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An Economic Evaluation of Zambia's Human Papilloma Virus (HPV) Vaccination Programme



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2195221

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ABSTRACT

This thesis presents an integrating narrative of five interrelated studies evaluating the cost-effectiveness of Zambia's national Human Papillomavirus (HPV) vaccination programme. It addresses a critical evidence gap in locally contextualised economic evaluations to inform sustainable policy and immunisation strategies in low- and middle-income countries. The research assessed costs and cost-effectiveness of three HPV vaccine delivery platforms—school-based, community outreach, and health facility—compared to cervical cancer screening alone, with additional analysis for HIV-positive subpopulations.

Using a Markov model informed by primary costing data, a systematic review, and programmatic insights, the study found that school-based delivery was the most cost-effective (ICER: $65 per DALY averted), followed by the combined approach (ICER: $263). Community outreach and health facility models were significantly less cost-effective. The research further explored how COVID-19 disrupted immunisation financing and delivery, which also affected HPV vaccine delivery at the time of the study. This represents an important contextual consideration in understanding programme performance, costs, and sustainability challenges.

The study underscores the need for locally driven health technology assessments (HTAs) and context-specific data to guide vaccine policy decisions. Its findings are intended to support Zambia's Expanded Programme on Immunisation (EPI), ZITAG, and other stakeholders in optimising delivery strategies as the country transitions from donor support.

DECLARATION

I, **Moses Simuyemba**, declare that this thesis, titled:

"An Economic Evaluation of Zambia's Human Papillomavirus (HPV) Vaccination Programme",

is my own original work. It is being submitted for the degree of Doctor of Philosophy (PhD) in Public Health at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Where other sources of information have been used, they have been appropriately acknowledged and referenced.

Signed: 

Moses Simuyemba

Date: 18th September 2025

DEDICATION

To God Almighty,

For Your unfailing guidance, strength, and presence throughout this journey. In the midst of life's challenges and uncertainties, You have been my refuge and source of hope. Thank You for granting me the wisdom, resilience, and courage to persevere through every trial. This work is a testament to Your grace and faithfulness, and I offer it in gratitude for the countless ways You have sustained me. May Your name be glorified through this accomplishment and all that it represents.

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- The views and interpretations presented in this thesis are solely those of the authors and do not represent the positions of Gavi, the Vaccine Alliance, or the UNC-UNZA-Wits Partnership for HIV and Women's Reproductive Health. Any errors are the full responsibility of the author

Conference Proceedings

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Workshops, Seminars and Meetings

1. Simuyemba, M.C. (2020, February 3–4). *Presentation of PhD methodology and theoretical framework*. Oral presentation at the UNZA–Vanderbilt Partnership for HIV–Nutrition Research Training (UVP), Lusaka, Zambia.
2. Simuyemba, M.C. (2021). *Preliminary findings on cost and sustainability of HPV vaccine in Zambia*. Oral presentation at the Expanded Programme on Immunisation Technical Working Group (EPI TWG) Meeting, Ministry of Health – Child Health Unit, Zambia
3. Simuyemba, M.C. (2020, September 30). *How COVID-19 has affected immunisation services at subnational level in Zambia*. Oral presentation at the Ministry of Health Multi-Stakeholders Dialogue Meeting on the Effects of the COVID-19 Pandemic on Immunisation Services, organised by GAVI/UNZA FCE and the Ministry of Health, Zambia.
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II. Simuyemba, M.C., Chama-Chiliba, C.M., Chompolola, A. et al. **An evaluation of the cost of human papilloma virus (HPV) vaccine delivery in Zambia.** BMC Infect Dis 24, 369 (2024). https://doi.org/10.1186/s12879-024-09222-2

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IV. Simuyemba, M. C., Chama-Chiliba, C., Chompola, A., Sinyangwe, A., Bchir, A., Asiimwe, G., & Masiye, F. (2025). **An evaluation of the consequences of Covid-19 on immunisation programme financing and service delivery in a lower-middle-income country: The case of Zambia.** *Medical Journal of Zambia, 51*(1), 1–11. https://doi.org/10.55320/mjz.51.1.466

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I. Chompolola A, Chama-Chiliba C, **Simuyemba MC**, Sinyangwe A, Bchir A, Asiimwe G, Masiye F. An assessment of fiscal space for immunisation financing in Zambia. BMC Res Notes 17, 152 (2024). https://doi.org/10.1186/s13104-024-06696-w

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III. **Simuyemba, M.C.**, Chama-Chiliba, C., Chompola, A., Sinyangwe, A., Bchir, A., Asiimwe, G., Masiye, F. (2022). Evaluating the functionality and effectiveness of ZITAG and related expanded programme on immunisation technical committees in Zambia. Vaccine: X, Volume 12(100193). https://doi.org/10.1016/j.jvacx.2022.100193

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VII. Kaluba, L., Malambo, M., Mutati, C., Chabinga, P., **Simuyemba, M**., Chilengwe, W., & Kafwamfwa, M. (2022). Can medicine be taught online? Cavendish University's transition from contact classes to online learning during the COVID-19 pandemic. Medical Journal of Zambia, 48(3), 171 - 180. Retrieved from https://mjz.co.zm/index.php/mjz/article/view/829

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ABBREVIATIONS AND DEFINITIONS

- **ACER:** Average Cost-Effectiveness Ratio
- **AGYW**: Adolescent Girls and Young Women
- **AIDS**: Acquired Immunodeficiency Syndrome
- **CBV**: Community-Based Volunteer
- **CEA**: Cost-effectiveness analysis
- **CHEERS**: Consolidated Health Economic Evaluation Reporting Standards
- **CHW**: Community Health Worker
- **CHWk**: Child Health Week
- **CIN**: Cervical Intraepithelial Neoplasia
- **CIN1**: Cervical Intraepithelial Neoplasia Grade 1 (Mild Dysplasia)
- **CIN2**: Cervical Intraepithelial Neoplasia Grade 2 (Moderate Dysplasia)
- **CIN3**: Cervical Intraepithelial Neoplasia Grade 3 (Severe Dysplasia/Carcinoma in Situ)
- **CSE**: Comprehensive Sexuality Education
- **DALY**: Disability-Adjusted Life Year
- **DREAMS**: Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe
- **EHT**: Environmental Health Technologist
- **EPI**: Expanded Programme on Immunisation
- **EPIC**: Expanded Programme on Immunisation Costing and Financing
- **FCE**: Full Country Evaluation
- **FGD**: Focus Group Discussion
- **FIC**: Fully Immunised Child
- **GDP**: Gross Domestic Product
- **GRZ**: Government of the Republic of Zambia
- **HIV**: Human Immunodeficiency Virus
- **HPV**: Human Papilloma Virus
- **hrHPV**: High risk Human Papilloma Virus
- **HTA:** Health Technology Assessment
- **ICER**: Incremental Cost-Effectiveness Ratio
- **KI**: Key Informant

- **KII**: Key Informant Interview
- **M&E**: Monitoring and Evaluation
- **MOH**: Ministry of Health
- **NGES**: National Girls' Education Strategy
- **NGO**: Non-Governmental Organization
- **PCV**: Pneumococcal Conjugate Vaccine
- **PEPFAR**: The U.S. President’s Emergency Plan for AIDS Relief
- **PATH**: Program for Appropriate Technology in Health
- **PCV**: Pneumococcal Conjugate Vaccine
- **QALY**: Quality-Adjusted Life Year
- **SAGE:** Strategic Advisory Group of Experts
- **SRHR**: Sexual and Reproductive Health and Rights
- **TOC:** Theory of Change
- **UNICEF**: United Nations International Children's Emergency Fund
- **USD**: United States Dollar
- **WHO:** World Health Organization
- **ZITAG**: Zambia Immunisation Technical Advisory Group
- **ZMW**: Zambian Kwacha

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1. INTRODUCTION

Cervical cancer contributes a large proportion of cancer-related illness and death globally and is mainly caused by the human papillomavirus (HPV) [1-3]. Zambia serves as a notable example of the significant cervical cancer burden on the African continent and globally. In Zambia, more than 4.7 million females aged above 15 are at risk of having cervical cancer in their lifetime [1, 4, 5]. It is the leading cause of cancer-related deaths among women in the country, with an age-standardized incidence rate of 66.4 per 100,000 women and a mortality rate of 44.5 per 100,000 women [1, 4, 5]. Cervical cancer rates are higher in urban populations than rural ones as well as in HIV positive populations compared to HIV negative populations [2, 6-8]. The mortality rate remains alarmingly high, almost 1400 deaths annually with an annual incidence of over 2300 cases, largely due to late-stage diagnosis and inadequate access to effective treatment options [1, 9-12].

The Cervical Cancer Prevention Program in Zambia (CCPPZ), implemented since 2006, is a cervical cancer screening programme in which trained health personnel, mainly nurses, provide screening through visual inspection with acetic acid (VIA) which is coupled with digital cervicography, with immediate treatment by ablation or, if clinically indicated, referral for surgical excision in the case of CIN or histologic examination in the case of suspected ICC [3, 13-15]. VIA-positive women receive same-day ablation whereas VIA-negative women receive counselling and are followed up for further advice [3, 13, 14].

Anogenital HPV infection is essentially sexually acquired and affects both men and women with risk factors relating to sexual behaviour characteristics such as early sexual debut and a large number of sexual partners [16]. Persistent infection of high-risk types of HPV has been established as a cause of early, non-cancerous, and late or cancerous lesions of the cervix as well as, to a lesser degree, cancers of the vulva and vagina, anus, and oropharynx [16].

In females, high risk HPV infection (hrHPV) can result in lesions on the cervix and over time these have the potential to progress to cervical cancer though cervical intraepithelial neoplasia (CIN) I, II and III stages, which are precancerous stages that

can be treated, and finally to invasive cervical cancer (ICC) [16]. High risk HPV genotypes 16 and 18 have been found to account for over 70% of the cervical cancer burden globally, while genotypes 6 and 11 cause genital warts [16]. Most women who acquire HPV infection are asymptomatic and only those with persistent infection are at risk for CIN and ICC [16]. Prevention of HPV infection, through vaccination for example, is thus a highly efficacious in preventing cervical cancer caused by oncogenic HPV genotypes.

There are currently three licensed, highly immunogenic, efficacious HPV vaccines for prevention of pre-invasive and invasive cancer of the cervix, vagina, and vulva caused by hrHPV [17]. The World Health Organisation recommends vaccination of girls aged 9-15, before they become sexually active [17]. Zambia's HPV vaccination efforts began with a demonstration project from 2013 to 2017, addressing its high cervical cancer burden caused by limited screening and treatment services, hrHPV prevalence, and a significant HIV burden [1, 2, 18, 19]. The project, supported by Gavi (the Vaccine Alliance), and other stakeholders, aimed to assess the feasibility of delivering HPV vaccines to adolescent girls and gather data for a national rollout [18-20]. It focused on vaccinating Grade 4 girls and 10-year-old out-of-school girls across urban and rural districts, achieving over 80% coverage in the demonstration districts [21].

The school delivery platform was trialled in the HPV demonstration project and the health facility and community outreach delivery models were not a major focus of the demonstration project and were not significantly utilised, although they were meant to cater for those out of school. Despite logistical challenges, vaccine hesitancy, and difficulty reaching out-of-school girls, the project demonstrated Zambia’s capability to deliver HPV vaccines, laying the groundwork for a national rollout [22-24].

Building on this success, Zambia launched its national HPV vaccination program in 2019, which targeted girls who were 9–14 years old [25-27]. The country was provided with US$1,138,490 of funding from Gavi (43% of the total budget of US$2,663,394) to introduce HPV vaccines nationally using the quadrivalent HPV vaccine (which is effective against HPV genotypes 6, 11, 16 and 18), targeting girls aged 9-14, commencing in June 2019 [18, 25]. Three delivery platforms are used

(school, facility and outreach) during child health weeks that are held twice a year [25, 28]. Strong public awareness campaigns and collaboration with traditional and religious leaders helped address vaccine hesitancy and improve acceptance [25]. By the end of the first year, administrative vaccination coverage data showed first dose coverage exceeding 70%, particularly in urban areas, and the program strengthened Zambia's immunisation infrastructure, including cold chain supply and capacity [18, 22].

At the time of recommending the introduction of the HPV vaccine in Zambia, cost-effectiveness evidence used by the Zambia Immunisation Technical Advisory Group (ZITAG) was from other countries, namely Canada, Brazil, and the United Kingdom [18, 29]. Gavi reports noted that the applicability of these findings from other countries was debatable, and that such decisions were often significantly shaped by worldwide agendas set by funders and donors [18, 21, 30]. PATH conducted a costing study during the demonstration project and this study worked out the financial cost per fully immunised girl to range between US$9.98 and US$10.40. However, the study did not assess the vaccine's cost-effectiveness [22]. Furthermore, Gavi's Full Country Evaluation (FCE) highlighted that there was need to look deeper at the sustainability and financial cost implications of introducing the HPV vaccine on a countrywide scale using locally produced evidence [18]. The report further went on to recommend that the MOH establish clear policies and guidelines for decision making on new technologies such as vaccines informed by economic evaluations of new vaccine introductions [18]. As Zambia moves forward with the national rollout a key implementation consideration is determining the most cost-effective delivery model among school, facility, and outreach delivery models [18].

