AN INVESTMENT CASE STUDY ON HPV VACCINATION IN VIET NAM

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ACKNOWLEDGEMENT

Today, cervical cancer remains a public health concern that continues to threaten the welfare and well-being of women and the entire population. According to the 2018 report, cervical cancer is the sixth most common cancer affecting Vietnamese women, with nearly 4,200 new cases and 2,420 deaths. It has been projected that without any intervention, about 200,000 Vietnamese women will die from cervical cancer by 2070.

Evidence from international studies also confirms that a strategic combination of a sufficient coverage of HPV vaccination for adolescent girls and a sufficient coverage of cervical screening and an appropriate treatment for all women can eliminate cervical cancer as a public health problem within our lifetime. Unfortunately, in Viet Nam, the HPV vaccination rate and the cervical cancer screening rate are low. Our study in 2021 shows that only 12% of women and girls aged 15-29 are vaccinated, and only 28% of women aged 30-49 have been screened so far.

In collaboration with National Institute of Hygiene and Epidemiology (Ministry of Health of Viet Nam) and Victoria University and Daffodil Centre, a joint venture between New South Wales Cancer Council and the University of Sydney (Australia), UNFPA undertakes an Investment Case Study on HPV Vaccination in Viet Nam to generate quality evidence to inform national and sub-national policies on roll out of HPV vaccination for adolescent girls and cervical cancer screening for women.

This report presents a range of different scenarios of HPV vaccination, cervical cancer screening and treatment. The findings show that depending on the extent and composition of the program, the number of deaths from cervical cancer will be reduced by up to 300,000 by 2100. The programme will return between around 5 and 11 times its cost in economic benefits, and between 8 and 20 times its cost in combined economic and social benefits.

We would like to extend our special appreciation to the extensive team of people who made this study possible for their commitment to complete the study despite travel restrictions and social distancing barriers during the COVID-19 pandemic. We also recognize the valuable assistance of the National Institute of Hygiene and Epidemiology, as well as experts from across Viet Nam for their advice and feedback on sources and quality of data for the modelling.

We hope that the findings of this investment case will prove useful and provide a signal for policy makers, health professionals, civil society organizations, researchers, and donors to advocate for cervical cancer prevention and control and align and accelerate efforts towards cervical-cancer free future for Viet Nam!

We must act now to not leave anyone behind, including women with, or at risk for cervical cancer, and ultimately eliminate cervical cancer as a public health problem in Viet Nam.

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LIST OF ABBREVIATIONS

BCR	Benefit-cost ratio
CCEMC	The WHO Cervical Cancer Elimination Modelling Consortium
CIN	Cervical Intraepithelial Neoplasia
DALY	Disability-Adjusted Life Year
GDP	Gross domestic product
HPV	Human papillomavirus
IARC	The International Agency for Research on Cancer
ICER	The incremental cost-effectiveness ratio
IVIR-AC	The WHO Advisory Committee on Immunization and Vaccine related Implementation Research
LFPR	Labour force participation rate
LYS	Life years saved
NIHE	The National Institute of Hygiene and Epidemiology
NNT	Number Needed to Treat
NPV	Net present value
PRIME	The Papillomavirus Rapid Interface for Modelling and Economics
QALY	Quality-Adjusted Life Year
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

Executive summary

In 2020, Victoria University in Melbourne, Australia agreed with UNFPA to undertake an Investment Case Study on HPV Vaccination in Viet Nam. This investment case has been done in conjunction with The Daffodil Centre, a joint venture between Cancer Council NSW and the University of Sydney.

In the report, we review previous studies analysing the economic case for vaccination and screening in Viet Nam and a number of multi-country studies that include Viet Nam.

We describe the epidemiological model Policy1-Cervix model developed by the Daffodil Centre in detail, as well as the economic modelling approach used by Victoria University.

The models used in this study have been based on a wide range of data sources, as much as possible, from Viet Nam. The study has been fortunate to receive valuable assistance and advice from experts in Viet Nam through individual consultations and a validation workshop held on-line in June 2021. This workshop was attended by experts from across Viet Nam, and they provided feedback and advice on sources and quality of data for the modelling. We thank all experts consulted and list them in the Appendix.

Thirteen scenarios of vaccination, screening and treatment were modelled, and their characteristics are shown in the table below.

SCENARIO CHARACTERISTICS

Scenario	Vaccine	Girls/Boys	Coverage	Screening	Treatment
0	No vaccine			VIA 28%	21.3%
1	HPV 4 only	Girls	90%	VIA 28%	21.3%
2	HPV 4 only	Girls	50%	VIA 28%	21.3%
3	HPV 4 only	Girls and boys	90%/60%	VIA 28%	21.3%
4	HPV 4 only	Girls and boys	50%/20%	VIA 28%	21.3%
5	No vaccine			10-yearly HPV 70%	90%
6	HPV 4 only	Girls	90%	10-yearly HPV 70%	90%
7	HPV 4 only	Girls	50%	10-yearly HPV 70%	90%
8	HPV 4 only	Girls and boys	90%/60%	10-yearly HPV 70%	90%
9	HPV 4 only	Girls and boys	50%/20%	10-yearly HPV 70%	90%
10	HPV 4 only	Girls	90%	3-yearly VIA 70%	90%
11	HPV 4 only	Girls	90%	5-yearly cytology 70%	90%
12	No vaccine			3-yearly VIA 70%	90%
13	No vaccine			5-yearly cytology 70%	90%

For both the cost-effectiveness and the return on investment analyses we compared the health outcomes, benefits and costs of each scenario with the base case scenario (scenario 0). The cost effectiveness analysis also compared different strategies with HPV vaccination together with screening and treatment scale up scenarios with scenario 5 (no vaccination, HPV screening and treatment scale up only). This allows identification of both effectiveness and cost-effectiveness of HPV vaccination, so when evaluating the cost effectiveness of HPV vaccination, the government could consider investment in scale up of HPV vaccination as well as HPV-based screening and precancer and cancer treatment.

Cost effectiveness analysis and timelines for cervical cancer elimination

If 90% vaccination coverage is reached in girls, and these girls continue to receive status-quo screening and cancer treatment in their lifetime (Scenario 1), 2-doses of the HPV vaccine are cost-effective at US$6.50 (ICER=US$136) or US$15.00 (ICER=US$281) per-dose, and are predicted to prevent 149,342 cancer cases and 108,926 cancer deaths by 2100 compared to status-quo (Scenario 0). This strategy can reach the elimination threshold by 2083. Adding males at 60% coverage (Scenario 3) is not cost-effective (ICER=US$4,640 at US$6.50 per-dose, ICER = US$8,463 at US$15 per-dose) and is predicted to prevent an additional 3,513 deaths (additional 3.2% compared to female-only) by the end of the century. Adding boys to this scenario (Scenario 3) had no noticeable impact on the timing of elimination compared to female-only vaccination.

If 90% HPV vaccination coverage is reached in girls, and these females receive 70% coverage of 10-yearly HPV-based screening and 90% cancer treatment scale-up (Scenario 6), HPV vaccination is cost-effective at either US$6.50 (ICER=US$738) or US$15.00 (ICER=US$1,547) per-dose and combined with increased screening and cancer treatment, is predicted to prevent 286,006 cancer cases and 301,846 cancer deaths by 2100 compared to status-quo. This scenario can reach the elimination by 2055 – around 30 years earlier than HPV vaccination only. Adding males at 60% coverage (Scenario 8) is not cost-effective and is predicted to prevent an additional 702 deaths (0.2% additional) by the end of the century and it has no noticeable impact on the timing of elimination, compared to female-only vaccination.

If only 50% coverage is reached in females and these females receive status-quo screening and cancer treatment in their lifetime (Scenario 2), 2-doses of the HPV vaccine are cost-effective at US$6.50 (ICER=US$125) or US$15.00 (ICER=US$262) per-dose and are predicted to prevent 91,997 cancer cases and 67,017 cancer deaths by 2100 compared to status-quo. Adding males at 20% coverage (Scenario 4) is also cost-effective (ICER= $717 at $6.50 per-dose, ICER= $1,347 at $15.00 per-dose) and is predicted to prevent an additional 6,581 deaths (additional 9.8%) by the end of the century. Both scenarios do not achieve elimination.

If 50% coverage is reached in females and these females receive 70% coverage of 10-yearly HPV-based screening and 90% cancer treatment scale-up (Scenario 7), HPV vaccination is cost-effective at either US$6.50(ICER=US$666) or US$15.00(ICER=US$1,426) and combined with the scale-up in screening and cancer treatment, is predicted to prevent 263,551 cancer cases and 294,551 cancer deaths by 2100 compared to status-quo. Adding males at 20% coverage (Scenario 9) is marginally cost-effective (ICER= $3,207 at $6.50 per-dose, ICER= $5,978 at $15.00 per-dose) and is predicted to prevent an additional 1,525 deaths (0.5% additional) by the end of the century. Timelines for elimination was not assessed for these scenarios.

When considering screening together with treatment scale up only (scenario 5, 12, and 13), 10-yearly HPV screening for women aged 30-50 years (three times in a lifetime) is predicted to achieve a similar impact on reduction of cervical cancer incidence and mortality rates to 5-yearly cytology screening (five times in a lifetime) and 3-yearly VIA screening (seven times in a lifetime). However, 10-yearly HPV screening requires fewer screening visits and substantially

fewer number of precancer treatment compared to VIA screening. When considering screening in unvaccinated cohorts, 10-yearly HPV screening is also cost-effective (ICER = US$ 164/LYS) (Scenario 5), compared to 3-yearly VIA and 5-yearly cytology screening (Scenarios 12 and 13). Similarly, 10-yearly HPV screening remains cost-effective in vaccinated cohorts with ICER = US$238 (at US$6.5 vaccine per-dose) and US$343/LYS with US$15 vaccine per-dose. All strategies which consider screening only (Scenario 5, 12, 13) do not achieve elimination.

Return on investment

The return on investment metrics indicate that the economic benefits from vaccination and screening are at least 5 times the cost of the programme and 8 times when both economic and social benefits are included.

RETURN ON INVESTMENT ANALYSIS

Scenario	Economic benefit (US$ million)	Social benefit (US$ million)	Cost (US$ million)	Economic benefit BCR	Economic and social benefit BCR
1	4,344	3,182	540	8.0	13.9
2	2,812	2,087	295	9.5	16.6
3	4,466	3,283	984	4.5	7.9
4	3,044	2,255	433	7.0	12.2
5	9,936	9,186	1,005	9.9	19.0
6	10,747	9,722	1,657	6.5	12.4
7	10,441	9,521	1,362	7.7	14.7
8	10,766	9,736	2,181	4.9	9.4
9	10,498	9,559	1,537	6.8	13.0
10	10,976	9,787	1,536	7.1	13.5
11	11,078	9,949	1,686	6.6	12.5
12	10,133	9,226	912	11.1	21.2
13	10,332	9,460	1,062	9.7	18.6

Both the cost-effectiveness and return on investment analysis produce results that are very sensitive to the discount rate used in calculating net present values.

These returns on investment are in line with those quoted above in the WHO strategy document – 3.2 and 26.0 for economic and social benefits. They are also similar to those found in a study of adolescent health and wellbeing for UNFPA, which found a BCR of 22.5 for economic and social benefits for low-income countries and an average of 17.0 across 75 low- and middle-income countries.

This study of an HPV vaccine, screening and treatment programme in Viet Nam has demonstrated that this is very worthwhile both in health and economic outcomes. Depending on the extent and composition of the programme, it will reduce the number of deaths among women from cervical cancer by up to 300,000. The programme will return between around 5 and 11 times its cost in economic benefits and between 8 and 20 times its cost in combined economic and social benefits.

At the prices assumed in this study, the modelling confirms the results of a range of other studies about the desirability of HPV vaccination and screening in terms of cost-effectiveness and as a return on investment. It also adds weight to previous studies advocating the introduction HPV vaccination in Viet Nam. The results of this study provide an impetus to the further development of the National Action Plan on Prevention and Control of Cervical Cancer in Viet Nam announced in 2016.

