered the same for both arms of the study once the vaccine had been stopped.

One-way sensitivity analyses were used to evaluate the impact of single assumptions on cost and outcomes and PSA with a bootstrapping technique determined the uncertainty in the model and evaluated the robustness of the results. The PSA was characterized by a second order, 1000 iteration Monte Carlo simulation yielding a range of plausible values for lifetime costs, QALYs and ICER. The PSA results were used to calculate the 95% confidence interval around the model outcomes, and these results were represented in the form of the CEAC. South Africa does not have a pre-defined WTP threshold and the GDP per capita (2012) was used as a proxy in accordance with the WHO Guide to Cost-Effective Analysis (537, 680, 681). The WTP threshold was thus defined as US$ 7 508 (ZAR 61 641) per QALY gained.

Participants were presumed sexually naïve at the start of the model. The model assumed that all children eligible for schooling were attending school and did not account for the drop-out rates. It was also assumed that HCT services were universally available in the school environment and easily accessible as prescribed by the national policy (295). The modelling exercise considered universal access to the national roll-out of the HIV vaccination strategy under the umbrella of an established school-based programme; providing comprehensive health care to all quintiles of learners. Lastly, the model presumed favourable uptake of the school-based programme by the learners considering that it would be provided in a presumably familiar and non-prejudicial environment without compromising school attendance. This assumption has not been validated as no formal pilot studies assessing uptake of care have been published.

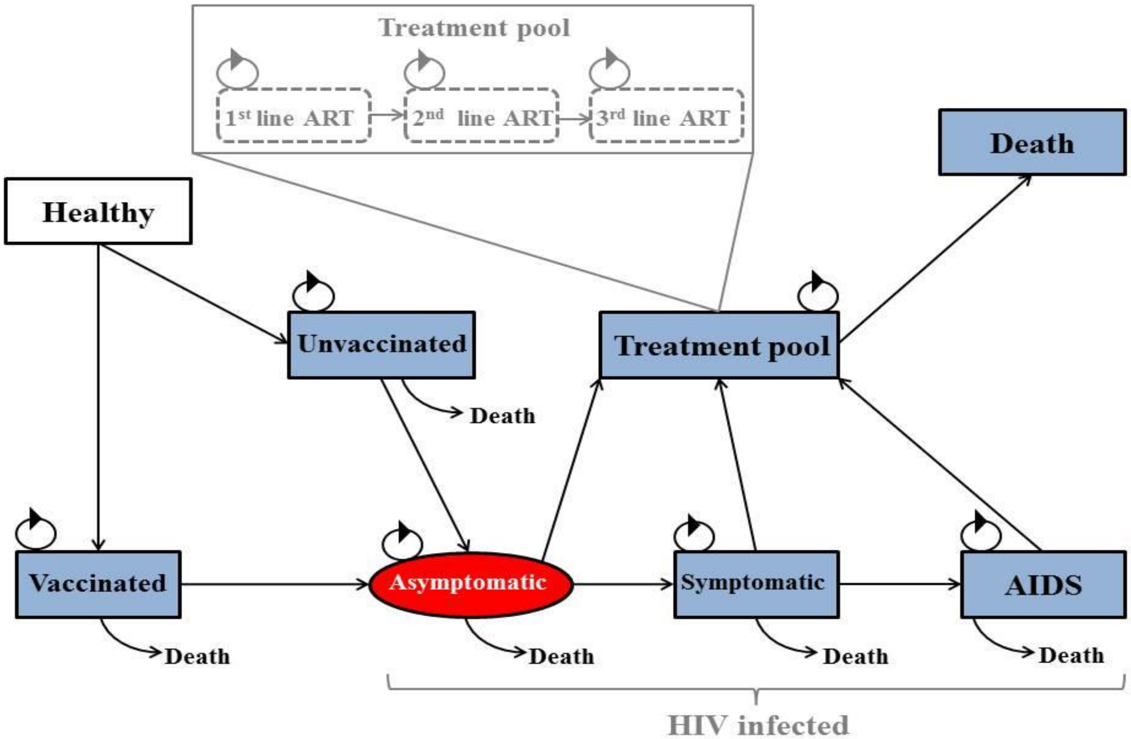

Figure 17. The semi-Markov model of the HIV vaccination strategy

Vaccinated and unvaccinated individuals may acquire HIV infection and transition to the HIV-positive state. Once HIV infected, individuals may transition to the accessing ART (treatment pool). Any states may transition to death but at a rate specific to that health state.

2.5 ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

3. RESULTS

3.1 COST-EFFECTIVENESS ANALYSIS

Table 22 shows the total costs and QALYs gained in the lifetime of the hypothetical cohort for HIV vaccine interventions. The introduction of the HIV vaccination in the general adolescent population resulted in the net cost of US$ 187 representing a nine percent increase in costs compared with the existing programme (which comprised no HIV vaccine prevention strategy). This translated to a gain of four QALYs and an ICER of US$ 43 per QALY gained (95% CI: US$ 39-47). The administration of the vaccine to females only yielded a 68% increase in QALYs gained to six (95% CI: 6-7) compared with administering to males only. The greater impact of the intervention among the female population was justified given their substantially higher burden of disease. Generally, the implementation of the HIV vaccine programme does represent an increase in total spending but with significant improvement in life-years.

Table 22. Cost-effectiveness of the HIV vaccine intervention

The vaccine programmes were compared with the standard of care (2012) which had no vaccination. All values are in US$.

	Vaccination program		Existing standard of care		ICER
	Cost	**QALY**	**Cost**	**QALY**	**per QALY gained**
Total	2341	9.47	2154	5.11	43.07
	(2222 – 2465)	(9.12 – 9.83)	(2030 - 2281)	(4.74 – 5.49)	(38.92 – 47.43)
Male	2043	8.27	1832	3.79	47.29
	(1935 – 2149)	(7.99 – 8.52)	(1725 – 1937)	(3.50 – 4.07)	(43.07 – 51.14)
Female	2628	10.60	2463	6.36	38.94
	(2479 – 2772)	(10.15 – 11.06)	(2306 – 2611)	(5.86 – 6.85)	(34.41 – 43.58)

Discount rate 3%. (95% uncertainty intervals).

ICER - incremental cost-effectiveness ratio, QALY - quality-adjusted life years.

3.2 SENSITIVITY ANALYSES

3.2.1 One-way sensitivity analysis

The one-way sensitivity analysis varies a single parameter to demonstrate its impact on the overall cost-effectiveness (682). Table 23 identified the improved ICER outcomes associated with increased duration of vaccine protection and lowered vaccine pricing strategies. The discount rate significantly influenced the cost-effectiveness with six percent discounting resulting in a 62% increase in the ICER value compared with 0% discounting. This was largely attributed to the investment for the intervention being made now (present costs) with benefits only being realised much later (future implications). Lastly the analysis proved that a partially effective vaccine or one that has coverage less than 50% would still prove cost-effective compared with the proxy WTP estimate considered for South Africa.

Table 23. Scenario analyses compared with base findings

One-way sensitivity analysis was done to systematically examine the impact of selected variables in the analysis by varying it across a plausible range of values with other variables remaining at their baseline level.

		Total	**Male**	**Female**
HIV vaccine – 3 years duration	Net cost	98.89	139.71	127.90
	QALYs gained	1.40	1.42	1.38
	ICER	70.67	98.25	92.84
HIV vaccine – 5 years duration	Net cost	104.11	159.99	137.28
	QALYs gained	2.27	2.32	2.23
	ICER	45.78	68.91	61.62
HIV vaccine price halved	Net cost	147.67	171.40	125.37
	QALYs gained	4.36	4.47	4.24
	ICER	33.90	38.30	29.59
Very low HIV vaccine price	Net cost	121.05	144.60	98.95
	QALYs gained	4.36	4.47	4.24
	ICER	27.79	32.31	23.35
Discount rate 0%	Net cost	128.03	162.96	99.31
	QALYs gained	4.18	4.33	4.04
	ICER	30.66	37.66	24.59
Discount rate 6%	Net cost	221.79	237.91	205.65
	QALYs gained	4.46	4.55	4.36
	ICER	49.73	52.24	47.16
Coverage 40%	Net cost	150.08	169.28	131.99
	QALYs gained	3.48	3.58	3.39
	ICER	43.07	47.29	38.94
RV144/Thai trial efficacy	Net cost	204.83	220.37	190.11
	QALYs gained	4.35	4.45	4.24
	ICER	48.07	49.47	44.82

HIV - human immunodeficiency virus, ICER - incremental cost-effectiveness ratio, QALY - quality-adjusted life year.

3.2.2 Two-way sensitivity analysis

Ideally, an intervention should be highly efficacious and affordable. The two-way analysis in Table 24 explored the effects of varying the vaccine cost and vaccine duration of protection on the ICER; under the optimized conditions of vaccine efficacy and vaccine coverage fixed at 70% each. Lower priced vaccines yielded more cost-effective results. Vaccines with a longer duration of protection (10 years) outperformed the shorter protecting vaccines (at five years or three years duration) irrespective of price.

Table 24. Two-way sensitivity analysis

Data based on assumed optimized coverage (70%) and vaccine efficacy (70%)

Vaccine cost*		**Cost per QALY gained by vaccine duration**		
Cost	**US$**	**3 years**	**5 years**	**10 years**
High	24	123.27	85.23	57.50
Medium	18	108.10	73.33	47.96
BASE	**12**	92.92	61.43	38.62
Low	6	77.74	49.53	29.27
Very low	2	67.62	41.59	23.05

*vaccine and vaccine delivery cost

QALY - quality-adjusted life year.

3.2.3 Probabilistic sensitivity analysis

Cost-effectiveness plane

The HIV vaccine programme implementation suggests improved health outcomes at a greater cost compared with the current standard of HIV care in the public sector. Bootstrapping analysis undertaken by repeated sampling (1000 iterations) estimated the uncertainty in model costs and effects (Figure 18). The majority of the iterations lying in the NE quadrant of the cost-effectiveness plane (an area of trade-off indicating greater health gain for added expenditure) raises the critical issue of determining how much a decision-maker is prepared to pay for an additional unit gain in health outcome. The limited vertical variation indicates limited variability associated with treatment costs. The reported ICERs for all three plausible interventions remained well below the WTP threshold and were thus deemed cost-effective.

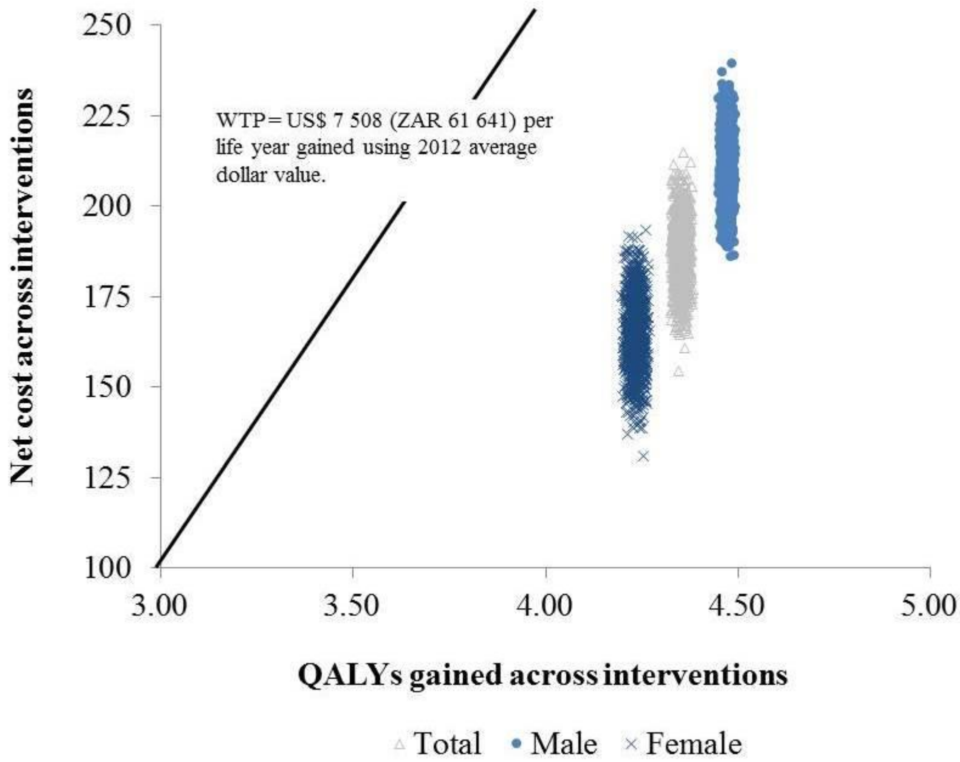

Figure 18. The cost-effectiveness plane

Costs and health outcomes are shown as a scatter plot in Figure 18. The values were generated from the probabilistic sensitivity analysis. The cost difference (ΔC) is the difference in costs between the comparator and intervention programme costs. The effect difference (ΔE) reflects the difference in health outcomes between the intervention and comparator effects. The unit of measure for the health outcomes are QALYs gained. All values falling below the WTP threshold indicated are cost-effective.

QALY - quality-adjusted life year, WTP - willingness-to-pay.

Cost-effectiveness acceptability curve

The CEAC (Figure 19) was constructed by calculating the probability that the intervention implemented in the general population represents the optimal choice across the 1000 simulations, for selected WTP governmental thresholds (x-axis: US$100 increments of cost per 1 QALY gained). The curve indicates the intervention to be cost effective, and supports the implementation of the vaccine programme as it has translated into improved health outcomes.

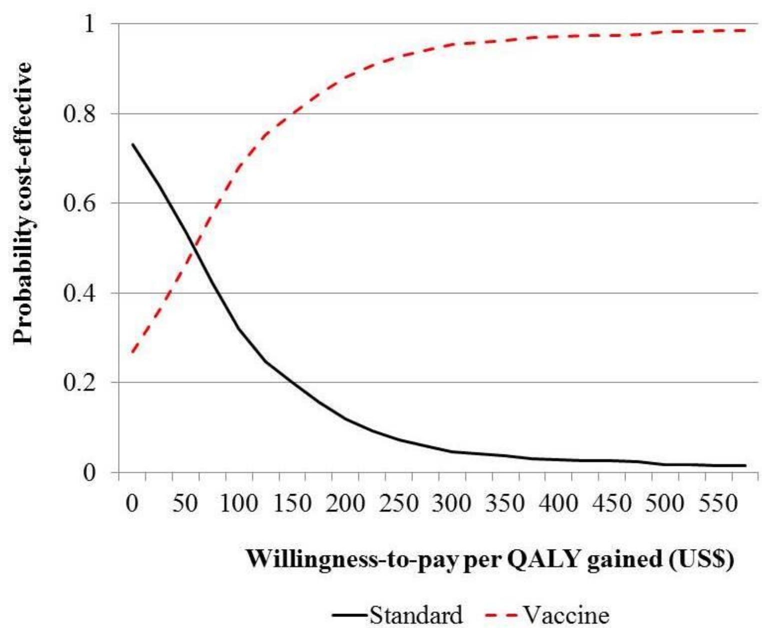

Figure 19. The cost-effectiveness acceptability curve

The CEAC shows the proportion of simulations that would be cost-effective (y-axis) given different threshold values of cost per QALY gained (x-axis). CEAC – cost-effectiveness acceptability curve, QALY - quality-adjusted life year.

4. DISCUSSION

This study evaluated the cost per QALY gained (expressed as the ICER) that was associated with school-based adolescent HIV vaccination services using a Markov modelling approach. The model, which was based on local costing data and transition probabilities derived from the literature, simulated annual cycles. These findings support that, even at relatively higher vaccine cost, the simultaneous implementation of the HIV vaccine programme in conjunction with the ART roll-out would prove cost-effective. These findings were validated by the cost-effectiveness plane and CEAC.

In the sensitivity analysis, the ICER was clearly sensitive to cost variations. Relatively lower prices were evaluated in the model as the South African government has successfully negotiated discounts with pharmaceutical companies in the past, notably with ART and HPV vaccines (644, 676). The impact of the effect that these discounts would have on cost-effectiveness is difficult to interpret as the discounts are frequently negotiated on volumes rather than prices (682). The cost-effectiveness was also particularly sensitive to variations in vaccine efficacy (683-685). In fact, even before the release of the RV144/Thai trial data, computer simulations of HIV transmission dynamics amongst South African adolescents already highlighted the significant role that a partially effective HIV vaccine could play (686). Work by Owens et al. concurred with this, illustrating that varying the degrees of vaccine efficacy for susceptibility, disease progression and infectivity still yielded substantial health benefits, even with only modestly efficacious vaccines (685). Based on the short-lived vaccine efficacy described by Rerks-Ngarm et al. (339), annual booster vaccinations were included in the study model. Booster vaccinations were not assessed in the RV144/Thai study, implying that the analyses of boosters in this evaluation remain hypothetical (339).

The two-way sensitivity analysis (Table 24) confirmed that HIV vaccines with longer duration of protection would provide more robust protection. Andersson did however caution against high numbers of booster vaccinations being required to maintain population coverage levels, despite having demonstrated significant impact on the South African epidemic when applying the RV144 vaccine using demographic projections (687). Modelling work with partially efficacious vaccines by Phillips returned similar health benefits in a southern African setting but offered no additional information on booster vaccinations (688). It should be borne in mind that the quadruple burden of NCDs, communicable, maternal and child health and injury-related disorders place insurmountable pressure on a restricted South African health budget (5), such that the implementation of a partially efficacious HIV vaccine requiring a series of several boosters should be weighed against the equity of scarce financial resource allocation.

These study findings should be considered in light of several limitations. The study considered heterosexual transmission of HIV only as there is a dearth of reliable data on same sex HIV transmission. Similarly, the study lacked more representative data on HIV risk and mortality profiles due to poor availability of data. Any potential benefit that may arise against disease acquisition and progression for vaccine recipients who become HIV-infected remains speculative. Importantly however, there were no significant differences documented between the vaccinated and unvaccinated arms of the RV144/Thai Trial participants who seroconverted in terms of viral load or CD4 T-cell counts (339). While the study assumed a high coverage rate (70%), it did not account for the potential benefits of herd immunity. The effect of herd immunity could play a major role in bolstering HIV vaccine coverage rates in a country where the childhood immunisation vaccine coverage rates fall significantly short of the required targets (674). The inclusion of herd immunity into the model could potentially equate to improved vaccine efficacy and cost-effectiveness. The analysis considered the provider perspective and not the societal perspective. South African health outcomes remain poor compared with similar middle-income counties despite the nine percent allocation of the country's GDP to health expenditure (3). While the nine percent expenditure exceeds the five percent recommendation of the WHO, middle-income countries such as Brazil report better health outcomes despite the same proportional expenditure (689). Vaccine implementation would significantly impact the health budget through direct medical costs implicated in the start-up of the programme. These costs include human resources and staff training, transport costs, appropriate refrigeration and medical supplies (not limited to vaccine, needles, safe disposal units etc.). This is a major consideration as the vaccine still proved cost-effective at higher prices in the sensitivity analysis. Importantly however, the assessment of the societal benefit would yield important information on increased economic productivity due to infections averted (684). The vaccine was modelled on evidence-based disease parameters as the candidate vaccine is still undergoing clinical trials. HIV vaccination as a preventive strategy was assessed in isolation in this study. It is must be considered that the simultaneous use of multiple HIV prevention strategies would prove more substantive in the clinical setting (690).

5. CONCLUSION

HIV vaccination among adolescents was evaluated to result in considerable health benefits and found to be cost-effective in the South African setting. The generalizability of these results is limited by two important cautions. Firstly, South Africa not having an established national WTP threshold excludes the WTP as an explicit national decision-making tool and serves to highlight the need for due consideration of the intervention by policy makers. Secondly, as the model was based purely on South African data that was modelled from a provider perspective, caution should be exercised when applying these results to other settings. The findings of this analysis suggest that at the conventionally defined WTP threshold in South Africa, the school-based implementation of the HIV vaccine programme would prove cost-effective should the HIV vaccine become commercially available. Understandably, the cost impacts and inefficiencies beyond those considered in this analysis may arise once the HIV vaccine is applied in a clinical setting. It would then be valuable to reassess the health economic impact of the HIV vaccine at that juncture.

CHAPTER 6

RESULTS: PROJECTED ECONOMIC EVALUATION OF THE NATIONAL IMPLEMENTATION OF A HYPOTHETICAL HIV VACCINATION PROGRAMME AMONG ADOLESCENTS IN SOUTH AFRICA

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1. INTRODUCTION

South Africa has the highest global prevalence of HIV reporting 6.4 million of its citizens living with HIV, 203 000 HIV-related mortalities and approximately 395 000 new infections in 2012 (97, 300, 637). Not surprisingly, the extensive HIV disease burden has impacted heavily on the life expectancy within the country (152). As such, life expectancy has been earmarked as a priority by the National Department of Health, with improvements documented from 2006 (53 years) to 2012 (61 years) (293). Much of this improvement has been attributed to the 'the largest ART roll-out in the world' that South Africa supports (691). Sustaining this achievement requires intensive planning. The increasing numbers of ART initiates have to be retained in care (with retention rates in the public sector reaching 75% after the first year of treatment) and the country needing to enrol more than 500 000 new patients onto ART annually to ensure that ART enrolment ratios are maintained in excess of 1.3 (152). Understandably, maintaining the ART programme in South Africa over the long term becomes a concern when considering the substantial injection of human resources and finances required to sustain it (672).

Young women aged between 15-25 years account for almost a quarter of all new HIV infections, solidifying this group as a considerable contributor to the epidemic. In fact, the HIV prevalence within this age group serves as a vital proxy for HIV incidence. Despite the documented HIV prevalence within this group declining by 18% between 2008 to 2012 (resulting in an impressive drop from nine to seven percent); there still remains an appreciable need to intensify prevention interventions (294). Women between 15-24 years of age are consistently reported to have the most limited access to life-saving ART treatment, despite the many accomplishments of the programme. Barriers still prevent young people from accessing public health services (95). This includes disregard for confidentiality and privacy of clinic attendees exacerbated by unfriendly, judgmental health care staff and inaccessible clinic hours (93, 692). It was these challenges that shape the re-engineering of PHC in South Africa, and in particular the development of the school-based SRH service, into an optimistic alternative (154).

Current HIV prevention strategies have enjoyed poor success in impacting the high incidence rate reported among South Africans, and the search for viable, alternative approaches becomes imperative. Vaccines are long been considered the one of the most cost-effective public health interventions (668). In Thailand (2009), Rerks-Ngarm et al. reported the only HIV vaccine to date (RV144/Thai Trial) to demonstrate vaccine efficacy (albeit moderate) in human subjects (339). The study assessed a prime-boosting strategy, priming with a recombinant canarypox vector (ALVAC-HIV[vCP1521]) with vaccine administration at weeks 0, 4, 12 and 24 and with additional boosts administered with the ALVAC at weeks 12 and 24. This prime-boost HIV vaccine regimen translated to a modest efficacy of 31% over 3.5 years (339). The protective effects were not sustained, but showed promise. Apart from changes to the protein and adjuvant, the HIV vaccine regimen was additionally modified to Clade C before entering South African clinical trials (Phase 1) at six key sites under the umbrella of the HVTN 100 study (345). Should the vaccine induce adequate immunogenicity, it will be entered into landmark Phase IIb/III HIV vaccine efficacy trials (provisionally scheduled for South Africa in 2016) called the HVTN 702 study.

This study aimed to provide guidance to decision-makers regarding the potential introduction of the HIV vaccine regimen among school-going South African adolescents. This study assessed the vaccine effect on HIV-associated burden of disease (and quantifies the health costs associated). The study also evaluated the cost-effectiveness and life expectancy effects based on the suggestion that school-based health care may contribute in resolving the difficulties associated with equity and access of health care that many South African adolescents face.

2. METHODS

The study methodology followed the principles set out in the reporting guidelines of the CHEERS statement (618).