Although the costs per fully vaccinated girl was established in 2014, this was for the demonstration project and costs during the scaled up national implementation are likely to be different and need to be investigated. Secondly, no prior studies have evaluated the cost-effectiveness of the different service delivery platforms (school, facility, and outreach) in the Zambian context. This is even more important given that over the past decade, Zambia has introduced a plethora of new vaccines countrywide (e.g. rotavirus, Pneumococcal conjugate vaccine, and measles-rubella),

which have been crucial in reducing the number of cases and deaths from these diseases but have significantly strained the national health system financially [18, 21, 31]. The logistical demands of maintaining cold chain infrastructure, reaching remote areas, and training personnel have stretched the health budget, with year-to-year funding gaps for the EPI programme's strategic plans ranging from 41% to 68% between 2017 and 2021 [18, 31]. The national introduction of the HPV vaccine in 2019, supported by Gavi, added to these financial concerns, particularly as Zambia prepares for its eventual transition from Gavi funding [20, 31].

HPV vaccination, which required two doses in initial recommendations (or three for HIV-positive girls), is more expensive than many other routine vaccines, and the associated costs of delivery, infrastructure, and rural outreach further exacerbate sustainability concerns [32-34]. As the government gradually increases its domestic co-financing of vaccines, there is a growing fear that the introduction of HPV, along with recent vaccine additions, could widen funding gaps and jeopardise Zambia's ability to sustain high immunisation coverage rates.

In light of the above, the aim of this study was *to evaluate the cost-effectiveness of Zambia's national Human Papillomavirus (HPV) vaccination programme, delivered through health-facility, outreach, and school-based platforms, compared to screening alone, in Zambian girls aged 9–14 years over a lifetime horizon, to inform decision-making on optimal delivery strategies.*

The specific objectives of the study were:

i. *To conceptualise an economic model for assessing the cost-effectiveness of HPV vaccine*
ii. *To establish the overall cost per fully vaccinated girl (having received 2 doses of vaccine) nationally and the cost per fully vaccinated girl across the three delivery platforms (school, facility and outreach) of HPV vaccine introduction in Zambia.*
iii. *To assess the cost-effectiveness of the three delivery platforms (school, facility and outreach) for HPV vaccine introduction in Zambia.*

iv. *To establish cost-effectiveness of HPV vaccination in Zambia across the HIV positive/negative and rural/urban subgroups (subgroup analysis).*

These questions are addressed through a series of five papers that form the basis of this thesis and are reproduced at the end of this integrating narrative. Papers I through III focus on addressing the key objectives, while Papers IV and V provide contextual factors and additional insights into the HPV implementation landscape in Zambia during the data collection period, which have a direct bearing on both the costs and cost-effectiveness of HPV vaccine delivery. Papers IV are V are thus important in interpreting the findings of the second, third and fourth objectives, or papers II and III, respectively. The connections between these five papers are illustrated in Figure 1 below.

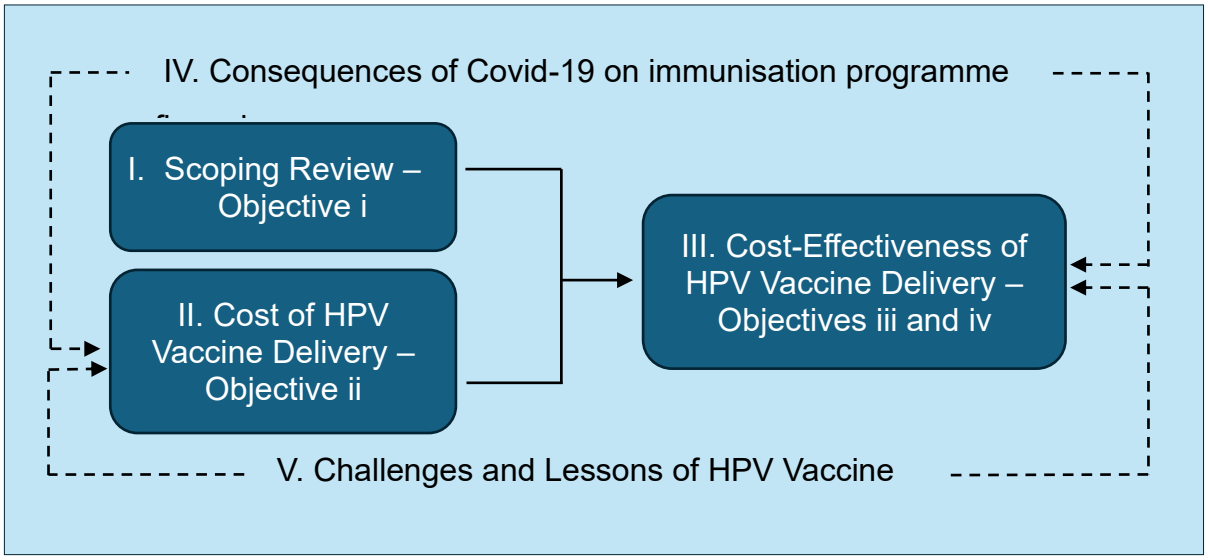

Figure 1: Relationships of the papers that constitute thesis on HPV Cost-Effectiveness in Zambia

This study aimed to explore these factors and develop evidence that can be useful for the EPI programme and its stakeholders to make evidence-based decisions for the sustainability of HPV vaccination in terms of choosing the most cost-effective delivery platform or mix of platforms. This evidence will be presented to the EPI team as well as other relevant stakeholders such as the Inter-Agency Coordinating

Committee (ICC) and its technical working groups (TWGs), and the ZITAG as the main policy bodies on immunisation to which the author has access through his work on the Gavi Full Country Evaluation. This study will thus help to inform future decisions on vaccine rollout and influence Health Technology Assessment (HTA) in Zambia.

Local evidence for cost-effectiveness studies is critical in guiding EPI stakeholders and policymakers in optimizing the allocation and utilisation of resources, identifying efficiency improvements, and ensuring equitable vaccine delivery. They can also quantify the long-term economic benefits of preventing cervical cancer compared to treatment costs, strengthening the case for continued investment in the HPV vaccination program as donor support from Gavi diminishes. Furthermore, these evaluations can help address sustainability concerns by informing financing mechanisms, such as integrating vaccination into existing health services or tailoring strategies for high-cost regions.

The remainder of this thesis is structured as an integrating narrative that brings together five interrelated papers. Chapter 2 provides background information on the burden of cervical cancer, HPV epidemiology, vaccine efficacy, and the policy context in Zambia. Chapter 3 outlines the theoretical and conceptual frameworks guiding the study, while Chapter 4 presents the aims and specific objectives. Chapter 5 details the methods used across all five papers, including data sources, analysis, and modelling approaches. Chapter 6 synthesises the findings from each paper, highlighting cost and cost-effectiveness results, contextual challenges, and implementation considerations. The final chapters discuss the implications of the findings, propose policy recommendations, and outline future directions for research and decision-making in HPV vaccination and broader immunisation financing in Zambia. The full versions of the five research papers are included as annexes to support and elaborate on the integrating narrative.

BACKGROUND

Cervical Cancer Burden and Challenges

As pointed out in the earlier, cervical cancer is a significant public health problem in Zambia and globally, particularly affecting women of low socio-economic standing in LMICs [35, 36]. This high global burden reflects the continuing challenge of preventing, detecting, and treating the disease effectively [36, 37]. However, there are marked disparities between high-income countries and low-income countries number of cases and deaths from cervical cancer, partly due to differences in healthcare provision and quality, availability of screening services for cervical cancer, and access to HPV vaccines [7, 37]. A large proportion of cervical cancer deaths, over 90%, occur in LMICs, which highlights the stark inequities in healthcare access, preventive care, and treatment [36, 38].

Africa in general, including Zambia, faces significant healthcare challenges that exacerbate the cervical cancer burden and impact, and these include limited access to screening, low vaccination coverage, weak healthcare systems, resource constraints; limited infrastructure for cancer treatment and prevention; A shortage of trained specialists, insufficient cancer awareness among healthcare workers, weak care-coordination structures, under-funded and under-resourced health facilities, sometimes even negative attitudes of healthcare personnel toward patients, and the high cost of both diagnosis and treatment and care services [9-12].

In addition to these structural challenges, HIV prevalence in Africa adds another layer of complexity to the cervical cancer burden [2, 7, 8, 14, 39, 40]. HIV positive women have an up to six-fold higher risk of developing persistent and unresolving hrHPV infections, significantly increasing their chances of developing cervical cancer [7, 8, 40]. The interplay between HIV and HPV poses a significant public health challenge in the region, where both infections are highly prevalent. There are also barriers on the client side such as patient's obligations related to family and personal commitments; lack of time; sexuality concerns about cervical cancer and its treatment, body image concerns and how they may affect relationships; as well as patient stigmatisation and discrimination [4, 11, 12, 39].

Efforts to address the cervical cancer burden in Zambia have been hampered by these systemic issues. Although the country has made strides in introducing HPV vaccination and improving cancer screening, coverage remains suboptimal [3, 5]. Screening coverage in one survey was as low as 16.4% [5, 15]. The country has an ambitious target of 65% screening for women above 30 and 90% for HPV vaccination by 2030 towards “Eliminating Cervical Cancer as a Public Health Problem” [5].

HPV Epidemiology and its Contribution to Cervical Cancer

HPV is one of the most common STIs globally and the major cause of cervical cancer morbidity and mortality [36, 41]. Of the more than 100 types of HPV, about 40 can infect the genitalia and surrounding tissues [16]. Of these, 14 are classified as high-risk, and likely to cause cancer, particularly cervical cancer [42]. HPV is highly transmissible, and it is estimated that people who are sexually active will acquire the virus at some point in their lifetime. However, most HPV infections and resolve spontaneously and are transient, within one to two years, without causing any significant harm [43, 44]. The concern arises when infections persist and do not resolve as is often the case with certain hrHPV types as highlighted earlier. Persistent infections, particularly with hrHPV types 16 and 18, which are highly oncogenic, are responsible for approximately 70% of cervical cancer cases globally [43, 44].

Zambia’s high cervical cancer prevalence is exacerbated by the country’s significant HIV burden, as HIV positive women are more susceptible to unresolving infections and development of cervical cancer [2, 6, 8, 40]. Additionally, at the time of this study it was recommended that girls who are HIV positive receive up to three doses of HPV vaccine, compared to two for those who were HIV negative [26, 34]. The high occurrence of both infections highlights the importance of strong prevention measures, such as vaccination and screening initiatives. [5].

Oncogenic hrHPV types cause cellular changes in the cervical epithelia, leading to the development of cervical intraepithelial neoplasia (CIN), which are precancerous lesions. If not detected early and subsequently and treated on time, they can evolve

to invasive cervical cancer. The two most significant hrHPV types are HPV-16 and HPV-18, which together account for approximately 70% of cervical cancer cases worldwide [45, 46]. In Zambia, some studies have noted prevalence levels of types 16 and 18 being as high as 68% of women with cervical cancer, 30% in those with Low-grade cervical lesions and 46% in those with High-grade cervical lesions [1]. Low-grade cervical lesions are mild cellular abnormalities typically caused by HPV (such as CIN 1), while high-grade cervical lesions are more severe precancerous changes (such as CIN 2 or CIN 3). These two types of hrHPV are particularly aggressive, contributing to both cervical and other cancers.

Persistent HPV infection is a key risk factor for the development of cervical cancer [16]. Over time, the virus can trigger cellular changes in the cervix, resulting in the development of precancerous lesions, known as cervical intraepithelial neoplasia (CIN), which may eventually progress to cervical cancer [16].

CIN classification is explained below:

- **CIN 1:** Mild abnormal cell growth confined to the lower third of the cervical epithelium. This condition is often temporary and may resolve without medical intervention.
- **CIN 2:** Moderate abnormal cell changes affecting up to two-thirds of the epithelial layer. This stage has a greater likelihood of progressing to cancer and may require treatment.
- **CIN 3:** Severe dysplasia or carcinoma in situ, where abnormal cells extend through the full thickness of the epithelium but have not yet invaded deeper tissues. If untreated, CIN 3 poses the highest risk of developing into invasive cervical cancer.
- **Cervical Cancer:** If CIN is left undetected and untreated, abnormal cells can penetrate the deeper layers of the cervix and spread to surrounding tissues, leading to invasive cervical cancer. This can manifest as either squamous cell carcinoma or adenocarcinoma [2, 8]. In most women, this progression typically occurs over 10 to 20 years or longer. However, in immunocompromised individuals, particularly those living with HIV, the transition from HPV infection to cervical cancer can happen more rapidly due

to a weakened immune system, which is less effective at controlling the virus [2, 6, 47]. Several studies in Zambia found a high burden of previously undiagnosed cervical disease in HIV positive women upon screening [2, 6, 47].

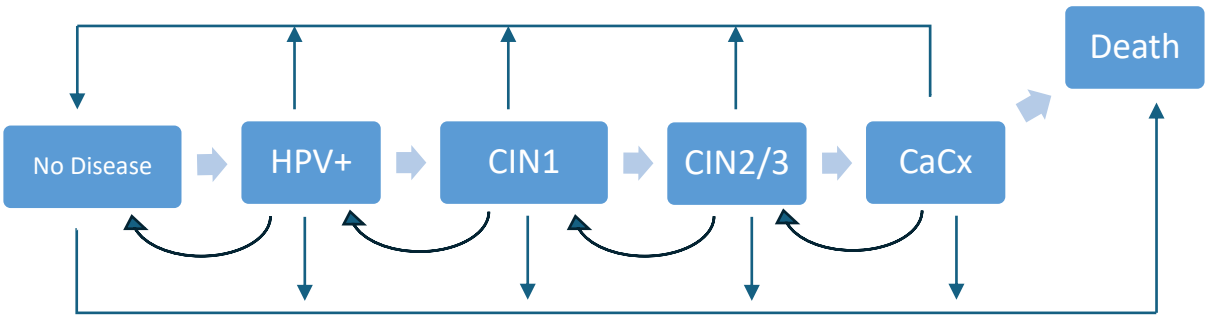

Figure 2: Cervical cancer disease states applied to Markov model

Invasive cervical cancer can spread to other areas of the body [48]. Treatment typically consists of a combination of surgery, complemented by radiation therapy, and often chemotherapy [48]. However, if the disease is diagnosed late, outcomes tend to be poor, a situation that is especially common in low-resource settings where access to early detection and timely treatment is limited [48].