In order to identify the most optimal HPV vaccination and cervical cancer screening strategies for Viet Nam, it is crucial to review all evidence regarding the benefits (effectiveness), harms (e.g., number of treatment needed to prevent a cancer death (NNT) for screening strategies), cost-effectiveness, and return on investment of each strategy. Additionally, budget estimates and timelines for cervical cancer elimination will also provide more information which will help the government to make decision for the most optimal strategies on cervical cancer prevention and control in Viet Nam.

1. INTRODUCTION

According to a recent report by UNFPA and the Cancer Council NSW (2020), cervical cancer is the sixth most common cancer in women in Viet Nam, with 4,177 new cases (7.1 per 100,000 women) and 2,420 deaths (4.0 per 100,000 women) in 2018. The burden of cervical cancer varies among regions in Viet Nam with higher rates in southern regions. It has been predicted that without any intervention, a total of 218,907 women in Viet Nam will die from cervical cancer by 2070 and 449,656 by 2120 (Canfell 2020).

Infection with the human papilloma virus (HPV) is the major cause of cervical cancer and its associated deaths, and a significant cause of vaginal and vulvar cancers in women, penile cancer in men, and anal, head and neck cancers, genital warts and recurrent respiratory papillomatosis (RRP) in both men and women.

In 2020, Victoria University in Melbourne, Australia agreed with UNFPA to undertake an Investment Case Study on HPV Vaccination in Viet Nam. This investment case has been done in conjunction with The Daffodil Centre, a joint venture between Cancer Council New South Wales (NSW) and the University of Sydney.

Vaccinating girls will result in fewer deaths among females from cervical and other cancers, but will also lead to fewer deaths among males due to lower HPV infection rates. In addition, vaccinating boys will further reduce their rates of infection, and consequently male deaths from HPV related causes.

In this study, we estimate the benefits, costs, cost-effectiveness and return on investment of vaccinating girls, as well as boys, taking into account the context of other preventive intervention methods, such as cervical screening, and cancer treatment. Given the interest in evidence on cervical screening techniques, analyses of the effectiveness, cost-effectiveness and return on investment of different cervical screening techniques are included.

One of the objectives of the study is to provide strong evidence to support the efforts of the Ministry of Health of Viet Nam and other agencies to scale up an HPV vaccination and cervical screening programme in Viet Nam, following the successful demonstration programmes in Thanh Hoa and Can Tho provinces over ten years ago.

In 2016 with technical assistance from the United Nations Population Fund (UNFPA), the Ministry of Health launched The National Action Plan on Prevention and Control of Cervical Cancer in Viet Nam for the period from 2016 to 2025. The plan aims to make sure as many as 60% of women between the age of 30 and 54 years receive cervical cancer screening, and at least 25% of women and girls receive the human papillomavirus (HPV) vaccine by 2025. The plan also strives to facilitate all provincial and municipal hospitals to conduct cytological tests on cervical cancer by 2025, and to educate at least 70% of mature adults with an understanding about the disease. The comprehensive national response to cervical cancer includes HPV vaccination, screening and treatment of cervical pre-cancer and cancer (Ministry of Health and UNFPA 2016).

In 2016, seven UN agencies under the United Nations Task Force on Non-Communicable Diseases established a 5-year Joint Programme to prevent and control cervical cancer. The Joint Programme provides global leadership, as well as technical assistance, to support governments and their partners build and sustain high-quality national comprehensive cervical cancer control programmes with women accessing services equitably (WHO 2016). Supporting this, UNFPA with other agencies has published programme guidance for countries (UNFPA 2011), and the World Health Organisation (WHO) has produced a toolkit for cervical cancer prevention and control programmes (WHO 2018), and a framework for strengthening and scaling-up services for the management of invasive cervical cancer (WHO 2020).

In 2020, WHO released its global strategy towards the elimination of cervical cancer as a public health problem (WHO 2020a). This strategy has the following targets to be achieved by 2030:

- 90% of girls fully vaccinated with the human papilloma virus vaccine by 15 years of age;
- 70% of women screened with a high-precision test at 35 and 45 years of age; and
- 90% of women identified with precancerous lesions and cervical disease receiving treatment and care.

This strategy has been supported by the International Papillomavirus Society (Garland et al 2019). Based on analysis by Bertram and Gauvreau (2021, in publication), the strategy claimed that:

Investing in the interventions to meet the 90-70-90 targets offers immense economic and societal benefits. An estimated US$ 3.20 will be returned to the economy for every dollar invested through 2050, owing to increases in women's workforce participation, with this figure rising to US$ 26.00 when societal benefits are incorporated.

In Section 2 of this report, we review previous studies analysing the economic case for vaccination and screening in Viet Nam and a number of multi-country studies that include Viet Nam. We describe the prominent epidemiological models used in these cases and the Policy1-Cervix model in detail, as well as the economic modelling approach used by Victoria University in previous studies in Section 3.

The models used in this study have been based on a wide range of data sources, including wherever possible, those from Viet Nam. The study has been fortunate to receive valuable assistance and advice from experts in Viet Nam through individual consultations assisted by Dr Dinh Tran and others from the National Institute of Hygiene and Epidemiology and members of UNFPA Viet Nam office, and a validation workshop held on-line in June 2021. This workshop was attended by experts from across Viet Nam, and they provided feedback and advice on sources and quality of data for the modelling. We thank all experts consulted and list them in the Appendix. The final sources of data are described in Section 4.

Thirteen key scenarios of vaccination and screening were modelled and the results from the modelling of these scenarios are described in Section 5. Adding HPV vaccination for boys is only cost-effective at either US$6.5 cost per dose or with a one-dose schedule. Compared to 3-yearly VIA and 5-yearly cytology screening, 10-yearly HPV screening strategy is effective, cost-effective and requires less resources for pre-cancer treatment. Additionally, exploratory scenarios considering the benefit, harm, and costs-effectiveness of different cervical screening technologies and nonavalent HPV vaccine (HPV9) were also performed.

The return on investment metrics indicate that the economic benefits from vaccination and screening are at least 5 times the cost of the programme and 8 times when economic and social benefits are considered. This is of similar magnitude to the results from WHO quoted above and are within the range of benefit-cost ratios (BCRs) from similar studies.

In Section 6 we discuss the support that the study results give to the implementation of a plan to eliminate HPV and cervical cancer in Viet Nam.

2. PREVIOUS STUDIES

There have been a range of studies of the benefits of an HPV vaccination programme in Viet Nam. A number of these have been in the context of multi-country studies which included Viet Nam.

Viet Nam studies

The National Institute for Hygiene and Epidemiology (NIHE) and PATH (PATH and NIHE 2009, 2010; LaMontagne et al 2011, 2014) undertook a five-year project entitled HPV Vaccines: Evidence for Impact. The first phase of the project, "Formative research for informing the introduction of HPV vaccine in Viet Nam," was conducted from 2006 to 2007 to understand the critical issues that may affect vaccine delivery and a supportive environment for individual acceptance and understanding of HPV vaccines among key stakeholders. In 2007 and 2008, they conducted research to identify the critical factors for HPV vaccine introduction. They focused on three provinces representing the geographical regions of Viet Nam, as well as the two most urbanized and populated cities in the country: Thai Binh province in the north, Nghe An province in the central region, Dong Thap province in the south, and Hanoi and Ho Chi Minh City.

The research findings indicated a supportive environment (from policymakers', health workers', and community members' perspectives) for the introduction of a cervical cancer vaccine in Viet Nam. Informed by these formative research findings, the second phase of the project was a two-year demonstration project to identify appropriate strategies for HPV vaccine delivery that could be integrated into the National Expanded Programme on Immunization (NEPI) in Viet Nam. The demonstration project was conducted in two districts in Thanh Hoa province (Nong Cong and Quan Hoa) and two districts in Can Tho city (Ninh Kieu and Binh Thuy).

Using a mathematical model of cervical cancer developed at Harvard University and applied to the northern and southern regions of Viet Nam, Kim et al. (2008) assessed the cost-effectiveness of cervical cancer prevention strategies and the trade-offs between a national and region-based policy in Viet Nam. With 70% vaccination of pre-adolescent girls and screening of older women, lifetime risk of cancer was reduced by 20.4–76.1%. When the cost per vaccinated girl was low (i.e., <US$25), vaccination combined with screening was favored in both regions; at high costs per vaccinated girl (i.e., >I$100), screening alone was most cost-effective. They concluded that HPV vaccination was an attractive cervical cancer prevention strategy for Viet Nam, provided that high coverage can be achieved in young pre-adolescent girls, that the cost per vaccinated girl is <$5 per dose, and that screening is offered at older ages.

Van Minh, My and Jit (2017) used the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model described below to evaluate the cost-effectiveness of HPV vaccine introduction in Viet Nam. A costing study based on expert panel discussions, interviews and hospital case note reviews was conducted to explore the cost of cervical cancer care. They found that with Gavi-negotiated prices of US$4.55 per dose, HPV vaccination was likely to be very cost-effective with an incremental cost per disability-adjusted life year (DALY) averted in the range US$780–1120. Under listed prices for vaccines, the incremental cost per DALY averted for HPV vaccination was significantly higher.

To assess intention to pay for human papillomavirus (HPV) vaccination, Le et al. (2020) conducted a cross-sectional study of 807 pregnant women in an urban and a rural district (Dong Da and Ba Vi) of Hanoi, Viet Nam in 2016. Most respondents expressed a firm intention to vaccinate, especially women in rural areas. However, on being informed of the current price of the HPV vaccine, their intention to vaccinate dropped to about one-fifth of overall respondents. Their findings underscored the need to develop a well-designed vaccination programme in Viet Nam to increase the adoption of HPV vaccination.

Tran et al. (2018) investigated willingness to pay for the HPV vaccine among those using services in an urban vaccination clinic in Hanoi, Viet Nam. They found that most of the 490 respondents were willing to pay for the HPV vaccine (86.6%), and willing to pay an average amount of US$4.93. Those aged 20–29 years and earning more than 22 million VND/month were more likely to pay for the HPV vaccine than people aged <20 years and earning <7 million VND/month.

Sharma, Sy and Kim (2016) estimated the health benefits and incremental cost effectiveness of HPV vaccination of preadolescent boys and girls compared with girls alone for preventing cervical cancer and genital warts in Southern Viet Nam. Vaccinating girls alone was associated with reductions in lifetime cervical cancer risk ranging from 20 to 56.9% as coverage varied from 25 to 90%. Adding boys to the vaccination programme yielded marginal incremental benefits (≤3.6% higher absolute cervical cancer risk reduction), compared with vaccinating girls alone at all coverages. At ≤25 international dollars (I$, i.e. US dollars adjusted for the difference in purchasing power when comparing prices in the USA with prices in Viet Nam) per vaccinated adolescent (I$5 per dose), HPV vaccination of boys was below the threshold of Viet Nam's

gross domestic product (GDP) per capita (I$2800), with ICERs ranging from I$734 per QALY at 25% coverage, to I$2064 per QALY for 90% coverage. Including health benefits from averting genital warts yielded more favourable ICERs, and vaccination of boys at I$10/dose became cost-effective at or below 75% coverage. Using a lower cost effectiveness threshold of 50% of Viet Nam's GDP (I$1400), vaccinating boys was no longer attractive at costs above I$5 per dose regardless of coverage. They concluded that vaccination of boys may be cost-effective at low vaccine costs but provides little benefit over vaccinating girls only. Focusing on achieving high vaccine coverage of girls may be more efficient for southern Viet Nam and similar low-resource settings.

Multi-country studies

Jit et al. (2014) developed an Excel-based model called PRIME to estimate the health and economic effect of vaccination of girls against HPV before sexual debut. They applied this to 179 countries for which sufficient data was available and compared the results to those from 26 individual countries and from a study of 72 GAVI-eligible countries (Goldie 2008). They concluded that HPV vaccination was very cost effective (with every disability-adjusted life-year averted costing less than the gross domestic product per head) in 156 of 179 countries. They compared the results from their modelling for Viet Nam to those of Kim et al. (2008) and concluded that in both cases that vaccination was very cost effective.