2.1 STUDY OVERVIEW

The vaccination strategy was introduced to ten year old South African school-going adolescents in 2012. The strategy finds it base in the national health initiative to provide school-based SRH services (154), targeting learners prior to sexual debut. The study population was modelled through a 70 year inclusive lifetime horizon which was greater than the current estimated 61 year life expectancy in South Africa (637). This was done considering the constantly improving life expectancy in the country, probably attributable to the availability of improved health care technologies. The HIV vaccine was assumed to be included into the South African EPI and administration would occur at schools. The perspective of the health care provider was used and the findings were hoped to provide objective baseline data for health planning. The HIV vaccine modelled was considered to a prevention intervention that would reduce the HIV-associated burden of disease and mortality. The standard of care (comparator model) included the availability of HCT, the national roll-out of ART, STI treatment and condom distribution currently applied in South Africa (247, 295). The intervention model would include the simultaneous delivery of the comparator care, given that ART would still be in use. Economic cost and health outcomes were discounted at 3% as recommended by the WHO-CHOICE guidelines (537). South African HIV epidemiology is described in Table 25.

Table 25. Age-stratified South African population exploring treatment access

The HIV epidemic in South Africa is detailed in Table 25. Treatment shortfall quantifies those who meet the ART eligibility criteria but remain unable to access the treatment.

Age groups	Population	Susceptible	Prevalence*	On ARV treatment*	Treatment shortfall†
10 - 19	10 264 690	9 982 612	282 078	78 176	163 605
20 - 29	11 010 305	9 386 287	1 624 018	411 831	941 930
30 - 39	9 008 794	6 521 402	2 487 392	775 604	1 442 687
40 - 49	4 479 445	3 329 718	1 149 727	358 501	666 842
50 - 59	3 367 397	2 883 570	483 827	204 740	280 620
60+	3 665 571	3 534 983	130 588	55 260	75 741
Totals	**41 796 202**	**35 638 572**	**6 157 630**	**1 884 112**	**3 571 425**

*Shisana O et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, HSRC Press. 2014, † UN Joint Programme on HIV/AIDS (UNAIDS). The Gap Report. 2014.

2.2 OUTCOME MEASURES

The LYG was used as the outcome measure because of the impact on mortality. The concept of the LYG is a modified mortality measure that quantifies life expectancy. The principle is that a younger person would accrue greater weight than would an older person, thus more life years are accumulated when saving the life of a younger person than with saving an older person. Thus, the life years are considered as the "remaining life expectancy at the point of each averted death" (548). Life expectancies are extracted from life-tables mostly and tend to be setting specific or standardized by geographical area.

The hypothetical HIV vaccine that was modelled was based on the vaccine currently being evaluated in Phase I/II clinical trials in South Africa. The characteristics of the HIV vaccine were based on the definition proposed by the P5, a diverse collaboration of organisations founded under the Global HIV Vaccine Enterprise to promote research based on the foundation of the RV144 trial and to draw collaboration globally to assess HIV vaccine candidates going forward (372).

The regimen modelled in this study mirrored HVTN 100 study, an adaptation of the ALVAC prime ALVAC/gp120/adjuvant boost of the RV144/Thai trial. In addition, a boost was given at month 12 to enhance the immune response that was described as diminishing in the 12 months following vaccination in the RV144/Thai trial.

Coverage was considered at 60% (range: 40-70%), representing an underestimation of the 3rd DTP3 dose of 68% (which serves as a proxy measure for national immunisation performance) (674). The HIV vaccine characteristics modelled were cost at US$ 12 per dose (base-case) (range: US$ 2-24), 50% vaccine efficacy (range: 30-70%) and a ten year duration of protection (achieved through the administration of annual boosters). The diminishing immune response in the RV144/Thai trial warranted the booster injections. The annual booster administration was not considered pragmatic but deemed necessary in light of the waning vaccine immune response reported. In economic terms, the annual booster merely represented a marginal increase in costs. The HIV vaccine price at US$ 12 approximated the price of the HPV vaccine procured by the South African government at US$ 17 per dose. Reduced vaccines pricing was considered possible given the successes in negotiating ART and HPV vaccines on government tender at markedly lower prices (644, 676). HIV/AIDS utilities were drawn from pooled meta-analysis data used to determine the cost-effectiveness of HIV-related interventions, (633).

2.3 STUDY INPUTS

Table 26 shows the input parameters of the model. A proposed vaccine coverage of almost 60% equated to approximately 6 million initial vaccine doses. Health service delivery was presumed to occur at the school. HIV-related costs were determined by using the treatment algorithms prescribed in the 2013 national HIV treatment guideline (247). PHC trained nurses would be responsible for the health care given and referral of complicated cases. Pharmaceutical costs comprised ART, STI treatment and condoms issued. Intervention costs would comprise comparator costs as well as vaccine (and its delivery) and associated human resource costs. The cost of laboratory tests were obtained from the National Health Services Laboratory. Human resource cost of medical personnel [derived from the Uniform Patient Fee Schedule (UPFS)] as well as pricing of medication, consumables and additional pharmaceuticals were obtained from the National Department of Health. Costs were inflation adjusted to the year 2012 using the CPI. The average exchange rate for the South African Rand (ZAR) to the United States dollar (US$) was applied. Costs were converted into the equivalent value for the 2012 US$ where (US$ 1 = ZAR 8.21) allowing for international comparison (591).

Table 26. Economic considerations and parameter costs modelled

The estimates were drawn from the South African literature for 2012. Costs are in US$.

HIV vaccine characteristics	Value	(Range)	Reference
Coverage	60%	(40 – 70)	assumption
Price (US$)	12	(2 – 24)	(274)
HIV vaccine efficacy	50%	(30 – 70)	assumption
Economics	**Value**	**(Range)**	**Reference**
Cost	3.0%	(0 – 6%)	(537)
Outcome	3.0%	(0 – 6%)	(537)
International comparison (ZAR: 1US$)	ZAR 8.21	-	(591)
HIV disease related costs	**Distribution**	**Value**	**Reference**
HIV prevention programme			
HIV vaccine	-	12	(372)
Vaccine delivery per dose *	Gamma	17	(638-642)
Existing prevention programme (incl. HR)	Gamma	65	(639-643)
HIV counselling and testing (HCT) (per test)	Gamma	23	(639, 640)
Cost of HIV rapid testing	Gamma	2	(639, 640)
Current HIV programme (annual costs)			
Asymptomatic treatment (not on ART)	Gamma	131	(247, 643)
Symptomatic treatment (not on ART)	Gamma	137	(247, 643)
AIDS treatment (not on ART)	Gamma	182	(247, 643)
Patient on ART (average)	Gamma	424	(247, 644)
ART cost (annual)			
First-line regimen	Gamma	10	(644)
Second-line regimen	Gamma	27	(644)
Third-line regimen	Gamma	173	(644)
Laboratory costs (annual)			
First-line regimen (first year)	Gamma	17	(247, 643)
First-line regimen (subsequent years)	Gamma	46	(247, 643)
Second-line regimen	Gamma	46	(247, 643)
Third-line regimen	Gamma	92	(247, 643)
Not on ART	Gamma	65	(643)

*Annexure A outlines the costing structures used

Table 27 shows the HIV disease transition probabilities derived from the South African published data.

Table 27. Transition probabilities showing annual disease progression risk

Disease transition from one health state to the next is shown in Table 27. The estimates were drawn from the South African literature for 2012.

Parameter	Distribution	Estimate	Reference
Change in HIV disease state			
Asymptomatic to symptomatic	Beta	0.32	(658)
Symptomatic to AIDS	Beta	0.20	(659)
AIDS to death	Beta	0.21	(658)
Change in drug regimens			
First-line to second-line	Beta	0.10	(659)
Second-line to third-line	Beta	0.01	(660)

2.4 MODEL-BASED ECONOMIC EVALUATION

2.4.1 Semi-Markov model development

Data was captured and analysed on Microsoft Excel® (Version 2010) (Microsoft Corp., Redmond, WA). The uncertainty analysis was performed with Ersatz version 1.2 (www.epigear.com). Ersatz is a boot-strap add-in application for Excel.

A semi-Markov simulation was constructed and run with annual cycles (Figure 20). The 'memoryless' nature of the semi-Markov model was countered by the addition of tunnel states. Vaccines were offered voluntarily to adolescents from ten years of age. The model consisted of eight health states. Individuals entered the model HIV uninfected and healthy (State 1). They then transitioned into a vaccinated (State 2) or unvaccinated (State 3) state depending on the coverage rate. Individuals in either of these states could enter into the asymptomatic HIV state (State 4). This is represented by the oval shape to emphasize that this is a primary endpoint. From an asymptomatic state, the disease of individuals may develop into a symptomatic (State 5) or AIDS (State 6) state. Once individuals were HIV-infected, they could advance into the ART pool where treatment could be accessed (State 7). The treatment pool was divided into first, second and third line ART regimens, each with a possibility of progressing to death. Each previously mentioned health state could progress to death with different transition probabilities (State 8). During each cycle, an individual could remain in the current health state or progress to another. The arrows delineate the transition probabilities between the states. Costs and utility measures were then added to each health state and the model was able to predict costs and QALYs over the 70 year period for the intervention and the comparator. Event rates were considered the same for both arms of the study once the vaccine had been stopped.

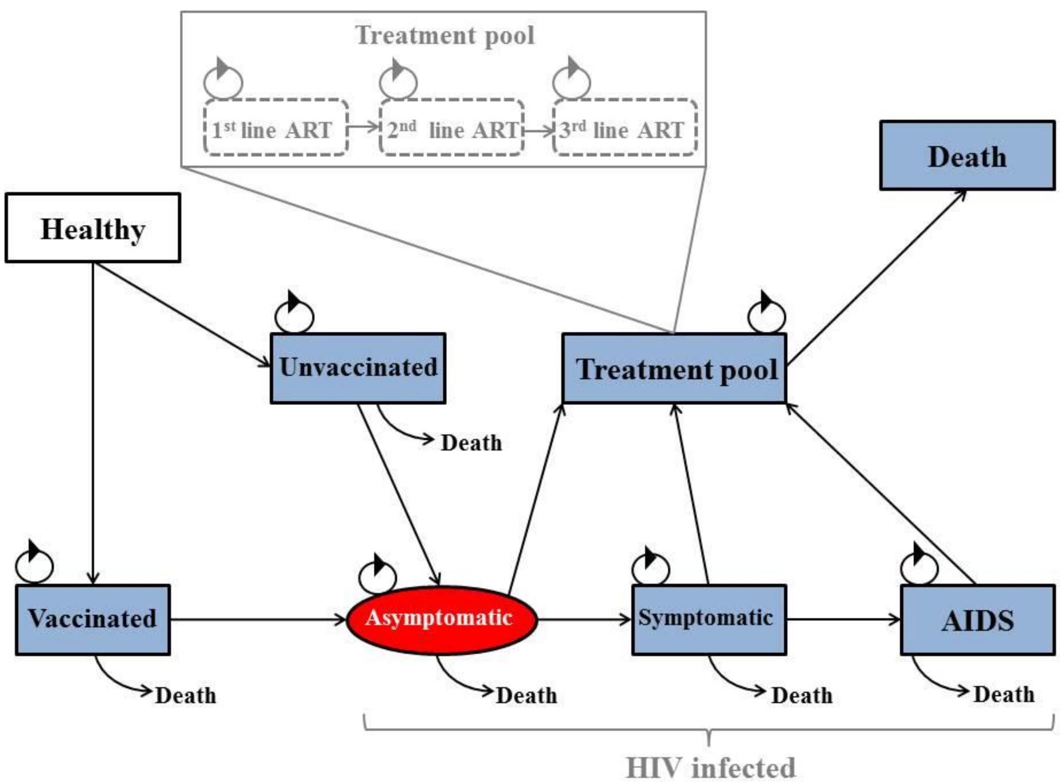

Figure 20. The semi-Markov model of the HIV vaccination strategy

Vaccinated and unvaccinated individuals may acquire HIV infection and transition to the HIV-positive state. Once HIV infected, individuals may transition to the accessing ART (treatment pool). Any states may transition to death but at a rate specific to that health state.

One-way sensitivity analyses were used to determine the impact of single assumptions on cost and outcomes. Bootstrapping techniques using a PSA of 1000 iterations explored the model uncertainty and the robustness of the results. Cost-effectiveness scatter plots and CEACs were used to display these results graphically. The PSA data generated determined if the intervention fell below the WTP threshold. South Africa has no nationally determined WTP threshold, thus 1 X GDP per capita (very cost-effective at the 2012 value) was used as a proxy as recommended by the WHO Guide to Cost-Effective Analysis (537, 680). The WTP threshold was defined as US$ 7 508 (ZAR 61 641) per QALY gained. The GDP per capita theoretically represents the value of an additional healthy life year and emanates from the 'value of statistical life' literature (587). In this study, the GDP is measured against the LYG instead of the QALY as no alternative exists to appropriately indicate cost-effectiveness in South Africa.

2.4.2 Model life-table analysis

The multi-state life-table described the differential mortality and morbidity of the model population under different interventions (693). This work comprised two model life-tables: the reference population with HIV and/or HPV associated mortality of the South African adolescent population under the current treatment strategies and the second table where the adolescent population was exposed to the vaccine interventions. Disease associated deaths were drawn from the literature as described in Table 26.

The cohort model life-table methodology applied calculated the probability of death of a generation (study population) during their lifetime. Age-specific mortality rates related to specific cohorts are used in cohort life-tables, and these allow for known, projected changes in mortality (694). National mortality data was used to determine the disease related mortality in the standard model life-table (as shown in Equation 19):

$$M_{tot} = M_{dis} + M_{other} \qquad \text{(Eq. 19)}$$

Where M_{tot} = total mortality identified in the age / sex group, M_{dis} = *mortality* attributed to the disease state and M_{other} = *mortality* attributed to all other causes.

HIV prevalence estimates was obtained from South African National HIV Prevalence, Incidence and Behaviour Survey, 2012 (97). The ratio between the comparator and the intervention groups was used to calculate the relative reduction in HIV-related mortality attributable to the intervention (reflected in Equation 19). This reduction was used in the model life-table ensuring that comparisons could be made including the individuals surviving, life expectancy and the cumulative years lived.

$$RR_m = \frac{M_i}{M_c} \qquad \text{(Eq. 20)}$$

Where RR_m = mortality risk reduction, M_i = mortality risk in the intervention group and M_c = mortality risk in the comparator group.

Figures entered into the model life-table determined the effect of the intervention on life expectancy and the number of life years gained. Generally, the model life-table generally estimates the mortality values in a population and determines life expectancy as calculated from birth (600). The life expectancy is evaluated using the following formula (Equation 21) (665):

$$e_x = \frac{T_x}{l_x} \qquad \text{(Eq. 21)}$$

Where e_x = life expectancy at age X, T_x = cumulative person years lived after age X and l_x = individuals alive at beginning of age X.

The LYG is simply the difference in the cumulative number of years remaining from the age (X) in the intervention group comparator groups.

$$\text{LYG} = T_{x(2)} - T_{x(1)} \qquad \text{(Eq. 22)}$$

Where $T_{x(1)}$ = cumulative number of years remaining from the age (X) in the comparator group and $T_{x(2)}$ = cumulative number of years remaining from the age (X) in the intervention group.

The ICER calculations used the values from the cumulative years lived in the intervention and comparator groups. The ICER calculates the difference in costs and divides it by the difference in effects (i.e. LYG) between strategies (Equation 23). The ICER is measured in US$ per LYG gained.

$$ICER = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \quad \text{(Eq . 23)}$$

Where C_1 and E_1 = costs and effects of the comparator, and C_2 and E_2 = costs and effects of the intervention.

2.4.3 Years of potential life lost

The YPLL measures the incidence of 'premature' mortality in a population to an age at when the death is regarded as unexpected (695, 696). The YPLL concept gives a quantitative value to the social and economic losses emanating from premature death, and is valuable in evaluating specified causes of death especially in younger populations (666). YPLL combines the age of death and by applying mathematically calculated weights, assigns values to deaths occurring at specific ages (Equation 22) (666, 696, 697).

$$YPLL = \Sigma({}_n d^i_x) \times [70 - (n \times 5)] \quad \text{(Eq. 24)}$$

Where ${}_n d^i_x$ = number of deaths due to HIV/AIDS from age x to age x + n and n is the width of the age interval (in this study ten-year age intervals were used) and *5* represents the number of years till the midpoint of the age interval is reached.

2.4.4 Cost consequence analysis

Absolute risk reduction (ARR) is expressed as a percentage. The ARR is the difference in the risk of an outcome of the intervention compared to the comparator. It was calculated as the difference in the mean values of the parameter of interest and the calculation formula (Equation 24).

$$\text{HIV incidence}_{\text{comparator}} - \text{HIV incidence}_{\text{intervention}} = \text{ARR } [\%] \qquad \text{(Eq. 25)}$$

Where the HIV incidence $_{\text{comparator}}$ and HIV incidence $_{\text{intervention}}$ represented mean percentages and the difference in values was the ARR percentage.

The difference in per capita costs between the intervention and comparator costs was then divided by the ARR obtained for HIV incidence and HIV mortality to yield the outcome value of cost per percentage reduction in disease. The outcomes for both the ARR and the percentage reduction in disease burden were analysed by gender to determine the area of greatest health impact.

2.4.5 Model assumptions

Participants were considered to enter the model prior to sexual debut. Children of school-going age were presumed to be attending school, and drop-out rates were not considered. The model assumed that HCT and the national HIV vaccination intervention were implemented as part of a school-based health care providing comprehensive health care to quintiles of learners. The model assumed favourable uptake of school-based care based on the fact that health care provision occurred in the familiar and non-prejudicial school setting without encroaching on school attendance. No formal pilot studies of school-based health care have been identified to date, thus these assumptions are speculative.

2.5 ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

3. RESULTS

3.1 COSTS OF MODELS

Per annum, the per capita cost of the intervention (US$ 89) represented an 11% increase on the per capita costs of the comparator which was US$ 80. Table 28 lays out the cost breakdown. There are no significant differences in human resources and laboratory costs, but the intervention does reflect a marginal saving on these costs. The pharmaceutical costs in the intervention group is 31% higher than in the comparator group, likely accounted for by the vaccine boosters required to ensure durable protection was attained. A vaccine price of US$ 12 was considered in Table 28.

Table 28. Comparison of costs and components of the HIV vaccination programme

Detailed costs of the intervention compared to the standard of care. The intervention includes the vaccine intervention and the comparator costs. Costs are shown in US$.

Cost category	Per capita expenditure			
	Intervention	Comparator	Difference	(% change)
Laboratory	**12.73**	**13.09**	**0.35**	**(-2.78)**
HIV rapid testing	1.06	1.41		
CD4 count	4.05	4.05		
Pap smear	1.13	1.13		
Viral load	5.95	5.95		
Creatinine	0.53	0.53		
Pharmaceuticals	**39.86**	**30.21**	**9.64**	**(+31.92)**
STI treatment	1.11	0.92		
Condom distribution	1.35	1.12		
Contraception	0.77	0.63		
Anti-retroviral therapy	27.34	27.34		
Vaccine	8.94	0.00		
Vaccine delivery*	0.15	0.00		
Bactrim® prophylaxis	0.20	0.20		
Human resources	**35.94**	**36.67**	**0.63**	**(-1.76)**
PHC nurse	20.70	22.24		
Counsellor	11.03	11.81		
Enrolled nursing assistant	1.68	0.00		
Medical officer	0.46	0.46		
Medical specialist	2.07	2.07		
Transport †	**0.47**	**0.00**	**-**	**-**
Total	**89.00**	**79.87**		

*Vaccine delivery includes the needle, syringe and alcohol swab for administration

†Calculated from average car rental cost incurred in providing a school-based service

3.2 DETERMINING THE COST AND COST-EFFECTIVENESS OF A NATIONAL HIV VACCINE PROGRAMME

Implementing the HIV vaccine programme nationally would be considered cost-effective at an ICER of US$ 5 per LYG. This would be at a base-cost of US$12 per dose [Table 29 – shaded area]. Against the criteria for cost-effectiveness recommended by the WHO, the national HIV vaccine programme would be considered highly cost-effective. Lower priced vaccines would positively impact the sustainability of the programme. Vaccines priced at US$ 6 per dose will reduce the programme cost by 5% (US$ 52 million) of the base vaccination programme; translating to an ICER of US$ 2 per LYG. Vaccines priced at US$ 2 per dose would produce more favourable outcomes – the ICER would be US$ 1 per LYG representing a 9% reduction (US$ 84 million) in the programmatic costs compared with using a vaccine at a cost of US$ 12 per dose.

Table 29. Cost-effectiveness of a national HIV vaccination program at varied vaccine prices

The programmatic costs were calculated if the vaccine costs were varied. The cost values reflect annual expenditure. At baseline (shaded) vaccine cost of US$ 12 per dose, the annual programmatic cost would be approximately US$ 1017 million representing a US$ 9 increase from the base cost per capita. All other evaluations are relative to the base vaccine strategy.

Vaccine pricing		**Program cost (millions)**			**Cost per**		
Structure	**Per dose**	**Total**	**Change from base (%)**		**Capita***	**LYG**	**Death averted**
Very low	2	933	-84	(-9)	1	1	421
Low	6	967	-50	(-5)	4	2	1106
Base cost	**12**	**1017**	**-**	**-**	**9**	**4**	**2131**
Medium	18	1067	50	(+5)	13	6	3161
High	24	1118	101	(+10)	18	8	4189

*increase in cost per capita

3.3 UNCERTAINTY ANALYSIS

3.3.1 The effect of coverage on cost and life expectancy

Table 30 shows how increased vaccine coverage would result in higher programme costs. Increasing vaccine coverage also results in improved life expectancy. The higher cost has to be considered against this improvement in life expectancy, prior to the vaccine strategy is deemed cost-effective. Other vaccine characteristics would also have to be factored before the decision is made.

Table 30. One-way sensitivity analysis of coverage on health outcomes

The coverage rate is varied in Table 30. Increasing the vaccine coverage results in increased programmatic costs.

	Cost (million US$)			
Coverage	**Comparator**	**Intervention**	**Increase in cost**	**Life expectancy**
40%	913	982	70	54.6 years
60%	**913**	**1017**	**104**	**55.5 years**
70%	913	1034	122	55.9 years

3.3.2 Probabilistic sensitivity analysis

ICER and WTP results

PSA was used to assess the uncertainty around the ICER. The HIV vaccine intervention resulted in an ICER of US$ 5 per LYG (95% CI ZAR 3-12). Projections of the intervention programme at national level were estimated at US$ 1017 million annually, representing a US$ 104 million (11%) increase on the comparator cost (US$ 913 million). The cost was driven by both the need for boosters and that the vaccine strategy would target approximately 6 million HIV uninfected adolescents aged between 10-19 year compared with ART provision to just under 80 000 adolescents of the same age in the comparator group. The intervention did yield a mean cumulative gain of 24 million LYG (95% CI 9 - 34 million years) in the total population. Figure 21 evaluated the cost-effectiveness of the vaccine strategy and assessed the effect of changing the vaccine efficacy on the ICER. At 30% vaccine efficacy (low), the intervention may not be cost-effective as the iterations appear on both sides on the WTP threshold. At higher vaccine efficacies (50% and 70% respectively), the iterations remained below the WTP threshold implying the strategies to be highly cost-effective (as per the WHO recommendation) (537).