Risk factors for progressing of hrHPV infection to cervical cancer include persistent HPV infection, with high-risk HPV-16 and HPV-18, is the most significant risk factor, HIV infection, which was incorporated into the modelling of this work, is another critical factor, HIV positive women have a higher risk of persistent HPV infection and progress faster progression to develop cervical cancer; in Zambia, 12.9% of cervical cancer patients were found to be HIV positive [8]. Smoking adversely affects the immune system and cervical epithelial cells and is also associated with a higher risk of cervical cancer, likely due to its, with a smoking prevalence of 4.7% among

cervical cancer patients in one study [1, 49]. Prolonged use of oral contraceptives has also been suggested to increase the risk of cervical cancer, likely due to hormonal influence on cervical epithelium coupled with less likelihood of using barrier methods of contraception, with nearly 12% of cervical cancer patients in Zambia reporting the use of oral contraceptives [1, 49]. Additionally, multiple full-term pregnancies appear to elevate risk; women with more than five live births were found to have a higher chance of developing cervical cancer in Zambia [8, 49]. This is likely due to hormonal changes during pregnancy, repeated cervical trauma from childbirth, prolonged exposure to hrHPV, and immune modulation that reduces the body's ability to clear persistent infections [50].

The gradual progression from HPV infection to cervical cancer presents important opportunities for prevention. HPV vaccination, especially for girls between the ages of 9 and 14, helps protect against infection from the most prevalent hrHPV strains, including HPV-16 and HPV-18.. However, as of 2022, only 13% of eligible girls globally were vaccinated, despite 60% of WHO member states introducing HPV vaccination into their vaccination programmes [51]. Routine cervical cancer screening, such as Pap smears and HPV testing, enables early detection and treatment of precancerous lesions before they develop into cancer [52]. However, in Zambia, screening coverage among women aged 25 to 49 remains alarmingly low, with rates below 16.4% [52]. Additionally, HIV prevention and effective treatment with antiretroviral therapy (ART) can reduce the risk of HPV progression in women living with HIV [52, 53].

As pointed out earlier, beyond cervical cancer, certain hrHPV subtypes are linked to various other cancers and non-cervical conditions. This underscores the wider health implications of HPV vaccination, emphasizing the need for broad vaccination coverage—not only to prevent cervical cancer but also to reduce the risk of other HPV-related cancers and diseases [43, 53-55].

HPV Vaccines and Their Efficacy Against Cervical Cancer

HPV vaccines have revolutionised cervical cancer prevention by targeting the primary cause of the disease, the human papillomavirus (HPV). Three HPV vaccines - bivalent (Cervarix), quadrivalent (Gardasil), and nonavalent (Gardasil 9) - provide different levels of protection against high-risk HPV strains [46]. These vaccines use virus-like particles (VLPs) to trigger an immune response, providing antibodies that neutralise the virus upon exposure, effectively preventing precancerous lesions and cervical cancer. Cervarix targets HPV-16 and HPV-18, which cause 70% of cervical cancers globally, with over 90% efficacy in preventing related infections and lesions [42, 46].Gardasil, which Zambia opted for, adds protection against HPV-6 and HPV-11, responsible for 90% of genital warts, while demonstrating over 98% efficacy in reducing high-grade cervical lesions [42, 46]. Gardasil 9 expands coverage to five additional high-risk types, protecting against nearly 90% of HPV-related cervical cancers worldwide, with over 95% efficacy [42, 46]. In addition, Gardasil has shown partial cross-protection against certain non-vaccine oncogenic HPV types such as HPV-31, which are prevalent in Zambia and disproportionately affect women living with HIV, thereby enhancing its potential cost-effectiveness in this setting [42].

HPV vaccines are most effective when administered before sexual debut, usually to girls and boys aged 9 to 14. Vaccination at this age triggers a stronger immune response and significantly reduces HPV infections, cervical abnormalities, and precancerous lesions [42, 46]. Countries with high vaccination coverage, like Australia, have observed over 90% reductions in hrHPV infections and precancerous lesions, with projections indicating decreased cervical cancer incidence and mortality over time [42, 46]. Long-term studies confirm the durability of vaccine protection for up to 10 years without waning immunity or a need for booster doses, and the vaccines exhibit excellent safety profiles [42, 43, 53]. In addition to preventing cervical cancer, HPV vaccines lower the risk of other HPV-related cancers and conditions, such as genital warts, further improving their cost-effectiveness and public health benefits. [36, 43, 56, 57].

Local and International Policies Guiding HPV Vaccination in Zambia

Global and national policies establish a strong foundation for guiding HPV vaccination efforts in Zambia. Internationally, the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer emphasizes vaccination, screening, and treatment, with a focus on vaccinating girls aged 9–14 years. This strategy aligns with the 90-70-90 targets, which aim to achieve 90% vaccination coverage of girls by age 15 [58]. The 90-70-90 targets for cervical cancer elimination aim for 90% of girls fully vaccinated with the HPV vaccine by age 15, 70% of women screened with a high-performance test by ages 35 and 45, and 90% of women identified with cervical disease receiving appropriate treatment [58]. In Zambia, Gavi provides support through financial assistance, including Vaccine Introduction Grants and Operational Cost grants, to ensure equitable access and effective vaccine rollout [18, 59-61]. The Gavi Co-financing model outlines the cost-sharing between Gavi and countries [61, 62]. Gavi's HPV national introduction theory of change (TOC) also provides some high level guidance on what key elements need to be in place for successful introduction and implementation of HPV vaccination programmes [18, 21].

At the national level, Zambia's National Health Strategic Plan (2022–2026) integrates HPV vaccination into broader health strategies, emphasizing preventive healthcare and universal coverage, while the National Cancer Control Strategic Plan (2022–2026) prioritizes vaccination as a key intervention to reduce cervical cancer incidence, with a target of vaccinating 90% of eligible girls [52, 61, 63]. Gavi's co-financing model further supports these efforts, gradually transitioning to domestic financing to sustain the program [61].

Critique of the policy documents

While the international and local policies provide a strong foundation for HPV vaccination in Zambia, there are several common gaps across the documents:

1. **Lack of Economic Evaluation Guidance**: None of the documents provide clear guidance on conducting economic evaluations or cost-effectiveness analyses, which are essential for ensuring that the vaccination program is financially sustainable in the long term. While the policies emphasize the importance of achieving high vaccination coverage, they do not offer tools or

frameworks for assessing the financial viability or cost-benefit of these programs in resource-limited settings like Zambia.

2. **Implementation Guidance**: Although the documents outline high-level targets and goals, such as achieving 90% vaccination coverage, they generally lack detailed, actionable steps for implementation at the national level. Limited practical guidance exists on addressing logistical challenges, such as reaching underserved communities and ensuring the seamless integration of HPV vaccination with other healthcare services, especially in rural areas.
3. **Sustainability of Programs**: While Gavi's co-financing model supports initial vaccine introduction, the long-term sustainability of the program as Zambia transitions to domestic financing is not thoroughly addressed. The lack of economic evaluation frameworks makes it difficult for the Zambian government to plan for future financial independence from Gavi's support, potentially jeopardizing the sustainability of the vaccination efforts.
4. **Prioritisation and Resource Allocation**: The existing documents do not provide clear criteria for prioritizing HPV vaccination relative to other health interventions. In a resource-constrained environment, where healthcare budgets must be carefully allocated, having tools to assess the comparative cost-effectiveness of HPV vaccination could help decision-makers make more informed choices.

Addressing these gaps requires incorporating economic evaluation frameworks into policy documents to support informed decision-making. This research aims to provide critical insights into the costs and cost-effectiveness of HPV vaccine delivery, offering methodologies applicable not only to HPV but to other vaccines and health technologies. Strengthened policies and economic guidance are essential for the sustainability and impact of vaccination programs in resource-limited settings like Zambia.

2. THEORETICAL FRAMEWORK

HPV introduction theory of change

Gavi's HPV programme implementation theory of change (TOC) is provided in Figure 3 below. This TOC was utilised to assess the HPV vaccine introduction in Zambia, and findings are presented particularly in the contextual Papers IV and V. The Gavi TOC for HPV vaccine introduction by countries outlines a structured pathway aimed at achieving high vaccination coverage and reducing the burden of cervical cancer. It begins with critical inputs such as funding support, technical assistance, and stakeholder engagement, which enable key activities including vaccine procurement, health worker training, and social mobilisation campaigns. These activities lead to immediate outputs like increased awareness, improved vaccine availability, and strengthened health systems for service delivery. In the intermediate stage, the focus shifts to ensuring equitable access, building trust in vaccines, and improving vaccine coverage rates among adolescent girls, particularly in underserved communities. The ultimate outcomes are higher vaccination rates, significant reductions in HPV prevalence, and the long-term goal of reducing cervical cancer morbidity and its associated mortality. The framework highlights the importance of integrating these efforts within existing health systems, fostering sustainability, and addressing

challenges such as vaccine hesitancy and logistical constraints.

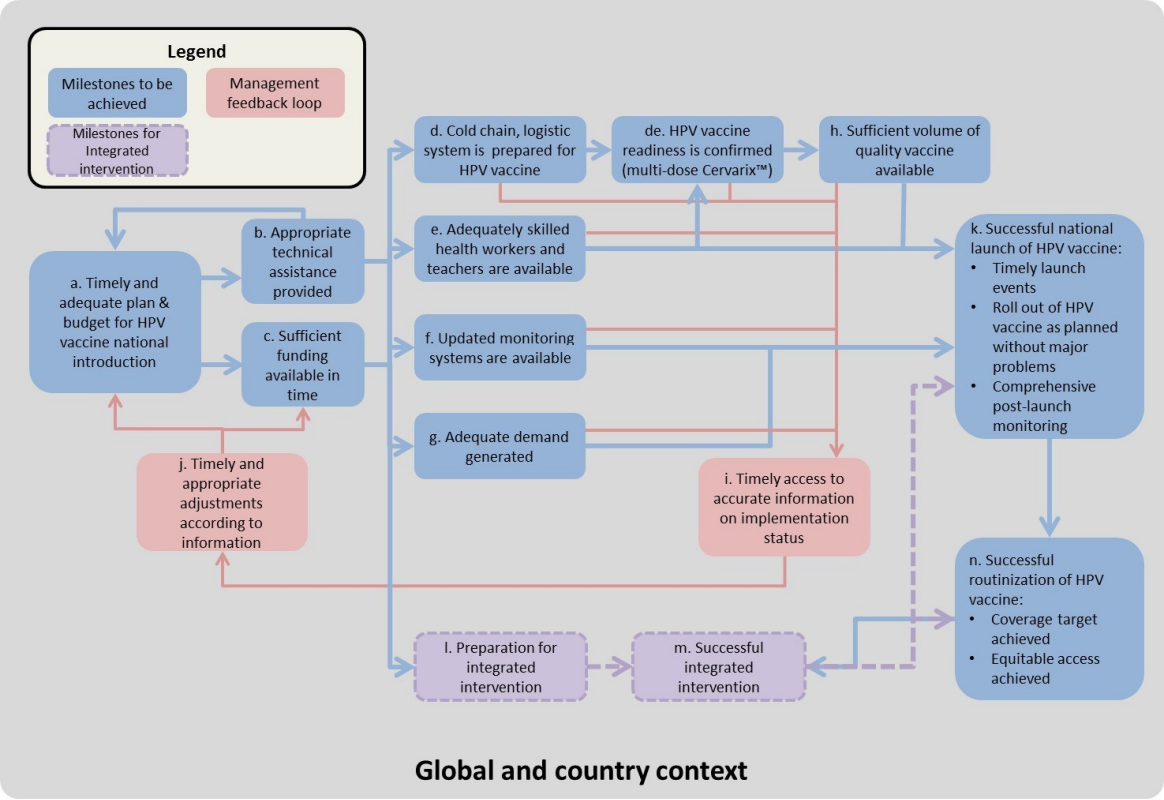

Figure 3: Gavi's HPV Vaccine introduction theory of change

The COVID-19 pandemic introduced additional challenges to immunisation programmes, including HPV vaccination. This study considers the financial and operational disruptions caused by the pandemic, such as increased costs for personal protective equipment (PPE) and reduced vaccination coverage due to school closures as detailed on Papers IV and V. These factors are integrated into the economic evaluation to provide a realistic assessment of the programme's cost-effectiveness under pandemic conditions.

Health Technology Assessment (HTA)

Health technology assessment (HTA) and economic evaluation are critical tools for assessing the value of healthcare interventions, particularly in resource-limited settings like Zambia [30, 64]. By systematically comparing the costs and outcomes of different healthcare delivery models, economic evaluations provide evidence for decision-makers to allocate limited resources efficiently [64]. The theoretical underpinning of this study is grounded in economic evaluation frameworks, Markov

modelling, and the broader principles of health economics, which together guide the analysis of Zambia's Human Papillomavirus (HPV) vaccination programme.