HPV vaccination was very cost effective (with every disability-adjusted life-year averted costing less than the gross domestic product per head) in 156 (87%) of 179 countries. Introduction of the vaccine in countries without national HPV vaccination at present would prevent substantially more cases of cervical cancer than in countries with such programmes… If 71 phase 2 GAVI-eligible countries adopt vaccination according to forecasts, then in 2070 GAVI Alliance-funded vaccination could prevent 200 000 cases of cervical cancer and 100 000 deaths in some of the highest-burden countries. (p. 406)

Using population-based and epidemiologic data for 72 GAVI-eligible countries, Goldie et al. (2008, 2008a) estimated averted cervical cancer cases and deaths, disability-adjusted years of life (DALYs) averted and incremental cost-effectiveness ratios (I$/DALY averted) associated with HPV 16,18 vaccination of young adolescent girls. At I$10 per vaccinated girl, vaccination was cost-effective in all countries using a per capita GDP threshold; for 49 of 72 countries, the cost per DALY averted was less than I$100 and for 59 countries, it was less than I$200.

For Viet Nam, they reported that the incremental cost effectiveness ratio (ICER) measured by cost per DALY averted for Hanoi was $50, $1200 and $2450 at a cost of $10, $25 and $50 per vaccinated girl. For Ho Chi Minh City, the ICERs were $70, $250, and $570.

Suijkerbuijk et al. (2017) undertook a systematic review of economic evaluations of HPV vaccination including non-cervical HPV-associated diseases. They assessed the influence of non-cervical HPV-associated diseases on the ICER of pre-adolescent HPV vaccination. They concluded that including non-cervical diseases in economic evaluations of HPV vaccination programs makes it more likely that the ICER falls beneath accepted cost-effectiveness thresholds, and therefore increases the scope for gender-neutral vaccination.

In a review of studies for the Lancet Commission on Investing in Health, Goldie and Sweet (2013) summarise the results of this modelling work as follows:

Pre-adolescent HPV vaccination at high coverage is more effective than an individual strategy of cervical cancer screening of adult women once or twice per lifetime. If the cost of vaccination is less than $25 per fully

vaccinated girl (~$5 per dose), inclusive of three doses, administration, wastage, and vaccine support and program delivery costs), then, for GAVI eligible (or formerly eligible) countries, pre-adolescent HPV vaccination is more cost-effective than an individual strategy of cervical cancer screening of adult women once or twice per lifetime. (p. 14)

A review by Fesenfeld, Hutubessy, and Jit (2013) of 25 cost effectiveness studies concluded that:

…vaccination can be cost-effective if the vaccine price is sufficiently competitive relative to the income level of the country being studied.

...However, the thresholds used to assess cost-effectiveness may not always correspond to affordability in the relevant countries, so there may be a need for more locally meaningful indicators of cost-effectiveness besides the commonly used GDP per capita-based thresholds.

We also find that vaccination is most cost-effective in settings where screening programmes are not yet in place. This highlights the importance of extending HPV vaccination beyond well-screened populations in high and upper middle-income settings where most vaccine introductions have so far taken place, to low-income countries where vaccine prices are now competitive, donor funding is available, cervical cancer burden is high and alternative preventive options are limited. (pp. 3793–3794)

3. MODELLING HPV VACCINATION AND SCREENING

Most of the studies cited above use models that have two parts. The first is an epidemiology model that calculates the impact of interventions such as vaccination, screening and treatment on health outcomes, typically deaths and morbidity associated with diseases that are caused by HPV. These health outcomes are usually expressed in terms of life years saved (LYS). The second part is an economic model that compares the cost of the vaccine, screening and treatment intervention programs, and the health costs saved by the interventions, with the health outcomes usually expressed as cost per life year saved. This cost-effectiveness analysis then compares the cost per life year saved with a benchmark value to assess the cost effectiveness of the intervention. This benchmark value is often calculated as a multiple of GDP per capita, although this is not recommended by recent WHO guidelines (WHO 2019).

Epidemiological model

There are a number of models of HPV vaccination that have gained prominence.

The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) involves three independent, dynamic models of HPV infection, cervical carcinogenesis, screening, and precancer and invasive cancer treatment (Brisson et al., 2020; Canfell et al., 2020). These models are the Policy1-Cervix model based at The Daffodil Centre, University of Sydney (CISNET 2020; Simms et al. 2019), the Harvard model at Harvard University (CSNET 2020a; Campos et al. 2017), and the HPV-ADVISE model from Laval University in Quebec (Brisson et al 2012).

The CCEMC models have been used recently to assess the impact of achieving the 90–70–90 triple intervention targets on cervical cancer mortality and deaths averted over the next century, and to assess the potential for the elimination initiative to achieve a one-third reduction in premature mortality from non-communicable diseases by 2030 (Canfell et al. 2020).

They found that in the next 10 years, a one-third reduction in the rate of premature mortality from cervical cancer in lower- and middle-income countries is possible, and over the next century, successful implementation of the WHO elimination strategy would reduce cervical cancer mortality by almost 99% and save more than 62 million women's lives.

Simms et al. (2019) did a statistical analysis of existing trends in cervical cancer worldwide using high-quality cancer registry data published by the International Agency for Research on Cancer (IARC). They used the Policy1-Cervix model to do a dynamic multi-cohort modelled analysis of the impact of potential scale-up scenarios for cervical cancer prevention, in order to predict the future incidence rates and burden of cervical cancer. They found that widespread coverage of both HPV vaccination and cervical screening from 2020 onwards had the potential to avert up to 12·5–13·4 million cervical cancer cases by 2069 and could achieve average cervical cancer incidence of around four per 100,000 women per year or less by the end of the century.

PRIME is a simpler static model intended for use by non-modeller users such as country programme managers and planners, and decision makers in low- and middle-income countries (Hickman, Jit and Hutubessy 2016; Jit et al. 2014). It was created by scientists at the London School of Hygiene and Tropical Medicine in London, Université Laval in Quebec, and Johns Hopkins Bloomberg School of Public Health in Baltimore, in conjunction with the World Health Organization in Geneva. It gives reliable, validated estimates for impact and cost effectiveness of HPV vaccination of adolescent girls prior to sexual debut.

A number of studies have used the model developed by Merck & Co (Elbasha et al. 2008; Elbasha and Dasbach 2010). The model has been used recently to estimate the impact of the HPV vaccine in Thailand (Termrungruanglert et al. 2021) and in France (Majed et al. 2021).

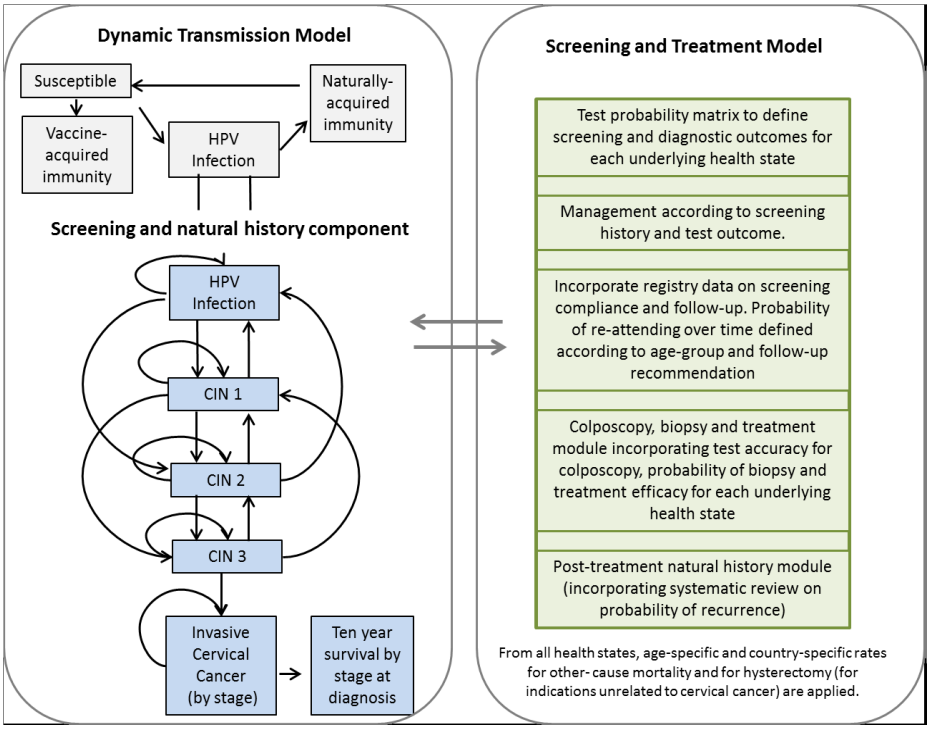
The model simulates the natural history of HPV infections and estimates the cost associated with all HPV-related diseases in both genders (i.e., cervical cancer, vaginal cancer, vulvar cancer, anal cancer, penile cancer, the associated precancerous lesions, head and neck cancer, genital warts and juvenile- and adult-onset recurrent respiratory papillomatosis, RRP).

The model used in this study is the Policy1-Cervix model based at The Daffodil Centre, University of Sydney.

Policy1-Cervix is a dynamic model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis, and treatment. It is shown schematically in Figure 1.

The model simulates HPV infection which can persist and/or progress to cervical intraepithelial neoplasia grades I, II and III (CIN1, CIN2, CIN3); CIN 3 can then progress to invasive cervical cancer. Progression and regression rates between states are modelled separately for types of HPV 16, HPV 18, other high-risk types (including HPV 31/33/45/52/58). The model platform captures the increased risk of CIN2+ recurrence in even successfully treated women (compared to the baseline risk of CIN2+ in the population).

FIGURE 1 POLICY1_CERVIX MODEL PLATFORM



To capture the impact of HPV vaccination, the model includes assumptions about median age of sexual debut for females and males, and a median lifetime number of sexual partners. Both males and females can move from an initial state of being susceptible to HPV infection, to being infected with HPV, recovering from an infection and being immune, and then returning to a state of being susceptible. In addition, women can potentially progress from infection with HPV to cervical intraepithelial neoplasia (CIN) and invasive cancer, or regress from precancerous states to a state where type-specific immunity to HPV has been conferred. Susceptible individuals can also become immune via vaccination against HPV. Additionally, individuals in any of the previously described states can die from other causes, and females can also undergo a benign hysterectomy.

The Policy1-Cervix model is an extensively validated model platform and has been used for a range of screening and vaccination evaluations across a range of countries. It was used to evaluate the impact of cervical cancer elimination targets in 78 low-and lower-middle income countries and was reviewed and endorsed by the WHO Advisory Committee on Immunization and Vaccines related Implementation Research (IVIR-AC). It has been used to predict the timeline to elimination of cervical cancer for 181 countries and to evaluate a range of screening strategies to inform WHO's updated cervical screening guidelines. It has been used for a range of government-commissioned studies on behalf of national cervical screening programs. It has also been used to evaluate the cost-effectiveness of alternative screening and vaccination approaches in China, Japan, Malaysia, and Papua New Guinea.

More details on the model structure, previous applications and calibration documentations for selected countries can be found on the Policy1 website (www.Policy1.org).

Economic model

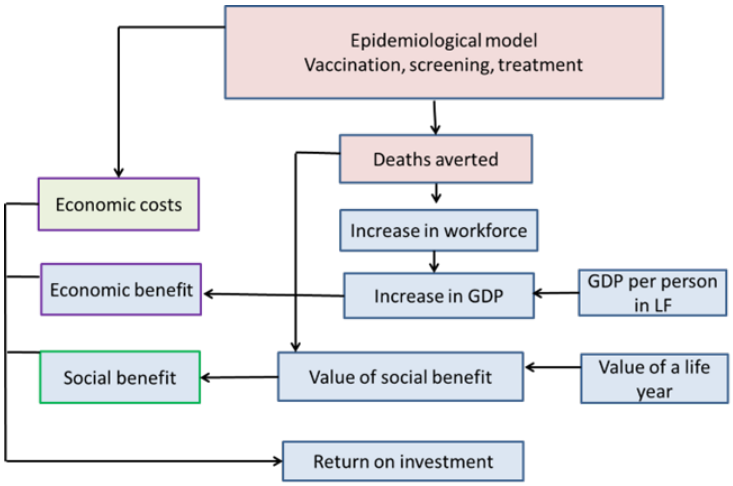
The health and cost outcomes can be used as inputs to an economic model that estimates the return on investment from each scenario. This approach has been used in a number of studies (Stenberg et al. 2014; Chisholm et al. 2016; Bertram et al. 2018; Sheehan et al. 2017; Sweeny et al. 2019). In a study for the UNFPA on the returns to investment for adolescent health, a simplified model was used to calculate the return on investment for an HPV vaccination programme for 75 low- and middle-income countries (Sheehan et al. 2017). A similar approach was used in a study for UNICEF on an adolescent investment case for Burundi (Rasmussen et al. 2019).