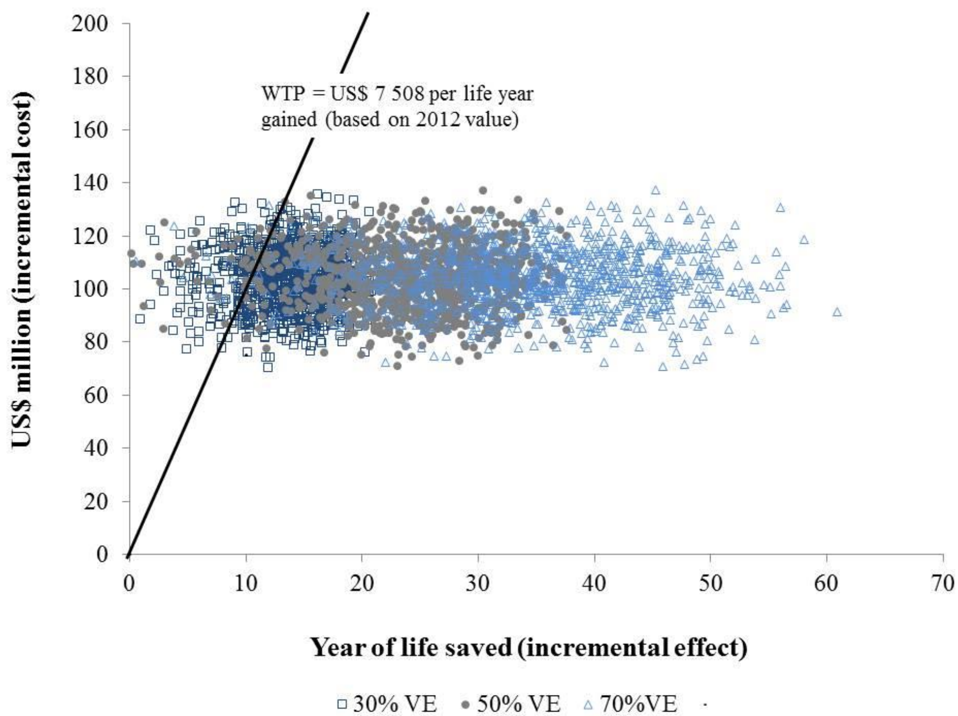

Figure 21. Willingness-to-pay analysis explored by varying vaccine efficacy

The scatter plot of the costs and health outcomes from the probabilistic sensitivity analysis are shown in Figure 21. Incremental cost represents the difference in cost between the comparator and the intervention programmes. Incremental effect reflects the difference in health outcomes between the comparator and intervention programmes. The unit of measure for health outcomes is years of life saved.

3.4 IMPROVEMENTS IN LIFE EXPECTANCY AND ASSESSING THE POTENTIAL YEARS OF LIFE LOST

The results of the model life-table simulation are shown in Table 30. Implementation of this intervention in the 10-19 year age group yielded a three year improvement in life expectancy, in addition to the significant increase in cumulative gain of years lived in the age group. The increase in life expectancy documented in the 10-19 year group, resulted in subsequent increases reported in the age groups that followed. The YPLL from the HIV/AIDS contribution to ‘premature’ death is also shown in Table 31. The years of life lost without the vaccine introduction (70 640) is greater than the years lost under the intervention (48 400), demonstrating the value of vaccine implementation.

Table 31. Model life-table analysis and years of potential life lost

The life-table tracks the movement of vaccinated individuals aged 10-19 years. Columns I_x describes the intervention impact on mortality reduction, columns T_x reflects the combined years lived with and without the intervention and columns e_x reflect the improvement in life expectancy as a result of the intervention.

Age (x)	**No vaccination (Comparator)**			**Vaccination (Intervention)**		
Life expectancy	**I_x**	**T_x**	**e_x**	**I_x**	**T_x**	**e_x**
	(millions)	(millions)		(millions)	(millions)	
10 – 19	10.0	529.1	**53.0**	10.0	553.6	**55.5**
20 – 29	9.8	429.9	**43.7**	9.9	454.4	**46.1**
30 – 39	9.3	334.4	**36.1**	9.4	358.2	**38.2**
40 – 49	8.3	246.8	**29.9**	8.6	268.3	**31.2**
50 – 59	7.1	170.0	**23.9**	7.6	187.2	**24.6**
60+	5.8	105.5	**18.2**	6.3	117.4	**18.6**
YPLL						
10 – 19		70 640			48 400	

I_x- individuals surviving, T_x - cumulative years lived, e_x - remaining life expectancy at age x

3.5 COST CONSEQUENCE RESULTS

The data generated was able to project the 10 year ARR in HIV-associated mortality and incidence seemingly offered by the HIV vaccine intervention. Table 32 outlines the detailed cost breakdown and in addition, highlights the vaccine impact by gender. The most notable reduction in HIV incidence was documented among females (0.53%), given their high disease burden. However, all scenarios reflected improvements in health outcomes.

Table 32. Reduction in disease risk and associated cost consequences

The ARR was evaluated over a 10 year period.

	10 year risk: Mean % (SE)				Absolute risk	Cost
	Intervention		Comparator		reduction	consequence*
Total						
Incidence	1.08	(0.08)	1.49	(0.15)	0.42%	20.87
Mortality	1.05	(0.01)	1.45	(0.04)	0.41%	21.36
Male						
Incidence	1.09	(0.09)	1.51	(0.15)	0.42%	20.67
Mortality	1.10	(0.02)	1.52	(0.05)	0.42%	20.45
Female						
Incidence	1.40	(0.12)	1.94	(0.22)	0.53%	16.29
Mortality	1.03	(0.02)	1.42	(0.04)	0.39%	22.05

*per 1% reduction in risk

HIV - human immunodeficiency virus, SE - standard error

4. DISCUSSION

This study attempted to determine the cost-effectiveness of a hypothetical HIV vaccine roll-out to South Africa school-going adolescents. The burden of HIV disease in South African is globally acknowledged as generalized with young people and adolescents disproportionately affected (698). Concerted nationally implemented HIV prevention efforts (including increasing ART coverage by 75% between 2009-2011 and establishing the largest condom distribution network globally) have been threatened by South Africa accounting for 16% of the global incidence of HIV in 2013 (97, 298). The high HIV incidence among adolescents reinforced the need to reach this key population with innovative HIV prevention interventions if HIV-associated mortality and incidence rates are to be curtailed (698). Without a doubt, the introduction of a potential HIV vaccine strategy in schools represents a sizable initial financial injection when considering the start-up costs required. The health benefits in terms of improved life expectancy, reduced potential years of life lost and decreased HIV mortality and incidence serve to justify the expenditure to an extent. Life expectancy was also sensitive to vaccine coverage rates, while cost-effectiveness was sensitive to vaccine efficacy.

The financial plausibility of HIV vaccine implementation was confirmed by both the model life-table findings and the cost-effectiveness analyses (537). Programmatic costs of higher priced vaccines remained cost-effective, but the programmatic costs were substantially higher. Much of the per capita cost of the intervention could be attributed to costs associated with the booster vaccinations. This requires a substantial investment considering the several competing burdens of disease that stakes claim to a limited South African health budget (5). Sustaining the ART programme in the long term is daunting, similarly financially sustaining a potential HIV vaccine programme over several years may prove equally concerning. The comparator cost includes those on treatment currently (excluding the 58% of people eligible but unable to access treatment (300)). Thus the comparator cost has been grossly underestimated, and the shortfall has to be covered. Scaling-up of ART is not a primary prevention strategy and is unlikely to definitively reduce the incidence of HIV as a primary strategy (e.g. vaccination) could. In addition to averted infections being cost-saving from the perspective of the provider, it may also translate to substantial financial savings by reducing ART demand (699). South Africa has enjoyed success in attaining lower prices for ART and the HPV vaccine, and this augurs well for the procurement of the HIV vaccine when it becomes commercially available (644, 676). If vaccine development fails to develop a longer-acting booster, then the more frequent administration of the booster (and the cost it entails) required to maintain the protective effect of the vaccine becomes a key factor in determining the cost-effectiveness of the intervention. Long term, the vaccine has the ability to impact health outcomes, apart from the economic benefits discussed. HIV vaccine implementation has the capacity to impact health outcomes long term. The mean cumulative increase in LYG demonstrates this by improving life expectancy in South Africa, a parameter considered a strategic output of the National Service Delivery Agreement (293).

While the South African HIV disease epidemic is assumed to be mostly heterosexual in nature, this work adopts a simplified assumption of a complex sexual network in South Africa. Individuals involved in high-risk behaviours remain susceptible to infection as a result of repeated exposure to risk almost negating the protection offered by the vaccine compared with those at seemingly low risk. A partially effective vaccine may still play a role in ‘avoiding’ or delaying infection even if it is unable to completely prevent the infection from establishing itself within the population (700). In fact, at population level, a partially effective vaccine modelled in the USA demonstrated temporal reductions in HIV infections and thus significant health benefit (690). Andersson et al. concurred with the USA findings when the RV144/Thai trial vaccine was modelled in the South African context, but warned that vaccines with shorter durations of protection would be effective in the scenario where coverage levels were high, corresponding to millions of vaccine doses being required (701).

Adolescents are an important target for the vaccine intervention. Apart from their major role in disease transmission, school-going adolescents appear to be easier to access than other high-risk populations (i.e. commercial sex workers) who are difficult to reach because of being marginalised and stigmatised (701). However, adolescents have documented historical challenges in accessing public health services in South Africa with concerns including confidentiality breeches and judgmental health care staff. With this in mind, it is not surprising that many do not return for continuation of care (95). The school setting is considered a “safe space” in terms of being free of prejudicial attitudes, a space that could be extended to include peer discussion and provision of relevant health services. However, neglecting adolescent health care and the failure to address the barriers to health care described by the adolescent could potentially undermine any success achieved by HIV prevention initiatives to date (172). Another potential deterrent to the uptake and coverage of HIV vaccines is the poor social acceptance of the HIV vaccines (often fuelled by perceived side-effects) (702). Understandably, it is virtually impossible for hypothetical models to emulate real-life behavioural changes but knowledge of these situations highlights the need to provide wide-ranging sexual counselling and risk reduction education; which may prove easier to deliver in the school setting (703).

There were several limitations identified in the study. Firstly, it is difficult to map the degree of behavioural risk-taking (if any) that could occur following vaccination and was thus not assessed in the evaluation. Having said this, sexual risk behaviour changes following HIV vaccination are generally difficult to grasp in the African situation (703). In high HIV prevalence communities such as South Africa, decreased condom use (even in the context of stable relationships) are likely result in increased in HIV acquisition (703). Data emanating from South African has suggested that there is a poor understanding of the 'low-efficacy' concept, which was additionally associated with a reported potential decrease in condom use. The degree of behavioural disinhibition is postulated to depend largely on how the HIV vaccine effects are marketed to the public (699). Behavioural disinhibition thus becomes an important consideration when exploring the low efficacy described in the candidate vaccines testing to date (703). Secondly, the herd immunity was not assessed but Long et al. has suggested that even partially efficacious vaccines may confer some protection to the unvaccinated population through herd immunity (690). The suggestion of benefit to those unvaccinated is critical when considering the modest coverage of childhood vaccinations in South Africa as it speaks directly to the country's capacity to successfully deliver the HIV vaccine (674). A 60% coverage rate implies that an unprecedented six million adolescents be vaccinated; further implying high initial implementation costs. Thirdly, the perspective of the provider was considered because the bulk of direct medical programme costs will be carried by the public health care sector. The societal costs were not formally assessed, but it is not unreasonable to suggest that the contribution would be significant and could thus contribute to the overall vaccine cost-effectiveness. Fourthly, the original RV144/Thai trial work did not assess booster vaccination (690). Therefore assuming that the booster vaccination affords the vaccine recipient the same protection as the initial vaccination is hypothetical. There have been rather limited discussions of the booster vaccinations or its potential efficacy evaluated in the literature (703). Annual boosters would drive up the administration costs and therefore drastically increase the programmatic costs. This is the key difference identified between the comparator and intervention cost. Targeting the relatively stable school population will hopefully contribute to minimising the attrition rates among vaccine recipients. Finally, this study evaluated HIV vaccination in isolation comparing it to the current standard of care (i.e. ART roll-out and condom distribution). It is most likely that the HIV vaccine would work in conjunction with other prevention strategies such as VMMC in a clinical setting; and an ideal "basket" of prevention interventions could be determined once newly validated information becomes available (690, 699). As the national HIV incidence has yet to be definitively curbed by public sector HIV prevention strategies, it becomes imperative to evaluate potential new interventions individually.

5. CONCLUSION

These findings suggest that the national programme of HIV vaccines administered to South African school-going adolescents would be a viable and cost-effective measure for reducing the considerable HIV disease and economic burden. Beneficial health outcomes associated with HIV vaccine implementation include reductions in HIV-associated mortality and incidence and improved life expectancy as shown by the model. Vaccines offering longer duration of protection (and thus requiring fewer boosters) would greatly drop programmatic costs. This work does provide those planning the health services with invaluable, relevant baseline South African data for considering the implementation of the HIV vaccine nationally. However, decision-makers would be able to judge the cost and disease implications more realistically once the actual vaccine efficacy, duration of protection and cost have been determined.

CHAPTER 7

RESULTS: COST-EFFECTIVENESS ANALYSIS OF DUAL HIV AND HPV VACCINE PROGRAMMES FOR SCHOOL-AGED GIRLS IN SOUTH AFRICA

1. INTRODUCTION

The global burden of HIV is disproportionately concentrated in Africa with disturbingly high rates of incident disease occurring among young women and adolescent girls (285). South African women of reproductive age (15-49 years) account for a staggering 18% of the national HIV prevalence and are two times more likely than males to be HIV-positive (97, 637). Not unexpectedly, cervical cancer ranks as the most prevalent cancer in the same age group (92). The link between HIV and HPV has long been established. HIV acquisition is enhanced in the presence of cervico-vaginal HPV disease (654, 655) and HPV detection increases rapidly within the first few years following HIV seroconversion (653). The relationship between HIV and HPV manifests clinically as a rapid progression of HPV disease to higher grades or invasive lesions, that often are refractory to treatment, in the presence of pre-existing HIV disease (651). This result is significant associated mortality and morbidity, and a disease burden particularly concerning to the National Department of Health.

South Africa has the highest cervical cancer incidence and mortality globally (92). The 2001 South African cervical screening guideline suggested an algorithm of 3 Pap smears in a lifetime – starting at age 30 and at ten year intervals. The programme was anticipated to reduce the cumulative incidence of cervical cancer by 64% but the guideline has been subject to intense scrutiny as it has yet to be updated in the wake of the HIV epidemic. Further, the programme has been marred by inadequate infrastructure, poorly trained staff and dismal uptake of screening and subsequent treatment (17). With cervical cancer defined as AIDS defining since 1993 (704) and the acknowledgement of the synergism between the diseases, the national HIV policy calls for annual cervical screening of HIV-positive individuals (247). Neither of the cervical screening programmes has been established; and the national cervical screening rate remains currently a mere 14% of the 70% anticipated (92). Conversely the HIV epidemic has received considerable attention. Massive campaigns have been initiated encouraging voluntary HIV testing (295). The mother to children transmission rate has been driven down to 2% in 2013/14 by offering PMTCT services at 98% of PHC facilities since 2010 (297). Most significantly, the South African ART programme expanding by 33% between 2010 -2013 has been internationally lauded (300).

The vaccine intervention reaching school-going girls is constrained by their ability to access health services. As a population group vulnerable to HIV and HPV disease, young girls have had to contend with inaccessible clinic hours and harsh judgment from health care staff regarding sexuality choices and contraception (151). It is at this juncture that the National Department of Health's re-engineering of PHC and, in particular, the development of school-based SRH services becomes a critical cog in preventive health care (154). A school-based programme allows the delivery of a comprehensive package of sexual health services in a safe and non-threatening environment. There is no intervention more cost-effective than vaccination (668). The HPV vaccination of young girls has been universally accepted as cost-effective in all settings (705). This cost-effectiveness has not been demonstrated in their male counterparts (281, 654). The situation is different regarding the HIV vaccine. Following the first successes demonstrated among human subjects in Thailand (339), the HIV vaccine regimen has undergone clade specific modification with the development of a new bivalent clade C protein and adjuvant (MF59); and has been entered into Phase I/II testing at six major sites in South Africa. Like the HPV vaccine, the HIV vaccine regimen would require a point of access into the health care system that will allow seamless integration of the vaccine into existing health services once it is commercially available. A school-based programme could opportunistically administer these vaccines to a stable population of vaccine recipients potentially prior to the onset of sexual activity.

The purpose of this economic evaluation was to assess the health impact, cost and cost-effectiveness of three vaccine interventions administered in a school-based programme targeting females: (1) HIV vaccination; (2) HPV vaccination and (3) dual HIV and HPV vaccination. The scenarios were compared with the standard of care provided at South African public sector health facilities. Sensitivity analyses of parameters considered in the model, including vaccine pricing, discount rates and vaccine coverage, were conducted.

2. METHODS

The study complied with the reporting guidelines of the CHEERS statement (618).

2.1 STUDY OVERVIEW

Uptake of the vaccine intervention was voluntary and aimed at all nine year old South African school-going females in 2012. This intervention was intended to be introduced as part of school-based SRH services – a focal initiative by the national health department (154), and was intended to target learners prior to their sexual debut. While the rationale for this was self-explanatory in the case of the HIV vaccine, the HPV vaccine was shown to have no effect on prevalent infection or disease (252). The hypothetical population was modelled through a 70 year lifetime horizon, congruent with current life expectancy in South Africa (637). It was assumed that these vaccines would be integrated into the EPI offered in the South Africa and be delivered at school health facilities. The adoption of the provider perspective was particularly relevant to the review of health service delivery and for exploring the financial implications of introducing health interventions in the public sector. Additionally, the provider perspective was used so that the information garnered would potentially guide national health decision-making regarding this issue. Economic costs and health outcomes were discounted at a rate of three percent, with an uncertainty range of zero to six percent, as recommended by the WHO-CHOICE (537).

The HPV vaccine was modelled as prevention against HPV-related cervical cancer and pre-cancerous HPV-related cervical states. The HIV vaccine used in the simulation was hypothetical and considered a prevention strategy aimed at reducing HIV-associated burden of disease and mortality. The intervention of vaccination was compared against the current standard of HIV care and prevention (comparator) in the South African public sector (viz. ART, STI treatment and condom distribution) (247, 295). Similarly, the cervical screening comparator was based on the 2001 National Guideline for Cervical Cancer Screening Programme which predicted a 64%

reduction in cumulative incidence of cervical cancer with three lifetime smears done at ten year intervals from age 30 years (246). The 2013 National HIV Treatment guideline argues for annual cervical screening of HIV-positive women given that increased incidence of cervical disease in the face of HIV (51, 268). In both instances, identified cervical disease is referred to public sector clinics or hospitals for further management. These two cervical screening policies discussed represent the standard of care associated with cervical disease in South Africa.

2.2 OUTCOME MEASURES

The validation of the EuroQol EQ-5D health outcome measurement tool for measuring HRQOL of HIV/AIDS in Africa validates the use of the QALY in the South African health environment (555). The QALY incorporates survival and HRQOL into a single summary measure of health that informs decision-making about the relative value for money of health care interventions (624). The QALY is estimated by calculating the total LYG from an intervention and then each year is multiplied by a quality of life score (where 0 = worst health and 1 = best health) to reflect the quality of life in that year (130). The computer simulation then determined the ICER of the current treatment strategies with and without vaccination (Equation 24):

$$\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \qquad \text{(Eq . 26)}$$

Where C_1 and E_1 = costs and effects of the comparator, and C_2 and E_2 = costs and effects of the intervention.

The bivalent vaccine [Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium)] contains the VLP types 16 /18 that have been implicated in 64% of cervical cancer is South Africa (92). The efficacy modelled in this evaluation was chosen from the PATRICIA as the study criteria closely resembled the economic evaluation (274). Table 33 presents effectiveness measures from the PATRICIA study.

Table 33. Assessing the Phase III efficacy HPV bivalent vaccine studies in young women

The PATRICIA efficacy measures (shaded) were adopted in the economic evaluation as the primary end-points and study inclusion criteria more closely reflected the parameters considered in model (274, 631).

	PATRICIA			Rationale for PATRICIA choice
Vaccine	Cervarix			Bivalent vaccine currently being implemented in SA government schools
VLP types	16/18			
No. study sites	135			Findings have greater generalisability with more study sites and countries
No. countries	14			
Age	15 - 25			Younger age group considered in analysis
Lifetime no. sexual partners	≤ 6			Reflects the assumed sexual naivety of the group
Primary endpoints	Incident HPV 16/18 associated CIN2+ or greater			Considered the long-term implications of HPV disease
Protection afforded	**Total Vaccine Cohort**			Health states integrated into the Markov model
		% Efficacy (95% CI)	Rate reduction	
	CIN2+	60.7 (49.6-69.5)	0.43	
	CIN3+	45.7 (22.9-62.2)	0.13	
	AIS	70.0 (-16.6-94.7)	0.02	

The hypothetical HIV vaccine described in the study is currently being evaluated in Phase I/II clinical trials in South Africa. The characteristics of the HIV vaccine discussed were proposed by the P5, a diverse collaboration of organisations founded under the Global HIV Vaccine Enterprise to promote research based on the foundation of the RV144 trial and to draw collaboration globally to assess HIV vaccine candidates going forward
(372).

HIV/AIDS related pooled utilities were drawn from a meta-analysis and applied to the cost-utility analyses of HIV prevention interventions (633). Similar pooled utility measures for HPV-related disease states do not exist in South Africa. Instead, quality of life weights were drawn from the available literature. The utility weights for both diseases appear in Table 34.

Table 34. Utility weights for HIV and HPV-related disease

The table describes the health-related quality of life weights for the different health states of both diseases.

Parameters	Estimate	Source
Full health	1	
HPV disease		
LSIL	0.91	(122)
HSIL	0.87	(122)
Cancer	0.65	(266)
Cancer survivor	0.84	(122)
HIV disease		
Asymptomatic	0.94	(633)
Symptomatic	0.82	(633)
AIDS	0.70	(633)

2.3 STUDY INPUTS

Table 35 lists the input parameters of the study. Transition probabilities relating to HIV and HPV disease states were drawn from the South African literature search. Costs were inflation adjusted to the year 2012 using the CPI. The average exchange rate for the South African Rand (ZAR) to the United States dollar (US$) was applied. Costs were converted into the equivalent value for the 2012 US$ where (US$ 1 = ZAR 8.21) allowing for international comparison (591).

Approximately 6 million girls would be vaccinated with the initial vaccine dose at an estimated coverage of 60%. The hypothetical HIV vaccine was modelled at a cost of US$ 12 per dose (base-case), had a 50% vaccine efficacy, 60% coverage rate and conferred 10 year duration of protection (requiring annual boosters). While the issue of annual boosters does not appear practicable, it was introduced into this analysis as a result of the immune response diminishing in the RV144/Thai trial 12 months following initial vaccine administration (339). In the context of this economic evaluation, the introduction of the boosters represents an overestimation of cost while still appropriately maintaining the desired vaccine effect. The HIV vaccine characteristics are hypothetical and based on the vaccine profile defined by the P5 drawn from major HIV vaccine clinical studies conducted thus far. The bivalent HPV vaccine was modelled as it is being administered in lower socio-economic schools as part of the government programme (650). The negotiated vaccine price was US$ 17 per dose and efficacy was determined by the documented clinical trials of the vaccine (274). The complete vaccine course ran over 2 years and was given concomitantly with the HIV vaccine to achieve a vaccine coverage of 60%. The duration of protection conferred by the HPV vaccine is assumed to be lifelong (662). The vaccine was delivered at schools in conjunction with the health care services that the national government envisions initiating in schools as part of the primary health care restructuring.

Relevant HIV-related cost components were drawn from the 2013 national treatment guideline adopted in the South African public health care sector (247). The costs associated with the treatment of cervical cancer and pre-cancerous lesions were drawn from previous economic analyses (130). Regarding the HIV treatment, it was assumed that PHC nurses would consult patients, and complicated cases would warrant upward referral to doctors or medical specialists. The cost of pharmaceuticals encompassed ART, treatment of STIs and condoms. The intervention costs comprised the comparator costs in addition to the costs associated with provision of the vaccine and its delivery (including accounting for consumables and human resources). The price of laboratory tests including Pap smears (provided by the NHLS), the cost of medication, consumables and additional pharmaceuticals and costs of human resources including medical personnel were based on the UPFS and derived from the National Health Department. Table 36 details these costing parameters.

Table 35. Model parameters pertaining to the female population

Disease transition from one health state to the next is shown in Table 35. The estimates were drawn from the South African literature for 2012.