Health Technology Assessment (HTA) is ideally designed as a multidisciplinary process in order to evaluate the clinical, economic, and social implications of healthcare interventions and technologies [64]. It relies on rigorous evidence to assess the effectiveness, safety, and efficiency of healthcare interventions, ensuring that decisions are based on validated data. HTA integrates insights from clinical medicine, epidemiology, economics, sociology, and ethics, ensuring a comprehensive view of a technology's impact, while tailoring assessments to specific contexts like Zambia's local epidemiological patterns and healthcare infrastructure [64].

Transparency in methods and findings, along with stakeholder engagement, promotes inclusivity and ensures diverse perspectives inform decisions. HTA explicitly addresses equity, evaluating the distribution of benefits and risks to ensure vulnerable populations are included [64]. Economic evaluation, particularly cost-effectiveness analysis, is the cornerstone, identifying interventions that maximize health outcomes within available resources. Ethical considerations ensure decisions align with societal values, while a lifecycle perspective evaluates technologies over time to maintain long-term effectiveness and sustainability [64].

HTA frameworks must be adaptable to emerging technologies and changing trends, ensuring interventions remain sustainable amid resource constraints. In LMICs like Zambia, prioritization of high-impact, cost-effective interventions is critical to addressing high-burden diseases such as cervical cancer.

Economic Evaluation Frameworks

Economic evaluations are a major component of HTA in healthcare that typically adopt one of several approaches, such as cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses [65, 66]. For this study, both cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) are used as the primary method due to its ability to assess the relative efficiency of alternative HPV vaccine delivery platforms (school-based, health facility-based, and community outreach) compared

to cervical cancer screening alone. CEA compares the incremental costs of an intervention to its incremental health outcomes in natural units such as number of girls vaccinated, while the outcome measures of CUA are disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) [64, 65]. CEA and CUA are often used interchangeably in the literature, and for simplicity in this study, CEA is also used in place of CUA. The major output of the CEA is the incremental cost-effectiveness ratio or ICER, a valuable decision-making tool when there are resource constraints [64, 65].

While CEA is widely used and offers valuable insights, it is not without limitations and the Second Panel on Cost-Effectiveness in Health and Medicine made the recommendation that all CEA studies and reports should outline such limitations [64-66]. One critique of CEA is its reliance on a single outcome measure, such as DALYs or QALYs, which may not capture all dimensions of health benefits or the broader societal impacts of an intervention [65, 67]. For example, while CEA focuses on health outcomes, it may overlook important economic or social benefits, such as increased productivity or reduced caregiving burden, which are better captured through cost-benefit analysis (CBA). Additionally, the choice of outcome measure can introduce bias; for instance, DALYs prioritize life-years saved and disease burden reduced, potentially undervaluing interventions that improve quality of life without significantly extending life expectancy.

Another critique lies in the assumptions inherent in CEA models, such as fixed cost structures, linear relationships between costs and outcomes, and uniform health state transitions [30, 65, 66, 68, 69]. These assumptions may not hold true in real-world settings, where costs can vary widely based on factors such as geographic location, healthcare infrastructure, and population demographics. For instance, the cost of delivering vaccines through community outreach may be significantly higher in rural areas with poor road networks compared to urban settings. Such variations can influence the cost-effectiveness of different delivery platforms and must be carefully accounted for through sensitivity analyses.

Moreover, CEA does not inherently address equity concerns (cite), which are particularly relevant in low- and middle-income countries (LMICs) like Zambia. By

focusing on average cost-effectiveness, CEA may mask disparities in access to interventions, such as the exclusion of out-of-school girls from school-based vaccination programmes. Equity-weighted analyses or complementary frameworks that explicitly incorporate equity considerations are needed to ensure that economic evaluations align with broader public health goals.

CEA commonly uses thresholds to assess whether an intervention offers is worthwhile or not in terms of its benefits compared to costs [68, 70, 71]. A commonly used benchmark is the WHO-recommended threshold, which considers an intervention cost-effective if its incremental cost-effectiveness ratio (ICER) is below three times the country's per capita gross domestic product (GDP). An intervention is classified as highly cost-effective if the ICER is below the per capita GDP [64, 68, 70, 71]. While this threshold is simple and widely applicable, it has been critiqued for being too broad and not reflecting the actual willingness or ability of countries to pay for health interventions [64, 68, 70, 71]. Critics argue that the threshold’s focus on GDP per capita fails to account for variations in health budgets, competing priorities, and opportunity costs within LMICs, where financial resources for the health sector are usually severely constrained [64, 68, 70, 71].

An alternative method, suggested by Woods, Revill, et al. (2015), advocates for using country-specific thresholds that reflect the opportunity cost of healthcare spending, providing a more context-sensitive approach to cost-effectiveness evaluation [68, 70]. This approach calculates thresholds as the marginal productivity of health spending, which is estimated by assessing the health gains forgone when funds are reallocated to a new intervention. These thresholds are often much lower than the WHO’s GDP-based thresholds and are argued to better reflect the real-world trade-offs policymakers face [68]. For example, in many LMICs, the opportunity cost thresholds are closer to 10-50% of GDP per capita, depending on the country’s healthcare system efficiency and budget constraints. While these thresholds provide a more context-specific basis for decision-making, they require detailed data on healthcare spending and outcomes, which may not always be readily available in resource-limited settings [68, 70]. This has led to ongoing debates about the appropriate balance between practicality, precision, and contextual relevance in setting CEA thresholds. However for this analysis the higher

end of Woods recommended threshold for Zambia of between $68 - $768 was utilised, which was still below the GDP per capita of approximately $958 in 2020 [72].

Despite these limitations, CEA remains a valuable tool for guiding resource allocation in healthcare. Its strengths lie in its ability to provide clear and actionable comparisons of interventions, facilitating evidence-based decision-making. In this study, the use of CEA allows for a more organised and recognised evaluation of the balance between costs and health outcomes across different HPV vaccine delivery platforms.

This study adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, ensuring the transparency and robustness of study and its findings as shown in Appendix 1 [73]. Incorporating the CHEERS checklist helps mitigate common issues such as incomplete reporting of costs, selective presentation of outcomes, and insufficient sensitivity analyses. In this study, adherence to the checklist ensures that all relevant aspects of the economic evaluation—from study design and data sources to analytical methods and results—are comprehensively documented. This transparency is particularly crucial in contexts like Zambia, where policy decisions based on economic evaluations must be robust and defensible to diverse stakeholders, including healthcare providers, funders, and policymakers.

While the CHEERS checklist enhances the methodological rigor of economic evaluations, it does not resolve all limitations inherent in these approaches [73]. For instance, the checklist focuses on reporting quality rather than the underlying assumptions or data quality, which remain critical factors in determining the validity of an evaluation. Furthermore, the emphasis on standardized reporting may inadvertently discourage innovative methodologies or context-specific adaptations, which are often necessary in LMICs like Zambia and as had to be done with certain aspects of costing for paper II of this work as described in the paper. Nonetheless, the CHEERS checklist represents a significant step forward in improving the consistency, transparency, and utility of economic evaluations in healthcare.

MARKOV MODELLING

Markov models are widely used in economic evaluations to simulate the progression of diseases and the impact of interventions over time, where there may be complex and multiple pathways the disease can follow in a population [74, 75]. These models are particularly suitable for chronic conditions, such as cervical cancer, where disease progression involves multiple health states [76]. The Markov model used in this study comprises distinct health states that reflect the natural history of HPV infection and of associated cervical cancer, as illustrated in Figure 2 above. Transitions between these states are governed by probabilities derived from epidemiological data and literature as outlined in Paper I. For example, the likelihood of progression from CIN I to CIN II or regression back to normal health is incorporated into the model. The analysis considers a lifetime time horizon for the cohort of girls aged 9–14 years, in accordance with the current life expectancy, allowing for the assessment of both the long-term benefits and costs associated with HPV vaccination.

To reflect the high prevalence of HIV in Zambia, the model incorporates adjustments for HIV-positive individuals, who have a higher risk of persistent hrHPV infection and a faster progression to cervical cancer. Additionally, it evaluates the effectiveness of various vaccine delivery platforms (school, outreach, health facility) in meeting coverage targets.

Application to HPV Vaccination

HPV vaccination is a key primary prevention strategy for cervical cancer. This study assesses the cost-effectiveness of three vaccine delivery platforms when integrated with cervical cancer screening, compared to screening alone, as outlined below:

1. **School-Based Delivery:** Leveraging school infrastructure to vaccinate enrolled girls.
2. **Health Facility-Based Delivery:** Administering vaccines through existing healthcare facilities.
3. **Community Outreach Delivery:** Extending services to hard-to-reach populations through mobile clinics and community health workers.

4. **All three delivery platforms combined:** This is the model that was being utlised by the EPI at the time of this work, combining all three delivery platforms (school, community, health facility).

Each platform is analysed for its cost, coverage, and impact on health outcomes, allowing for a comprehensive comparison of their cost-effectiveness. Key metrics include the incremental cost-effectiveness ratio (ICER), which expresses the additional cost per DALY averted.

Conceptual Framework

The conceptual framework guiding this study integrates the economic evaluation of HPV vaccination with the broader goals of Zambia's immunisation programme. Key components include:

1. **Health Outcomes:** Measured in DALYs averted, capturing cervical cancer morbidity and mortality.
2. **Cost Components:** Including vaccine procurement, delivery, and operational expenses, stratified by delivery platform.
3. **Equity Considerations:** Addressing disparities in vaccine access, particularly for out-of-school girls and HIV-positive individuals.
4. **Sustainability:** Evaluating the financial viability of the programme as Zambia transitions away from donor funding.

The theoretical framework underpinning this study reflects a comprehensive approach to evaluating the cost-effectiveness of HPV vaccination in Zambia. By combining HTA principles, economic evaluation methodologies, and Markov modelling, the study provides robust evidence to inform policy decisions and optimize resource allocation, which can contribute to the long-term sustainability and equity of Zambia's immunisation programme.

This framework is complemented by concepts from implementation science and health systems thinking, particularly the WHO health system building blocks and the equity-efficiency trade-off lens, which highlight the importance of balancing cost-effectiveness with equitable access and system resilience.

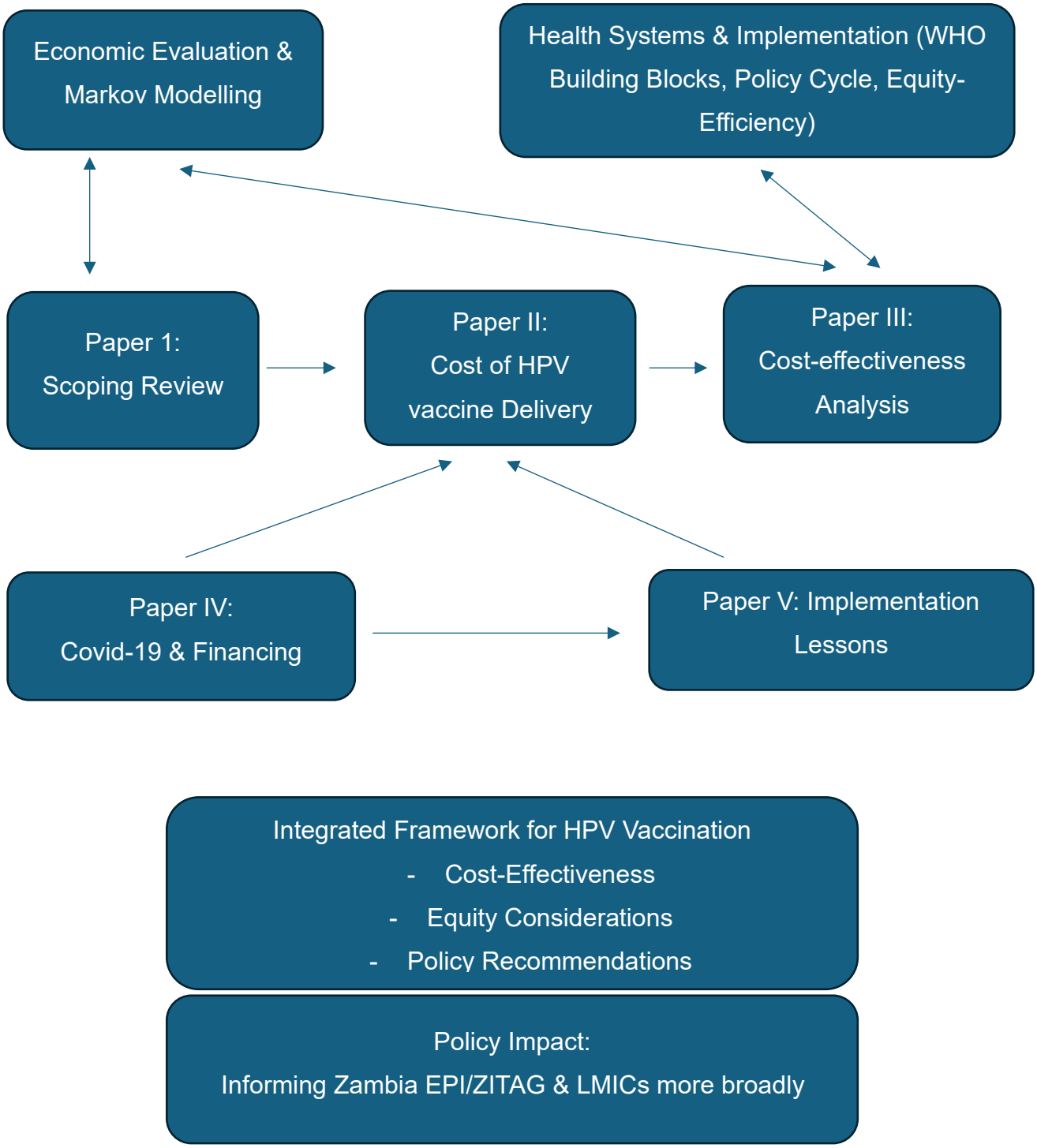

Figure 4: Conceptual Framework Diagram

Figure 4 presents the conceptual framework guiding this thesis. At the foundation are principles of economic evaluation and Markov modelling, complemented by broader health systems and implementation science perspectives, including the WHO health system building blocks, the policy cycle, and the equity–efficiency trade-off. These frameworks collectively emphasise both efficiency and fairness in health resource allocation.