The model is shown schematically in Figure 2.

The economic benefits are calculated by following over their lifetimes the cohort of people whose deaths are averted for each year of the intervention program. As the people in each cohort age, they are subject to death rates for their country, age and sex using estimates from the most recent UN World Population Prospects (UN 2019) projections to the year 2100.

The number of these people that are in the labour force is calculated by using the most recent labour force participation rate (LFPR) projections from the ILO (2021) for the period to 2030. For each year and age and sex cohort, the number of people in the labor force is calculated by applying the LFPR estimate appropriate for each estimate of the numbers of people in that year by age and sex. The economic contribution from these people in the labor force is calculated by multiplying the number by an estimate in that year of the GDP per person in the labor force, and a factor estimating the productivity of their age compared to average productivity. GDP estimates are obtained from the World Bank for the most recent year (World Bank 2021) and labor force from the ILO. Average productivity is obtained by dividing GDP by the labor force and this is allowed to increase each year by a rate depending on the country's World Bank income status.

FIGURE 2 RETURN ON INVESTMENT MODEL



The results are, for each cohort, their contribution to GDP each year in which they are in the labor force. Summing across all the cohorts gives a measure of the GDP resulting from the deaths averted by the intervention program.

Estimates of the overall GDP in each year can be calculated by multiplying the estimated average productivity in that year by the estimate of the overall labor force in that year. GPD per capita in a particular year can be obtained by dividing GDP by the estimated population in that year.

It is common when estimating the benefits of improved health to put a value on being alive. This is usually done by estimating the value of a statistical life year. Building on the results of Viscusi and Aldy (2003), Jamison et al. (2013) estimated the value of a life year as between 1.4 and 4.2 times GDP per capita, averaging 1.6 globally.

Stenberg et al. (2014) modified this approach by assuming the value of a life year of 1.5 times GDP per capita and assuming the economic benefit represented 1 times GDP per capita, leaving a residual value of 0.5 times GDP per capita as the social benefit. Following this approach, a value of 0.5 times the GDP per capita is assigned to each healthy life year gained from the interventions to estimate the social benefit of improved health.

In order to compare the economic benefits and costs associated with the intervention program, both are expressed as net present values (NPV) using the standard World Bank discount rate of 3%. A common investment metric is the benefit cost ratio (BCR), and this is calculated by dividing the economic and social benefits by the cost, both in NPV terms.

The WHO guide for standardization of economic evaluations of immunization programmes (WHO 2019; Bertram et al. 2017), recommends that:

In the absence of national guidelines, two analyses using the following discount rate schemes are recommended to be used: (i) 3% and 0% discounting for consumption and health respectively, (ii) 3% discounting for both health and consumption. (p. 67)

The modelling results reported below discount costs and economic and social benefits by 3%.

4. ASSUMPTIONS AND DATA FOR MODELLING THE INVESTMENT CASE

Both the epidemiology and economic model require country-specific information to produce accurate outcomes. Table A1 in the Appendix lists in detail the assumptions used in this evaluation.

Vaccine price and other cost data

This analysis aims to inform the government on the optimal scenarios to invest in HPV vaccination and cervical cancer screening, so costs were estimated from a service provider or government perspective. Any costs incurred by patients (direct non-medical costs such as transportation and time lost) were not included.

All scenarios assume the use of the HPV4 vaccine (Gardasil 4, quadrivalent) as this has been officially selected by the Ministry of Health in Viet Nam in the implementation plan 2019-2025. In alternative scenarios (1A-9A), HPV9 vaccine (nonavalent vaccine) was assumed to be used after 2025.

We assume that the HPV4 vaccine cost is US$6.50 for the period 2022-2025 consisting of the GAVI price of US$4.50 for the vaccine and US$ 2.00 for other indirect costs, including UNICEF administrative fees, storage and transportation to service delivery points and disposals. After 2025, the price of HPV4 vaccine is estimated at US$12.00 through direct negotiation between the government and manufacturers (based on the current negotiated price for middle income countries in Southeast Asia and Latin America) plus US$3.00 for indirect costs that make up the total US$15.00 per dose from 2026 onward. In the alternative scenarios, we assumed HPV9 vaccine costs would be US15 per dose – the same price as HPV4 vaccine after 2025. Additionally, the registered price for HPV9 vaccine of US$122.8 was included in the cost-effectiveness analysis.

For other costs associated with cervical cancer screening, diagnosis and treatment, only direct medical costs were considered and were originally assessed in Viet Nam Dong (VND) (Viet Nam currency) and converted to US$, using the 2022 exchange rate (1US$ = VND 23,201, 28th July 2022, State Bank of Viet Nam). Cervical screening, diagnosis, and treatment costs were estimated based on the government prices for medical services for patients with public health insurance. Costs associated with screening tests and diagnosis were calculated as costs for the test itself plus administration fees as is common practice in public health facilities in Viet Nam. Cervical cancer treatment costs were estimated as a sum of associated costs for major clinical procedures and services that need to be included in each treatment, based on clinical guidelines for each treatment procedure. Costs of chemotherapy drugs were based on market prices, given most of these drugs were not covered by public health insurance.

For a sensitivity analysis of budget impact and return on investment, we considered additional 20% increase of the current total costs to capture potential indirect costs associated with administration, planning and supervision costs to be able to deliver HPV vaccination, cervical screening, and cancer treatment.

Table A1 in the Appendix lists all costs and their sources.

Sexual activity behaviour

Nguyen et al (2019) conducted a detailed review of sexual behaviour in Viet Nam. Findings from two rounds of a national youth survey conducted in Viet Nam in 2003 and 2009, which included 17,628 married and non-married males and females aged 14-25 years in 42 out of 63 provinces/cities across Viet Nam, showed that on average sexual puberty began at the age of 14-14.5 years in females and 15.4-15.7 years in males. Across the two surveys it was found that the mean age at sexual debut commenced around 18-20 years. Evidence from other studies also showed an increased rate of premarital sex and the acceptance of premarital sex in younger Vietnamese (Ghuman 2006).

The increased evidence of premarital sex was also reported in the UNFPA National survey on sexual and reproductive health among Vietnamese adolescents and young adults aged 10-24 years (UNFPA 2016). This survey revealed that 20.5% males participating in the survey reported ever having premarital sex, compared to 9.3% in females. In urban areas, 15.3% of respondents reported ever having premarital sex compared to 14.7% living in rural regions. In terms of age, 36.8% respondents who reported having premarital sex were 19-24 years of age and 7.5% were aged 15-18 years. This survey also revealed the average number of sex partners the respondents ever had was 2.1.

This evidence implied that sexual behaviour is changing in Viet Nam over the last few decades and this change in sexual behaviour is leading to increased risk of HPV infection and transmission. Given the limitations on data on sexual behaviour in the Vietnamese population, when modelling the transmission of HPV infection, a generic dynamic transmission model was

used. This generic transmission model was originally calibrated to reflect the sexual behaviour patterns in the Asia-Pacific region. In this model, at each age the transmission model captures the number of women infected with type-specific HPV in the cohort. From this the predicted age-specific prevalence by HPV types can calculated and compared to the observed age-specific HPV prevalence reported for Viet Nam (Pham et al, 2003; Vu et al, 2013), and to the observed cervical cancer incidence in Viet Nam.

HPV prevalence and cervical cancer

Because there are significant differences in HPV prevalence, cervical cancer incidence, and data availability, between Hanoi (northern urban) and Ho Chi Minh City (southern urban) and rural areas in Viet Nam, three separate models for northern urban; southern urban and rural regions were developed. The model was calibrated to the cervical cancer incidence and HPV prevalence reported for Hanoi and Ho Chi Minh City, based on the International Agency for Research on Cancer (IARC) certified cancer registry data (Parkin et al 2002, 1997) and HPV prevalence surveys (Pham et al 2003, Vu and Bui 2012, Vu, Bui and Le 2013). Based on IARC's uncertified cervical cancer rates reported by local cancer registries for semi urban provinces, which were as low as the incidence reported for Hanoi, rural regions were assumed to have a similar burden of disease as Hanoi. The overall national modelling outcomes were estimated as weighted 15% for the northern urban region, 15% for the southern urban region, and 70% for the rural region.

Screening

Where screening is included in the modelling, it assumed that 70% of women aged 30-50 years are screened 10-yearly (three times in a lifetime) by 2030 and 90% by 2045.

Based on discussions with country experts, it is assumed that HPV screening, triaging with visual inspection with acetic acid (VIA) ('HPV screen, triage and treat' modality) would be suitable for urban regions, while 'HPV screen and treat' modality would be more suitable for rural regions.

Given cytology and VIA screening would be potentially in health facilities/settings where resources for HPV screening would be not available, these screening options were also included in the modelling. These screening management pathways follow WHO recommendations (WHO 2021b).

Based on data from a literature review of treatment resources for cervical precancerous lesions, a 75% compliance rate among women who were referred to precancerous treatment was assumed as current treatment status. We assumed this compliance rate would reach 90.0% in scenarios where cervical cancer screening and treatment achieved the WHO 2030 targets for cervical cancer elimination.

The test characteristics for primary HPV testing, cytology and VIA were obtained from an international systematic review on the sensitivity and specificity to inform the model inputs (WHO 2021b).

We assumed a sensitivity to CIN2+ of 94.7% and a specificity of 88.7% for primary HPV testing. We assumed a sensitivity of 67.0% for primary cytology testing. For VIA, test performance was based on a combination of evidence from cross-sectional studies and larger scale population-level longitudinal studies. We assumed 39.5% sensitivity to CIN2+.

Further descriptions of the alternative screening types are included in the Appendix.

Hysterectomy rate, treatment access rate and survival rates

Although in clinical practice, hysterectomy is being conducted on benign conditions, this information is not well documented or not published, it was assumed there was no background hysterectomy for benign conditions.

The current treatment access rate for women diagnosed with cervical invasive cancer was estimated at 21.3%, based on the access rate to radiotherapy estimated for Viet Nam in Datta et al (2014). In scenarios which assume screening and treatment scale-up, cancer treatment access rates were increased to 50% and 90% by 2023 and 2030, respectively.

The survival rates used in the modelling were the same as those reported for Viet Nam in Canfell et al (2020) and are based on the treatment access rate to radiotherapy. Table 1 shows these survival rates under the current rate and for treatment scale up to 50% and 90%.

TABLE 1. MODELLED CERVICAL CANCER SURVIVAL RATES BY STAGE

a. Current access to radiotherapy treatment - 21.3%

	5-year survival rate		10-year survival rate	
	Symptomatic cancer	Screen-detected cancer	Symptomatic cancer	Screen-detected cancer
Stage 1	0.668	0.735	0.195	0.214
Stage 2	0.534	0.587	0.173	0.19
Stage 3	0.187	0.187	0.114	0.114
Stage 4	0.031	0.031	0.02	0.02

b. Access to radiotherapy treatment - 50% rate

	5-year survival rate		10-year survival rate	
	Symptomatic cancer	Screen-detected cancer	Symptomatic cancer	Screen-detected cancer
Stage 1	0.750	0.828	0.434	0.481
Stage 2	0.630	0.696	0.385	0.426
Stage 3	0.355	0.355	0.290	0.290
Stage 4	0.065	0.065	0.045	0.045

c. Access to radiotherapy treatment - 90% rate

	5-year survival rate		10-year survival rate	
	Symptomatic cancer	Screen-detected cancer	Symptomatic cancer	Screen-detected cancer
Stage 1	0.869	0.954	0.783	0.859
Stage 2	0.774	0.825	0.693	0.739
Stage 3	0.599	0.599	0.522	0.522
Stage 4	0.117	0.117	0.081	0.081

5. RESULTS

The Policy1-Cervix model was used to calculate the impact of various scenarios for addressing HPV and cervical cancer in Viet Nam. A further 9 scenarios are considered later in this section.