Parameters	Base-case estimate	Reference
Vaccine characteristics		
Coverage	60%	assumption
HPV vaccine efficacy	70%	(274)
HIV vaccine efficacy	50%	assumption
Treatment uptake		
Cervical screening	13.60%	(92)
ARV therapy	29.00%	(300)
HPV treatment	35.30%	(250)
Transition probabilities (represented as percentages)		
HIV-negative		
Development of LSIL	3.00	(651)
Progression of LSIL to HSIL	1.69	(651)
Progression of HSIL to cancer	3.84	(250)
HIV-positive		
HIV incidence in general population	2.28	(97)
HIV incidence in HPV disease	5.39	(651)
Development of LSIL	14.00	(51, 268)
Progression of LSIL to HSIL	6.00	(51, 268)
Progression of HSIL to cancer	8.10	(651)
Mortality		
Mortality in general population	1.16	(637, 678)

Table 36. Unit cost of screening, diagnosis and treatment of HPV disease in 2012

The estimates were drawn from the South African literature for 2012. Costs are in US$.

Economics	**Value**	**Range**	**Reference**
Cost	3.0%	(0 – 6%)	(537)
Outcome	3.0%	(0 – 6%)	(537)
International comparison (ZAR: 1US$)	ZAR 8.21	-	(591)
HIV disease related costs	**Distribution**	**Value**	**Reference**
HIV programme			
HIV vaccine	-	12	assumption
Vaccine delivery per dose*	Gamma	17	(638-642)
Existing prevention programme (incl. HR)	Gamma	65	(639-643)
HIV counselling and testing (HCT) (per test)	Gamma	23	(639, 640)
Cost of HIV rapid testing	Gamma	2	(639, 640)
ART treatment	Gamma	310	(640, 643, 644)
Not on ART	Gamma	65	(643)
HPV-related disease	**Distribution**	**Value**	**Reference**
HPV prevention programme			
Cervical screening	Gamma	82	(640, 643)
HPV vaccine	-	17	(706)
Vaccine delivery per dose	Gamma	17	(638, 640)
Treatment costs			
HSIL	Gamma	942	(130)
Cervical cancer	Gamma	7329	(130)

*Initial course comprises 6 doses

2.4 MODEL-BASED ECONOMIC EVALUATION

Data capture and data analysis was done using conducted in Microsoft Excel® (Version 2010) (Microsoft Corp., Redmond, WA). Ersatz version 1.2 (www.epigear.com) was used to perform the uncertainty analysis. Ersatz is a boot-strap add-in application for Excel. Movement between health states shown in Figure 22 was modelled on the basis of transition probabilities and the effectiveness values of the treatment options in the model.

The core model was a semi-Markov simulation with annual cycles (Figure 22). Semi-Markov models, in particular, were chosen as it allowed for the addition of tunnel states to counter the 'memoryless' nature of the Markov model and also allowed for recurrent disease to be modelled. The study population started the model HIV and HPV disease free and each year were exposed to the risk of acquiring each disease. The two diseases were not able to be acquired in a single year. The rate of acquisition of the second disease was adjusted for depending on the primary infection acquired. The model was constructed using socio-demographic data of the proportion of the population that accesses public health care in South Africa (707). The model accounted for the interaction of one disease in the presence of another (i.e. HIV risk was increased in the presence of HPV disease vice versa). The dual vaccination programme was offered to nine year old school-going girls on a voluntary basis. Several health states were used to construct the model. A proportion of these healthy individuals would be vaccinated against HIV and HPV disease, and the rest would remain unvaccinated. Each year, these healthy individuals were exposed to the risk of acquiring each disease.

Healthy individuals could develop HPV disease starting from LSIL to HSIL which may then progress to cervical cancer. At each HPV-related health state, an individual may die (not represented graphically) or become HIV-infected (in which case they would progress on the lower HIV-positive spectrum). HIV-positive, HPV-infected individuals that were treated for HPV disease could potentially develop recurrent HPV disease. The model allowed for females with HPV disease both treated and untreated to acquire HIV disease. There was a higher probability of transition to more serious HPV states among the HIV-positive vs. the HIV-negative individuals. All individuals who were HIV-positive could enter the HIV treatment pool. Every health state, including the healthy individuals without HIV or HPV disease, could progress to death at rates dependent on their current health state but also with background mortality independent of their current health state. These mortality transitions were excluded from Figure 22 as they rendered the model excessively ‘bushy’ and concealed the key message the diagram was intended to convey. The arrows represented the transition probabilities from one state to another. Costs and utility measures were then added to each health state and the model was able to predict costs and QALYs over the 70 year period for the intervention and the comparator. Upon cessation of the HIV vaccine, event rates were still considered lower among those individuals who received the HPV vaccination compared with those who did not. The protection conferred by the HPV vaccine was considered lifelong (662).

One-way sensitivity analyses was used to assess the influence of single assumptions on cost and health outcomes. Model uncertainty was explored using PSA with a bootstrapping technique. In addition, the PSA examine the robustness of the results. Cost-effectiveness scatter plots and CEACs were used to graphically display the findings. The PSA data was also used to determine if the intervention fell below the WTP threshold. South Africa has not adopted a formal WTP threshold and the GDP per capita (2012) was used as a proxy measure for this purpose as per the recommendation of the WHO (537, 680). The South African WTP threshold thus equated to US$ 7 508 (ZAR 61 641) per QALY gained.

The model was constructed under various assumptions. All participants were considered sexually naïve at the start of the model. The model assumed that all nine year old children that were eligible for schooling were indeed attending school, and that consent was obtained from parents and was reflected in the coverage rates. The efficacy of dual vaccination strategies was considered as multiplicative (625) as there is rarely evidence available from clinical trials reporting the efficacy of two prevention interventions that were simultaneously introduced. Individuals were exposed to the risk of both diseases during each cycle but could only acquire a single condition per year. Once *disease 1* was acquired, the rate of acquisition of *disease 2* changed accordingly. The model assumed global uptake and provision of HCT in the school environment as stipulated by the national policy (295). Despite the generally poor uptake of cervical screening services (92), it was assumed that those diagnosed with LSIL would return for repeat assessments given the convenience of attending a school health service. The modelling exercise assumed the national roll-out of the dual vaccination strategy under the auspices of an established school-based programme providing comprehensive health care to quintiles of learners. Favourable uptake of school-based health care services was assumed by the model, given that the health care provision occurred in the familiar and non-prejudicial school setting without impacting on school attendance. There have been no formal pilot studies of school-based health care provision in South Africa and as such, the validation of this assumption is speculative.

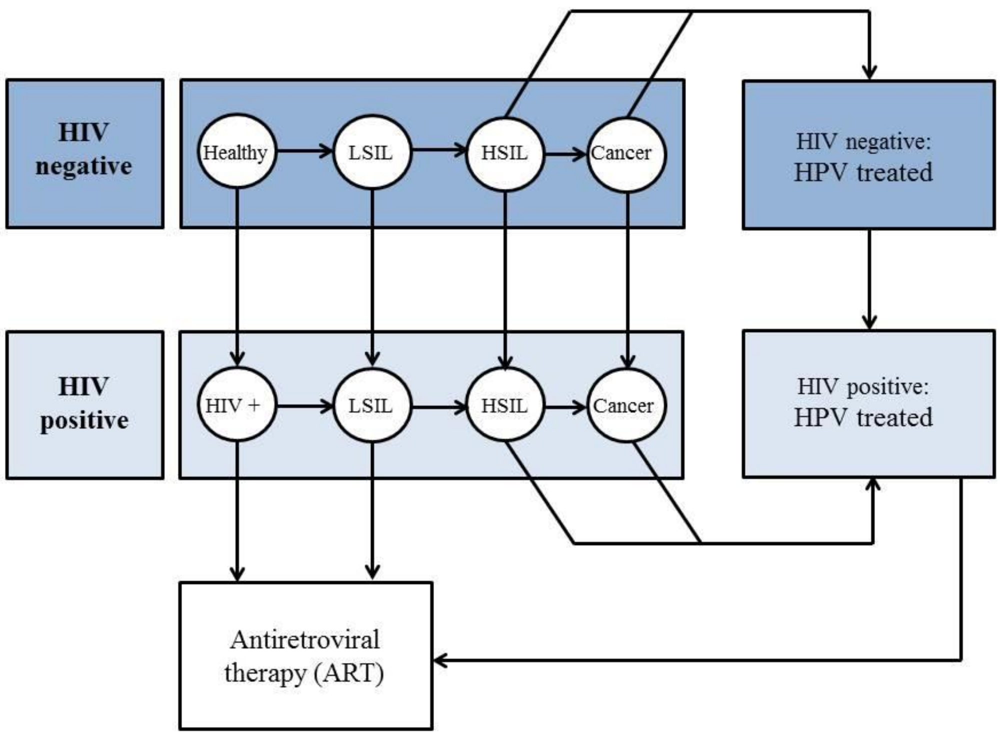

Figure 22. Semi-Markov model for HPV- and HIV-related disease states

Healthy individuals (vaccinated and unvaccinated) may remain uninfected or transition into HPV or HIV disease. Those acquiring HPV disease are at risk of HIV infection (if unvaccinated against HIV). Each state may progress to death during any cycle, the rate of which depends on the state from which the individual progresses. LSIL – low-grade intraepithelial neoplasia, HSIL – high-grade intraepithelial neoplasia

2.5 ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

3. RESULTS

The results are described below in terms of: (1) the cost and cost-effectiveness of the models; (2) one-way sensitivity analysis; (3) probabilistic sensitivity analysis and, finally, (4) disease risk reduction.

3.1 COST AND COST-EFFECTIVENESS

The total costs and QALYs gained in the lifetime of the hypothetical cohort for the three vaccine interventions are shown in Table 37. Compared with the existing programme (which has no vaccination), the introduction of the HIV vaccination among female learners resulted in the additional net cost of US$ 436. This translated to four QALYs gained and a cost-effective ICER of US$ 95 per QALY gained (95% CI: US$ 88 – 102). Our analysis of the implementation of the HPV vaccination concurred with the global literature that found the HPV vaccine to be highly cost-effective. The intervention yielded a 44% increase in QALYs gained to 33 (95% CI: 33-34) compared to the existing HPV disease standard of care. The HPV vaccine programme cost 8% less than the existing cervical screening programme. This is not surprising considering the substantial financial implications of treating HPV-related cervical cancer or the associated pre-cancerous lesions. The negative ICER associated with the HPV programme implies an improvement in life-years as well as a reduction in costs. Dual HIV and HPV vaccine implementation represents an 18% net increase in QALYs gained over the HPV programme alone. With a negative ICER, the dual intervention also represents significant improvement in life-years associated with reductions in cost.

Table 37. Cost-effectiveness analysis of three vaccine interventions

The vaccine programmes were compared with the standard of care (2012) which had no vaccination. All costs are reflected in US$.

	Vaccination programme		Existing standard of care		ICER
	Cost	**QALY**	**Cost**	**QALY**	**per QALY gained**
HIV	2509 (2367 – 2642)	12.09 (11.95 – 12.24)	2097 (1955 – 2235)	7.76 (7.61 – 7.91)	95.22 (88.19 – 102.38)
HPV	1792 (1664 – 1915)	33.35 (33.03 – 33.67)	1937 (1794 – 2074)	23.19 (22.72 – 23.67)	Dominant
DUAL	4295 (4215 – 4497)	35.87 (35.54 – 36.18)	7507 (7088 – 7966)	23.93 (23.47 – 24.36)	Dominant

Discount rate 3%. (95% uncertainty intervals)

The HPV vaccine is considered cost-saving when it is implemented alone and in combination with the HIV vaccine. It becomes pertinent to understand the cost-drivers behind the HIV vaccine strategy. Table 38 is a breakdown of costs per capita associated with HIV vaccine and the current standard of care (no vaccination). The actual vaccine (listed under pharmaceuticals) is accountable for the considerable outlay in costs (an increase of 29%), and questions of individual vaccine cost or the need for several booster injections will need to be determined.

Table 38. Comparison of costs and components of the HIV vaccination programme

Detailed costs of the intervention compared to the standard of care. The intervention includes the vaccine intervention and the comparator costs. Costs are shown in US$.

Cost category	Per capita expenditure			
	Intervention	Standard	Difference	(% change)
Laboratory	**12.73**	**13.09**	**0.35**	**(-2.78)**
HIV rapid testing	1.06	1.41		
CD4 count	4.05	4.05		
Pap smear	1.13	1.13		
Viral load	5.95	5.95		
Creatinine	0.53	0.53		
Pharmaceuticals	**39.86**	**30.21**	**9.64**	**(+31.92)**
STI treatment	1.11	0.92		
Condom distribution	1.35	1.12		
Contraception	0.77	0.63		
Anti-retroviral therapy	27.34	27.34		
Vaccine	8.94	0.00		
Vaccine delivery*	0.15	0.00		
Bactrim® prophylaxis	0.20	0.20		
Human resources	**35.94**	**36.67**	**0.63**	**(-1.76)**
PHC nurse	20.70	22.24		
Counsellor	11.03	11.81		
Enrolled nursing assistant	1.68	0.00		
Medical officer	0.46	0.46		
Medical specialist	2.07	2.07		
Transport †	**0.47**	**0.00**	**-**	**-**
Total	**89.00**	**79.87**		

*Vaccine delivery includes the needle, syringe and alcohol swab for administration

†Calculated from average car rental cost incurred in providing a school-based service

3.2 UNCERTAINTY ANALYSIS

3.2.1 One-way sensitivity analysis

Model outputs were scrutinized using differing assumptions of parameters (Table 39). The duration of protection offered by the HIV vaccine influences its cost-effectiveness. Vaccines of longer protective duration are associated with improved ICER values. Reduced HIV vaccine pricing showed a significant improvement in ICER values with a 12% reduction when the vaccine price was halved and a 20% reduction at low vaccine prices compared to the baseline cost of US$12 per dose. A discount rate of zero percent was applied and resulted in a 15% reduction in the ICER value associated with the HIV vaccine programme. This was attributed to the differential timing of health gain (in future) and costs (upfront). Conversely, the doubling of the discount rate (six percent) increased the ICER values for the HIV vaccine programme by seven percent. When a lower coverage rate (40%) was examined for both vaccines, the ICER value for HIV vaccine implementation was driven up by 36%. Finally the implementation of a partially efficacious HIV vaccine (31% as described by Rerks-Ngarm (339)) was modelled resulting in a seven percent increase in ICER value ("Present" efficacy). Through each of these scenarios, the ICER values for the HPV and dual vaccine programmes were altered but remained cost-saving.

Table 39. Scenario analyses compared with base findings

One-way sensitivity analysis was done to systematically examine the impact of selected variables in the analysis by varying it across a plausible range of values with other variables remaining at their baseline level.

		HIV	**HPV**	**DUAL**
HIV vaccine – 3 years duration	Net cost	259.50	n/a	Dominant
	QALYs gained	1.58	-	10.71
	ICER	163.73	-	Dominant
HIV vaccine – 5 years duration	Net cost	305.02	n/a	Dominant
	QALYs gained	2.47	-	11.09
	ICER	123.31	-	Dominant
HIV vaccine price halved	Net cost	369.56	n/a	Dominant
	QALYs gained	4.33	-	11.93
	ICER	85.31	-	Dominant
Very low HIV vaccine price	Net cost	342.73	n/a	Dominant
	QALYs gained	4.33	-	11.93
	ICER	79.12	-	Dominant
Discount rate 0%	Net cost	340.16	Dominant	Dominant
	QALYs gained	4.10	10.14	11.91
	ICER	83.04	Dominant	Dominant
Discount rate 6%	Net cost	454.06	Dominant	Dominant
	QALYs gained	4.47	10.17	11.94
	ICER	101.65	Dominant	Dominant
Dual coverage 40%	Net cost	375.24	Dominant	Dominant
	QALYs gained	2.89	6.78	7.96
	ICER	129.93	Dominant	Dominant
“Present” efficacy	Net cost	447.37	Dominant	Dominant
	QALYs gained	4.41	10.16	11.30
	ICER	101.48	Dominant	Dominant

3.2.2 Probabilistic sensitivity analysis

The cost-effectiveness plane showing the plots of all 1000 simulations for each intervention is depicted in Figure 23. The plane shows considerable overlap in the three clouds of net costs by QALYs gained. It is clear though that a considerable proportion of the 1000 simulations per intervention results in a negative ICER indicating net cost-savings. The implementation of the HPV vaccine alone resulted in a net cost-saving of eight percent and when administered in combination with the HIV vaccine, resulted in 43% reduction in health care costs. The impact on costs is most pronounced in the dual vaccine intervention.

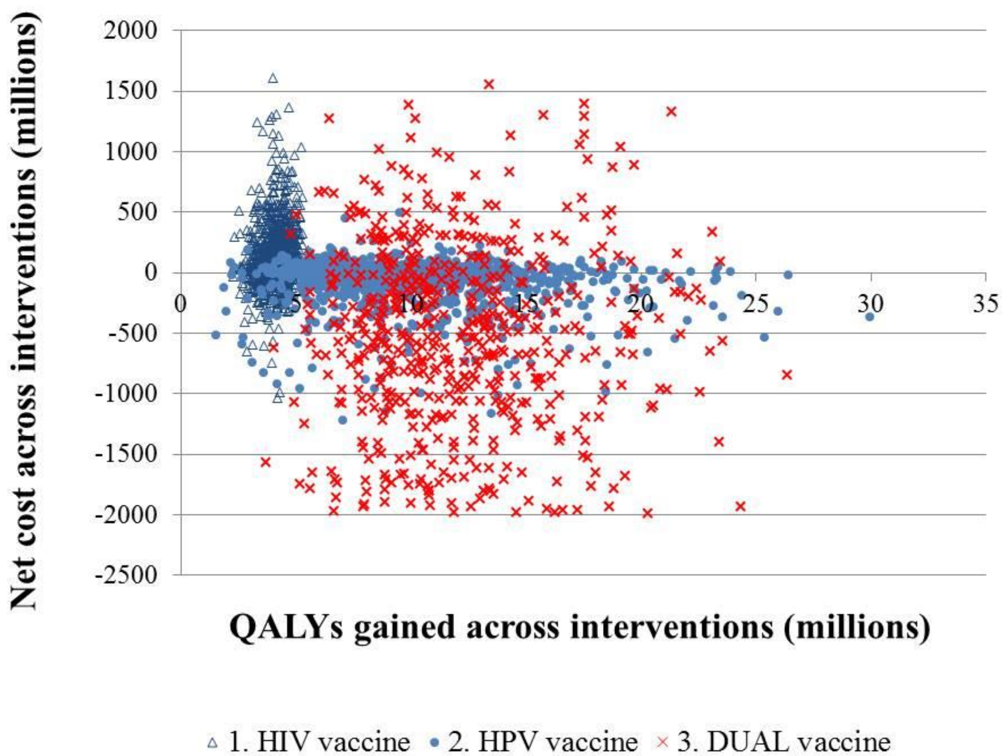

Figure 23. Cost-effectiveness plane for the three vaccine interventions compared to no vaccination

All three interventions are simultaneously plotted to reflect their relative cost-effectiveness. The y-axis shows the QALYS gained by each intervention and compares it to the net cost of each intervention (y-axis).

CEACs (Figure 24) were then applied to determine the optimal intervention in cost-effectiveness terms. The curve is constructed by calculating the probability that any of the interventions (compared with current standard of care) represents the optimal choice across the 1000 simulations, for selected WTP governmental thresholds (x axis: US$100 increments of cost per 1 QALY gained). The curves indicate all interventions to be cost-effective, and support the implementation of either vaccine programme. The HPV vaccine and the dual intervention seem to be cost-effective at low government spends per QALY gained, implying improved health outcomes with either of these interventions.

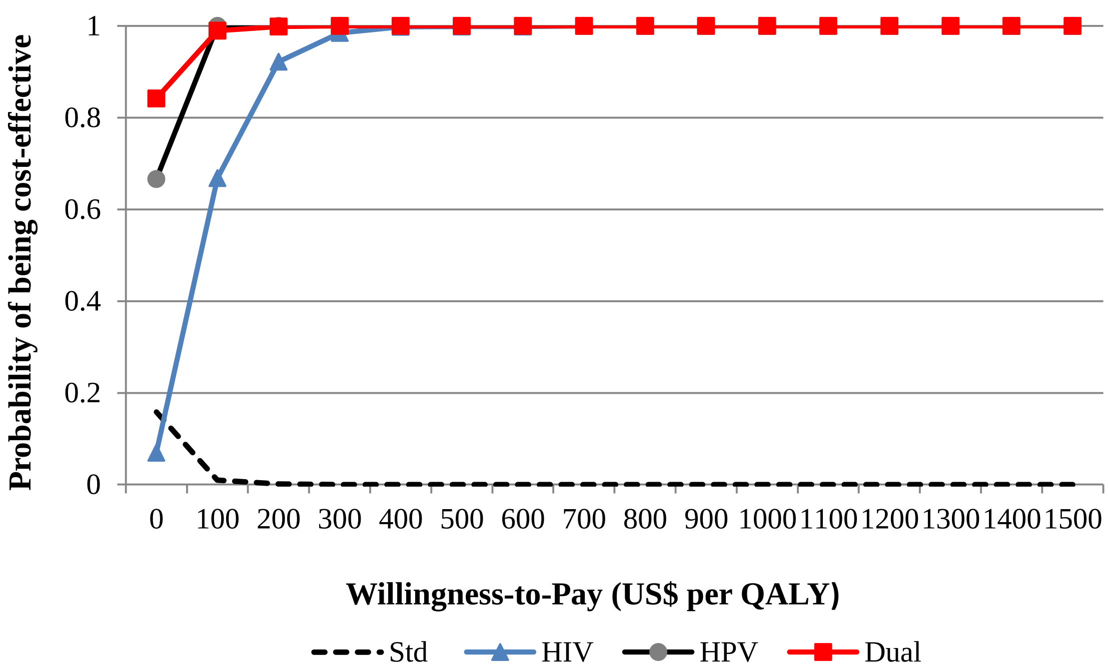

Figure 24. Cost-effectiveness acceptability curves for the three vaccine interventions

The x-axis describes the amount (US$) that a provider is willing to pay for an increase in unit of health gain (QALY). This is compared to the probability that the intervention would be cost-effective (shown on the y-axis).

3.3 DISEASE RISK REDUCTION

The ten-year ARR of HIV disease and HPV-related cervical cancer offered by the interventions were projected in Table 40. Individual disease incidence and dual mortality were the outcomes analysed. The introduction of the HIV or HPV vaccine programme showed improved outcomes related to their disease burdens. However, due to the mutual synergism of these diseases, the mortality and incident outcomes showed evidently greater risk reductions in the dual vaccine intervention.

Table 40. Reduction in disease risk and associated cost consequences

The table shows the ARR percentage calculated over a 10 year period. The effects of the dual intervention have marked health impacts over the vaccine implemented individually.

	10 year risk: Mean % (SE)				Absolute risk reduction
	Intervention		Comparator		
HIV					
Incidence	4.24	(1.25)	5.44	(1.38)	1.20%
Dual mortality	1.26	(0.07)	1.30	(0.10)	0.04%
HPV					
Incidence	0.26	(0.18)	0.40	(0.26)	0.14%
Dual mortality	1.28	(0.08)	1.30	(0.10)	0.02%
DUAL					
HIV incidence	0.20	(0.49)	5.44	(1.38)	5.24%
HPV incidence	0.00	(0.00)	0.40	(0.26)	0.39%
Dual mortality	0.09	(0.25)	1.30	(0.10)	1.21%

4. DISCUSSION

The study demonstrates the potential utility of developing a school-based approach to HIV and HPV vaccine delivery within the South African public health care sector. Adoption of this vaccination model could contribute significantly to improving the life expectancy among a highly vulnerable population (adolescent females) and strategically impact on several health burdens of the national government in a cost effective manner.

South Africa accounts for a significant proportion of the global burden of HIV disease and HPV cancer-related diseases with adolescents, particularly young girls, inadvertently responsible for the propagation of the epidemic (285). Driven by the magnitude of the problem, the national health department has weighed in with significant contributions of time and resource investment to enhance treatment services, but not prevention ones. While the issue of the HIV vaccine remains explorative and hypothetical, the response to the HPV-related diseases has been staggered and haphazard. The national cervical screening programme currently promulgated preceded the HIV epidemic and makes no amendment for screening practices based on the impact of HIV on HPV-related cervical disease (246). The national HIV guideline stipulates annual cervical screening for HIV-positive females, essentially undermining the national cervical screening guideline (247). The private health care sector adopts its own approach, separate from these. Couple these inefficiencies to the inadequate infrastructure for screening, abysmal uptake of cervical screening services since the introduction of the programme in 2001, and a neglected uptake of treatment among those with pathological screening findings and the management of cervical diseases is rendered dire (708).