Each of the five studies is mapped onto this framework to demonstrate their interdependence and cumulative contribution. Paper I (Scoping Review) synthesised existing evidence and identified key gaps to inform parameter selection. Paper II (Cost of HPV Vaccine Delivery) provided locally relevant costing inputs essential for modelling. Paper III (Cost-Effectiveness Analysis) integrated these inputs within a Markov model to evaluate vaccination strategies. Paper IV (Covid-19 & Financing) and Paper V (Implementation Lessons) contributed contextual insights, highlighting how system shocks and implementation challenges affect delivery and sustainability. Together, these studies form an integrated evidence base on the cost-effectiveness, equity considerations, and policy implications of HPV vaccination in Zambia. The bottom tier of the framework shows how this integration generates actionable recommendations for national decision-makers, particularly the Expanded Programme on Immunisation (EPI) and the Zambian Immunisation Technical Advisory Group (ZITAG), while also providing lessons relevant to other LMICs transitioning to domestically financed immunisation programmes.

3. AIMS AND OBJECTIVES

Aim: To evaluate the cost-effectiveness of Zambia's national Human Papillomavirus (HPV) vaccination programme, delivered through health-facility, outreach, and school-based platforms, compared to screening alone, in Zambian girls aged 9–14 years over a lifetime horizon, to inform decision-making on optimal delivery strategies.

The specific objectives of the study were:

i. To conceptualise an economic model for assessing the cost-effectiveness of HPV vaccine
ii. To establish the overall cost per fully vaccinated girl (having received 2 doses of vaccine) nationally and the cost per fully vaccinated girl across the three delivery platforms (school, facility and outreach) of HPV vaccine introduction in Zambia.
iii. To assess the cost-effectiveness of the three delivery platforms (school, facility and outreach) for HPV vaccine introduction in Zambia.
iv. To establish cost-effectiveness of HPV vaccination in Zambia across the HIV positive/negative and rural/urban subgroups (subgroup analysis).

The linkages between the objectives and published papers are described in detail in the introduction section and illustrated in Figure 1.

METHODS

STUDY SETTING

The study was conducted in Zambia, focusing on the national introduction of HPV vaccination for girls aged 9–14 years combined with cervical cancer screening for women aged 30–70 years. The intervention was HPV vaccination for girls aged 9–14 years combined with cervical cancer screening for women aged 30 and above, while the comparator was cervical cancer screening alone. Screening coverage for women aged 30–70 was 16.4% [15, 52]. A cohort of 3,103,000 girls was modelled from age 9 until age 70, reflecting Zambia's female life expectancy [77]. HIV prevalence was incorporated using age-specific rates from national statistics [77].

DATA COLLECTION

Wherever possible, locally derived data were used to inform the costing, coverage, and epidemiological parameters. These included primary cost data collected across delivery platforms in Zambia and national HIV prevalence estimates. Where no Zambian data were available, high-quality international estimates (such as long-term vaccine protection duration and progression rates from CIN to cervical cancer) were incorporated, consistent with approaches in other HPV economic evaluations. Each source is clearly referenced in the relevant papers. Data collection spanned five papers in this research and included:

Scoping Review (Paper I)

A scoping review was conducted to gather epidemiological and economic parameters through a comprehensive and systematic search conducted across PubMed, Embase, Scopus, Web of Science, and the Cochrane Library to identify studies on the cost-effectiveness of HPV vaccination in Africa using Markov models. The search was limited to English-language articles published from 2010 onward and employed a carefully designed strategy incorporating relevant keywords and subject headings. Studies were included if they were original research conducted within Africa, focused on HPV vaccination cost-effectiveness, provided detailed Markov model parameters, and adhered to the CHEERS checklist. Exclusions were applied to studies not focused on HPV vaccination, those lacking sufficient model

detail, non-African studies, and publications such as reviews, abstracts, commentaries, and editorials.

Two independent reviewers evaluated titles and abstracts to determine eligibility, followed by a full-text review for a more detailed assessment. Any disagreements were resolved through discussion. Data extraction was carried out independently by both reviewers using a standardized form to capture study characteristics, intervention details, model structure, and key parameters such as transition probabilities, costs, and effectiveness measures. Quality assessment using the CHEERS checklist ensured the reliability and applicability of selected studies for developing a Zambia-specific Markov model. Finally, a narrative synthesis was conducted to analyse key parameters, identify literature gaps, and propose recommendations for future research.

Costing of HPV Vaccine Delivery (Paper II)

The financial and economic costs of HPV vaccine delivery were assessed using both top-down and micro-costing approaches. Data was gathered from eight districts across four provinces—Lusaka (Lusaka and Chongwe), Copperbelt (Ndola and Lufwanyama), Central (Kabwe and Mkushi), and Muchinga (Mpika and Chinsali). This study combined the EPI Costing and Financing Project (EPIC) sample with an additional province selected in consultation with the Ministry of Health.

Key data sources included:

- **Document Reviews**: Routine EPI reports, HPV vaccination microplans, budgets, and Expanded Programme on Immunisation (EPI) meeting minutes.
- **Key Informant Interviews (KIIs)**: Conducted at national and district levels with health officials, EPI staff, and stakeholders.
- **Focus Group Discussions (FGDs)**: Held with community-based volunteers (CBVs) to explore their roles in vaccine delivery and social mobilisation.

An Excel data extraction tool was utilised to compile the cost data gathered using all these sources. The costing analysis covered planning, social mobilisation, vaccine delivery, and service supervision activities, with costs stratified by the three delivery

platforms—school, health facility, and outreach. Financial and economic costs were collected for 2019 and adjusted for inflation to 2020 values. Economic costs were drawn from EPIC data, and costs per dose and per fully vaccinated girl were calculated for each platform. These costs were used in the Markov model for Paper III.

Cost-Effectiveness Study (Paper III)

The primary objective of **Paper III** was to evaluate the cost-effectiveness of HPV vaccination for girls aged 9–14 years combined with cervical cancer screening once they are aged 30 and above, compared to cervical cancer screening alone from 30 years old. This study adhered to the CHEERS checklist to ensure transparent and comprehensive reporting of economic evaluations. A cost-effectiveness analysis was conducted using TreeAge Pro software, employing a Markov model with microsimulation trials and probabilistic sampling to evaluate the impact of HPV vaccination in Zambia. The analysis compared HPV vaccination combined with cervical cancer screening to cervical cancer screening alone over a lifetime horizon, with results assessed using the incremental cost-effectiveness ratio (ICER). Four vaccine delivery strategies—school-based, community outreach, health facility delivery, and a combination of all three—were compared to the standard of care (cervical cancer screening), factoring in HIV prevalence and varying delivery platform probabilities. HPV vaccination coverage was assumed at 80%, and cervical cancer screening coverage was set at 16.5%.

Costs included vaccination, screening, and cervical cancer treatment, all adjusted to 2024 values, and health outcomes were measured in DALYs. The healthcare provider perspective was adopted, and both costs and utilities were discounted at a 3% annual rate. The study incorporated a wide range of parameters, including age-specific HIV prevalence, transition probabilities, health states, and economic costs. Probabilistic sensitivity analysis and Monte Carlo simulations were performed to account for individual variability and parameter uncertainty, with sensitivity analyses exploring variations in key parameters such as costs, discount rates, and disability weights. This robust approach ensured reliable conclusions about the cost-

effectiveness of HPV vaccination strategies in Zambia, providing insights into the economic and health outcomes of different delivery models.

HPV Implementation and effect of Covid-19 (Papers IV and V)

Papers IV and V extended the analysis by focusing on implementation challenges and equity in vaccine delivery, particularly in underserved areas, in order to answer questions relating to objectives II (costing), and III (cost-effectiveness) of this study, comprehensively, given the unique challenges of the time.

- **Document Reviews**: Similar to Paper II, this included microplans, EPI budgets, and routine reports. Additionally, Gavi reports, operational guidance, and theories of change were reviewed for insights into vaccine rollout strategies.
- **Key Informant Interviews (KIIs)**: Conducted at the national and district levels with health workers, programme managers, and community leaders. These interviews explored implementation challenges, vaccine delivery logistics, and social mobilisation strategies.
- **Focus Group Discussions (FGDs)**: Held with community-based volunteers (CBVs) and health workers, the FGDs explored barriers to vaccine uptake, vaccine hesitancy, and strategies to improve community engagement.

For **Paper IV**, the focus was on understanding operational challenges across the three delivery platforms and in particular any deviations from the HPV theory of change. For **Paper V**, the focus was on understanding the cost implication of the Covid-19 pandemic and how this would affect overall costs for HPV vaccination.

4. Summary Results

Paper I - Scoping Review for Markov Model

The initial search resulted in a total of 100 articles, with 27 identified as duplicates. After reviewing the titles and abstracts of the remaining 73 articles, 59 were excluded for not meeting the inclusion criteria. Full-text reviews were conducted for 13 potentially relevant articles, of which 8 were ultimately included in the scoping review, as outlined in Table 3. The primary reason for exclusion was insufficient methodological detail, which was a key focus of the review. The selected articles analysed the cost-effectiveness of HPV vaccination programmes in various African countries and settings..

Health States and Utilities: The health states modelled across studies generally range from normal health to HPV infection and its progression through stages of cervical intraepithelial neoplasia (CIN) to cervical cancer. For example, *Li et al. (2015)* models transitions from normal health to CIN and persistent HPV infections, while *Wondimu et al. (2022)* includes susceptibility, cervical cancer, and death. Utilities assigned to these states, such as those used by *Michaeli et al. (2022)*, reflect the burden of each condition on quality of life [78-80].

Transition Probabilities: Several studies, like *Li et al. (2015)*, provide specific transition probabilities between health states, such as the likelihood of HPV progressing to CIN1 or CIN2/3. Other studies, such as *Wondimu et al. (2022)*, do not explicitly specify these probabilities [78, 79].

HIV Adjustments: Only *Li et al. (2015)* incorporates an HIV-adjusted model to reflect the interaction between HPV and HIV, whereas other studies, including *Wondimu et al. (2022)* and *Michaeli et al. (2022)*, do not adjust for HIV status [78-80].

Costs: Costs considered in the studies include both direct costs, such as vaccine costs and cancer treatment, and broader health service costs. *Li et al. (2015)* factors in the cost of routine Pap smears and treatment, while *Wondimu et al. (2022)*

includes vaccine costs and cancer treatment expenses [78, 79]. Most studies used USD values, and cost estimates varied depending on country and health system.

Outcome Measures: Most studies measured the outcomes in terms of Quality-Adjusted Life Years (QALYs), which reflect the quality and quantity of life gained through vaccination programmes. However, *Ekwunife and Lhachimi (2017)* used Disability-Adjusted Life Years (DALYs), and *Kiatpongsan and Kim (2014)* considered life expectancy as the primary outcome [81, 82].

Vaccine Coverage Rates and Efficacy: Coverage rates varied across studies, from 0.532 in *Wondimu et al. (2022)* to full coverage (1.0) in *Li et al. (2015)*. Vaccine efficacy was consistently high, with most studies assuming effectiveness rates close to 1 or reporting specific efficacy percentages for different HPV strains, such as 54.64% for quadrivalent vaccines in *Michaeli et al. (2022) [78-80]*.

Time Horizon and Discount Rates: Most studies modelled outcomes over a lifetime or extended period (e.g., 100 years in *Wondimu et al. (2022)*) [79]. Discount rates, which adjust future costs and benefits to present value, were typically set at 3% or 5%.

Delivery Strategies and Strains of HPV: Delivery strategies ranged from school-based programmes, such as in *Wondimu et al. (2022)*, to less specified models. The strains of HPV included in the models generally focused on hrHPV strains like HPV-16 and HPV-18, although some studies, such as *Wondimu et al. (2022)*, modelled multiple strains [79].

Herd Immunity and Duration of Protection: None of the studies modelled herd immunity effects. The duration of vaccine protection varied, with some studies assuming lifelong protection, while others, like *Li et al. (2015)*, included waning immunity over 5 to 50 years [78].

Cost-effectiveness Models and Perspectives: Most studies used Markov models or similar frameworks to simulate the progression of disease and the impact of

vaccination. All studies took a healthcare provider perspective for costing, though *Kiatpongsan and Kim (2014)* also considered societal costs [82, 83].

While the models differ in specific parameters, they generally assess the cost-effectiveness of HPV vaccination by considering health outcomes, costs, and vaccine efficacy across varied time horizons and delivery models.

PAPER II - COSTING OF HPV VACCINE DELIVERY

The delivery model for HPV vaccination involved three main types of sites. Health facilities accounted for 327 sites, representing 15.8% of the total. Community outreach sites contributed 641 sites, making up 30.9%, while schools were the largest contributor with 1108 sites, comprising 53.3% of the total. In total, there were 2076 sites used across all delivery models, covering 100% of the vaccination effort across the eight sampled districts. This was used as a means of apportioning costs across the three delivery platforms.