To assess the impacts of HPV vaccination, screening and treatment the study compared the outcomes from a number of combinations of these with a base case scenario (0) in which there is no HPV vaccination and the current VIA screening rate of 28% and a cervical cancer treatment rate of 21.3%. The characteristics of the different scenarios assessed in the main analysis are listed in Table 2.

Vaccination is assumed to commence in 2023 at age12.

Scenarios

A total 13 key scenarios have been assessed at the base case analysis in the main analysis.

The first scenario assumes 90% coverage of the quadrivalent vaccine (Gardasil) for girls only while the second scenario assumes 50% coverage.

The third scenario assumes 90% coverage of the quadrivalent vaccine (Gardasil) for girls and 60% for boys while the fourth scenario assumes coverage rates of 50% and 20% respectively.

These first 4 scenarios assume a VIA screening rate of 28% and a cervical cancer treatment rate of 21.3%.

The fifth scenario has no vaccination but HPV screening for 70% of women aged 30-50 years 10-yearly (three times in a lifetime) and a cervical cancer treatment rate of 90%.

Scenarios 6 to 9 replicate scenarios 1 to 4 but with HPV screening for 70% of women aged 30-50 years 10-yearly (three times in a lifetime) and a cervical cancer treatment rate of 90%.

Scenarios 10 and 11 are the same as scenario 6 but replace HPV screening with 3-yearly VIA screening and 5-yearly cytology testing respectively.

Scenarios 12 and 13 are the same as scenario 5 (i.e., no vaccine) but replace HPV screening with 3-yearly VIA screening and 5-yearly cytology testing respectively.

Taking Scenario 0 as the base case (ie the current situation), we compared each of the other scenarios with this base case and calculated the number of deaths averted, life years saved, the incremental costs, the economic and social benefits accrued. The results are reported in both cost-effectiveness terms as cost per QALY averted and as BCRs. Table 3 shows the deaths averted and life years saved.

TABLE 2. SCENARIO CHARACTERISTICS

Scenario	Vaccine	Girls/Boys	Coverage	Screening	Treatment
0	No vaccine			VIA 28%	21.3%
1	HPV 4 only	Girls	90%	VIA 28%	21.3%
2	HPV 4 only	Girls	50%	VIA 28%	21.3%
3	HPV 4 only	Girls and boys	90%/60%	VIA 28%	21.3%
4	HPV 4 only	Girls and boys	50%/20%	VIA 28%	21.3%
5	No vaccine			10-yearly HPV 70%	90%
6	HPV 4 only	Girls	90%	10-yearly HPV 70%	90%
7	HPV 4 only	Girls	50%	10-yearly HPV 70%	90%
8	HPV 4 only	Girls and boys	90%/60%	10-yearly HPV 70%	90%
9	HPV 4 only	Girls and boys	50%/20%	10-yearly HPV 70%	90%
10	HPV 4 only	Girls	90%	3-yearly VIA 70%	90%
11	HPV 4 only	Girls	90%	5-yearly cytology 70%	90%
12	No vaccine			3-yearly VIA 70%	90%
13	No vaccine			5-yearly cytology 70%	90%

TABLE 3. DEATHS AVERTED AND LIFE YEARS SAVED COMPARED TO BASE SCENARIO

Scenario	Deaths averted	Life years saved
1	114,856	3,265,297
2	73,691	2,082,637
3	118,456	3,360,983
4	80,112	2,264,590
5	282,437	7,206,818
6	301,819	7,754,213
7	294,545	7,546,952
8	302,506	7,769,401
9	295,951	7,584,703
10	300,315	7,784,000
11	305,109	7,884,609
12	279,833	7,211,110
13	286,910	7,377,805

Table A2 in the Appendix shows the change in the cervical cancer incidence rate, mortality rate and cervical cancer cases averted.

Under the base case scenario, the modelling predicts that the age-standardised rate of incidence and mortality would be 7.9 per 100,000 women and 5.7 per 100,000 women, respectively in Viet Nam.

Assuming two-dose HPV vaccination could achieve 90% coverage in cohorts of females, it was predicted that the cervical cancer incidence and mortality reduced by around 66% in the longer term. Adding HPV vaccination for males had a minor impact on health outcomes, which the incidence and mortality rates were reduced 2% - 3% further only. If only 50% HPV vaccination was achieved for females, the incidence and mortality rates were reduced by around 40% compared to no vaccination. Adding HPV vaccination for males in this low-female-coverage scenario could reduce cervical cancer incidence and mortality rates by an additional 3-4%. However, adding males still remained less effective than when 90% coverage is achieved in females.

When considering two-dose HPV vaccination at 90% coverage in cohorts of females who receive high-coverage HPV-based screening and high access to cervical cancer treatment later in their lifetime, then the combined impact of these interventions is predicted to reduce cervical cancer incidence and mortality reduced to 1.3/100,000 (83.2% reduced) and to 0.4/100,000 (92.5% reduced) respectively compared to current rates of cancer. Assuming 50% HPV vaccination is achieved for females, but that screening and cancer treatment coverage remains high, the incidence and mortality rates were reduced to 2.1/100,000 (73.5% reduced) and 0.7/100,000 (88.6% reduced). Adding HPV vaccination for males had a minor impact on health outcomes, reducing cancer incident and mortality rates, at most, by a further 1%.

Alternative scenarios

Several other scenarios requested by UNFPA were undertaken. These scenarios are outlined in Table 4 and are the same as those listed in Table 2 except that the HPV4 vaccine is replaced by the HPV9 vaccine in 2026 and the screening scenarios assume 5-yearly HPV screening at 70% coverage. In addition, two variations of vaccine price are modelled. The first assumes that the price of HPV9 is the same as the price of HPV4, namely US$15.00. The second assumes a price of US$122.80, the registered price in Viet Nam.

Table A7 in the Appendix shows the number of deaths averted and life years saved for each scenario when compared to the base scenario.

TABLE 4. ALTERNATIVE SCENARIO CHARACTERISTICS

Scenario	Vaccine	Girls/Boys	Coverage	Screening	Treatment
0	No vaccine	Girls		VIA 28%	21.3%
1A	HPV 4 then HPV9	Girls	90%	VIA 28%	21.3%
2A	HPV 4 then HPV9	Girls and boys	50%	VIA 28%	21.3%
3A	HPV 4 then HPV9	Girls and boys	90%/60%	VIA 28%	21.3%
4A	HPV 4 then HPV9		50%/20%	VIA 28%	21.3%
5A	No vaccine	Girls		5-yearly HPV 70%	90%
6A	HPV 4 then HPV9	Girls	90%	5-yearly HPV 70%	90%
7A	HPV 4 then HPV9	Gái	50%	5-yearly HPV 70%	90%
8A	HPV 4 then HPV9	Girls and boys	90%/60%	5-yearly HPV 70%	90%
9A	HPV 4 then HPV9	Girls and boys	50%/20%	5-yearly HPV 70%	90%

5.1 COST-EFFECTIVENESS ANALYSIS

As discussed above, the cost-effectiveness analysis considered HPV4 vaccine prices in two scenarios: 1) remaining at US$6.5 per dose after 2025 and 2) US$15 per dose after 2025.

In a sensitivity analysis, a total twenty-three (23) key scenarios were assessed, considering one-dose and three-dose HPV vaccination at current screening and treatment (status quo) and at screening and treatment scale-up.

For cost-effectiveness analysis, we assumed 3% discount rate for both effects and costs in sensitivity analyses. Results are presented in Table 5 and Tables A3 and A4 in the Appendix.

Additionally, in order to provide evidence to identify optimal screening strategies for Viet Nam, the analyses of benefits, harms and cost-effectiveness of cytology and VIA screening were performed.

To evaluate the cost-effectiveness of various HPV vaccination strategies, in investment case 1, we compared each of scenarios 1,2,3,4 with the status-quo and calculated the life-years saved (LYS), costs and the incremental cost-effectiveness ratio of groups of these scenarios. Table 5, part I summarizes the reduction in cervical cancer incidence, mortality, cases averted over 100 years and the incremental cost ratios (ICER) of each strategy.

Similarly, in investment case 2 evaluating the cost-effectiveness of HPV vaccination together with screening and treatment scale-up to the WHO 2030 targets, we compared each of scenarios 6,7,8,9 with scenario 5 (screening and treatment scale-up only). Results are presented in Table 5, part II.

To provide evidence for the government to identify the most optimal cervical screening strategies for Viet Nam, taking Scenario 0 as status-quo, we compared each of scenarios 5, 12, and 13 (with no HPV vaccination and cervical screening and cancer treatment scale up only) and scenarios 6, 10, and 11 (with HPV vaccination and screening and treatment of cases diagnosed with cervical cancer) with the status-quo. Results are presented in Table A4 in the Appendix.

Investment case 1: Investing in HPV4 vaccination with current rates of screening and treatment

Table 5, part I (Investment case 1) summarizes the incremental cost-effectiveness ratios (ICER) for various HPV vaccination strategies at current screening and treatment status, considering different vaccine dose-schedules, vaccine prices, vaccination coverage rates, and discount rates.

Female-only two-dose vaccination was cost-effective up to 3 times the GAVI-supported vaccine price (US$4.5 per dose), at US$15 per dose at both 50% and 90% coverage (ICER <= US$281/LYS). If 90% coverage is achieved in females, adding males was not cost-effective at either 0% or 3% discounting for effects (ICER = US$ 4,640-US$43,491/LYS).

If only 50% coverage is achieved in females, adding HPV vaccination for males was cost-effective only when the discount rate was assumed to be 0% for effects (ICER = US$717 - US$1,347/LYS).

For one-dose HPV4 vaccine, female-only HPV4 vaccination remained cost-effective at US$15 per dose regardless of the coverage reached (ICER = US$109 - 119/LYS). HPV4 vaccination for females and males was not cost-effective at high coverage rates (90% for females and 60% for males) at US$15 per dose and when 3% discounting for effects was considered (ICER = US$4,212 - US$21,643/LYS).

For the three-dose vaccine schedule, female-only HPV4 vaccination remained cost-effective at US$15 per dose regardless of the vaccine coverage reached (ICER = US$412/LYS - US$442/LYS). Adding HPV4 vaccination for males was marginally cost-effective at low vaccine coverage (50% for females and 20% for males) and at 0% discount rate for effects (ICER = US$1,103 – US$2,047/LYS). At 3% discount rate for effects, adding HPV vaccination for males was not cost-effective (ICER= US$5,669/LYS - US$10,521/LYS).

Investment case 2: Investing in HPV4 and assuming vaccinated cohorts are offered improved screening and cancer treatment during their lifetime, according to the WHO targets for cervical cancer elimination.

Table 5, part II (Investment case 2) summarizes the incremental cost-effectiveness ratios (ICER) for various HPV vaccination strategies at 10-yearly HPV screening and treatment scale-up, considering different vaccine dose-schedules, vaccine prices, vaccination coverage rates, and discount rates.

If HPV4 vaccine was provided from 2023, combined with 10-yearly HPV-based screening for women aged 30-50 years established and scaled up as well as cancer treatment access was increased, two-dose female-only HPV4 vaccination with 10-yearly HPV screening for women aged 30-50 years and treatment scale up was cost-effective at US$15 per dose at either 90% (ICER = US$1,547/LYS) or 50% coverage (ICER = US$1,426/LYS).

Two-dose HPV4 vaccination for females and males at screening and treatment scale-up was marginally cost-effective at US$6.5 per dose, low coverage (50% females and 20% males), and at 0% discount rate for effects only (ICER = US$3,546/LYS).