It is under these circumstances that a school-based programme becomes highly plausible and relevant for several reasons. Adolescents are a key risk group for HIV and HPV preventive strategies. As a key population, school-going adolescents are more easily accessed than other commonly identified groups at high risk of HIV including commercial sex workers (who are more difficult to access as a result of stigmatisation) (701). The barriers encountered by adolescents in attempting to access health care services is well documented ranging from confidentiality breaches to the judgmental attitudes of health care staff, making it unsurprising that many opt not to come back for continuation of care (95). The setting of the school may potentially negate this negativity by providing a "safe space" that offers peer discussion and accessible and pertinent health care services. Neglecting the health care needs of adolescents and ignoring the barriers to care they face in accessing care will serve to challenge any success enjoyed by HIV prevention initiatives to date (172).

However, to view the HIV and HPV cancer-related disease burden in isolation is blinkered. While the findings of this study point inextricably to the cost-effectiveness of the vaccine scenarios, it does not address matters of cost. South Africa has to contend with several burgeoning epidemics in health care over and above HIV and HPV cancer-related disease including maternal and child health and NCDs - all competing for the same dwindling financial resources (5). A comprehensive body of work exists supporting the implementation of the HPV vaccine among females only (709). Much of this work concentrates on matters of cost-effectiveness where the female burden of HPV-related disease considerably outweighs that of the males. When health spending has to be focused on imminent health needs, it makes sense that the female school-going adolescents are targeted for HPV vaccination. This is contrary to HIV disease, where the spread amongst the genders are far more "democratic" and the opportunity costs of not treating males are far too great.

All three vaccine initiatives examined in this study were deemed cost-effective using the South African GDP per capita as an indication of society's WTP threshold. Further scrutiny of the results indicates that dual vaccine implementation would have the most substantive impact on HIV and HPV incidence respectively and on mortality associated with these diseases over a ten year period. The reason for this is anything but implicit – compared with HIV-negative women, HIV-positive women are reported to have higher HPV prevalence and incidence, higher HPV viral loads, more persistent disease and a greater prevalence of oncogenic subtypes (710-713). As such, targeting both diseases would prove synergistic. However, preventive interventions are often associated with uncertainty in projecting health gains, particularly those associated with an infectious disease (714). This modelling exercise suggests uncertainty around HIV vaccine pricing - an important consideration in light of the success achieved in procuring HPV vaccines at lower pricing by the South African government for the public sector (676). This would effectively decrease the ICER values. Further cost reductions may be imminent in HPV vaccine strategies as data emerges of the two dose regimen having equivalent efficacy to the three dose schedule (715) – a factor that could easily translate to considerable reduction in HPV vaccine delivery costs.

When Rerks-Ngarm documented the first HIV vaccine regimen to demonstrate any efficacy in human subjects, it spurred a series of discussions on the impact and role of a partially efficacious HIV vaccine. Data from the USA emphasizes that even a partially effective vaccine could provide temporal reductions in HIV incidence at the population level (690). So while the findings of this study suggest that a partially effective vaccine is cost-effective and warrants merit (Table 38: "Present" efficacy), it should be borne in mind that Andersson et al. modelled the vaccine used in the RV144/Thai trial in the context of South African and demonstrated similar health benefits but warned that a vaccine of limited efficacy had the potential to translate to millions of doses required at exceedingly high coverage levels (701). Data from this study also places much emphasis on the duration of protection afforded and the impact this has on cost-effectiveness. The real question remains however: can we honestly afford not to?

The social paradigm of these diseases further strengthens the case for vaccine implementation Poor health outcomes of HIV and HPV disease have long been linked with lower socio-economic circumstances (14). Given the exceptional vulnerability of women (particularly young women) to these diseases, coupled with the vast majority of the disenfranchised South Africans having erratic and ineffective access to health care, it is not inconceivable to view vaccine implementation as an equitable and necessary societal intervention.

This work highlights several pivotal areas of research that remain questioned. From a public health perspective, there is an urgent need to consolidate the national cervical screening practices in South Africa. Holding all health care providers to a defined, evidence-based standard of practice will allow for greater accountability and evaluation of practice. The impact of HPV vaccination of boys needs to be contextualized in the South African epidemic, as they serve as an important reservoir of disease. Finally, with the success achieved in negotiating reduced HPV vaccine prices with the manufacturers, it becomes imperative to consider the impact of the quadrivalent and nonavalent HPV vaccine implementation.

There are several limitations that apply to the study which are governed by data availability and the assumptions made. Firstly, vaccine implementation would result in significant societal benefits not captured by this model, thereby underestimating the full benefit of the intervention. Collection of societal data is labour intensive and difficult to acquire and thus not considered. Secondly, the intervention was limited to females based on comparative disease burdens. Males represent a significant reservoir of disease and could play a key role in the development of herd immunity (716). Thirdly, it would be difficult to quantify and therefore assess the impact of risk compensation – where adolescents engage in increased sexual risk-taking activities based on the perceived protection of the vaccine. Fourthly, the vaccine was assumed to be administered to sexually naïve adolescent females (prior to sexual debut), bearing in mind the relevance of early sexual debut among South African adolescents (99) and the high incidence of sexual abuse of children in South Africa (254). The fifth concern was that cost measurement relied largely on the UPFS and NHLS pricelists. There are obvious limitations in applying such generic measures of costs but limited available South African costing data provided little alternative. Lastly, the characteristics applied to the HIV vaccine are hypothetical, as there is no commercially available vaccine. These assumptions, and the uncertainty around them, were applied to determine plausible entry points of the vaccine into the health sector when they become viable.

5. CONCLUSION

The findings of this study support the implementation of the HPV or dual HIV and HPV vaccine programmes administered to school-going females as a cost-effective and imperative primary prevention strategy targeting the considerable burden of HIV and HPV cervical cancer-related diseases in South Africa. The social paradigm of these diseases further strengthens the case for vaccine implementation as an equitable societal intervention.

CHAPTER 8

RESULTS: THE PRICE OF PREVENTION - COST-EFFECTIVENESS OF BIOMEDICAL HIV PREVENTION STRATEGIES IN SOUTH AFRICA

1. INTRODUCTION

Despite several campaigns by national government to control the HIV disease burden, South Africa remains the focus of the HIV pandemic accounting for 18% of the global prevalence of disease (300). The national HCT campaign launched in 2010 saw a 15% increase in numbers of people having HIV tests between 2008-2012 (97). This is a noteworthy achievement considering that data from modelling studies estimate that the universal implementation of HCT among South Africans from the age of 15 years could result in a 1% HIV prevalence reduction over a 50 year period (296). Additionally, by 2010, 98% of public health facilities were offering PMTCT which translated to a reduced annual infections rate of two percent in 2013/2014 (297). Other interventions included the national distribution of 506 million condoms in 2013/2014 alone, representing the most established condom distribution programme globally (297). HIV and AIDS education has become a core component of primary and high school curriculums through a Life Skills Education Programme. The dynamic programme was developed to support those children already living with HIV in addition to preventing new infections through education. Lastly, South Africa is home to the most expansive ART treatment programme in the world, a programme that accounted for a third of new ART drug recipients globally between 2010 and 2013 (300). Contrary to these efforts, 58% of South Africans are unable to access the life-saving ART treatment, despite demonstrated eligibility (300). Thus the massive initiatives made by government to ease the HIV disease burden have been consistently undermined by high HIV incidence rates over the years (South Africa accounted for 16% of the global incidence of HIV in 2013) (300).

The major advances achieved in biomedical interventions in the last decade have urged clinicians and decision-makers to strongly rethink their choice of HIV prevention packages. Observations arising from clinical trials investigating VMMC (717) and oral PrEP (263-265, 267) have demonstrated some degree of success in decreasing sexual transmission of HIV. The general consensus remains that a 'multi-faceted combination prevention' approach is probably the best option and is critical to curbing the progression of the epidemic (108, 718, 719). Clinical trials investigating combination interventions are rarely documented given the financial, ethical and feasibility complexities that surround them; yet they are crucial to defining an optimal portfolio of prevention. In the context of this study, we have considered the cost-effectiveness of the implementation of PrEP, HIV and HPV vaccinations and VMMC programmes against the scaling-up of the coverage of ART.

The legitimacy of PrEP as a HIV prevention intervention was endorsed by the encouraging findings of several HIV PrEP trials and cemented by the observed 96% reduction in HIV transmission rates associated with early ART use in serodiscordant couples (HPTN 052) – data that has stimulated critical policy discussions regarding the use of ART in HIV prevention (325, 720). The first significant findings were reported among men and transgender women who had sex with men in the iPrEX trial, which effectively yielded a 44% reduction in HIV acquisition with a daily dose of TDF/FTC (319). Following which, two large trials found PrEP to be equally effective (between 63-73%) in reducing heterosexual HIV transmission in the Partners PrEP conducted in Kenya and Uganda (TDF or TDF/FTC daily) and TDF2 (TDF/FTC daily) studies conducted in Botswana (320, 322). Similar results were not reproducible in the South African setting as FEM-PrEP (recruiting heterosexual women in South Africa, Tanzania, and Kenya for daily TDF/FTC) and the oral arm of the VOICE trial (recruiting women in South Africa, Uganda, and Zimbabwe) were prematurely closed for futility (315). The VOICE trial stopped its gel arm when it became evident that the daily use of the gel was safe but ineffective (316). The CAPRISA 004 trial (a proof of concept study supporting pericoital vaginal microbicide application) did enjoy a measure of success when the use of a one percent TDF vaginal gel decreased HIV-1 incidence by 39%, but this success was short lived (313). The FACTS 001 study, a study conceptualised to generate supporting data for microbicide licensure in South Africa, was found to be ineffective alluding again to the poor adherence patterns derived and questioning the future use of this prevention modality (314, 316). Despite these reservations regarding adherence, oral PrEP is being introduced in many developing countries including South Africa and due consideration must be given to how this intervention will feature financially, programmatically and politically in the South African prevention efforts (332, 721, 722).

VMMC represents another promising HIV prevention initiative in South Africa. Data garnered from observational studies (723-725) and three RCTs conducted in Kenya, South Africa and Uganda (63-65) prove conclusively that circumcised men are afforded a significantly lower risk of acquiring HIV infection. The strong epidemiological evidence base for VMMC has been strengthened by the plausible biological basis for the protective effects of VMMC (726) and the cost-effectiveness, or even cost-saving, of the intervention has been reinforced by several studies (717, 727-729). In addition to the public health benefits of the HIV prevention strategy that reported high efficacy (approximating 60%), VMMC is a once-off medical procedure with partial but potentially durable effects (569). The coverage rates for VMMC still remain surprisingly low, with 3% coverage reported in a sample of 14 SSA countries (730). Heeding the global call to improve coverage, South Africa had conducted just over three million VMMCs by 2012 (97). It should be remembered that countries continuing to report low circumcision rates have extensive scope to draw the benefits of the intervention going forward (731).

Vaccines are considered one of the most cost-effective intervention in public health. Despite several early HIV vaccine failures (337, 342), Rerks-Ngarm (2009) demonstrated the first HIV vaccine (RV144/ Thai trial) to demonstrate any efficacy in human subjects (339). The HIV vaccine regimen was then optimized by undergoing modification to make it Clade C specific, followed by changing the adjuvant and the protein, and then entered into Phase I clinical trials to assess safety and immunogenicity at six major South African clinical research sites as part of the HVTN 100 study (345). The cost information garnered from the evaluation exercise regarding the implementation of the vaccine into the EPI would represent a key advocacy tool for decision-makers should this vaccine become commercially available (669, 670). For the purposes of this study, we are considering the dual implementation of the HIV vaccine and the HPV vaccine. The biological relationship between HIV and HPV has long been established. The acquisition of HIV is enhanced in the presence of cervico-vaginal HPV disease (654, 655) and the detection of HPV is known to increase drastically post HIV seroconversion (653). The clinical manifestation of the HIV-HPV relationship is rapidly progressive disease (651), associated with significant mortality and morbidity that remains a major concern to the national health department. Given the intimate relationship the pathologies share, it is not inconceivable that the HPV vaccination could potentially play a role in reducing HIV transmission on the biological basis that HPV infection increases the acquisition of HIV infection (463). South Africa has the highest cervical cancer incidence and mortality globally (92), and the HPV vaccine has already been rolled out to a proportion of school-going female learners (732).

The implementation of the most efficient portfolio of HIV prevention strategies requires considered evaluation of the comparative costs and benefits of the alternate strategies. The economic evaluation of these interventions individually and in combination with others can provide insight into our understanding of their potential synergistic effects (733), without the financial challenges of multi-intervention clinical trials. Additionally, CEA can guide decision-makers in the efficient allocation of limited health budgets. Few studies in the past have considered evaluating multiple interventions (625) due to ethical, financial and feasibility constraints; and have chosen rather to concentrate on individual interventions. There has been no previous evaluation of the HIV vaccine in this context. The aim of this study was to conduct an economic evaluation on individual and combination HIV preventive strategies and compare their impact against both the current roll-out of ART and a potential scaling-up of the ART programme.

2. METHODS

The methods used in this study complied with the reporting guidelines of the CHEERS statement (618).

2.1 STUDY OVERVIEW

The evaluation included South African school-going adolescents in 2012. The programme was suggested for school-based implementation in accordance with the national health initiative to support school-based SRH services (154). The intention was to target learners prior to their sexual debut, thus preventing HIV exposure and potential acquisition. A lifetime horizon of 70 years was modelled as it was considered congruent with current South African life expectancy. The provider perspective was adopted. The data generated from this evaluation would be used to explore health service delivery and decision-making; and review the financial consequences of introducing these health interventions in the public sector. The interventions were considered prevention strategies that could reduce the HIV-associated burden of disease and mortality. The vaccine intervention was modelled and compared to the standard of HIV care and treatment in South Africa comprising HCT, ART, STI treatment and condom distribution (247). The current coverage achieved by the national ART programme was estimated at 29% (300). Economic costs and health outcomes were discounted at a rate of three percent, and adopted an uncertainty range of zero to six percent, as recommended by the WHO-CHOICE guidelines (537).

2.2 OUTCOME MEASURES

The validation of the EuroQol EQ-5D health outcome measurement tool for measuring HRQOL of HIV/AIDS in Africa, has essentially validated the use of the QALY in the South African health context (555). The QALY combines survival and HRQOL into a single health summary measure informing decision-making regarding the relative value for money of health care interventions (624). The estimation of the QALY is derived from calculating the total LYG from an intervention, then multiplying each year by a quality of life score, where 0 = worst health and 1 = best health, thus reflecting the quality of life achieved in that year (130). The ICER of the interventions compared to the standard of care was measure using Equation 25:

$$\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \qquad \text{(Eq. 27)}$$

Where C_1 and E_1 = costs and effects of the comparator, and C_2 and E_2 = costs and effects of the intervention.

HIV/AIDS pooled utilities derived from a meta-analysis and applied to the cost-utility analyses of HIV-related interventions (633). The utility weights for HIV disease appears in Table 41.

Table 41. HIV-related utility weights

The table describes the health-related quality of life weights for the different HIV-related health states where full health carries a weight of one (1).

Parameters	Estimate	Source
Full health	1	
HIV disease		
Asymptomatic	0.94	(633)
Symptomatic	0.82	(633)
AIDS	0.70	(633)

2.3 STUDY INPUTS

Input parameters concerning both HPV and HIV disease were assessed in the model to demonstrate the impact of the dual vaccine strategy (Table 42). Only HIV-related costs were included in the model. The model was constructed and parameterized using transition probabilities drawn from South African published literature. Costs were inflation adjusted to the year 2012 using the CPI. The average exchange rate for the South African Rand (ZAR) to the United States dollar (US$) was applied. Costs were converted into the equivalent value for the 2012 US$ where (US$ 1 = ZAR 8.21) allowing for international comparison (591).

The standard HIV treatment was assumed to be delivered by PHC nurses who consulted patients. Complicated cases would be referred to doctors or medical specialists depending on the nature of the condition. Pharmaceutical costs included ART, treatment of STIs and condom delivery. Additionally, the intervention cost comprised the intervention cost (vaccine, vaccine delivery and related costs) in addition to the comparator cost as both services would run concurrently in the intervention group. Laboratory test prices were obtained from the NHLS and medication, consumables, additional pharmaceuticals and valuations of medical personnel costs were derived from the UPFS sourced from the National Department of Health. These parameters are detailed in Table 43. Implementing the interventions accrued the annual estimated costs comprising included human resources (e.g. consultation with a PHC nurse and counsellor); pharmaceuticals (e.g. drugs, STI treatment and condoms) and laboratory costs (e.g. regular HIV testing, creatinine monitoring and pregnancy testing) – as directed by the pertinent guidelines.

Table 42. Model parameters pertaining to the study population

Disease transition from one health state to the next is shown in Table 42. The estimates were drawn from the South African literature for 2012.

Parameters	Base-case estimate	Reference
Vaccine characteristics		
Coverage	60%	assumption
HPV vaccine efficacy	70%	(274)
HIV vaccine efficacy	50%	assumption
Treatment uptake		
Cervical screening	13.6%	(92)
ARV therapy	29.0%	(300)
HPV treatment	35.3%	(250)
Transition probabilities (represented as percentages)		
HIV-negative		
Development of LSIL	3.00	(651)
Progression of LSIL to HSIL	1.69	(651)
Progression of HSIL to cancer	3.84	(250)
HIV-positive		
HIV incidence in general population	2.28	(97)
HIV incidence in HPV disease	5.39	(651)
Development of LSIL	14.00	(51, 268)
Progression of LSIL to HSIL	6.00	(51, 268)
Progression of HSIL to cancer	8.10	(651)
Mortality		
Mortality in general population	1.16	(637, 678)

Table 43. Unit cost of screening, diagnosis and treatment of HPV disease

The estimates were drawn from the South African literature for 2012. All costs are reflected in US$.

Economics	**Value**	**Range**	**Reference**
Cost	3.0%	(0 – 6%)	(537)
Outcome	3.0%	(0 – 6%)	(537)
International comparison (ZAR: 1US$)	ZAR 8.21	-	(591)
HIV disease related costs	**Distribution**	**Value**	**Reference**
HIV programme			
HIV vaccine	-	12	assumption
Vaccine delivery per dose [a*]	Gamma	17	(638-642)
Existing prevention program (incl. HR)	Gamma	65	(639-643)
HIV counselling and testing (HCT) (per test)	Gamma	23	(639, 640)
Cost of HIV rapid testing	Gamma	2	(639, 640)
ARV treatment	Gamma	310	(640, 643, 644)
Not on ARV	Gamma	65	(643)
Other HIV prevention interventions	**Distribution**	**Value**	**Reference**
HPV vaccine	-	17	(706)
Vaccine delivery per dose	Gamma	17	(638, 640)
Annual PrEP cost	Gamma	140	(734)
Voluntary medical male circumcision	Gamma	79	(735)

[a] Initial course comprises 6 doses

*Annexure A outlines the costing structures used

2.4 INTERVENTIONS CONSIDERED

2.4.1 HIV vaccine

As there is no commercially available HIV vaccine, the vaccine characteristics considered in this evaluation are hypothetical. The characteristics were based on the available literature and determined by the characteristics suggested by the P5 (a research collaboration dedicated to expanding research from emanating from the RV144/Thai trial) (372). The HVTN 100 vaccine regimen was applied in this evaluation adapting the ALVAC prime ALVAC/gp120 boost of the RV144/Thai trial but with an additional boost at month 12. The purpose of the boost was to counter the declining immune response described in the RV144/Thai trial a year following the vaccine administration. Should the vaccine induce adequate immunogenicity, it will be entered into landmark Phase IIb/III HIV vaccine efficacy studies (provisionally scheduled for South Africa in 2016) called the HVTN 702 study.

The HIV vaccine coverage estimated 60% receiving the initial course. This was a roughly approximated to the 68% coverage achieved for the 3rd dose of DTP (DTP3) (674). The DTP3 coverage has been validated as a proxy for immunisation system strength and performance nearly globally in the recent decades (675). The coverage range was then explored in the sensitivity analysis. The HIV vaccine was estimated at a cost of US$ 12 per dose (base-case), vaccine efficacy was 50% (Range: 30-70%) and the vaccine duration of protection spanning ten years (achieved through the administration of annual boosters). The rationale for the booster was the declining immunity documented in the RV144/Thai trial 12 months after the vaccine was given for the first time. The model countered the diminishing immunity by applying the conservative approach of annual boosters. While this may not represent a pragmatic solution, it merely translated to an overestimation of costs in the context of an economic evaluation. The HIV vaccine price of US$ 12 roughly corresponded to the public sector pricing of the HPV vaccine pricing (US$ 17). Lower vaccines prices were considered appropriate considering the great strides made in the public sector in negotiating reduced pricing for ART and HPV vaccines (644, 676) and given the extensive disease burden in the country. The price assumption was additionally tested in the sensitivity analysis. The bivalent HPV vaccine was modelled as it is already being administered in lower socio-economic schools as part of the government initiative (650). The negotiated vaccine price was US$ 17 per dose and efficacy was determined by the documented clinical trials of the vaccine (274). The HPV vaccine course was completed over two years and was administered concomitantly with the HIV vaccine to achieve vaccine coverage of 60%. The HPV vaccine was assumed to confer lifelong protection, as per the indications in the literature (662). Health service delivery occurred at schools in the model. Relevant HIV-related cost components were identified from the 2013 national treatment guideline that are adopted in the South African public health care sector (247).

2.4.2 HPV vaccine

The implementation of the HPV vaccine was considered in this study considering the synergistic relationship HPV disease shares with HIV disease (268). Reporting the global highest disease burden for both these diseases, it makes programmatic sense for South Africa to integrate their responses to these diseases. Progression to cervical cancer is drastically increased in the presence of HIV infection and the bivalent vaccine [Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium)] targets the VLP types 16/18, that have been implicated in the aetiology of 64% of cervical cancer in South Africa (92). The vaccine was considered at 60% coverage, but limited to the female population only.

2.4.3 Voluntary medical male circumcision

It has been definitively proven that VMMC can reduce female to male sexual transmission of HIV by 60% (Range: 28-66%) (64). These findings informed the WHO decision to launch the exceptional public health initiative in 2009 proposing 80% coverage of voluntary, safe, culturally appropriate and affordable VMMC by 2016 (63). South Africa conducted 150 000 VMMCs by April 2011, averting one infection for every five procedures done in an attempt to observe the call from the WHO (329). However, the services in South Africa have been limited as initially, the procedures could only be performed by doctors and the procedures were marred by inadequate health facilities and poor surgical care (330). The introduction of PrePex (an elastic ring device requiring no local anaesthetic that can be placed and removed by a mid-level health care worker) in South Africa since has proved promising and may hold the key to increasing the amount of VMMCs performed without impacting on the limited numbers of health care workers available. VMMC is considered a highly cost-effective intervention (735). Being a once-off procedure that has potential lifelong benefit, VMMC holds the promise of being a significant player in the South African fight against HIV (735). The model assumed VMMC coverage of 60%, and this was evaluated in the sensitivity analysis. The model itself was adjusted for VMMC inclusion but running the model exclusively with the male epidemiological parameters. This model was then compared to the gender integrated model. The cost evaluation considered the PrePex system for VMMC, as this was a cheaper procedure that negated the need for the formerly used surgical procedures (735).