In 2020, across the eight sampled districts, schools achieved the highest vaccination coverage, averaging 93% for both the first and second doses. Community outreach sites contributed 6.0% to the overall coverage, while health facilities accounted for only 1.0%. This is illustrated in Table 1 below.

Table 1: Doses administered and coverage across delivery platforms

Dose	Doses administered	Percentage by site	Percentage of total doses administered
First Dose	**22,896**		**53.7%**
Schools	21,874	95.5%	
Community Outreach Sites	947	4.1%	
Health Facilities	76	0.3%	
Second Dose	**21,460**		**46.3%**
Schools	19,390	90.4%	
Community Outreach Sites	1,706	7.9%	
Health Facilities	364	1.7%	
All Doses Total	**44,356**		**100%**
Schools	41,264	93.0%	
Community Outreach Sites	2,653	6.0%	
Health Facilities	440	1.0%	

Table 2 shows the total costs for the HPV vaccination programme in the sampled districts are broken down into various categories, including both financial and economic costs. The total cost, including human resources, was USD 1,022,337, with an average of USD 119,082 per district. The second dose accounted for 46% of the total costs.

Financial Costs:

- **Planning and Training**: Microplanning cost USD 47,595, with an average of USD 5,949 per district, accounting for 4.7% of the total. Training cost USD 23,266 (2.3%), and orientation/training added another USD 8,424 (0.8%).
- **Social Mobilisation and Service Delivery**: Social mobilisation cost USD 5,535 (0.5%), while service delivery and outreach expenses totalled USD 48,162 (4.7%). Supervision, monitoring, and evaluation amounted to USD 4,602 (0.5%), and communication costs were minimal at USD 436.
- **Vaccines and Supplies**: Safety supplies such as boxes, needles, and syringes cost USD 77,909 (7.6%), while vaccine co-financing was USD

25,902 (2.5%). Health cards and other materials added USD 3,224, and distribution cost USD 956 (0.1%).

- **Delivery Model Specific Costs:** School Outreach delivery model incurred additional costs of USD 9,545, while health facility incurred USD 4,308, and community outreach incurred USD 5,355. Specific of these costs varied from district to district in terms of their specific use.

Economic Costs:

- **Cold Chain**: Maintenance and utilities totalled USD 19,838 (1.9%), and equipment cost USD 60,332 (5.9%). Energy for the cold chain added USD 32,373 (3.2%), with other equipment totalling USD 86,001 (8.4%).
- **Building and Vehicles**: Building overhead was the largest single cost at USD 121,317 (11.9%), followed by vehicles at USD 105,458 (10.3%), with maintenance costs at USD 19,293 (1.9%).
- **Human Resources**: Human resource costs were the largest overall at USD 274,220 (26.8%).

The financial cost alone (excluding economic costs) was USD 266,201, with an average of USD 33,275 per district.

Table 2: Costs attributable to HPV Vaccination in Zambia, 2020

COSTS	Sum	Average/District	Dose 2 Costs (46%)	% of total costs
Financial costs				
Planning and Training				
Microplanning	47,595	5,949	22,018	4.7%
Training	23,266	2,908	10,763	2.3%
Orientation				
Orientation/Training	8,424	1,053	3,897	0.8%
Social Mob and Service Delivery				
Social Mobilisation	5,535	692	2,561	0.5%
Service delivery/Outreach	48,162	6,020	22,281	4.7%
Supervision & M&E	4,602	575	2,129	0.5%
communication	436	54	202	0.0%
Vaccines and Supplies				

Supplies (safety boxes, needles, syringes etc)	77,909	9,739	36,043	7.6%
Vaccines Co-finance	25,902	3,238	11,983	2.5%
Health Cards + Registers + Tally Sheets + Other materials	3,224	403	1,491	0.3%
Distribution	956	119	442	0.1%
Other costs	982	123	454	0.1%
Delivery model specific costs				
School Outreach	9,545	1,193	4,416	0.9%
Health Facility	4,308	539	1,993	0.4%
Community Outreach	5,355	669	2,477	0.5%
Economic costs apportioned				
Cold chain maintenance and utilities	19,838	2,480	9,177	1.9%
Sterilisation and Waste management	37,304	4,663	17,159	3.6%
Cold chain equipment	60,332	7,541	27,911	5.9%
Cold Chain Energy Costs	32,373	4,046	14,891	3.2%
Other equipment	86,001	10,750	39,786	8.4%
Building overhead	121,317	15,165	56,124	11.9%
Vehicles	105,458	13,182	48,787	10.3%
vehicle maintenance	19,293	2,412	8,925	1.9%
Human Resources	274,220	34,277.50	126,860	26.8%
TOTAL (USD) including HR	**1,022,337**	**119,082**	**472,957**	100.0%
Financial Cost	**266,201**	**33,275**	**122,452**	

Table 3 gives the estimated costs per dose and per fully immunised child across the delivery platforms and overall. These costs were calculated by allocating the costs obtained in Table 2 to each deliver platform using the number of sites utlised by each delivery platform as outlined in the first part of the results section. These figures were divided by the number of relevant doses to arrive at the cost per dose. For cost per fully immunised child only the costs were divided by second dose figures, regardless of the first dose coverage.

Table 3: HPV vaccinations cost per dose and per fully immunised child in Zambia

Costs apportioned to delivery model	Cost (USD)	Doses administered	Cost per dose (USD)	Cost per Fully Immunised Child (2 doses, USD)
Economic Cost				
TOTAL	1,022,337 (100%)	44,356	23.0	47.6
Health facilities	161,033 (15.8% of total)	440	365.7	441.8
Outreach	315,664 (30.9% of total)	2,652	119.0	185.0
Schools	545,640 (53.4% of total)	41,264	13.2	28.1
Financial Cost				
TOTAL	266,202 (100%)	44,356	6.0	12.4
Health facilities	41,931 (15.8% of total)	440	95.2	115.0
Outreach	82,194 (30.9% of total)	2,652	31.0	48.2
Schools	142,077 (53.4% of total)	41,264	3.4	7.3

PAPER III - COST-EFFECTIVENESS OF HPV VACCINE DELIVERY

The findings for the four scenarios modelled are summarised below:

All-Inclusive Delivery Models: The combined HPV vaccination and screening using all delivery platforms yielded an Incremental Cost-Effectiveness Ratio (ICER) of $263, significantly below the WTP threshold, indicating high cost-effectiveness. Without HIV factored into the model, the ICER increased slightly to $284, maintaining its cost-effectiveness profile.

The Cost-Effectiveness Acceptability Curve (CEAC) below compares the probability that either HPV vaccination with combined with cervical cancer screening, or cervical cancer screening alone is cost-effective across a range of willingness-to-pay (WTP) thresholds. At low WTP levels (below approximately $200), cervical cancer screening is the more cost-effective option, with nearly 100% of simulation iterations favouring it. However, as WTP increases, the cost-effectiveness of screening declines sharply while that of HPV vaccination rises. Around the $200–$350 threshold, the preference shifts, and beyond $400, HPV vaccination consistently emerges as the most cost-effective intervention in nearly all simulations. This suggests that in low-resource settings with tight budget constraints, screening may be the preferred strategy, while in contexts where higher investments in health are feasible, HPV vaccination offers greater value for money and becomes the optimal choice.

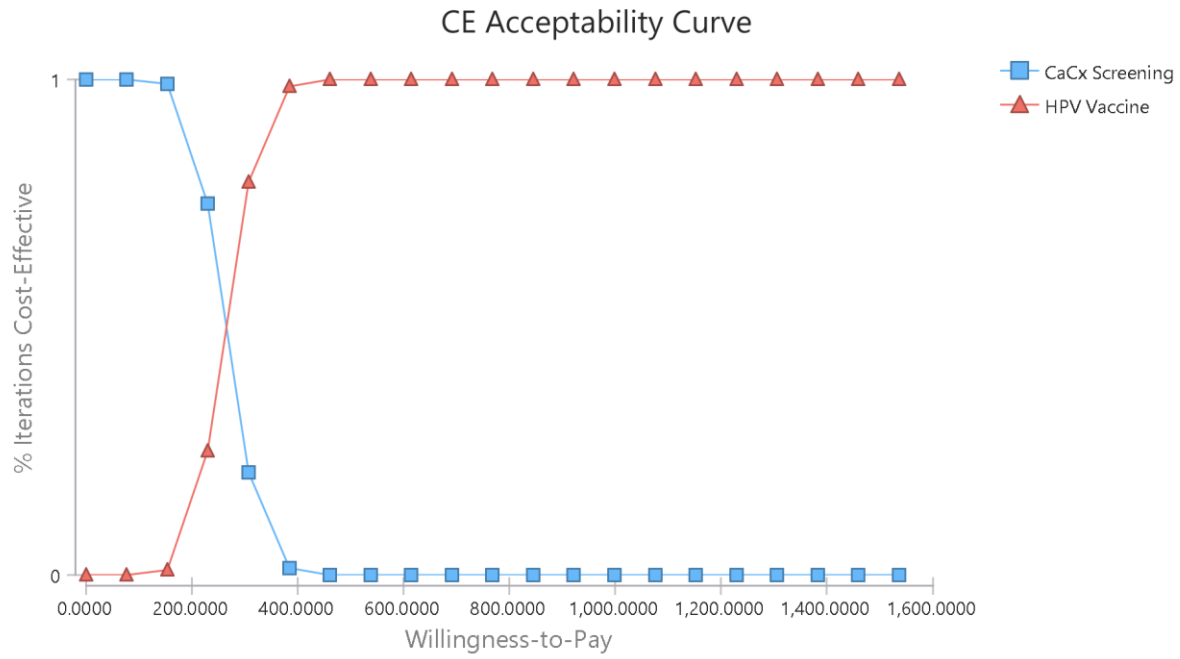

Figure 5: Cost-Effectiveness Acceptability Curve

School-Only Model: This presented excellent cost-effectiveness with an ICER of $65, well below the WTP threshold. Excluding HIV in the model resulted in a modest increase in ICER to $85, while still indicating high cost-effectiveness.

Community Outreach-Only Approach: This exhibited an ICER of $2,362, exceeding the WTP threshold and suggesting lower cost-effectiveness. Removing HIV considerations slightly increased the ICER to $2,408, underscoring its limited cost-effectiveness.

Health Facility-Only Strategy: Registered the highest ICER at $6,225, far surpassing the WTP threshold and indicating very low cost-effectiveness. Exclusion of HIV resulted in a marginal increase in ICER to $6,229, further emphasizing its economic inefficiency.

Overall, the school-based delivery model shows the lowest costs and most favourable ICER, particularly when HIV is considered, while community and health facility models were not cost-effective on their own as shown in Figure 6.

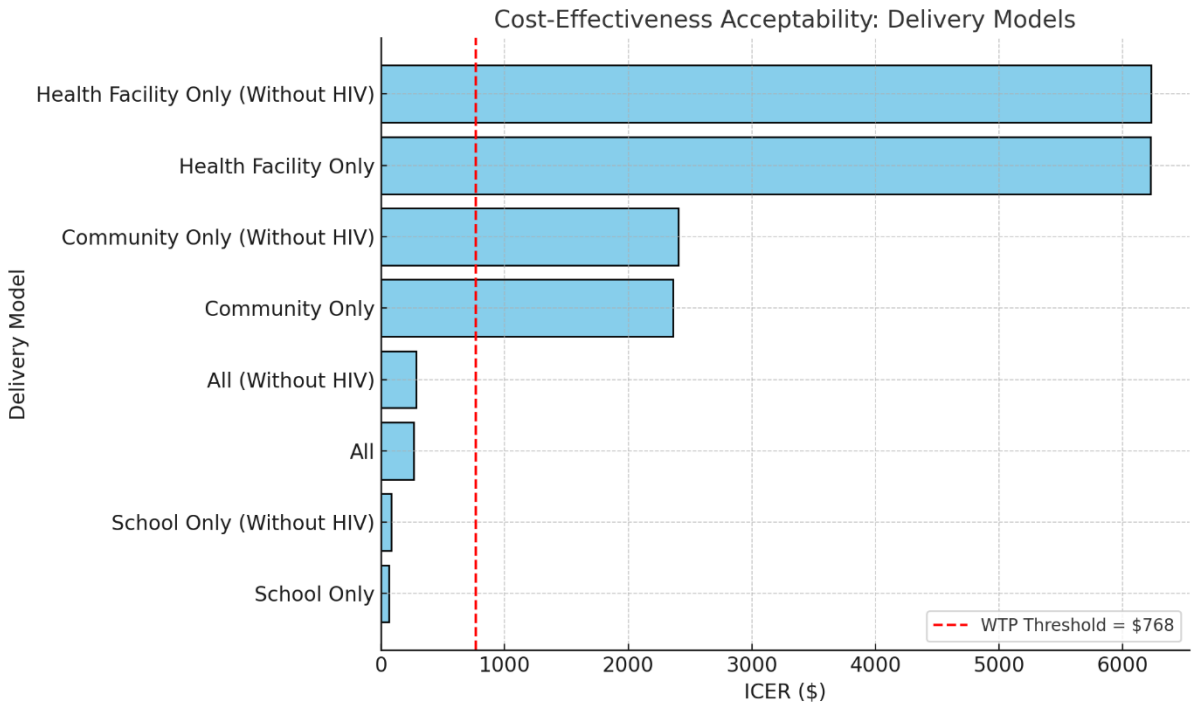

Figure 6: Cost-Effectiveness Acceptability: Delivery Models

When extrapolated to population level analysis using the projected population of 3,100,000 girls aged 9-14 at 80% coverage total costs for all delivery models combined are USD 4,571 million, with cervical cancer screening alone costing USD 2,957 million [84]. Overall ICER remains unchanged at USD 290, which reduces to USD 269 when HIV is excluded. The school-based delivery model is the most cost-effective, with a cost of USD 3,606 million for HPV vaccination and screening, compared to USD 2,914 million for cervical cancer screening alone, resulting in an ICER of USD 131. When HIV is excluded, the ICER further reduces to USD 35, making this the most favourable option.