Offering one-dose HPV vaccination for females only and providing 10-yearly HPV screening and treatment scale-up was cost-effective at US$15 per dose regardless of coverage reached (ICER = US$581-647/LYS). Adding males to this strategy could be cost-effective (ICER = US$1,511-2,896/LYS) at US$6.5 per dose, low coverage, and at 0% discount rate for effects only; at 3% discount rate for effects, adding HPV vaccination to males was not cost-effective. (ICER = US$7,548-14,471/LYS).

For three-dose vaccination, when considering HPV vaccination in screening and treatment scale-up, female-only vaccination remained cost-effective regardless of coverage reached (ICER = US$1,680-2,447/LYS) at US$15 per dose and adding males was not cost-effective. (ICER = US$7,871- 14,452). At 3% discounting rate for effects, three-dose HPV4 vaccination was not cost-effective.

Effectiveness and cost-effectiveness of cervical cancer screening strategies

We compared three cervical cancer screening strategies that have been recommended by WHO, namely 10-yearly HPV screening, 3-yearly VIA and 5-yearly cytology. These were considered in two scenarios: 1) cervical cancer screening only for unvaccinated women aged 30 years; and 2) cervical cancer screening for cohort of women who were vaccinated and compared to current situation (no vaccination, current screening and treatment). The results are shown in Table A3 and A4 in the Appendix.

Comparing different screening strategies, Table A3 presents the reduction in cervical cancer incidence, mortality and number of precancer treatment needed as well as number needed to treat (NNT) to prevent a cancer death for each screening strategy.

Considering screening in unvaccinated women, the incidence was reduced by 58.1%, 56.7% and 58.7% for 10-yearly HPV screening, 3-yearly VIA, and 5-yearly cytology screening, respectively. Similarly, the mortality was predicted to reduce by 81.9%, 81%, 82.2%, respectively as the impact of increased cancer treatment access rate. The number of precancer treatments required over a lifetime of 100,000 cohort was ~10,000, ~7,500, and ~130,000 for 10-yearly HPV screening, 5-yearly cytology, and 3-yearly VIA, respectively. The number needed to treat (NNT) to prevent a cervical cancer death was 15, 11, and 197 for 10-yearly HPV screening, 5-yearly cytology, and 3-yearly VIA, respectively.

Considering offering cervical screening for vaccinated women, a similar pattern of reduction in incidence and mortality was predicted in scenarios considering screening for women who received vaccination. The pre-cancer treatment number remained the same as in unvaccinated women, however, the NNT to prevent a cancer death was reduced due to the impact of HPV vaccination.

In terms of cost-effectiveness, for unvaccinated women, 10-yearly HPV screening strategy was cost-effective (ICER = US$164/LYS). When considering screening in vaccinated women, 10-yearly HPV screening remained cost-effective at US$15 per dose (ICER=US$238-343/LYS).

Alterative scenario results

The alterative scenarios assume switching from HPV4 to one-dose HPV9 vaccination after 2025 for girls or girls and boys from age 12 years old and providing primary 5-yearly HPV screening (five times in a lifetime) for women aged 30-50 years.

Investment case 1: Investing in HPV4/HPV9 vaccination with current rates of screening and treatment

Table A5 Part I (Investment case 1) in the Appendix summarizes the incremental cost-effectiveness ratios (ICER) for switching from HPV4 vaccination to one-dose HPV9 strategies (HPV4/HPV9) at current screening and treatment status, considering different vaccine prices and vaccination coverage rates. Only 0% discounting for effects and 3% discount for costs were considered.

Assuming 90% one-dose female-only HPV4/HPV9 vaccination and at current screening and cancer treatment status (Scenario A1) was cost-effective at price US$15 per dose (ICER=US$29/LYS) and at US$122.8 per dose (ICER=US$776/LYS). Adding 60% one-dose HPV4/HPV9 vaccination for males (Scenario A2) was not cost-effective at the vaccine price of either US$15 per dose (ICER=US$5,652) or US$ 122.8 per dose (ICER=US$38,454/LYS).

If only 50% one-dose HPV4/HPV9 vaccination coverage is achieved in females (Scenario A3), this strategy was cost-effective at either US$15 per dose price (ICER = US$18/LYS) and US$122.8 per dose (ICER=US$705/LYS). Adding 20% one-dose HPV4/HPV9 vaccination for males (Scenario A4) was cost-effective only when considering US$15 per dose for HPV9 price (ICER= US$717/LYS).

Investment case 2: Investing in HPV4/HPV9 vaccine and assuming vaccinated cohorts are offered 5-yearly HPV screening and cancer treatment scale up during their lifetime, according to WHO elimination targets

Table A5 Part II (Investment case 2) in the Appendix summarizes the incremental cost-effectiveness ratios (ICER) for switching from HPV4 vaccination to one-dose HPV9 strategies (HPV4/HPV9) at 5-yearly HPV screening and treatment scale-up, considering different vaccine prices and vaccination coverage rates. Only 0% discounting for effects and 3% discount for costs were considered.

If switching from HPV4 vaccine to one-dose HPV9 vaccine after 2025, combined with 5-yearly HPV-based screening for women aged 30-50 years and cancer treatment scaled up, 90% one-dose female-only HPV4/HPV9 vaccination with 5-yearly HPV screening for women aged 30-50 years and treatment scale up (Scenario A6) was cost-effective at price US$15 per dose (ICER = US$498/LYS) but not cost-effective at the vaccine price of US$122.8 per dose (ICER=US$5,261/LYS). Adding 60% vaccination for males to this strategy (Scenario A7) was not cost-effective at either vaccine price of US$15 per dose (ICER=US$67,020/LYS) or US$122.8 per dose (ICER=US$452,376/LYS).

If 50% one-dose female-only HPV4/HPV9 vaccination combined with 5-yearly HPV screening and cancer treatment scale up (Scenario A8) was cost-effective at the vaccine price of US$15 per dose (ICER = US$174/LYS) and at US$122.8 per dose (ICER=US$547/LYS). Adding 20% vaccination for males to this strategy (Scenario A9) was marginally cost-effective at US$15 per dose (ICER=US$3,620/LYS) and not cost-effective at US$122.8 per dose (ICER=US$26,577/LYS).

TABLE 5. EFFECTIVENESS AND COST-EFFECTIVENESS OF HPV4 VACCINATION STRATEGIES

I. Investment case 1: Investing on HPV4 only with current screening and treatment

Scenarios	Scenario name	Two-dose ICER US$/LYS 0% (3%) discount rate for effects		One-dose ICER US$/LYS 0% (3%) discount rate for effects		Three-dose ICER US$/LYS 0% (3%) discount rate for effects	
		US$ 6.50	US$ 15.00	US$ 6.50	US$ 15.00	US$ 6.50	US$ 15.00
Group 1: High coverage reached							
0	Current screening and treatment (status quo) - comparator	-	-	-	-	-	-
1	HPV4 vaccination for girls (90%) at current screening and treatment	136 (690)	281 (1,428)	47 (237)	119 (606)	224 (1,140)	442 (2,248)
3	HPV4 vaccination for girls (90%) and boys (60%) at current screening and treatment	4,640 (23,845)	8,463 (43,491)	2,300 (11,820)	4,212 (21,643)	6,979 (35,868)	12,714 (65,337)
Group 2: Lower coverage reached							
0	Current screening and treatment (status quo) - comparator	-	-	-	-	-	-
2	HPV4 vaccination for girls (50%) at current screening and treatment	125 (640)	262 (1,338)	41 (208)	109 (557)	208 (1,063)	412 (2,110)
4	HPV4 vaccination for girls (50%) and boys (20%) at current screening and treatment	717 (3,686)	1,347 (6,921)	333 (1,709)	647 (3,327)	1,103 (5,669)	2,047 (10,521)

ICER: Incremental cost-effectiveness ratio; Willingness-to-pay threshold: 1GDP per capita: US$ 3,640 (2021)

II. Investment case 2: Investing on HPV4 vaccination with 10-yearly HPV screening and treatment scale up

Scenarios	Scenario name	Two-dose ICER US$/LYS 0% (3%) discount rate for effects		One-dose ICER US$/LYS 0% (3%) discount rate for effects		Three-dose ICER US$/LYS 0% (3%) discount rate for effects	
		US$ 6.50	US$ 15.00	US$ 6.50	US$ 15.00	US$ 6.50	US$ 15.00
Group 1: High coverage reached							
5	10-yearly HPV screening and treatment scale up only - comparator	-	-	-	-	-	-
6	HPV4 vaccination for girls (90%), at 10-yearly HPV screening and treatment scale up	738 (3,546)	1,547 (7,436)	243 (1,116)	647 (3,110)	1,233 (5,927)	2,447 (11,761)
8	HPV4 vaccination for girls (90%) & boys (60%), at 10-yearly HPV screening and treatment scale up	not cost-effective	not cost-effective	not cost-effective	not cost-effective	not cost-effective	not cost-effective
Group 2: Lower coverage reached							
0	10-yearly HPV screening and treatment scale up only - comparator	-	-	-	-	-	-
7	HPV4 vaccination for girls (50%), at 10-yearly HPV screening and treatment scale up	666 (3,211)	1,426 (6,877)	201 (967)	581 (2,800)	805 (3,884)	1,680 (8,099)
9	HPV4 vaccination for girls (50%) & boys (20%), at 10-yearly HPV screening and treatment scale up	3,207 (16,022)	5,978 (29,868)	1,511 (7,548)	2,896 (14,471)	7,871 (39,325)	14,452 (72,210)

ICER: Incremental cost-effectiveness ratio; Willingness-to-pay threshold: 1GDP per capita: US$ 3,640 (2021)

5.2 RETURN ON INVESTMENT ANALYSIS

Table 6 set outs the return to investment analysis comparing the base scenario (0) with the 13 intervention scenarios listed in Table 2. We assume two dose vaccination at a cost of US$ 6.50 in 2023 changing to US$ 15.00 in 2025, as described earlier.

The economic benefit, social benefit and costs for these intervention scenarios are shown in millions of US dollars (US$) expressed in net present value terms at a discount rate of 3%. The economic benefit cost ratio is the economic benefit divided by the cost while the economic and social benefit is the sum of the economic and social benefits divided by the cost.

Scenarios 1 and 2 which only incudes vaccines for girls at coverage rates of 90% and 50% have high economic BCRs of 8.0 and 9.5 respectively and economic and social BCRs of 13.0 and 16.6. Scenarios 3 and 4 which include boys as well as girls have somewhat lower economic BCRs of 4.5 and 7.0 respectively and economic and social BCRs of 7.9 and 12.2.

Scenario 5 includes HPV screening but not vaccines and has a high economic BCR of 9.9 and economic and social BCR of 19.0. Scenarios 6 to 9 are the same as scenarios 1 to 4 but with 10-yearly HPV screening and 90% treatment rates. Their BCRS are a little lower for the girls only vaccine scenarios and similar to the girls and boys scenarios.

Scenarios 10 and 11 are the same as scenarios 6 but with 3-yearly VIA and 5-yearly cytology screening replacing 10-yearly HPV screening. The BCRS are a little higher for scenario 10 and virtually the same for scenario 11.

Scenarios 12 and 13 are similar to scenario 5 in that they do not include vaccines but replace 10-yearly HPV screening with 3-yearly VIA and 5-yearly cytology screening. The BCRS are higher for scenario 12 and virtually the same for scenario 13.

TABLE 6. RETURN ON INVESTMENT ANALYSIS

Scenario	Economic benefit (US$ million)	Social benefit (US$ million)	Cost (US$ million)	Economic benefit BCR	Economic and social benefit BCR
1	4,344	3,182	540	8.0	13.9
2	2,812	2,087	295	9.5	16.6
3	4,466	3,283	984	4.5	7.9
4	3,044	2,255	433	7.0	12.2
5	9,936	9,186	1,005	9.9	19.0
6	10,747	9,722	1,657	6.5	12.4
7	10,441	9,521	1,362	7.7	14.7
8	10,766	9,736	2,181	4.9	9.4
9	10,498	9,559	1,537	6.8	13.0

10	10,976	9,787	1,536	7.1	13.5
11	11,078	9,949	1,686	6.6	12.5
12	10,133	9,226	912	11.1	21.2
13	10,332	9,460	1,062	9.7	18.6

Both the cost-effectiveness and return on investment analysis produce results that are very sensitive to the discount rate used in calculating net present values. Unlike many other health interventions, HPV vaccination only has a significant impact on deaths from cervical and other cancers after a considerable delay. Vaccinating girls at age 11 or 12 only prevents them developing cervical and other cancers in their 50s, 60s and 70s.