2.4.4 Pre-exposure prophylaxis

ART chemoprophylaxis has shown great promise in preventing HIV acquisition. In 2010, the landmark iPrEx study demonstrated an encouraging 44% reduction in HIV incidence among MSM using daily doses of TDF. Data from this work forms the basis for the MSM ART chemoprophylaxis standard of care in South Africa (318). The model employed in this evaluation study uses the algorithms of this guideline to determine the costs implicated in a national PrEP programme. (The new South African guideline was released after this manuscript was submitted for consideration (736)). HPTN 052, a pivotal study conducted in 2011, was associated with a 96% reduction in HIV transmission to the HIV-negative partner when ART was initiated early (in people with a CD4 T-cell count between 350-550 cells/mm^3) in the HIV-positive partner of a serodiscordant couple (325). Oral PrEP (a combination of TDF/FTC) has been approved for use in South Africa since late 2015, though the indications for use and the extent of the roll-out have yet to be properly defined. The monthly cost of the drug used in this analysis was determined by the current tender price that the drug is available to the South African government (US$ 6 per month in 2012) (734). Oral PrEP, not vaginal microbicidal formulations, was considered in the analysis. The study assumed coverage of 60%, with effectiveness of 67% (Range: 44-81%) for high adherence and 21% (Range: -31-52%) for low adherence (319, 320, 322, 737). Lower price estimates, coverage and effectiveness measures were assessed in the sensitivity analysis.

2.4.5 Antiretroviral therapy

The model considered the HIV prevention interventions discussed against the 2012 roll-out of ART (29% coverage) (300) and against a potential increase in the roll-out to cover the 58% treatment gap cited by UNAIDS (300).

2.5 ASSESSING COMBINATION INTERVENTIONS

As mentioned the combined effectiveness of two interventions (such as VMMC and PrEP) has rarely been assessed in a clinical trial setting. In the absence of published data, mathematical modelling techniques were used to determine the combined effectiveness under different assumptions (625). The methodology for the calculation of the combined intervention effectiveness was adopted from a similar study conducted by Long and Stavert (625). They suggested that the efficacy may be multiplicative (e.g. if VMMC is assumed to be 60% effective and PrEP 67% effective, then the combined effectiveness would be calculated as in Equation 26:

Combined effectiveness = (1-[(1- 60%)*(1- 67%)] = 86.8% (Eq. 27)

2.6 MODEL-BASED ECONOMIC EVALUATION

The data capture and analysis was performed in Microsoft Excel® (Version 2010) (Microsoft Corp., Redmond, WA). Ersatz version 1.2 (www.epigear.com) was used to perform the uncertainty analysis. Ersatz is a boot-strap add-in application for Microsoft Excel. Figure 25 shows the semi-Markov model simulation with annual cycles that was developed. Semi-Markov models were considered in this evaluation as it allowed for the addition of tunnel states that counter the 'memoryless' nature of the Markov model and permitted the modelling of recurrent disease episodes. The study population commenced the model disease free and each year was exposed to the risk of acquiring either HPV or HIV disease with the rate of disease acquisition adjusted for based on which primary infection was acquired. The model was built using socio-demographic data of the proportion of the population that accesses public health care in South Africa (707). The study aggregated simulated data of individuals representing a 69% coverage rate, the estimated access rate to PHC services (707). The dual vaccination programme was specifically offered to female learners on a voluntary basis. Among males, the impacts of HPV disease/HPV vaccination were omitted. A proportion of healthy individuals (coverage) would be vaccinated against HIV and HPV disease, while the rest remained unvaccinated. Annually, healthy individuals were exposed to the risk of acquiring each disease.

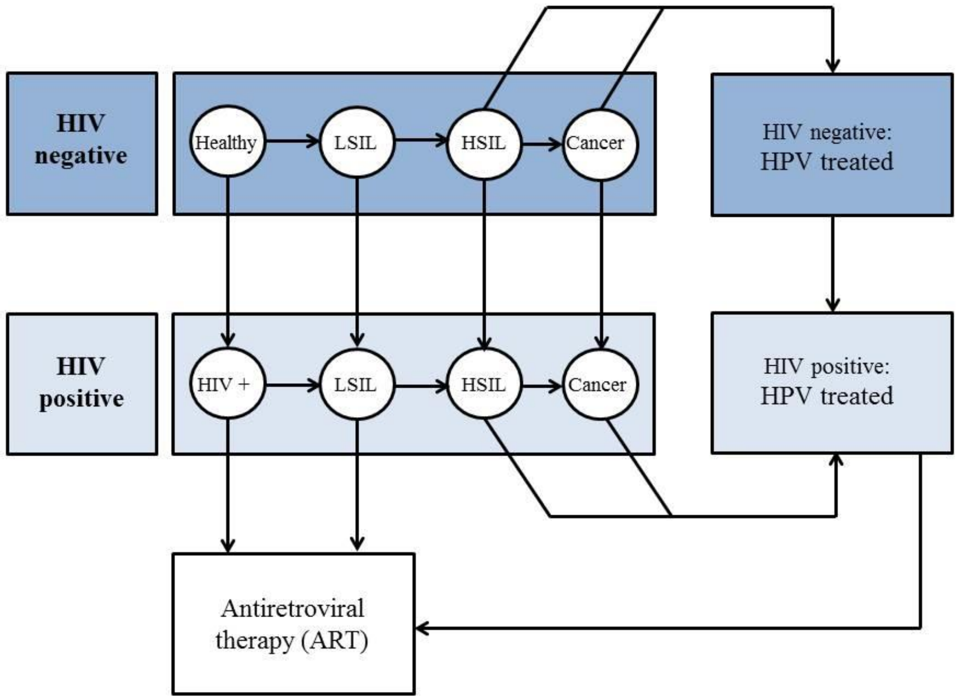

Figure 25. Semi-Markov model for HPV and HIV-related disease states

Healthy individuals (vaccinated and unvaccinated) may remain uninfected or transition into HPV or HIV disease. Those acquiring HPV disease are at risk of being HIV infected (if unvaccinated against HIV). Each state may progress to death during any cycle, the rate of which was dependent of the state from which they progressed. LSIL – low-grade intraepithelial neoplasia; HSIL – high-grade intraepithelial neoplasia

Where the dual vaccination strategy was being considered, healthy individuals could acquire HPV disease from a LSIL to HSIL, which has the potential to progress to cervical cancer. At each proposed HPV-related health state, an individual may die (not represented graphically) or acquire HIV infection (which would see them progress on the lower 'HIV-positive' spectrum of disease). HIV-positive, HPV-infected individuals that were treated for HPV disease could potentially develop recurrent HPV disease. The model allowed for females with treated and untreated HPV disease to acquire HIV infection. There was a greater risk of transition to more serious HPV states among those HIV-positive vs. those HIV-negative. HIV-positive individuals could potentially enter the HIV treatment pool. Every health state, irrespective of disease status, could progress to death at a rate determined by their current health state with consideration to the background mortality independent of their current health state. Mortality transitions were excluded from Figure 25 as they rendered the model excessively 'bushy' and concealed the key message of the diagram. The arrows represented the transition probabilities from one state to another, with costs and utility measures then added to each health state to predict costs and QALYs over the 70 year duration of the intervention and the comparator. Following HIV vaccine cessation, the HIV event rates were adjudged to be lower among those who received the HPV vaccine than among those who had not (51, 268). HPV vaccine protection was considered lifelong (662).

One-way sensitivity analyses were run to evaluate the influence of single assumptions on cost and health outcomes. The model uncertainty and robustness of the results were evaluated using PSA with a bootstrapping technique. Cost-effectiveness scatter plots were used to display the findings graphically. Data from the PSA was used to determine the cost-effectiveness of the intervention. South Africa has not formally adopted a WTP threshold, and the GPD per capita (2012) was applied as a proxy measure as recommended by the WHO (537, 680). The WTP threshold was defined as US$ 7 508 (ZAR 61 641) per QALY gained. Given the lack of sensitivity of the GDP as a measure of cost-effectiveness, a benchmark intervention was additionally used as a threshold established by analysis of existing practice (585). In the case of South Africa, VMMC had been established as a cost effective intervention in several analyses (738, 739). To validate the finding of this analysis, the cost-effectiveness was assessed against both the GDP and the benchmark intervention.

The study participants were considered sexually naïve at the start of the model. The model assumed that children eligible for schooling were attending school, and that the consent obtained from parents was reflected in the coverage rates. The efficacy of dual interventions was considered multiplicative (625) as there is rarely data obtained from clinical trials reporting the efficacy of two prevention interventions simultaneously introduced. The model conformed to the principle of global uptake and provision of HCT in schools as stipulated by the national policy (295). The exercise modelled the roll-out of HIV preventive interventions under the umbrella of the comprehensive school-based programme to be delivered to all learners, irrespective of socio-economic status. Lastly, the model assumed relatively high uptake of the health services delivered at schools, given that the care was provided in a safe and familiar setting, without impacting negatively on school attendance. There have been no formal studies to validate this assumption.

2.7 ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. The study did not involve any direct patient contact. Rather, the study drew transitional probability data (input parameters) from the relevant, published South African data. No individual data records were accessed, and the information used could not be linked back to any specific individual that would have been involved in these published data. As such, patient records were considered anonymized and de-identified prior to analysis.

3. RESULTS

3.1 SINGLE INTERVENTIONS

The implementation of individual HIV prevention interventions was compared with the cost of ART in the public sector (Table 44). The coverage of ART in 2012 was considered at 29% and included HCT, condoms and STI treatment being offered at facilities (300). Scaling-up the coverage of the current ART programme to 58% to meet the demands of the existing deficit in South Africa would likely prevent new infections through possible herd immunity but was associated with a minimal decrease in mortality. However, this improvement in health outcomes comes at an appreciable cost with a marginal improvement in the QALYs gained as the intervention influences incidence indirectly. Similar results were obtained from the HPV vaccine which shares a synergistic relationship with HIV, and reduces HIV incidence indirectly (51, 268). The health effects of the HPV vaccine and HIV vaccine administered in combination to women is marked. There is a reduction in HIV incidence, HIV associated mortality documented and the intervention is significantly cost-effective at US$ 7.02 per QALY gained. Individually, the HIV vaccine and VMMC has similar health benefits to the dual vaccine initiative, but the VMMC project is more cost-effective given that it represents a once-off procedure with no further follow-up required, in the absence of complications. PrEP is an expensive option, with an ICER of US$ 257 per QALY gained. By the standards of the WHO CHOICE, every intervention would be deemed cost-effective as the ICER values are below the GDP defined threshold of cost-effectiveness (US$ 7 508). The ICER for VMMC could also serve as a proxy to benchmark intervention cost-effectiveness in South Africa, as it has been the validated through several independent research studies in South Africa as a cost-effective medical intervention (585). By virtue of this benchmark, only the dual vaccination strategy would then be deemed cost-effective. The dual vaccine strategy offered the largest gain in health benefits for US$ 7 per QALY gained.

Table 44. Health outcomes and cost-effectiveness of individual HIV prevention interventions

Single interventions are compared with the status quo (i.e. continuing to treat HIV infection with ART at 29% coverage (300)).

	HIV infection (over 10 years) (%)			Incremental		
	Incidence	**Infections averted**	**Deaths**	**QALYS**	**COST**	**CER**
Status quo	5.44	-	0.43	12.53	6 467.96	-
Upscale ART	-	-	0.42	+ 0.56	+ 461.27	823.21
HIV vaccine	4.28	21.24	0.34	+ 4.80	+ 445.41	92.77
HPV vaccine	5.30	2.54	0.41	+ 3.68	+ 488.20	132.53
Dual vaccine	3.95	29.00	0.30	+ 14.30	+ 100.42	7.02
VMMC	3.97	27.39	0.32	+ 12.52	+ 379.50	30.32
PrEP	3.79	30.24	0.31	+ 13.04	+ 2 247.83	172.41

ART – antiretroviral therapy; HIV – human immunodeficiency virus; HPV – human papillomavirus; Dual vaccine – HIV and HPV vaccinations; VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis (ART scale-up covers the ART deficit of 58%; HIV and HPV vaccine quoted at 50% and 70% vaccine efficacy respectively; VMMC efficacy is 60%, PrEP efficacy is 67% (Range = 21-67%); all coverage = 60%.)

The graphical representation of these results displays the dual vaccine strategy to be the most economically efficient strategy (Figure 26). The price of the PrEP intervention is undetermined at this point, but the assumption made reflects a rather optimistic scenario: markedly reduced pricing

(US$ 220 per annum) with high adherence (67%) and high coverage (60%). Despite this, the implementation of PrEP remained one of the least cost-effective strategies, even at the current low tender price in South Africa.

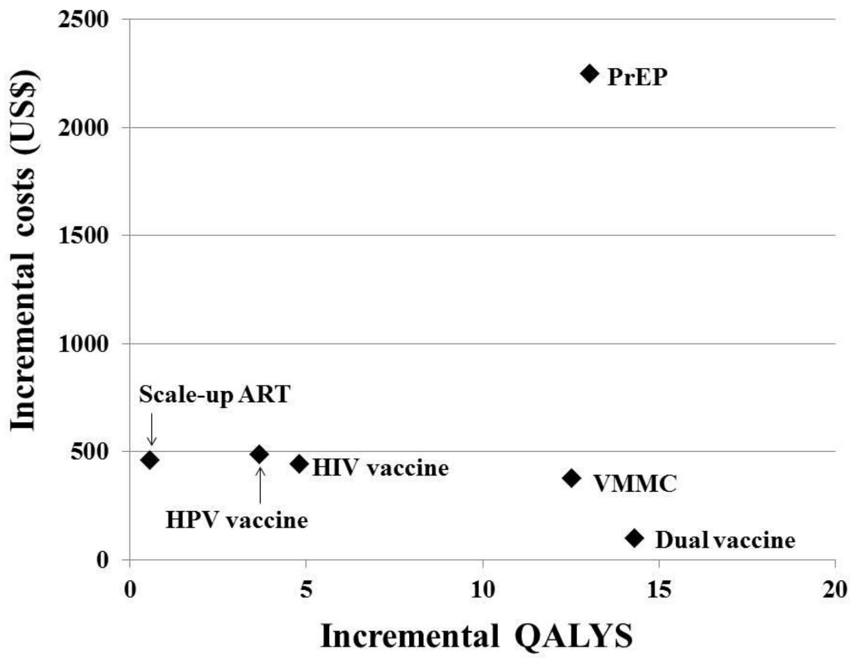

Figure 26. Cost-effectiveness analysis for the individual HIV prevention strategies

Discounted incremental costs and QALYS over 10 years are displayed for the single interventions.

ART – antiretroviral therapy; HIV – human immunodeficiency virus; HPV – human papillomavirus; Dual vaccine – HIV and HPV vaccinations; VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis

3.1.1 Sensitivity analysis of single interventions

A one-way sensitivity analysis demonstrates the impact of varying a single parameter on the overall cost-effectiveness (682). Table 45 identified the markedly improved ICER outcomes associated with VMMC and the dual vaccine strategy compared with the implementation of the HIV vaccine alone or with an intervention that involved the use of PrEP. Unsurprisingly, decreased cost and increased intervention effectiveness and coverage rates were associated with improved ICER values across all interventions. The higher discount rate, at 6%, was also associated with an improve ICER value. This could be explained by the investment for the intervention being made now (present costs) with benefits only being realized at a later date (future implications).

Table 45. Scenario analyses compared with base findings

One-way sensitivity analysis systematically examined the impact of selected variables in the analysis by varying it across a plausible range of values with other variables remaining at their baseline level.

			HIV Vaccine	Dual vaccine	PrEP	VMMC
Discount rate	0%	Net cost	4.81	14.28	13.06	12.54
		QALYs gained	447.38	84.42	2 236.88	370.65
		ICER	93.05	5.91	171.22	29.56
	6%	Net cost	4.80	14.31	13.03	12.51
		QALYs gained	446.76	107.58	2 254.96	385.58
		ICER	93.10	7.52	173.05	30.82
Cost	High	Net cost	4.80	14.30	13.04	
		QALYs gained	532.55	193.14	2 247.83	n/a
		ICER	110.92	13.50	172.41	
	Low	Net cost	4.80	14.30	13.04	
		QALYs gained	399.66	51.73	1 723.95	n/a
		ICER	83.24	3.62	132.23	
	Very low	Net cost	4.80	14.30	13.04	
		QALYs gained	373.12	23.48	1 400.79	n/a
		ICER	77.71	1.64	107.44	
Effectiveness	High	Net cost	4.69	15.03	13.04	
		QALYs gained	426.61	99.47	2 253.37	n/a
		ICER	90.97	6.62	172.83	
	Low	Net cost	4.92	13.61	10.19	
		QALYs gained	464.96	101.02	1 869.09	n/a
		ICER	94.58	7.42	183.50	
Coverage	High	Net cost	5.60	16.68	15.21	14.60
		QALYs gained	486.72	84.23	2 557.83	371.64
		ICER	86.89	5.05	168.16	25.45
	Low	Net cost	2.40	7.15	6.52	6.26
		QALYs gained	321.49	148.99	1 339.99	403.06
		ICER	133.92	20.84	205.55	64.41

HIV – human immunodeficiency virus, PrEP – pre-exposure prophylaxis, VMMC – voluntary medical male circumcision, Dual vaccine – HIV and HPV vaccinations

3.2 MULTIPLE INTERVENTIONS

The evaluation of combined interventions is shown in Table 46. Simultaneously increasing the ART coverage and adding another recognized HIV prevention intervention results in a reduction in HIV incidence exceeding 50%. The synergism between the interventions in decreasing the HIV incidence rates was also noted. Interventions involving PrEP had significantly higher cost implications and thus higher ICER values. The implementation of VMMC in combination with the HIV vaccine proved more cost-effective than the implementation of VMMC with an increased ART coverage. The only combination of interventions that resulted in cost-saving employed the use of the dual HIV and HPV vaccination strategies in combination with the VMMC roll-out.

The graphical representation of the combined interventions is displayed in Figure 27. Interventions involving PrEP are shown to involve a significantly higher incremental cost. Combinations involving VMMC and the HIV vaccine demonstrate a larger gain in QALYS and are associated with lower incremental cost increases. The introduction of the dual vaccine strategies in combination with VMMC proved to be the most economically efficient strategy, increasing QALYs gained while decreasing costs, relative to the standard of care. This strategy is the only cost-saving one.

Table 46. Health outcomes and cost-effectiveness of combination HIV prevention interventions

Combined interventions are compared with the status quo (i.e. continuing to treat HIV infection with ART at 29% coverage (300)).

			HIV infection (over 10 years) (%)			**Incremental**		
			Incidence	**Infections averted**	**Deaths**	**QALYS**	**Cost**	**CER**
	Status quo		5.44	-	0.43	12.53	6 467.96	-
Scenario	**Combinations**	**ART**						
1.	VMMC	Upscale	2.56	52.49	0.31	+ 13.13	+ 361.10	27.50
2.	VMMC + HIV vaccine	Current	3.46	36.39	0.28	+ 18.24	+ 206.52	11.32
3.	VMMC + HIV vaccine	Upscale	2.25	58.71	0.27	+ 18.87	+ 581.11	30.80
4.	VMMC + PrEP	Current	3.24	40.35	0.27	+ 30.78	+ 2 062.08	67.00
5.	VMMC + PrEP	Upscale	2.11	61.28	0.26	+ 31.42	+ 2 433.94	77.46
6.	HIV vaccine + PrEP	Current	3.15	41.99	0.26	+ 19.02	+ 2 188.01	115.08
7.	HIV vaccine + PrEP	Upscale	2.06	62.11	0.25	+19.65	+ 2 563.53	130.42
8.	Dual + VMMC	Current	3.04	44.11	0.24	+ 42.68	Dominant	Dominant

ART – antiretroviral therapy; HIV – human immunodeficiency virus; HPV – human papillomavirus; Dual vaccine – HIV and HPV vaccinations; VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis (ART scale-up covers the ART deficit of 58%; HIV and HPV vaccine quoted at 50% and 70% vaccine efficacy respectively; VMMC efficacy is 60%, PrEP efficacy is 67% (Range = 21-67%); all coverage =60%.)

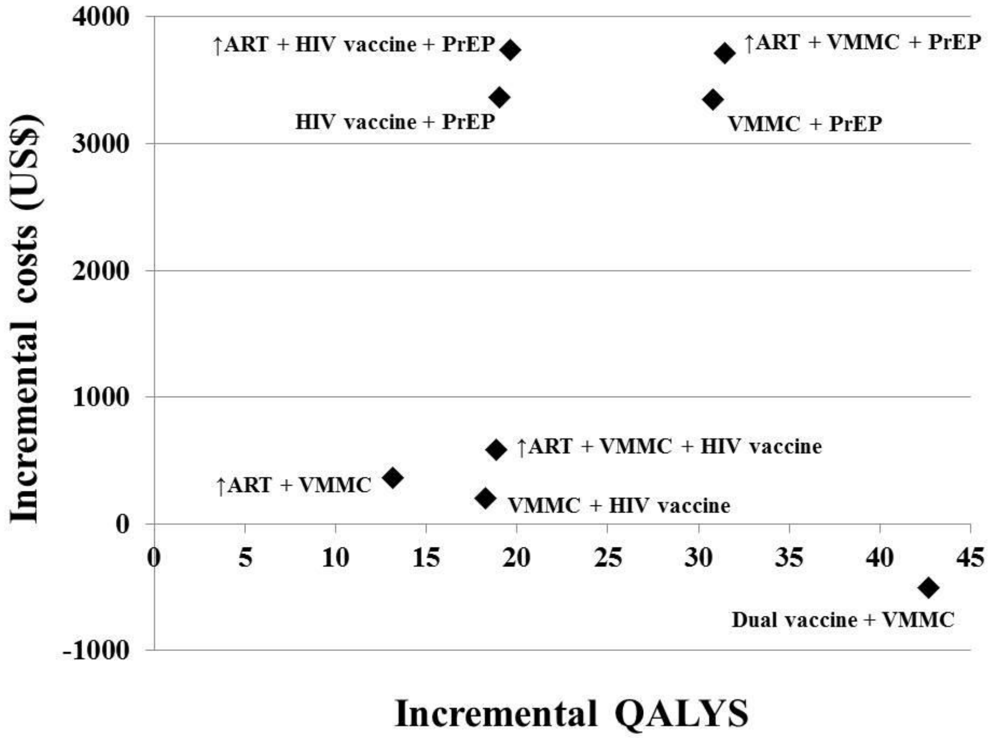

Figure 27. Cost-effectiveness for combination HIV prevention strategies

Discounted incremental costs and QALYS over 10 years are displayed for combined interventions.

ART – antiretroviral therapy; HIV – human immunodeficiency virus; HPV – human papillomavirus; Dual vaccine – HIV and HPV vaccinations; VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis

3.2.1 Probabilistic sensitivity analysis

The interventions included under combinations 1, 2 and 3 are associated with improved health outcomes at a greater cost compared with the current standard of HIV care in the public sector. Bootstrapping analysis was conducted by repeated sampling (1000 iterations) to estimate the model uncertainty regarding costs and effects (Figure 28). The majority of the iterations lying in the north east (NE) quadrant of the CE plane (an area of trade-off indicating greater health gain for added expenditure) raises the critical issue of determining how much a decision-maker is prepared to pay for an additional unit gain in health outcome. The limited vertical variation indicates limited variability associated with treatment costs. The reported ICERs for all three interventions included in combinations 1, 2 and 3 remained well below the WTP threshold and were thus deemed cost-effective. The iterations of combination 4 appear in the SE quadrant implying treatment dominance i.e. the elements of combination 4 implemented concurrently would prove to be a more effective and less costly (cost-saving) measure.