In contrast, the community-based model is significantly more expensive, costing USD 16,182 million, with an ICER of USD 2,333, which remains high even when HIV is not considered (USD 2,325). The health facility-based model has the highest costs, with HPV vaccination and screening reaching USD 35,782 million and an ICER of USD 5,911, which increases to USD 6,149 without HIV. Overall, the school-based model stands out as the most cost-effective, while the community and health facility models are more costly with higher ICERs.

PAPER IV - EFFECT OF COVID-19 ON IMMUNISATION FINANCING

Paper IV, "An Evaluation of the Consequences of COVID-19 on Immunisation Programme Financing and Service Delivery in a Lower Middle Income Country: The Case of Zambia" explored how the pandemic affected Zambia's immunisation efforts. Key findings included:

1. **Funding Challenges**: Although regular disbursements of operational grants improved in 2020, the pandemic created competition for limited resources. Funds were diverted from routine immunisation to COVID-19-related activities, resulting in reduced financial support for immunisation. Districts faced additional costs for implementing COVID-19 safety measures, such as PPE and sanitization, but did not receive extra funding to cover these expenses. Table 4 shows additional costs of Covid-19 supplies and compliance and illustrates that a health facility would have needed nearly USD 250 per month. This amount may seem small, but for already financially strained districts and health facilities it is substantial.
2. **Immunisation Service Delivery**: There was a significant decline in both facility-based and outreach immunisation services. Caregivers avoided health facilities due to fears of contracting COVID-19, and many outreach sessions were cancelled due to restrictions. Additionally, the enforcement of social distancing and other preventive measures led to slower service delivery, further discouraging attendance.
3. **Human Resources**: Immunisation staff were reallocated to COVID-19 response tasks, such as contact tracing and patient screening, which led to a shortage of staff available for immunisation activities. This increased the workload and stress levels of the remaining staff, many of whom were working longer hours under difficult conditions, with insufficient protective equipment.
4. **Vaccine Supplies**: Although most vaccines were available, there were stock-outs of Bacillus Calmette-Guérin (BCG) and oral polio vaccines (OPV) due to global supply chain disruptions. There was also concern that other vaccines might run out if the situation persisted.
5. **Equity Issues**: The focus on high-density areas during the pandemic exacerbated existing inequities in immunisation coverage, leaving children in remote areas even more underserved than before.

Table 4: Additional cost for Covid-19 supplies at health facility level

Category	Unit Cost	Quantity	Total Kwacha	US$
A1. PPEs				
Disposable PPEs per staff for 5 staff (MCH, vaccinator, EHT, CHW.)	10	220	2200	118.92
Gloves-two pairs per staff	2.5	220	550	29.73
	Sub-total		**2750**	**148.65**
A2. Sanitary supplies				
Hand wash sanitizer-one each day	7	22	154	8.32
Hand wash soap for caregivers	15	3	45	2.43
Water-20 L	0.5	0	0	0
Water bucket-replacement at 6 months	18	2	37	1.98
	Sub-total		236	12.74
B1. PPEs				
Disposable PPEs for outreach team of 5	15	40	600	32.43
Gloves for outreach team of 5	1.5	70	105	5.68
	Sub-total		**705**	**38.11**
B2. Outreach Sanitary supplies				
Sanitizer	7	7	49	2.65
Hand wash soap for caregivers	15	3	45	2.43
Water	0.5	120	60	3.24
Water bucket-replacement at 6 months	18	2	37	1.98
Waste bag-disposable	3	12	36	1.95
	Sub-total		**226.67**	**12.25**
B3. Outreach transport and logistics				
Fuel	275.2	4	1100.8	59.5
Allowances-lunch	100	20	2000	108.11
Vehicle hire	0	200	0	0
	Sub-total		**3100.8**	**167.61**
	TOTAL		**4,330.16**	**246.45**

PAPER V - EFFECT OF COVID-19 ON IMMUNISATION PROGRAMME

Paper V, "An Evaluation of Successes and Challenges of Human Papillomavirus (HPV) Vaccine Programme Implementation in the Covid-19 Era: Are Lower Middle-Income Countries Like Zambia on the Right Path?" provided insights into the implementation of Zambia's HPV vaccine programme, especially during the COVID-19 pandemic. This was important to fully understand whether the programme was implemented according to the theory of change as shown in Figure 3. Given the unique challenges presented by the COVID-19 period, it was critical to interpret the cost and cost-effectiveness findings in Objectives II and III within the context of how the programme was actually implemented during that time. The pandemic may have introduced disruptions and inefficiencies that impacted both delivery costs and programme effectiveness in ways not initially anticipated. As such, any future policy or funding decisions based on these findings must consider these contextual factors to ensure accurate interpretation and appropriate planning for sustainable implementation.

Key findings included:

1. **Community Trust and Engagement**: The involvement of healthcare workers and traditional leaders fostered trust in the vaccine, especially in rural areas. Previous vaccine campaigns (like PCV and rotavirus) had built a foundation of trust, which made the introduction of the HPV vaccine easier. However, urban areas faced challenges with inconsistent volunteer engagement, affecting community trust in some districts.
2. **Persistent Myths and Misconceptions**: Despite overall success in community engagement, myths and misconceptions surrounding the HPV vaccine persisted. These included fears that the vaccine could cause cancer, infertility, or COVID-19, and that it might promote promiscuity among girls.
3. **Leadership and Coordination**: Strong leadership was evident at the national level, supported by stakeholders such as WHO and UNICEF. However, coordination with the Ministry of General Education (MoGE) was inconsistent at subnational levels, leading to a lack of awareness and engagement in some districts, especially with school-based vaccination.

4. **Impact of COVID-19 on Coverage**: In 2019, the school delivery platform achieved the highest vaccine coverage. However, in 2020, school closures due to COVID-19 led to lower overall coverage, with significant reliance on community outreach to maintain vaccine uptake. While the outreach model helped boost coverage, data inaccuracies were noted, as some girls vaccinated at outreach sites were still recorded under schools.
5. **Logistical Challenges**: Despite adequate cold chain capacity, there were delays in vaccine and supply delivery to districts and health facilities in both 2019 and 2020, partly due to waiting for supplementary materials like vaccination cards and registers.
6. **Inconsistent Approach to HIV-positive Girls**: There was confusion and inconsistency in vaccinating HIV-positive girls, with some facilities offering additional doses while others did not. This lack of clear guidance and the absence of a linked HPV and HIV system made it difficult to identify HIV-positive girls and ensure appropriate vaccination protocols.
7. **Underutilization of Adolescent Health and Cancer Prevention Services**: These services, which could have served as additional vaccination points and funding sources, were underutilized. Greater integration of HPV vaccination with adolescent health and cervical cancer services was recommended as a missed opportunity to improve programme reach.

DISCUSSION

This thesis integrates five interdependent studies within a broader economic evaluation and health systems framework. By combining local costing, cost-effectiveness modelling, and contextual analyses on COVID-19 and implementation challenges, it provides a holistic evidence base for HPV vaccination in Zambia. The framework not only strengthens national decision-making but also offers transferable lessons for other LMICs balancing efficiency, equity, and sustainability in immunisation programmes.

The results of the studies provide critical insights into the cost-effectiveness, challenges, and opportunities associated with HPV vaccination programmes in Zambia and similar settings. This discussion synthesises findings from the scoping review, costing and cost-effectiveness analyses, and evaluations of the impact of COVID-19 on immunisation programmes, highlighting implications for policy, programme design, and implementation. This work is also unique in the African context as it explored costs and cost-effectiveness associated with community outreach and health facility delivery models, whereas most studies in the African context, and all those that were selected as part of the scoping review in paper I, considered school-based delivery only [78-83, 85-87].

Cost of HPV Vaccine Delivery

The costing analysis in paper II provided detailed insights into the economic and financial costs of HPV vaccine delivery. School-based delivery, which accounted for over 53% of vaccination sites, was the least costly platform, with an economic cost per dose of USD 13.2 and a cost per fully immunised child (FIC) of USD 28.1. In contrast, health facility-based delivery had the highest costs, with an economic cost per dose of USD 365.7 and a cost per FIC of USD 441.8. These findings emphasise the need to optimise resource allocation by prioritising school-based delivery while addressing the inefficiencies in community and health facility-based delivery models, which are largely driven by their larger costs and suboptimal coverage.

The analysis also revealed significant cost components. Human resources were the largest contributor (26.8%) to total costs, followed by building overheads (11.9%) and vehicles (10.3%). This suggests a need to explore innovative approaches, such as digital tools for planning and training, to reduce these cost drivers . Additionally, the low financial cost of social mobilisation (USD 5,535) and communication (USD 436) raises concerns about whether adequate efforts were made to engage communities and counter vaccine hesitancy. Indeed it can be argued that the major reason community and health facility-based delivery had such high cost per dose and per fully immunised child was the low coverage achieved using these platforms. Thus, if coverage were to be increased, through greater community mobilisation and messaging targeted at these platforms, their costs would be less and they would achieve greater efficiency.

Cost-effectiveness of HPV Vaccination Delivery Models

The scoping review underscored the importance of using Markov models to evaluate the cost-effectiveness of HPV vaccination in various African settings. The health states, transition probabilities, and outcomes measured in these models provide a comprehensive framework for assessing the benefits of vaccination programmes. However, the lack of consistency in incorporating HIV interactions, herd immunity, and the duration of vaccine protection in these models highlights significant gaps in existing research. For example, only one study in the scoping review included HIV adjustments, despite the high prevalence of HIV in many African countries, which may affect the progression of HPV-related diseases and the effectiveness of vaccination [78]. This work addressed this by incorporating HIV into the Markov model and illustrated that this has significant bearing not only on the costs of the intervention, but also on the health benefits. The findings from this work show that including HIV in the vaccination model increased costs but achieved greater health impact due to the higher risk of HPV progression in HIV-positive individuals. This resulted in lower incremental costs across all delivery platforms when HIV was considered as shown in paper III. This makes HIV-inclusive strategies cost-effective and essential in high HIV prevalence settings, while broad school-centric approaches may suffice in low HIV prevalence areas. This was in contrast to the scoping review paper by Li et al that showed higher incremental costs with HIV included, which is interesting as South Africa has a higher HIV prevalence than Zambia [78].

This could possibly be partially explained by the use of TreeAge software. Using software like TreeAge for Markov modelling offers significant advantages over traditional manual or spreadsheet-based approaches to modelling health outcomes and economic evaluations. One of the key advancements offered by TreeAge is its ability to incorporate microsimulation and probabilistic sampling techniques, which enhance the realism and applicability of Markov models. Microsimulation allows the model to simulate individual patient-level trajectories, capturing variability in disease progression and intervention effects that traditional cohort-based models may overlook. This results in more detailed and accurate estimates of outcomes, that better reflect the heterogeneity of real-world populations. Similarly, probabilistic sensitivity analysis (PSA) enables the inclusion of uncertainty in input parameters, such as transition probabilities and costs, by assigning distributions to these variables and sampling from them iteratively. This approach produces a range of possible outcomes, providing decision-makers with confidence intervals and a clearer understanding of the robustness of model results. The combination of microsimulation and probabilistic sampling is more akin to real-world conditions and offers better model results.

From the cost-effectiveness perspective, the results clearly indicate that school-based delivery is the most efficient model. This approach achieves the lowest ICER and highest vaccine coverage. The ICER for the school-based model (USD 263 per DALY averted) is significantly lower than for community-based (USD 2,362) or health facility-based models (USD 6,225). This underscores the importance of leveraging schools as a primary delivery platform, particularly in settings where resources are constrained.

While school-based vaccination is the most cost-effective and aligns with public health goals, it faces challenges in reaching out-of-school girls from marginalised communities. In addition, in the Zambian context, concerns such as HIV-related stigma may arise in school settings when identifying girls who require additional doses or follow-up, which can inadvertently discourage disclosure and participation. To address these gaps, complementary strategies are essential. Community health workers, who have long played a pivotal role in Zambia’s immunisation and HIV programmes, are well-positioned to support outreach, sensitisation, and follow-up for

out-of-school girls. Their involvement not only improves equity and coverage but also builds trust within communities, making HPV vaccination more accessible to vulnerable groups. Extending services to HIV-positive girls through community outreach, mobile clinics, and local social mobilisation can ensure equitable access and improved health outcomes. In essence, a combination of school-based delivery and community outreach would be more equitable, beyond the cost-effectiveness considerations. However for such a hybrid model it would be imperative to increase coverage for the community outreach model by increasing social mobilisation and messaging efforts.

As pointed out earlier, optimising vaccine coverage is key to improving cost-effectiveness across all delivery platforms. Enhanced social mobilisation efforts and resource allocation can make community outreach and health facility-based delivery more viable. A hybrid approach combining school-based and community outreach models promotes comprehensive coverage, supporting long-term cervical cancer prevention and equitable health outcomes.