These returns on investment are in line with those quoted above in the WHO strategy document – 3.2 and 26.0 for economic and combined economic and social benefits respectively. They are also similar to those found in a study of adolescent health and wellbeing for UNFPA (Sheehan et al. 2017), which found a BCR of 22.5 for economic and social benefits for low-income countries and an average of 17.0 across 75 low- and middle-income countries. For an adolescent investment case for Burundi, the BCR was 4.8 (Rasmussen et al 2019).

Tables A8 and A9 in the Appendix give the economic and social benefits, the costs, and the benefits cost ratios associated with each scenario for the two assumptions about vaccine price. As might be expected the higher price assumption for HPV9 vaccine leads to increased costs and to lower benefit cost ratios. These range from 1.1 to 4.0 for economic benefits for those scenarios with vaccination, and 1.9 to 7.5 for economic and social benefits.

Replacing HPV4 with HPV9 at the same price gives benefit cost ratios ranging from 6.3 to 16.3 for economic benefits only and from 12.1 to 28.6 when both economic and social benefits are included.

5.3. ESTIMATED 5-YEAR BUDGET IMPACT

Table A6 in the Appendix presents 5-yearly undiscounted financial costs associated with HPV4 vaccination, cervical cancer screening, precancer treatment and cancer treatment for the 13 main scenarios. In this analysis, one-dose HPV4 vaccination was considered with the assumed vaccine price of $15 per dose.

The estimated financial costs include costs directly incurred in HPV4 vaccination (vaccine cost and vaccine delivery cost), cervical cancer screening, precancer treatment, and cancer treatment. We considered an increase of 20% of the estimated costs to capture potential indirect costs (administration, planning, supervision) to support the delivery of these services. The estimated costs do not include capital costs of existing infrastructure and equipment of the current national immunization system, cervical screening, and precancer and cancer treatment. It also does not include start-up costs which will usually be required at the beginning stage of the introduction of a new vaccine into a national vaccination program and a new established cervical screening program, for example costs for integrated vaccine monitoring and reporting system for HPV4 vaccination, costs for establishment of cervical cancer screening registry system, and costs for training and education for services providers.

At current status (no HPV vaccination, current ineffective cervical screening with low coverage and low cancer treatment access rate), it was estimated that 5-year (2023-2027) undiscounted financial costs of ~US$795 million would be spent on diagnosis and treatment of cervical cancer. (Table A6)

If one-dose HPV4 vaccination reached 90% coverage in females aged 12 years old from 2023 (scenario 1) and there is no further scale-up of cervical screening or cancer treatment access, an estimated 5-year undiscounted financial costs US$1,089 million would be required. Adding 60% HPV4 vaccination for males to this strategy (scenario 3) would require 5-year cost of ~US$1,294 million. If one-dose HPV4 vaccination was provided for only 50% females aged 12 years old (scenario 2), it was predicted that a 5-year cost of ~US$961 million would be needed. Adding 20% HPV4 vaccination for males to this strategy (scenario 4) would require ~US$1,025 million for 5-year costs.

If the government could invest in HPV4 vaccination and also established 10-yearly HPV screening and increased cancer treatment access rate (investment case 2), the estimated 5-year cost would be US$ 1,556 million if 90% females aged 12 years old were provided with HPV4 vaccine from 2023 (scenario 6). Adding 60% HPV4 vaccination for males to this strategy (scenario 8) would require ~US$1,759 million in the 5-year budget. If HPV4 vaccine was provided to 50% females aged 12 years old from 2023 and invested on 10-yearly HPV screening and increased treatment access rate (scenario 7), the 5-year budget would be ~US$1,427 million. If adding 20% HPV4 vaccination for males this strategy (scenario 9) would require US$ 1,493 million in the 5-year budget.

Comparing different cervical screening strategies, the 10-yearly HPV screening and cancer treatment scale up strategy (Scenario 5) would require a 5-year budget of ~US$1,260 million for the period 2023-2027, while 5-yearly cytology screening (Scenario 13) would need US$1,714 million and VIA screening strategy (Scenario 12) would need US$1,233 million. In strategies that require HPV4 vaccination, cervical screening and treatment scale up, 90% HPV4 vaccination combined with 10-yearly HPV screening and cancer treatment scale up (Scenario 6) would require US$1,556 million over the five-year period (2023-2027), while a similar strategy involving 5-yearly cytology screening (Scenario 11) would need US$2,014 million. Surprisingly, HPV vaccination combined with VIA screening and cancer treatment scale up (Scenario 10) would require US$1,539 million, which is similar to the budget required for a similar scenario using 10-yearly HPV screening (Scenario 6).

Assuming an 20% increase of the total current estimated costs would be added to cover associated administrative, planning and supervision to be able to deliver HPV vaccination, cervical screening and precancer and cancer treatment, the upper bound 5-year and annual budgets were estimated in Table A6.

5.4. TIMELINES FOR CERVICAL CANCER ELIMINATION

In November 2020, a global strategy to eliminate cervical cancer as a public health problem was launched. The strategy recommends that countries implement the '90-70-90' intervention targets by 2030 which are:

1. 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by 15 years of age.

2. 70% of women screened using a high-performance test (currently, primary HPV screening) by 35 years of age and again by 45 years of age; and

3. 90% of women identified with cervical precancer or invasive cervical cancer are provided with access to adequate treatment and care.

Countries will be considered to have eliminated cervical cancer as a public health problem when rates of new cases fall below 4 per 100,000 women-years.

To inform elimination timing for Viet Nam, we have updated Table A10 and A11 in the appendix to include the age-standardised rates (ASR) of cervical cancer incidence using the 2015 World Female population and the year when the elimination threshold is reached by each strategy, as used in previous elimination timing evaluations (Simms et al 2019, Brisson et al2020, Canfell et al 2020).

Assuming HPV4 vaccine coverage of 90% for girls aged 12 years old and assuming cervical screening and treatment remain unchanged from status-quo (Scenario 1, Table A10), we predicted that the ASR incidence of cervical cancer would decrease to fewer than 4 new cases per 100,000 women by 2083. Adding boys to this scenario (Scenario 3) had no noticeable impact on the timing of elimination compared to female-only vaccination. Assuming HPV4 vaccine coverage of 50% for girls aged 12 years old and assuming cervical screening and treatment remain unchanged from status-quo (Scenario 2), we predicted that cervical cancer rates would remain above the elimination threshold of 4 new cases per 100,000 women (the ASR incidence remains above 6 per 100,000 women by 2100); Adding boys to this scenario (Scenario 4) does not help achieve elimination.

Assuming HPV4 vaccine coverage of 90% for girls aged 12 years old and assuming 10-yearly HPV screening and precancer and cancer treatment is scaled-up to reach the WHO target for cervical cancer elimination (Scenario 6), we predicted that the ASR incidence of cervical cancer would decrease to fewer than 4 new cases per 100,000 women by 2055 (note we also found this scenario was cost-effective). This is more than 30 years earlier than HPV vaccination alone. Adding boys to this scenario (Scenario 8) had no noticeable impact on the timing of elimination. Two other scenarios (Scenario 10 and 11) which assume HPV4 vaccine coverage of 90% for girls aged 12 years old and either 3-yearly VIA screening or 5-yearly cytology produced similar elimination timing as Scenario 6 (2057 and 2055, respectively). However, these scenarios were not cost-effective.

Strategies which consider cervical screening only (Scenario 5, 12, and 13 assume 10-yearly HPV, 3-yearly VIA or 5-yearly cytology, respectively) do not achieve elimination. Note that 10-yearly HPV screening was cost-effective but 3-yearly VIA and 5-yearly cytology were not cost-effective as identified (Table A3, Appendix).

Table A11 presents the timeframe for elimination of 9 alternative scenarios. Providing HPV4 vaccine for 90% girls from 2023 and switching to HPV9 vaccine from 2026 (HPV4/9 vaccination) and maintaining cervical cancer screening and treatment as current (Scenario 1A) will decrease the ASR incidence to less than 4 new cases per 100,000 women by 2073 and is cost-effective. Adding boys to this scenario (Scenario 3A) is predicted to bring forward elimination by one year (2072). Providing HPV4/9 vaccination for 50% girls (Scenario 2A) only or 50% girls and 20% boys (Scenario 4A) and maintaining the current screening and treatment status would not eliminate cervical cancer.

Providing HPV4/9 vaccination for 90% girls in combination with 5-yearly HPV screening and precancer and cancer treatment scale up (Scenario 6A), would decrease the ASR incidence to less than 4/100,000 by 2047. Adding HPV4/9 vaccination for 60% boys (Scenario 8A) still could reach the elimination by the same year (2047), however, this scenario was not cost-effective. In two other similar scenarios (Scenario 7A and 9A) with lower HPV4/9 vaccination coverage (50% for girls or 50% girls and 20% boys), the elimination threshold could be reached by 2050, however, we found these strategies were marginally cost-effective.

6.IMPLEMENTING THE CERVICAL CANCER ELIMINATION STRATEGY

This study of an HPV vaccine, screening and treatment program in Viet Nam has demonstrated that this is worthwhile both in health and economic outcomes. Depending on the extent and composition of the program, it will reduce the number of deaths among women from cervical cancer by up to 300,000. The program will return between around 5 and 11 times its cost in economic benefits and between 8 and 20 times its cost in combined economic and social benefits.

At the prices assumed in this study, the modelling confirms the results of a range of other studies about the desirability of HPV vaccination and screening in terms of cost-effectiveness and as a return on investment. It also adds weight to previous studies advocating the introduction HPV vaccination and screening in Viet Nam.

The study has several limitations. We have only estimated the benefits arising from cervical cancer deaths averted. HPV vaccination also prevents a range of other conditions including vulvar cancers in women, penile cancer in men, and anal, head and neck cancers, genital warts and recurrent respiratory papillomatosis (RRP) in both men and women. This study therefore underestimates the total benefits from HPV vaccination as it does not include the benefits arising from deaths and morbidity averted from these other conditions. This is particularly the case for those scenarios which include vaccination for boys. The scarcity of epidemiological data on these rarer conditions means they are more difficult to model.

The assumptions for vaccine prices in this study include a markup for certain indirect costs including UNICEF administrative fees, storage and transportation. The modelling does not include other indirect vaccination costs or the indirect costs involved in screening and treatment. This is common in this type of analysis particularly when considered from the perspective of the Ministry of Health rather than other stakeholders.

To address this, some studies include indirect cost by adding a percentage markup to the direct costs. For instance, if total indirect costs represent 20% of direct costs, then the cost estimates in this study could be adjusted by multiplying by 1.2. Similarly, the benefit cost ratios could be adjusted downwards by dividing them by 1.2.

Modelling HPV and cervical cancer necessarily relies on a range of data.

For Viet Nam some of that data on cancer incidence and mortality is limited and from surveys a number of years ago. The modelling uses GLOBOCAN2018 estimates. For some assumptions no data is available, for instance rates of hysterectomy.

The results of this study provide an impetus to the further development of the National Action Plan on Prevention and Control of Cervical Cancer in Viet Nam announced in 2016.

The WHO Global strategy sets out a plan to eliminate cervical cancer as a public health problem with three major components:

- a national HPV vaccination program aimed at 90% of girls fully vaccinated with the human papilloma virus vaccine by 15 years of age.
- a national cervical cancer screening program to ensure that 70% of women are screened with a high-precision test at 35 and 45 years of age; and
- a national program aimed at 90% of women identified with precancerous lesions and invasive cervical cancer are provided with access to adequate treatment and care.