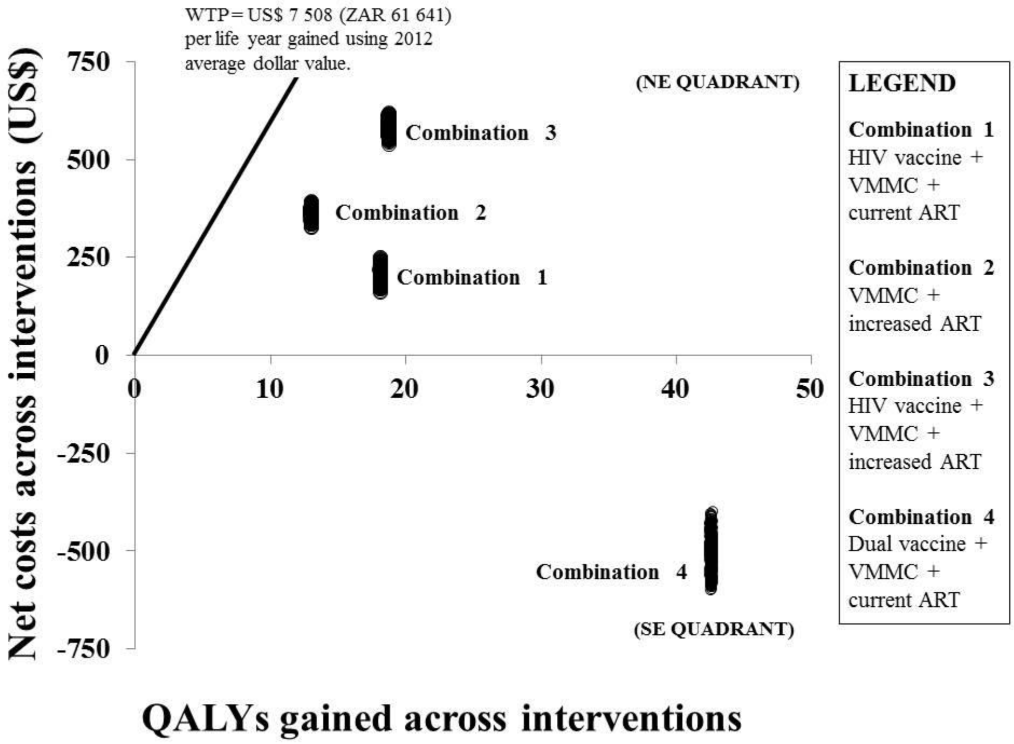

Figure 28. Cost-effectiveness plane for combination HIV prevention interventions

Incremental costs and effects were graphically demonstrated on the incremental cost-effectiveness plane. The x-axis represents the plane according to incremental cost (positive above, negative below), while the y-axis represents the plane according to incremental effect (positive to the right, negative to the left), thus dividing the incremental cost-effectiveness plane into 4 quadrants through the origin. Values falling below the WTP threshold indicated are cost-effective.

ART – antiretroviral therapy; HIV – human immunodeficiency virus; HPV – human papillomavirus; Dual vaccine – HIV and HPV vaccinations; VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis

4. DISCUSSION

Globally, it was reported that nearly two million people were newly infected with HIV in 2014 (740). More than 25 years into the epidemic, international public health programmes are still unable to sufficiently curb the HIV incidence. This study aimed to generate insights into potential biomedical HIV prevention strategies regarding their financial and health implications when implemented individually and in combination. Previous modelling studies confirm that no single option can curtail the epidemic but rather, a structured portfolio of complementary prevention and treatment options designed around the specific needs of specific populations should be sought (741). Biomedical interventions specifically, comprise chemical and physical strategies targeting biological and physiological processes responsible for HIV acquisition and transmission (742).

The hypothetical HIV vaccine was found to be cost-effective and biologically feasible, averting 21% of new infections in a ten year period. Work done by Harmon et al. showed a similar reduction in HIV incidence in LMICs from 2.0 million in 2014 to 550 000 in 2070 (741). The HIV vaccine proved cost-effective even at lower coverage rates and at lower effectiveness rates in the sensitivity analysis. This is important when considering that even a partially effective vaccine could contribute to a sustainable response to HIV/AIDS (743). However, the issues of cost become critical in developing countries as cost-effectiveness estimates are sensitive to market prices, uptake of services and intervention efficacy (744). The HIV vaccine in combination with the HPV vaccine resulted in a considerably improved ICER of US$ 7 per QALY gained. Considering the burden of HPV disease in South Africa, this finding is particularly relevant implying the indirect effect of the HPV prevention strategy on HIV acquisition (92, 268).

Scaling-up of ART coverage has been shown throughout the study to be a necessary, but significant financial, investment. Apart from preventing the progression to AIDS, ART can reduce the number of new infections by decreasing the amount of circulating virus in the body of an infected individual (325). In 2014, UNAIDS' proposed the "90-90-90" campaign where 90% of all people living with HIV know their HIV status, 90% of those HIV-positive people who are aware of their status should receive ART, and 90% of all people receiving ART have achieved and sustained viral suppression by 2020 (745). However, it is acknowledged that ART distribution extends beyond mere provision of ART drugs. ART access and adherence represents logistical, financial and behavioural challenges between people knowing their status and achieving complete viral suppression, even in high income countries (746). Recent updated guidance by the WHO recommends initiation of ART at the time of a positive HIV diagnosis, and 16 million people living with HIV (less than half of the total) accessing treatment by June of 2015 (741). However, it was noted in this study and others that scaling-up ART programmes provided greater value than untargeted PrEP programmes (721). Further to this, the implementation of a PrEP programme could never supersede increasing ART coverage to those individuals already infected with HIV.

PrEP has been proven to reduce HIV infection among MSM in several large clinical trials, in clinical implementation and in a PrEP demonstration project (747). To some extent, the financial implications of introducing PrEP negates the optimism of ‘real world’ data, even at the lower prices considered. The drug price influences the affordability of PrEP programmes greatly, and is thus instrumental in determining overall cost-effectiveness (748, 749). Apart from the drug price, the validity and utility of estimates must encompass the associated service costs, including regular blood monitoring, potential drug toxicity and the development of resistance (315). User adherence to the medication and potential impacts on other preventive mechanisms (such as reductions in patterns of condom use) represent additional major concerns (750). As a relatively new intervention in South Africa, careful consideration has to be given to marketing the intervention, including towards improving provider knowledge (751). In the South African context, where HIV stigmatization is rife, the association between PrEP and high-risk behavioural practices should not be underestimated as an implementation challenge (752-755). This highlights the need for solid pre-implementation counselling that addresses PrEP education, myth reduction, potential social prejudices and an accurate assessment of patient obligations as standard (752, 756). Ultimately however, as these study findings concur, PrEP remains a relatively low value alternative in the general population despite its demonstrated effectiveness (721). From an economic perspective, the findings of this study demonstrate that the implementation of a PrEP programme may result in significant opportunity costs.

Overall, the use of the HIV vaccine with the HPV vaccine (females) and VMMC (males) proved to be the only dominant strategy. Comparatively, the use of VMMC proved more cost-effective as an individual intervention compared with the HIV Vaccine, alluding to the impact the pricing of the vaccine may have going forward. The use of the dual vaccine approach in females makes sense. Apart from the highest HPV incidence and mortality in the world, the HIV incidence in young women and girls in SSA is twice that of their male counterparts (741). Similarly among males, VMMC has been demonstrated to be a highly cost-effective, highly effective HIV prevention strategy in RCTs and in cost-effectiveness studies conducted in areas with generalized epidemics (65, 448, 569, 742). In fact several studies have shown VMMC to be cost-saving due to moderate implementation costs, high and durable protective effects, and the resulting averted HIV care costs (569, 757). Further, unlike most other HIV prevention strategies, VMMC is a once-off procedure conferring potentially lifelong protection with no compelling evidence of increased sexual risk-taking reported among circumcised men (64).

Several limitations were identified in this study. Firstly, models are accepted as simplifications of reality, as an approximation of the true nature. As such much of the detail is simplified to aid understanding and computation. A glaring example of this would be the oversimplification of the complex sexual networking patterns that exist in South African society (758, 759). Secondly, the affordability of an intervention must be discerned from its cost-effectiveness. Most interventions, as demonstrated with PrEP and scaling-up of ART services, require a substantial financial investment. The analyses presented were unable to predict the availability of the resources to implement such interventions but rather to highlight the options that present a greater return on investment. Thirdly, the analysis considered the South African population as a whole considering the generalized state of the HIV epidemic in South Africa. Stratification by risk groups (MSM or commercial sex workers for example) may potentially yield differing results even in a high prevalence setting. The scenario differs in low prevalence settings where the risk of contracting HIV among the higher risk groups mentioned could be up to 12-19 times higher than in the general population (741). Fourthly, the potential complications of the interventions and its associated costs were not accounted for. These included complications of VMMC (including infections and surgical complications) and the development of drug resistance from the use of PrEP. Fifthly, with the development of any economic model is the ensuing problem of parameter uncertainty. It is unclear if trial-derived data will differ from those documented in actual clinical practice. Frequently, factors such as risk compensation and adverse events impact negatively on the cost-effectiveness of an intervention. As more data is made available in the literature, particularly in the case of the HIV vaccine, the model would have to be restructured and refined. Lastly, it should be remembered that the value of the ZAR had essentially halved as a currency by 2015/2016 implying that costs are much greater in 2015/2016 than previously.

5. CONCLUSION

This analysis does not purport to provide the optimal combination of biomedical HIV prevention strategies to be applied in the South African setting. On the contrary, this evaluation was intended to stimulate discussion on potential HIV prevention research, intervention options and funding opportunities for delivery mechanisms. The allocation of limited financial and human resources for HIV control measures in South Africa remains a priority. It is the findings of this body of work that the adoption of a multi-intervention biomedical approach could avert a significant proportion of new HIV infections and present a more cost-effective use of resources; particularly in the absence of large scale multi-interventional RCTs.

CHAPTER 9

DISCUSSION

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1. INTRODUCTION

This body of work aimed to establish an evidence-base for universal HIV and HPV vaccination administered individually and in combination to school-going children as part of the school-based health programme envisioned under the restructuring of PHC services, a fundamental arm of the NHI social reform plan currently underway. The vaccine strategies were considered pertinent considering the high burden of HPV- and HIV-related disease harboured by the adolescent age group. Furthermore, adolescents were identified at particularly high risk of disease acquisition, and hence the vaccination programme was considered as a vital part of the school-based SRH platform that was hoping to be developed at schools. However, there still remain large gaps in the literature regarding uptake of services, potential delivery mechanisms and parental attitudes regarding vaccination. As the scope of the discussion extends beyond a health economic evaluation, the gaps identified in the literature are defined under several broad headings:

- Addressing issues of equity
- Youth access of health services
- Generation of health data
- School health care services to adolescents
- Impact on HIV/HPV disease burden

This chapter begins with a discussion of the information generated by this thesis and the impact this has on planning school-based HIV and/or HPV vaccine services for adolescents in South Africa. The implications of these findings on school-based HIV and/or HPV vaccine services for adolescents are then discussed in relation to the primary objectives of the study. Overarching limitations of the thesis are presented, followed by suggestions for important areas of future research. The final conclusions are then made.

2. CONTRIBUTION OF THE LITERATURE FINDINGS ON SCHOOL-BASED ADOLESCENT HIV AND HPV VACCINE SERVICES

The literature review carefully outlined the vulnerability of adolescents to acquiring HIV and HPV disease and how their prevailing social and economic circumstances contribute to this acquisition. The implementation of school-based vaccination services requires considered co-operation among various sectors including the Departments of Health and Basic Education along with involvement of parents and the adolescents themselves. The results of this PhD have demonstrated the economic, financial and health benefits of the vaccine intervention. Based on the conceptual framework (Chapter 1), several key areas were considered for further discussion and are described in Table 47.

Table 47. Summary of the gaps in the literature and findings that contribute to the understanding of school-based dual vaccine programmes among adolescents

TOPIC	EXISTING GAPS IN KNOWLEDGE TO BE ADDRESSED	BRIEF SUMMARY OF LITERATURE FINDINGS
Addressing issues of equity	1. Apartheid, rural health and diseases of the poor 2. The quintile system in schools 3. Moving health care into the schools 4. The move to Prevention Medicine 5. Empowering women	Historically, the bulk of HIV and HPV disease are concentrated among the poor, rendering the universal access that school-based health services offer vital. School-health services represent an established level of care, tailored to the needs of adolescents at their socio-economic level that brings the services to the child. Apart from SRH, education services will have to address the empowerment of women in sexual decision-making. Preventive medicine is the highest echelon of health care and is a long overdue shift from hospicentric care to more primary prevention.
Youth access of health services	1. The impact of a historically fragmented health service on adolescents 2. The inadequacy of rural health care	The health system of South Africa was left socially and economically fragmented under Apartheid. The rural health system bore the brunt of the poor health service delivery. The NHI represents social reform and health care finance restructuring that seeks to address the health care inequities of the

	3. The problems with traditional health services for adolescents 4. The vulnerability of women and young girls 5. The effects of co-payments on health care delivery 6. Acknowledging the gap in health care provision to adolescents 7. The need for SRH services for adolescents	past. To some extent, it will negate the need for financially draining co-payments that depletes the family's financial resources. A key arm of this endeavour is the re-engineering of PHC, particular targeting school-based health care. This is important as adolescents have long endured challenges accessing traditional health care services in the form of judgemental staff and poor quality of services. The inherent vulnerability of women and young girls to HIV disease as well as IPV, early sexual debut and sexual exploitation are well documented. There is a dire need for SRH that target empowering women and improve links to community support structures. School-based health care bridges the chasm between established childhood health services and adult services, where adolescent health care is relatively neglected. While this body of work explores the health care provider perspective, the long-term impact on disease burden alludes to improved productivity going forward.
Generation of health data: **(Adolescent epidemiological data)**	1. Identification of adolescents as an independent risk group for disease 2. How interventions impact on disease burden in the adolescent group 3. Assessing the need for SRH and promoting uptake of the services	The literature review explains why adolescents are considered high risk. It alludes to issues of early sexual debut, 'sugar-daddies', multiple and concurrent partners, drug and alcohol use and sexual exploitation. School-based health care has been shown to be universally useful and parental involvement in the SRH development is encouraged. While disease manifestation may only occur decades later, it is imperative that we target adolescents early and prior to sexual debut.
Generation of health data: **(Use of health economic data in health care planning)**	1. Health economics, as a discipline, is not widely established in South Africa 2. Understanding the implications of the vaccines vs. increase in ART provision vs. the value of VMMC 3. Costing the programme options, assessment of the opportunity costs and the cost consequences	It is often the case that due to lack of expertise on health economics, decision-makers extrapolate regional data for the purposes on planning. This PhD embodies work based on the local data in South Africa and is thus locally relevant. It allows for the comparison of the vaccine interventions against validated biomedical interventions in a head to head comparison. We also explored how these interventions measured up against potential up-scaling of the ART services currently provided in the country.
School health care services to adolescents	1. Organised health services provides specialised care for children and adults, but miss adolescence	Adolescents comprise 25% of the world's population and their dynamic health needs warrant specific attention. The development of a school-based programme extends beyond mere vaccination provision but requires a clear understanding of their sexuality. Although much

	2. Catch-up of adolescent vaccines and opportunity for establishing SRH at schools 3. The interaction of health and education: facing concerns of poor nutrition, abject poverty and the resultant developmental delays	research has been undertaken, the project requires practical translation. The staff implementing the service needs to be trained to comfortably handle discussions on sexuality and disease processes. Given the sensitivity involved in the subject matter, it would be advisable for parents to assume a more active role in curriculum development.
Impact on HIV / HPV disease burden: **(HIV vaccine concerns)**	1. Identifying and prioritising adolescents as a group at high risk for HIV 2. The need for HIV vaccine bridging studies among adolescents 3. Addressing the economics of the HIV vaccine including vaccine characteristics and pricing structures 4. Predicting the health impacts of the HIV vaccine 5. Proposing vaccine delivery mechanisms	The literature review identified the challenges facing adolescents in post-Apartheid South Africa, and their particular vulnerability to HIV disease. The complexities surrounding the South African legislature regarding adolescent involvement in clinic trials was then outlined. Based on these legalities, the value of bridging studies among adolescents was discussed, particularly citing the example of the HPV vaccine. The literature review further cited the value of school-based health services for adolescents, including SRH and HCT. Lastly, based on the target product profile of the P5, vaccine characteristics were assessed in differing scenarios and then tested against other biomedical interventions targeted at HIV prevention.
Impact on HIV / HPV disease burden: **(HPV vaccine concerns)**	1. Improving HPV vaccine coverage 2. Improving HPV vaccine uptake 3. The cost implications of improving uptake and coverage 4. Assessing the impact of dual vaccination services 5. Establishing the HPV disease burden among adolescents 6. A dissection of the existing services 7. Addressing the myths of promiscuity associated with vaccination	Currently the HPV vaccine programme is being delivered to quintiles one and two schools. This PhD assessed the cost consequences and health implications of universal coverage at schools, based on the foundations of the school-based service of SRH. By doing so, this work demonstrates the universal cost-effectiveness and improved health outcomes of HIV and HPV disease as a result of a dual vaccination programme. The poor uptake of the existing cervical screening programme is noted and explained. The poor uptake of screening services further justifies moving the service to adolescents in a school environment. Additionally, the HPV vaccine alone and in combination with the HIV vaccine are weighed against existing biomedical prevention strategies employed to compare their impact on disease burden and cost-effectiveness. The myths surrounding the HPV vaccine promoting promiscuity is explored, and debunked. Marketing of the HPV vaccine as a primary cancer prevention tool is considered to address issues of stigma and improve uptake.

2.1 ADDRESSING ISSUES OF EQUITY

Ensuring young people remain in school is dependent on many factors – gender, socio-economic circumstances, conflict, rural areas, poverty, disability, HIV/AIDS and ethnicity (760). In SSA, the persistent disadvantages in access to education persist; perpetuating the cycle of poverty (761).

Gender remains the seed for much inequity. In southern Africa, young women aged 15-24 years comprise nearly 30% of all new HIV infections in the region (331, 347). Within South Africa, this translates to approximately 113 000 new infections among women annually, roughly four times the amount contributed by their male counterparts (97). Many young girls' first sexual experience involves some level of coercion, with those aged 15-19 years at high risk of physical and sexual violence compared with older women. Many adolescent girls have considerable age differences with their partners, rendering them susceptible to exploitative relationships (762). As such, many women realise that once sexual relations have been initiated, the power dynamic in the relationship shifts to the male (763, 764). This shift in control is a characteristic feature of the HIV epidemic in the region, where young women acquire HIV disease five to seven years earlier than males; often at sexual debut (97, 98, 765).

Despite the risk of disease in young women, there remain limited evidence-based interventions available to this population. Sadly the options of abstinence, behaviour change and condom use has been negated by the challenging power dynamics highly prevalent in the southern African environment (350). Many SRH programmes relay a generic message targeting a wide range of individuals (e.g. different genders, population groups and varying levels of sexual experience). Research conducted among the youth in Cape Town suggest that tailoring the sexual and reproductive education curriculum to targeted groups such as young women has the added benefit of allowing young women to align their perception of risk to their understanding of the disease process (766).

2.2 YOUTH ACCESS TO HEALTH SERVICES

Epidemiology, knowledge, and behavioural data describes limited success in global prevention efforts with considerable ground to cover before universal access to critical prevention services and support for adolescents (including provision of age-appropriate information, access to condoms, HCT); and essential SRH and treatment services can be established (767).

However, consistent with several studies was the finding that most youth perceived themselves to be at little or no risk of HIV or other STIs (768-773). Adolescence is characterised physical, sexual, emotional and psychological change that influences the development of autonomy, increased impulsivity and vulnerability to peer influence. These changes may be closely linked to poor adherence to chronic medications required for conditions such as diabetes, asthma and HIV. Often poor adherence extends beyond simple forgetfulness and difficulty integrating medication into busy school or extra-mural activities. During the adolescent period, serious consideration has to be given to issues of stigma, unresolved psychological barriers and substance abuse (698, 774-776). Additionally, structural barriers include limited socio-economic resources for transportation, inaccessible clinic hours and other demanding responsibilities like caring for younger children (777). The situation is exacerbated by legislation and nursing staff that criminalize the behaviour of adolescents and foster further discrimination and violence, thus hindering access to these critically needed services (767). Little is understood about the factors determining the success or failure of school-based adolescent SRH services, apart from the differential uptake by the genders, limited availability of materials and the high turnover of trained teaching staff (405).

The transition from childhood to adolescence is fraught with emotional and psychological changes that require specialised understanding and services. However, these expertise are often unavailable. Comprehensive care requires SRH counselling, contraceptive and risk-reduction counselling, and treatment of STIs, provision of ART and access to social welfare systems (776). It is little wonder that adolescent access to these essential services remains constrained. Investment in a school-based programme that provides education linked to screening service and care has great potential to reach the marginalised youth but also to reduce costly hospital admissions and the social impact this has on families and communities (776).

2.3 GENERATION OF HEALTH DATA

The global view of adolescent health is inconsistent, with major data gaps (778). South Africa collects very little data on the health of its adolescents routinely. This is partly attributed to the poor access to health services by adolescents and partly because of the age bands adopted by the District Health Information System (DHIS) (767, 774). This lack of data is concerning as several determinants of poor health in adults such as alcohol and cigarette use, poor diet and lack of physical activity stems from the adolescent years (774). Ultimately, poor data gathering mechanisms are being compounded by inadequate analysis and reporting systems, resulting in the health outcomes of adolescents that cannot be tracked or monitored in a meaningful way. There is no standardisation of data, and the existing data does not lend itself to international comparison nor for use in improving the health outcomes in adolescents (767).

South African health data sets need to capture vital information pertaining to adolescents. This will allow for determining trends and patterns in adolescent health that would ultimately inform interventions that are responsive to the needs of adolescents. This would require an overhaul of national data sets, district data collection forms and clinic registers; and sufficient training of health care staff to understand the rationale for the change and effect the new documentation (779). It should be remembered that this problem is not confined to South Africa. Internationally, there is no agreed set of indicators specifically for adolescent health (780).

2.4 SCHOOL HEALTH SERVICES TO ADOLESCENTS

Research has shown that school-based health services have significant advantages for the delivery of interventions based on the ability to reach large numbers of young people (781, 782). Many South African youth are confused by the contradictory messaging they receive regarding HIV/AIDS which they feel schools themselves are unable to clarify (783). It is often the case that schools are delegated the bulk of the responsibility by African society to develop the safe sexual practices of the youth. To this end, the South African Department of Education (2001) has integrated HIV/AIDS into the Life Orientation curriculum at all schools (784). However, the indifferent attitudes of learners and teachers alike raises concerns on how to overcome the ignorance surrounding HIV disease and how to avoid possible infection (784).

Several challenges have been described in school-based SRH services; not limited to inadequate time allocation for sexual education, poor resources and unmanageably large numbers of students per class (431). The situation is further exacerbated by disparate cognitive and developmental maturity between males and females, frequent student absenteeism and high levels of violence (785). Teachers themselves pose barriers due to absenteeism, conservative personal beliefs and concern regarding their own HIV status (431, 786-788). While the knowledge of HIV transmission was considered acceptable among most youth, the several misconceptions about the disease were alarming. Coupled with low education levels and substance abuse among males was the belief among females that condoms 'get in the way' of sexual intercourse. The result among South African youth was high levels of high risk sexual practices, particularly among the youth residing in socio-economically deprived areas (789).

Adopting the principles of school mentors and participatory learning approaches from the school sector could assist the implementation of interventions in schools and have significant potential in improving the current preventive models being employed for adolescents.

2.5 IMPACT ON HIV/HPV DISEASE BURDEN

The 2006 position paper on HIV/AIDS in adolescents issued by the Society for Adolescent Medicine noted that despite the scientific advancements made in the diagnosis and treatment of HIV/AIDS, the HIV/AIDS epidemic among adolescents was burgeoning; with almost 50% of new infections documented among the youth and young adults (790, 791). UNAIDS estimated that approximately 300 000 new infections occurred among adolescents aged 15–19 years in 2012, which constituted 13% of the two million new infections globally in 2012 ~ roughly translating to 830 adolescents being infected daily in 2012 (767). Despite this, the uptake of HCT among adolescents in South Africa remains poor, with only 20% reporting ever having had a HIV test (97).

The second decade of life has been marred by an increased vulnerability to HIV infection for those transitioning from childhood to adolescence (792). This highlights the critical importance of youth-focused HIV prevention strategies (792, 793). Adolescence is developmental phase with complex psychosocial, behavioural, physiological and cognitive interactions that challenges the boundaries of treatment adherence, social and sexual behaviour and health seeking tendencies (794-797). It is a period characterised by experimentation, risk-taking and significant peer pressure with a need to assert an identity separate from that of caregivers – a period that lends itself to experimentation and risk including early sexual debut, sexual coercion and violence and abuse of substances (798, 799). It is these behavioural characteristics that result in adolescents committing early to sexual relationships amidst growing concerns of anxiety, guilt, fear and vulnerability to STIs and abortions (800).