Impacts of COVID-19 on Immunisation Programmes

The findings from Papers IV and V highlight the profound impact of the COVID-19 pandemic on immunisation financing and service delivery. The diversion of funds to COVID-19-related activities and additional costs for PPE and sanitisation created financial constraints that disrupted routine immunisation programmes. For instance, the estimated additional monthly cost of COVID-19 compliance (USD 250 per health facility) may appear small but posed a substantial burden for already strained health systems.

Service delivery challenges, including reduced facility-based and outreach immunisation sessions and staff reallocation to COVID-19 tasks, further undermined immunisation efforts. The decline in vaccine coverage during school closures demonstrates the vulnerability of school-based delivery to external disruptions, highlighting the need for complementary delivery platforms to ensure continuity. However, it also demonstrated the resilience of the health system and its adaptability as a few days into the child health week, many districts realised the low turnout at schools and switched strategies to social mobilization for community outreach. This

helped to improve uptake and coverage, although the monitoring system was les adaptable and still accounted for the girls reached through community outreach as having been vaccinated at schools as they had already been registered at schools. This is a contamination factor in this work that has to be considered. However, since both 2019 and 2020 coverage figures across platforms were utilised in this work this minimises its overall effects as Covid-19 was only experienced in the 2020 vaccination period.

Thus, A key lesson from this work is the importance of embedding vaccination programme resilience into broader pandemic preparedness planning. The COVID-19 experience in Zambia highlighted how fragile routine immunisation can become when health systems are disrupted by emergencies. School closures, supply chain interruptions, and diversion of health resources led to gaps in HPV vaccine delivery, particularly affecting adolescent girls and other marginalised groups. Strengthening resilience means ensuring that vaccination platforms are flexible and adaptable during crises—for example, by integrating school-based delivery with community outreach mechanisms, maintaining buffer stocks and robust cold-chain systems, and leveraging digital tools for tracking and follow-up. Incorporating such strategies into national pandemic preparedness frameworks can safeguard continuity of essential vaccination services, reduce long-term setbacks in disease prevention, and protect the significant investments already made in programmes such as HPV vaccination.

Addressing Gaps in Policy through this Research

This thesis addresses critical gaps identified in both international and local policy that guides HPV vaccination efforts in Zambia. While these policies provide a solid foundation, they often lack practical tools and guidance to ensure the financial sustainability and effective implementation of vaccination programmes. One significant gap is the absence of economic evaluation frameworks, which are crucial for evidence-based decision-making. This research fills that void by employing robust methods, including CEA and Markov modelling, to evaluate the financial and health impacts of HPV vaccination. By providing detailed cost estimates and ICERs for various delivery platforms—school-based, community-based, and health facility-based—this study offers a practical framework for assessing the financial viability of these approaches, particularly in a resource-constrained setting like Zambia.

The thesis also addresses the lack of detailed implementation guidance in policy documents. Although high-level targets such as achieving 90% vaccination coverage are set, the policies often fail to outline actionable steps to achieve them. This research evaluates delivery models, identifying school-based vaccination as the most cost-effective approach while emphasizing the importance of community outreach to reach underserved populations. It further recommends integrating HPV vaccination with adolescent health and cervical cancer screening services to enhance efficiency and coverage. Other implementation evidence includes the important role that social mobilisation efforts play in influencing coverage of the various delivery platforms and how this in turn influences costs and cost-effectiveness. These insights provide policymakers with evidence-based strategies to overcome logistical barriers and improve implementation.

Sustainability is another area of concern in existing policies, particularly as Zambia transitions from Gavi funding to domestic financing. The research highlights the importance of integrating local economic evaluations into policy planning to guide resource allocation and financing strategies. By quantifying the costs and benefits of HPV vaccination under various scenarios, the study offers a roadmap for sustaining high vaccination coverage while minimizing financial strain on the health system. Furthermore, it emphasizes the need for clear prioritization criteria to guide decision-making in resource-constrained environments. The findings demonstrate the added value of combining HPV vaccination with cervical cancer screening, showing significant health benefits, particularly when HIV considerations are included.

Overall, this thesis bridges critical gaps in HPV vaccination policy and implementation in Zambia. By addressing issues related to economic evaluation, implementation guidance, sustainability, and prioritization, it provides policymakers with the evidence and tools necessary to strengthen immunization strategies. The findings contribute not only to national policy but also to global discussions on sustainable and effective vaccination programmes in low-resource settings.

Generalisability of Findings to Other LMICs

Although this thesis is primarily focused on Zambia, several key findings have broader relevance for other low- and middle-income country (LMIC) contexts. The demonstrated cost-effectiveness of school-based HPV vaccination, balanced against the equity challenges of reaching out-of-school girls, is a dynamic likely to be shared across many LMICs where school enrolment is high but incomplete. The influence of HIV prevalence on both vaccine effectiveness and delivery strategies is similarly applicable in sub-Saharan Africa, where overlapping HIV and cervical cancer burdens are common. Furthermore, the role of community health workers in extending access, and the importance of programme resilience during health emergencies such as COVID-19, are lessons that resonate widely. While the exact costs, delivery logistics, and health system structures will differ by country, the methodological framework applied here—including Markov modelling with HIV-adjusted parameters and equity considerations—offers a transferable approach for economic evaluations of HPV vaccination elsewhere. As such, this work contributes evidence not only to Zambia but also to other LMICs navigating similar resource constraints, competing health priorities, and equity challenges in the pursuit of cervical cancer elimination. This also offers lessons for other LMICs, particularly those transitioning from donor-supported to domestically financed immunisation programmes, where balancing efficiency, equity, and sustainability is a common challenge.

Methodological Considerations

Despite robust findings, there are several limitations that have to be acknowledged with this study. Firstly, not all data inputs could be drawn from local sources. While key costing, delivery, and HIV-related data were generated within Zambia, certain parameters such as long-term vaccine efficacy and natural history transition probabilities were adapted from international literature. Although a proportional breakdown of local versus external inputs is not feasible given the integrated nature of the model, the thesis has clearly outlined data sources and justified assumptions for transparency. Future work could expand locally generated epidemiological data to further strengthen the evidence base and reduce reliance on external estimates.

Another limitation is that some of the cost and benefit assumptions were taken from other studies as Zambia did not have any economic evaluation guidelines in place. The data collection for this study was done after only one cohort of girls had been fully immunised, and another partially immunised with one dose. The national introduction was in the early phase where a lot of resources were likely allocated towards the programme than when it becomes more routine as has been the case with previous vaccine introductions in which vaccine introduction grants were given by Gavi. Thus, some of the costs may be higher than once the vaccination becomes more routine. Further, assumptions had to be made about lifelong protection of HPV vaccine as the evidence for this is still evolving given that the vaccine is a relatively recent development [86, 88]. Additionally, it was not possible to determine how individuals in the target population moved across delivery platforms as one individual may utilise more than one platform in reality.

The healthcare perspective did not reflect the full costs or benefits of HPV vaccination as would be derived from a societal perspective. Other benefits of HPV vaccination in preventing cancers other than cervical cancer as well as herd immunity effects in protecting males were also not considered and thus the benefits may be under-estimated. Lastly, the model study does not account for future improvements in cervical cancer screening and treatment, which are likely to occur over the lifetime horizon.

5. Policy Implications

The findings of this study highlight the critical importance of economic evaluation and modelling in supporting health technology assessment (HTA), vaccine introduction, and implementation decisions. These tools provide policymakers with evidence-based insights to optimise delivery strategies, ensure financial sustainability, and address equity concerns in immunisation programmes. Incorporating local cost-effectiveness studies into decision-making processes is particularly crucial, as such studies generate country-specific data that reflect Zambia's unique context. This enables policymakers to design strategies that maximise health benefits while considering the country's resource constraints. For example, identifying cost-effective delivery models and balancing efficiency with inclusivity ensures that

immunisation programmes are both impactful and equitable, particularly in reaching underserved populations.

Local economic evaluations also serve as essential inputs to HTA frameworks, providing decision-makers with the tools to allocate resources more effectively and sustainably. These frameworks are vital for guiding not only HPV vaccination programmes but also the introduction of other health technologies, ensuring that policies and decisions are grounded in locally relevant evidence. Additionally, as Zambia transitions from donor-funded vaccination programmes to domestic financing, integrating economic evaluation findings into financial planning becomes critical. Innovative financing mechanisms, such as public-private partnerships and integrating vaccinations with broader health services, can provide sustainable solutions to address funding gaps while maintaining high vaccination coverage. The integration of vaccination programmes with other health services, such as adolescent health and cervical cancer prevention, offers an opportunity to enhance efficiency and extend reach. Strengthened collaborations across health sectors can reduce redundancies and improve access, especially for vulnerable groups. Furthermore, insights from economic modelling can guide investments in logistics and supply chain systems, building resilience in immunisation infrastructure to mitigate disruptions caused by emergencies such as pandemics. Policymakers must also prioritise equity in vaccine access by adopting strategies that address disparities and ensure no population is excluded.

To support effective implementation, economic evaluation findings can inform the development of clear and actionable guidance for overcoming logistical barriers, such as reaching rural and hard-to-reach populations and maintaining cold chain infrastructure. Evidence-based advocacy is also critical for aligning national immunisation goals with global strategies, such as the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer. By leveraging local data and insights, policymakers can strengthen their case for continued investment in HPV vaccination and other public health interventions, ensuring that programmes remain impactful, equitable, and sustainable. Integrating these approaches into policy and decision-making processes will maximise health outcomes and enhance the long-term viability of vaccination efforts in Zambia.

Policy Recommendations with prioritisation:

This study highlights several policy implications for Zambia's HPV vaccination programme. To maximise impact, these can be prioritised into short-term urgent actions, medium-term feasible steps, and long-term structural reforms.

- **Urgent actions (immediate priority):** Sustain high coverage in school-based vaccination while strengthening outreach for out-of-school girls, particularly through community health workers. Clear communication strategies should be reinforced to reduce stigma and vaccine hesitancy, especially among girls living with HIV.
- **Feasible, near-term actions (1–3 years):** Institutionalise routine monitoring of vaccine coverage disaggregated by HIV status, schooling, and geographic location to improve equity. Establish sustainable financing mechanisms for HPV vaccines as Gavi support transitions, including integrating HPV vaccine procurement into national budgets.
- **Long-term structural reforms:** Embed health technology assessment (HTA) processes into national immunisation decision-making to ensure sustainability of new vaccine introductions. Strengthen integration of HPV vaccination within adolescent health services, linking with HIV, SRHR, and cervical cancer screening platforms to ensure a comprehensive approach.

By distinguishing urgent actions from medium- and long-term priorities, these recommendations provide policymakers with a clearer roadmap for implementation.

FUTURE PERSPECTIVES

This study highlights critical areas for future research and policy development to strengthen the implementation and sustainability of HPV vaccination programmes in Zambia and similar settings. One key area is the need for longitudinal studies to evaluate the long-term health and economic outcomes of HPV vaccination, particularly as new cohorts are vaccinated and programmatic efficiencies evolve. Future research should also explore the integration of HPV vaccination with other adolescent health services, such as HIV prevention and cervical cancer screening, to enhance programme reach and cost-effectiveness.

Additionally, there is a need to develop robust HTA frameworks tailored to Zambia's context. These frameworks will enable policymakers to systematically evaluate the cost-effectiveness of health interventions and prioritise resources effectively. Further exploration of innovative financing mechanisms, including public-private partnerships and domestic funding strategies, is essential to address the sustainability challenges identified in this study, particularly as donor funding decreases.

Lastly, future efforts should focus on strategies to strengthen the resilience of immunisation systems to external shocks, such as pandemics, and improve equity in vaccine access. Hybrid delivery models that balance cost-efficiency with inclusivity will be crucial for ensuring that all eligible girls, including those in marginalised and hard-to-reach populations, benefit from HPV vaccination. By addressing these areas, Zambia can continue to make significant strides toward eliminating cervical cancer as a public health threat.

6. Conclusion

The findings of this study emphasize the interconnected nature of costs, cost-effectiveness, and contextual challenges in implementing HPV vaccination in Zambia. While school-based delivery remains the most cost-effective strategy, the disruptions caused by the COVID-19 pandemic revealed the limitations of relying solely on this model. Community outreach, though more expensive, plays a critical role in addressing equity gaps and maintaining coverage during crises.

The inclusion of HIV-positive girls in the analysis underscores the importance of tailoring vaccination strategies to address the unique needs of high-risk populations. Equitable access to HPV vaccination, particularly for out-of-school girls and HIV-positive individuals, is essential for achieving Zambia's public health goals.

The contextual challenges highlighted in this research demonstrate the need for resilient immunisation programmes that can adapt to external shocks. Strengthening collaborations between health and education sectors, integrating HPV vaccination with broader health services, and investing in robust logistical systems will be critical

for ensuring the long-term sustainability and impact of the HPV vaccination programme in Zambia.

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8. Appendices

Wits Ethics Approval

UNZABREC Ethics Approval

NHRA Approval

9. Publications

Evaluating the cost-effectiveness of HPV vaccination in Africa: a scoping review for Markov model development.

An evaluation of the cost of human papilloma virus (HPV) vaccine delivery in Zambia.

Cost-effectiveness Analysis of Human Papilloma Virus (HPV) Vaccination in Zambia: Comparing School, Community Outreach, and Health Facility Delivery Models, with HIV Status Consideration.

An evaluation of the consequences of Covid-19 on immunisation programme financing and service delivery in a lower-middle-income country: The case of Zambia.

Challenges and lessons from the implementation of the HPV vaccination programme in Zambia during the COVID-19 pandemic.