Adolescents and young adults are particularly vulnerable to the sexual transmission of infection (347, 794). HPV infection represents one of the most common STIs among adolescents, sharing many of the same risk factors and health seeking concerns of HIV. HPV infection poses substantial health risks; and the nature and course of the disease remains highly unpredictable. While genital warts are the most common clinical manifestations of HPV infection, it is with persistent infection that the risk of CIN and subsequent cervical cancer becomes a possibility (801). The prevalence of HIV/AIDS among Nigerian youth remains one of the highest globally, and studies conducted among this group confirm the disjuncture between HIV/AIDS knowledge and the adoption of protective sexual behaviour (802). Apart from poor availability or poor interpretation of knowledge of sexual matters among adolescents in SSA, their vulnerability to STIs is exacerbated by inaccessible health services and poor education and life skills orientation (389, 803). The crux of the matter is that HIV prevention and care services in the region need to be modified and adapted to adequately address the specific needs of the escalating disease burden among adolescents.

3. IMPLICATIONS FOR SCHOOL-BASED ADOLESCENT HIV AND HPV VACCINE SERVICES

The findings of this thesis provided unique insights into the environmental factors that influence the decisions made by adolescents, explored school-based health services as a delivery mechanism for the HIV and HPV vaccine, and quantified the cost-effectiveness and financial implications of the vaccine interventions. The implications are presented under these sub-themes, and are discussed in Table 48.

Table 48. Summary of the implications for school-based dual vaccine programmes among adolescents

THEME	SUB-THEME	IMPLICATIONS SCHOOL-BASED DUAL VACCINES AMONG ADOLESCENTS
Addressing issues of equity	The vulnerability of women	South African women have long suffered a disproportionately high burden of HIV- and HPV-related disease. There often exists a social and cultural barrier that limits the access of women to health care including issues of disease associated stigma and family influence on whether health care should actually be accessed. While the implementation of the dual vaccination strategy does not directly translate to improved sexual decision-making and empowerment among women, it is hoped that this point is inadvertently achieved through the sexual health education and counselling that would be administered prior to vaccination and as part of the informed consenting process.
Youth access of health services	Establishing youth-friendly services	Youth-friendly health services should be tailored to the needs of adolescents. The curriculum for the school-health services should be developed in collaboration with the Departments of Basic Education and Health, in consultation with parents and teachers and with adolescent representatives. The school-based services should be linked to the wider societal services available in the community such as social welfare and counselling services, if required. The service provided should be non-judgmental with teachers (that provide the education) and nurses (that provide the health-care services) undergoing sensitivity training. The service should be provided from an adolescent perspective and be accessible during reasonable hours at the school so as to not interrupt educational activities. By targeting schools universally, and not based on socio-economic status, the developmental milestones of the youth can be assessed, and deficiencies and delays identified and rectified.

	Accessing health care	As discussed in the literature review, the health system has been fragmented by Apartheid. The reforms of the NHI have prioritized school-health services and concentrated particularly on PHC delivery. The focus of this PhD is to establish the HIV and HPV vaccine programme as part of the school-based services under implementation of the national government. As such, the infrastructural and human resource requirements for the delivery of these vaccines would be potentially provided by the school-service were it established.
Generation of health data	Adolescent epidemiological data	As youth health services have generally been a neglected field, the development of school-health services creates the opportunity to establish a database of health information, with subsequent follow-up data to determine trends in disease patterns. The information garnered will guide health planning by determining uptake and coverage, as well as identify areas of need and areas requiring improved service delivery.
	Use of health economic data in health care planning	The PhD compared the cost-effectiveness of different interventions under different scenarios where the HIV and HPV vaccines individually and in combination were weighed against a range of biomedical interventions. The affordability and opportunity costs of the various options were considered by gauging the cost consequences of the interventions. As the question of treating ourselves out of the HIV epidemic constantly arises in academic discussion, the scenario of increasing the ART treatment threshold to cover the treatment shortfall described by UNAIDS was assessed.
Impact on HIV / HPV disease burden	Vaccine interventions	Individual or dual vaccination strategies are shown to be universally cost-effective. This is an important consideration when planning health care services as it describes a shift from curative, secondary disease prevention to primary prevention strategies, in keeping with the national restructuring of health care being proposed. Although this PhD considers the provider perspectives of the vaccine implementation, the reduction in disease burden would more than likely result in improved productivity and better health outcomes when considering the societal perspective.
	Disease burden	The landscape of the HIV and HPV disease burdens are changed with vaccine implementation. Besides the improvement noted in life expectancy, there are decreases noted in disease incidence, particularly when the dual vaccination strategy is used.

3.1 ADDRESSING ISSUES OF EQUITY

Addressing inequities among adolescents of South Africa extends far beyond the conventional 'temperamental nature of teenagers' into years of societal fragmentation orchestrated by Apartheid. Black adolescents, in particular those residing in female headed households are more likely to live in poverty, have poor access to water and sanitation, experience hunger regularly and are unlikely to complete secondary level education (804).

In general adolescents need social, emotional, spiritual, and often material support (805). The situation is exacerbated among HIV-infected adolescents as they are often alienated from their peers (806). It is at this juncture that the need for support groups becomes imperative, as peer support may not be forthcoming (775). As discussed throughout this PhD, adolescent girls are especially vulnerable in the South African context as they are unable to negotiate monogamy, condom use and/or male circumcision (176). There is a significant association between the early onset of sexual relations and poor condom use among females. Often early onset of sexual initiation renders young women incapable of negotiating safer sexual practices with their partners highlighting the need for gender focused programmes, particularly focussing on the sexual empowerment of female adolescents (802, 807). A vast array of comprehensive biomedical, structural and behavioural interventions need to be made available to young women if the HIV epidemic control is to be properly addressed. Until such time that this is achieved, existing HIV prevention strategies need to be practically integrated into wider school-based SRH services as a priority (176).

Structured social norms grant more privileges to males than females and promote models of male masculinity that justify their subjugation of women (808). This access to social and financial resources can impact on nutrition, education, employment, and income with girls less likely to enrol in schools and more likely to drop-out (809). Women are thus frequently economically dependent on their male counterparts, which within a sexual relationship results in threats of violence (physical, sexual and psychological), diminished ability to negotiate safer sexual practices (e.g. condom use) and the decreased likelihood of accessing HIV testing services because of fear of disclosing their status (810-812).

The HIV/AIDS epidemic has resulted in an unprecedented shift in focus to gender inequality and women's vulnerability (813). Women need to be empowered to realise their sexual and reproductive rights and health within the health system and beyond it through intersectoral-collaboration including school-based reproductive health services (814, 815). It is inevitable that gender inequities practiced in everyday South African life inadvertently filters into the classroom. As an example, young girls falling pregnant while at school are expelled and unfairly discriminated against (809). SRH services remains central to addressing issues of gender equity. The access to these services remains inadequate to both males and females which has serious health consequences for all, particularly for women and girls in areas with HIV prevalence (814). School-based interventions need to be cognisant of multiple structural factors such as social norms, gender inequality, and poverty; and integrate these components with comprehensive sexuality and behaviour change, open communication and parental involvement (816).

3.2 YOUTH ACCESS OF HEALTH SERVICES

Millions of adolescents are sexually active in areas with high disease burden of HIV, and are thus at risk of acquiring HIV. Adolescence presents a prime opportunity to engage these children prior to sexual activity, and implement interventions targeted at reducing their risk (767).

School-based adolescent SRH programmes have been shown to positively impact on HIV/AIDS knowledge, behaviours and attitudes, and have been promoted for implementation widely (389, 390, 403, 817-819). The benefit of channelling health services through the school system is that it enables large numbers of young people to be accessed, and has significant potential for scale-up of interventions (440). Integrated adolescent-friendly, school-based health services has the potential to bridge the gap between availability and access to general and reproductive health counselling services (233). Attempts to strengthen more traditional clinical based services by providing comprehensive youth-friendly SRH services have often fallen short due to clinic inaccessibility for several reasons including clinic hours and hostile staff (331, 407). 'Youth-friendly health services' have adopted several innovative strategies such as combining interventions that see training of service providers, outreach activities and mobile health services.

Yet these services fall prey to the same limitations experienced by traditional services (389, 396, 820, 821).

3.3 GENERATION OF HEALTH DATA

There is undoubtedly a need to strengthen the development of strategic information to effectively address educational and health developmental outcomes of young people including access to comprehensive SRH services. The persistent lack of good quality research and evaluation of adolescent health interventions limits the ability of the country to address major health concerns facing adolescents (822). Well-developed information systems have underpinned advances in health in other age groups and evidence suggests a similar response in younger age groups, particularly regarding the school context for health development (823-825). Further, age-disaggregated data generated would allow for ongoing monitoring of results, with a focus on scrutinizing and responding to inadequacies in access, coverage, and quality of high-impact interventions and to track progress on implementation of current guidelines (441, 826). Comprehensive data are essential to shaping accurate HIV-related messages and services and sexual education curricula before risky behaviours start developing and become entrenched (767). Adequate documentation of adolescent health programmes are needed so that the programmes may be evaluated and improved upon where required (779). School-based health surveys may present a novel option for adolescent data collection, particularly considering the improvements made in learner enrolments in South Africa (780).

The relentless spread of the HIV among South African youth means that policy and interventions require careful attention. These programmes need to be evaluated rigorously and the long-term impact needs to be studied (779).

3.4 IMPACT ON HIV/HPV DISEASE BURDEN

As one of the most common STIs globally, HPV prevention through vaccination is a public health priority aimed at reducing cancer and HPV-associated disease burden (827). The HPV vaccine has repeatedly been proven to be cost-effective and highly immunogenic (274, 709). Prevention through vaccination has been proven to be a lifesaving intervention that decreases the burden of HPV-related cancers and other HPV-associated diseases (827). In fact, results from projects conducted in South Africa demonstrated how the adolescent HPV programmes could be used to control cervical cancer among the mothers by offering information and screening (828). Yet unwarranted fears (mostly by parents) of increased sexual promiscuity has stagnated vaccine uptake in many areas (829-832). In reality, few adolescents adopted more risky sexual practices post HPV vaccination. However, several misperceptions regarding the HPV vaccine exist among adolescents and comprehensive education and active communication between young girls and their mother is needed to address this (833). Even countries with established access to HPV vaccines like the USA have experienced difficulty maintaining coverage rates. Some of the reasons quoted for this include parental concerns about safety, necessity, and timing (834). Adolescent issues around consent are another drawback to vaccination. If vaccine coverage among unaccompanied, adolescent minors is to be considered, then the political, legal and policy frameworks need to accommodate their ability to make this decision (835, 836). This concept of adolescent consent is vital when considering the vaccine hesitancy sometimes displayed by paediatric health care providers. Educational interventions have to be tailored to improve vaccine confidence (837).

A similar set of arguments and could potentially arise should the HIV vaccine become available. For now, HIV prevention remains a key area of focus in adolescent health care particularly considering their dynamic social, physiological and psychological needs as they transition from childhood to adulthood. Ignoring their sexual and reproductive needs at this formative stage may result in irreparable damage to them, and dire consequences to the HIV/AIDS epidemic of the country (767). The onus is on health care providers to enhance vaccine utilization by engaging in more active discussion with their patients. Strategies include education and advocacy for receiving the vaccine, maximizing access to the vaccine, and implementing new strategies for vaccine-delivery, including school-based services (834, 838).

4. LIMITATIONS

The methodological limitations of the study have been presented in Chapter 4 and in the individual chapters for the studies (Chapters 5-8). There are still a few overarching limitations that need to be considered regarding the study population and the methodology.

The adolescent population of South Africa is heterogeneous displaying considerable economic, social, behavioural and cultural diversity. This research has incorporated the analysis of demographic information and data on sexual risk behaviour that will hopefully portray a more comprehensive picture of adolescent sexual risk behaviour in this country. However, the studies assumed the population to be sexually naïve at the start of the model to simplify the conditions of the simulation. This is often not the case as many young South Africans are documented to have an early sexual debut, and many have fallen prey to non-consensual sexual activity. The complexity of the sexual networking that is occurring is also not explored in extensive detail. Future studies could factor in the high rates of concurrency and multiple partners to more adequately represent the sexual interactions among adolescents. A school-based intervention was modelled. This study did not consider drop-out rates; this was to ascertain a more thorough estimation of cost using a complete school-based adolescent population. Lastly, the analysis used a static model and was thus unable to determine the influence of the vaccines on secondary transmission (herd immunity).

The work presented in this PhD addresses several data gaps in South African adolescent vaccination interventions and represents an important contribution to the literature. However, as many of the parameters were not routinely collected and sourced from the literature, the generalizability of these findings would need to be validated. Important data parameters that were difficult to access included the rates of transition among the ART regimens, the actual numbers of people on each ART regimen, average drop-out rates and accurate mortality estimates across the age-bands. Data gaps that specifically pertained to adolescents included the numbers that accessed ART, average ART enrolment rates in this age bracket, accurate school enrolment figures, current uptake of traditional health services and the demand for reproductive health services among this age group. Finally, to facilitate both planning and future research, a more comprehensive description of the school health services envisaged under the NHI would prove most useful.

The HIV vaccine is hypothetical and thus its parameters were assumed, based on work completed thus far. The study did not account for potential side-effects of the vaccine as these would be speculative. While the findings of this PhD would have to be validated when a vaccine became available, the results do provide important information regarding vaccine implementation in a high risk population. Parameter uncertainty was evaluated using sensitivity analyses. Lastly, the vaccine effectiveness was expressed in terms impact on disease burden and health outcome which are theoretical endpoints. Programme effectiveness considering adolescent uptake of services, acceptability of the standard of care by the learners and parents alike and relevance to the South African context would have to be assessed qualitatively.

5. FUTURE RESEARCH

Further research questions arose from the findings of this thesis, its limitations and the suggested implications for dual vaccination strategies for school-based adolescents. Regarding the impact on HIV/HPV disease burden, economic evaluations of potential adolescent interventions need to be conducted to advise health planning going forward. Accurate costing data are often difficult to access, and programmes should concentrate on more fully estimating the costs of adolescent health interventions. The integration of services for HIV and HPV should be explored as part of the PHC reengineering to offer more comprehensive care. Importantly, this strategy would have to be evaluated against the *test-and-treat* ART strategy that is being globally implemented. Lastly, once the HIV vaccine is commercially available, a more accurate costing exercise should be undertaken particularly concentrating on the impact of vaccine pricing structures and the overall financial implications of the vaccination programme. Regarding youth access to health services, there is still a need to enhance the understanding of the risk and protective factors influencing the behaviour of adolescents, including important concerns such as vaccine hesitancy. Vaccine hesitant individuals may accept vaccines but report continued concerns about them or may delay or refuse vaccines altogether (839). The WHO has characterised vaccine hesitancy as "a behaviour, influenced by a number of factors including issues of confidence (i.e. do not trust a vaccine or a provider), complacency (do not perceive a need for a vaccine or do not value the vaccine), and convenience (access) (840). The concept translates clinically into failure to achieve or sustain herd immunity (841), making it a vital area of future research. In the context of this work, vaccine efficacy could be included as a confounding effect on vaccine coverage. Other potential impacts of the hesitancy are included in Table 49.

Table 49. Potential effects of vaccine hesitancy on model parameters and outcomes

Parameter	Potential impact
Coverage	Decrease the coverage as people potentially refuse to be vaccinated.
Duration of protection	Indirectly impacts herd immunity levels, and thus decreases duration of protection
Cost of vaccine	No impact
Transmission rates	Unvaccinated individuals are more susceptible to disease and could potentially increase the transmission rates.
Vaccine effectiveness	Hesitancy or refusal may diminish the "effectiveness" of a vaccine in a real world setting.
Study outcomes	**Potential impact**
Cost-effectiveness of : - HPV Vaccine - HIV vaccine - Dual vaccine	Decrease the cost-effectiveness as fewer people will be prevented from acquiring disease.
Potential inclusion of adolescents in vaccination programmes	One of the areas of major impact. Parents rarely relinquish their autonomy over their children and the potential is that fewer adolescent would be vaccinate, increasing your susceptible pool.
Development of school health programmes	Vaccine hesitancy would impact the immunisation arm of the school health programme. The impact on the other services offered will have to be assessed.

Much has been achieved in this regard but emphasis needs to be placed on the refinement of this knowledge and its incorporation into programmes and policies. The inherent drawbacks of traditional clinic services have been described in the literature. Research now needs to concentrate on making these services more responsive to the needs of the adolescent, and integrating their input into the delivery mechanisms. To this end, a cost-effectiveness analysis by province and / or by racial groups would prove most useful.

The deleterious effects of inequity will be felt for generations to come in South Africa. The broader social determinants of health have been largely described and now need to be addressed through improvements in service delivery, alleviation of poverty and development of infrastructure. Mechanisms to achieve this have to be researched. Additionally, strategies have to be developed to collect data on socially marginalised young people particularly those who have dropped out of school and those in correctional facilities. There is a global paucity of relevant adolescent health data. An internationally agreed upon set of indicators needs to be developed to assess programme effectiveness and areas of priority. In South Africa specifically, the age thresholds used in the DHIS need to be redefined. Neglected areas of adolescent health, such as mental health and health system functioning, need regular and appropriate measurement.

School health services to adolescents have already been prioritised by the national government in restructuring PHC. While the initiative has government will, the implementation of these services have been lagging. The HPV vaccination has been successfully rolled out to quintiles one and two schools. These successes need to be built on. The platform that has been established through the HPV programme needs to be developed, expanded and assessed going forward. There are several policy documents endorsing school health services. To ensure the success of the programme, adolescents need to detail their requirements and expectations of the service; thereby improving accessibility and making the services more meaningful to the youth. From an economic evaluation perspective, the costs implications of a national school health programme would need to be assessed. There were several misconceptions associated with HPV vaccination including concerns of promiscuity of adolescent girls post vaccination by parents and trepidation regarding side-effect profiles. The lesson that should be learned from this is the need for culturally appropriate marketing strategies for the HIV vaccine once it becomes commercially available. Uptake of the HIV vaccine would hinge on how adolescents perceive the vaccine, and we should endeavour to understand this prior to implementation.

6. CONCLUSION

'The adolescent population in sub-Saharan Africa is expected to double in 2050, a region where HIV infections are also highest, and adolescents already account for 23% of the current population. Although data improvements are needed, the current evidence makes clear that adolescents are more vulnerable to HIV than persons in older age groups, invoking an obligation to take action' (767).

This thesis has shown that universal dual HIV and HPV vaccination of adolescent girls through a school-based health care system in South Africa represents a plausible and cost-effective strategy for addressing the high incidence of HIV and HPV disease that this young age group is particularly susceptible to. Apart from being cost-effective, the universal implementation of the HIV vaccine to adolescent boys and girls through the same delivery mechanisms, yielded substantial health gains by reducing the HIV disease incidence and improving life expectancy across all age groups. The thesis provided evidence that substantiated these findings and thus has implications for adolescent health planning in South Africa going forward. The strength of the economic evaluation findings is that it is based on locally 'sourced' South African data, and is thus representative of the current health situation in the country and not merely an extrapolation of regional or international findings. Furthermore, apart from being locally relevant, the findings may have significance to other LMICs where high HIV and HPV disease burdens persist, with a dearth of reliable health information generated to guide planning. The comprehensive establishment of school-health services is complex and using this conduit for the implementation of the HIV and/or HPV vaccine services remains challenging; but international (and now locally relevant) evidence exists that supports this initiative as viable and cost-effective. Much work still remains to be done in the field.

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ANNEXURE A. COSTING STRUCTURES CLARIFIED

(i) Micro-costing for vaccine delivery costs per participant (US$ 1 = ZAR 8.21)

Cost assignment	Line item	(ZAR)	US$	Notes
Pharmaceuticals	STI treatment	(7.54)	0.92	- Cost per one unit of treatment - Assigned for potential STI syndromic management. - Negotiated reduced pricing on government tender.
	Contraception	(14.39)	1.75	- Cost includes two units of male condoms (pack of 20 each) and hormonal contraception (hormonal contraception distributed to every second child, if requested). - Negotiated reduced pricing on government tender.
Human Resources	Lay counsellor (per 20 minute session)	(27.78)	3.38	- Pre- and post- test counselling allocated.
	PHC* nurse (per 30 minute session)	(54.93)	6.69	- Duties include co-ordination of health services, health promotion, treatment and referral (as required) and administration of vaccines.
	ENA* (per 15 minute session)	(18.78)	2.29	
Laboratory	HIV testing	(9.21)	1.12	- Rapid testing kits used as per government tender.
Miscellaneous	Transport	(5.31)	0.65	- Vehicle leasing costs used to calculate the transport costs per school visit.
Totals		**(137.94)**	**16.80**	

*ENA – Enrolled nursing assistant, PHC – Primary health care

(ii) Vaccine costing structures

	Very low	Low	BASE	Medium	High
(ZAR)	(20)	(50)	(100)	(150)	(200)
US$	2.44	6.09	12.18	18.27	24.36

ANNEXURE B. ETHICS APPROVAL
(UNIVERSITY OF THE WITWATERSRAND)

R14/49 Dr Nishila Moodley

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140472

NAME: (Principal Investigator)	Dr Nishila Moodley
DEPARTMENT:	School of Public Health Chris Hani Baragwanath Academic Hospital Perinatal HIV Research Unit
PROJECT TITLE:	The Impact of Dual HIV and HPV Vaccine Strategies among Adolescents in a Resource Contrained Setting
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Glenda Gray, Dr Melanie Bertham and Dr Alex Welte
APPROVED BY:	[signature] Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/05/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature ____________ Date ____________

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ANNEXURE C. TITLE APPROVAL
(UNIVERSITY OF THE WITWATERSRAND)

Faculty of Health Sciences
Private Bag 3 Wits, 2050
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Reference: Ms Thokozile Nhlapo
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25 April 2014
Person No: 9602853F
PAG

Dr N Moodley
Postnet Suite 213
Private Bag X1
Northcliff
2115
South Africa

Dear Dr Moodley

Doctor of Philosophy: Approval of Title

We have pleasure in advising that your proposal entitled *The impact of dual HIV and HPV Vaccine strategies among adolescents in a resource contrained setting* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

ANNEXURE D. TURNITIN REPORT

Explanatory note:

The similarity percentage calculated by Turnitin represents a guideline and has been interpreted as such (rather than a threshold). There are very legitimate reasons why the similarity was assessed at 23% that does not constitute plagiarism. The reasons for the high index of similarity include:

1. The thesis comprises 2 published peer reviewed papers and one non-peer reviewed paper. Turnitin is currently picking up each item of every table as a direct reproduction of the paper. It is not possible for me to paraphrase quantitative data.
2. The thesis has referenced 819 different papers / sources and each of these contribute to the similarity index.
3. Each paper I have submitted to the University of the Witwatersrand's Wits-elearn programme for the plagiarism scan has been archived. Thus, if the report is re-run, the similarity index actually increases and is documented under the category *Student Paper*.

The plagiarism report has been discussed with my supervisor, Prof Glenda Gray, and she has approved the submission of the Turnitin report and the thesis.

____

Prof Glenda Gray

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ORIGINALITY REPORT

%23	%10	%14	%5
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Nishila Moodley, Glenda Gray, Melanie Bertram. "Projected economic evaluation of the national implementation of a hypothetical HIV vaccination program among adolescents in South Africa, 2012", BMC Public Health, 2016 Publication	%7
2	Submitted to University of Witwatersrand Student Paper	%3
3	www.ncbi.nlm.nih.gov Internet Source	%1
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5	www.biomedcentral.com Internet Source	%1
6	www.bmj.com Internet Source	%1
7	Belhadj, Hedia, Jennifer J.K. Rasanathan, Lynette Denny, and Nathalie Broutet. "Sexual and reproductive health and HIV services: Integrating HIV/AIDS and cervical cancer prevention and control", International Journal of Gynecology & Obstetrics, 2013. Publication	%1
8	Xin Sun. "Decision-analytical modelling in health-care economic evaluations", The European Journal of Health Economics, 11/2008 Publication	%1
9	www.childlinesa.org.za Internet Source	<%1
10	www.jiasociety.org Internet Source	<%1