To aid the development and implementation of these plans, UNFPA and Cancer Council NSW (2020) have developed a checklist of 23 items to guide decision makers based on the WHO global strategy recommendations. This is included in the Appendix.

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APPENDIX

LIST OF LOCAL EXPERTS FOR THE CONSULTATION MEETING-HPV INVESTMENT CASE, JUNE 2021

No.	Name	Organization
1	Prof. Nguyen Vu Quoc Huy	Department of Obstetrics and Gynecology, Hue University of Medicine and Pharmacy
2	A/Prof. Tran Thi Thanh Huong – Vice Director	National Institute for Cancer Control, Hanoi
3	Representatives	National Hospital of Obstetrics and Gynecology, Hanoi
4	Representatives	Tu Du Hospital – TP Ho Chi Minh
5	Ms. Nghiem Xuan Hanh	Department of Maternal and Child Health Ministry of Health
6	A/Prof. Nguyen Thi Thi Tho	National Institute of Hygiene and Epidemiology, Hanoi
7	Dr. Bui Duc Tung	Center of Cervical Cancer Registry – Ho Chi Minh, Ho Chi Minh Cancer Hospital
8	Dr. Nguyen Thi Mai Lan	Vice-Director, Hanoi Oncology Hospital
9	Dr Pham Hoang Anh	Epidemiologist, former staff at National Institute for Cancer Control, Hanoi
10	Dr. Le Thi Nga	Epidemiologist, Health Bridge, Canada
11	Dr. Scott LaMontagne	Epidemiologist and director of HPV vaccine programs at PATH
12	Dr. Hoang Van Minh	Health Economist, Vice Dean Hanoi School of Public Health
13	Dr. Dat Duong	UNFPA
14	Dr Lai Duc Truong Technical Officer (NCD)	WHO Viet Nam
15	Pham Duy Quang	Head of Training and Science Centre, Hochiminh City Pasteur Institute

Types of screening

The WHO (2021b) describes the three screening tests as follows:

The traditional method to screen women for cervical cancer has been cytology (the Papanicolaou test, also known as the Pap smear or smear test). When cytology results are positive, the diagnosis is confirmed by colposcopy, and appropriate treatment is informed by biopsy of suspicious lesions for histological diagnosis. In countries with effective cytology-based cervical cancer screening and treatment programmes, the mortality from cervical cancer has been reduced fivefold over the past 50 years. This screening approach has not been as successful in low- and middle-income countries.

Newer screening tests introduced in the last 15 years include visual inspection with acetic acid (VIA), and molecular tests, mainly high-risk HPV DNA-based tests,3 which are suitable for use in all settings.

Visual inspection of the cervix with acetic acid

Visual inspection of the cervix with acetic acid (VIA) is an effective, inexpensive screening test

Visual inspection of the cervix, using acetic acid (white vinegar; VIA) or Lugol's iodine (VILI) to highlight precancerous lesions so they can be viewed with the "naked eye", shifts the identification of precancer from the laboratory to the clinic. This method is also referred to as direct visual inspection or cervicoscopy. Such procedures eliminate the need for laboratories and transport of specimens, require very little equipment and provide women with immediate test results. A range of medical professionals - doctors, nurses, or professional midwives - can effectively perform the procedure, provided they receive adequate training and supervision. As a screening test, VIA may perform as well as or better than cervical cytology in accurately identifying pre-cancerous lesions. This has been demonstrated in various studies where trained physicians and mid-level providers correctly identified between 45% and 79% of women at high risk of developing cervical cancer. Though VIA has limited specificity and low positive predictive value (~10%), it is economical, requires little equipment, and provides immediate results.

Cytology

Cytology tests (including the Papanicolaou smear test and liquid-based cytology [LBC]) identify atypical cells on the cervix through the preparation and interpretation of slides using microscopy by a trained expert. LBC requires sophisticated processing to create slides from liquid specimens. The threshold used in this guideline to identify the need for further evaluation or treatment is a cytological result of atypical squamous cells of undetermined significance (ASCUS) combined with the presence of high-risk HPV,

With a Pap smear, cells collected using a spatula are smeared onto a slide for examination under a microscope. In liquid-based cytology, a sample of cells is taken using a small brush. The cells are put into a container of liquid and analysed for abnormalities. Cervical cells to be tested for HPV are collected in a similar way.

HPV testing

These tests identify a group of high-risk carcinogenic HPV genotypes. HPV16 and 18 are the highest-risk genotypes and are the most common in cancers. Some of the tests on the market provide information about specific HPV genotypes, such as HPV16 and 18. We refer to HPV tests with partial genotyping when they report HPV16 and 18 (including HPV45 in some cases) and other carcinogenic types separately. Other HPV tests may provide extended genotyping, when

they report additional types, or groups of types, such as HPV31, 33, 35, 45, 52 and 56.

Studies of the accuracy of HPV testing report:

sensitivity 88% to 91% (for detecting CIN 3 or higher) [30] to 97% (for detecting CIN2+)

specificity 73% to 79% (for detecting CIN 3 or higher) [30] to 93% (for detecting CIN2+)

Studies of the accuracy of conventional cytology report:

sensitivity 50%,

specificity 94%

TABLE A1. EPIDEMIOLOGICAL MODEL INPUTS AND ASSUMPTIONS

Parameters	Baseline value (%)	Range for sensitivity analysis	Sources
Pre-intervention burden of disease			
Northern urban	ASR-W#= 6.8/100,000	N/A	Assumption that cervical cancer burden in northern urban is similar to the incidence reported by Hanoi cancer registry data (1993-1997), reported by IARC in CIV Vol. VIII[29]
Southern urban	ASR-W#= 28.8/100,000	N/A	Assumption that cervical cancer burden in southern urban is similar to the incidence reported by Hochiminh City cancer registry data (1995-1998) and (2009-2012), reported by IARC in CIV Vol. VIII[29]
Rural	ASR-W#= 6.8/100,000	N/A	Based on cancer registry data that reported in Vietnamese Oncology Journal in which the cervical age-standardized incidence rates in rural regions were as low as the rate reported in Hanoi.
Screening participation and compliance			
Screening participation rate (%)	Current status (status quo): Scale-up: 70% (selected from the 90% ever-screeners)	N/A	Current status: 2020 SDG children and women survey UNFPA and UNICEF Scale-up: WHO 2030 target for cervical cancer elimination
Rate of loss to follow-up for same-day treatment with thermal ablation	5%	N/A	Assumption
Rate of loss to follow-up after screening, diagnosis or treatment (if follow-up does not perform on the same day) (%)	Current status (status quo): 30% for urban and 50% for rural, making a national level of 25% loss-to-follow up Scale-up: 10% for urban and rural	N/A	Current status (status quo): Assumed based on local context. Scale-up: in-line with WHO targets for cervical cancer elimination

HPV vaccination			
Vaccine types and implementation year	HPV4 start from 2023	N/A	Based on discussions with country and international experts
Target groups	Girls only and Girls and boys	N/A	Based on discussions with country experts
Vaccination age	12	N/A	Based on discussion with country experts
Vaccine schedule	2 doses	1 dose, 3 doses	WHO[35]
Vaccination coverage rate	50-90%		Assumption based on Viet Nam HPV vaccine demonstration project[20] and assessment of current local context
Type-specific vaccine efficacy in HPV naive	100%	N/A	Paavonen et al., 2007[36]; FUTUREII group, 2007[37]; Joura et al, 2015[38]
Protection duration of HPV vaccine	Lifelong	N/A	Assumption based on the possibility that a booster dose would be provided by vaccine company if needed with no extra costs. A similar assumption on vaccine efficacy has been used in other models of cost-effectiveness analysis of HPV vaccine
Vaccine cross-protection against non-vaccine included types			
Quadrivalent	No	N/A	
Screening test characteristics #			
Primary HPV	Sensitivity CIN2+: 94.7% Specificity: 88.7%	N/A	Published systematic review(Koliopoulos et al., 2017)
Primary VIA/VIA triage	Sensitivity CIN2+: 94.7% Specificity: 88.7%	N/A	Combined evidence from systematic reviews(Kelly, unpublished) and population longitudinal data.(Sankaranarayanan et al., 2009; Shastri et al., 2014)
Primary cytology (LSIL cut-off)	Sensitivity CIN2+: 94.7% Specificity: 88.7%	N/A	Published systematic review(Koliopoulos et al., 2017)
Ablative treatment success rate	84.3-92.4% for CIN1-3; 0% for cancer	N/A	Randall et.al., 2019(Randall, Sauvaget, Muwonge, Trimble, & Jeronimo, 2019)
LEEP treatment success rate (%)	93.6	N/A	Ryu et al., 2012[32]; Martin-Hirsch et al., 2013[31]; Zhu et al, 2015[33]
% cancer treatment access to radiotherapy	At status quo: 22.3% (national) Intervention: 2023: 50%, 2030: 90%	N/A	At status quo: based on Datta et al., 2014[27] Intervention: in-line with WHO targets for elimination

% cancer treatment uptake for screened detected cancers	100% for urban and rural regions	N/A	Assumption that when a nationally organized cervical screening program is established, 100% screened detected cancers will be referred to cancer treatment
5-year survival rates by FIGO stage (%) for symptomatic cancer		N/A	
At status quo (current)			Datta et al., 2014 (Datta, Samiei, & Bodis, 2014)
FIGO I	66.8		
FIGO II	53.4		
FIGO III	18.7		
FIGO IV	3.1		
At 50% treatment access rate			
FIGO I	75.0		Canfell et al, 2020(Canfell et al., 2020)
FIGO II	63.0		
FIGO III	35.5		
FIGO IV	6.5		
At 90% treatment access rate			
FIGO I	86.9		
FIGO II	77.4		Canfell et al, 2020(Canfell et al., 2020)
FIGO III	59.9		
FIGO IV	11.7		
Health economic parameters ~			
Costs for HPV vaccination			
Vaccine delivery cost (US$)	3,9 USD/dose*	N/A	Levin et al., 201340 PATH's Global HPV vaccine project - Vietnam40
Vaccine price per dose (US$)			
2023-2024			
Quadrivalent (HPV4)	$6.5		Based on discussions with country experts
Nonavalent (HPV9)	Not available in Viet Nam yet		Based on discussions with country experts
From 2025-2100			
Quadrivalent (HPV4)	$15		Based on discussions with country experts
Nonavalent (HPV9)	$15		assuming HPV9 at same price as HPV4 from 2025
Nonavalent (HPV9)	$122.8		Registered price for Viet Nam market
Nonavalent (HPV9)	$61.4		assuming 50% of the registered market price

Screening, diagnosis, and treatment for precancerous lesions (US$)			
HPV test cost/+- HPV genotyping	$17.2		Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
VIA test cost	$4.8		Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
Cytology test cost	$15.8	N/A	Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
Colposcopy	$4	N/A	Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
Biopsy	$18.6		Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
Cryotherapy	$7.2	N/A	Costs for cancer treatment by FIGO stage were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
LEEP	$64.6	N/A	Costs were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019)
Cancer treatment costs (US$)			
FIGO I	$3871.6		Costs for cancer treatment by FIGO stage were estimated based on the government prices for medical services for health insurers, issued in 2019(Viet Nam Ministry of Health, 2019) (Circular 13/2019/TT-BYT). NOTE: Only 22.3% of the cancer costs will be applied in the status-quo because of the assumption that this is the proportion of women who get access to adequate treatment and care in Viet Nam.
FIGO II	$5898.5		
FIGO III	$5965.8		
FIGO IV	$5896.77		
Threshold for considering HPV vaccine to be "very cost-effective"	US$3640(1xGDPpc)	N/A	General Statistics Officer of Viet Nam (2016)45

(#) ASR-W: Age-standardized rate to world population; VIA: Visual Inspection with acetic acid; LEEP: Loop Electrosurgical Excision Procedure; HPV: Human Papilloma virus; GDP: Gross Domestic Products; FIGO: International Federation of Gynaecology and Obstetrics; WHO: World Health Organization

Note: (#) This table presents the test characteristics of different cervical screening and diagnosis tests which were reported from original studies, considering the proportions of pre-cancerous lesions (CIN1, CIN2, CIN3) in the population. For each test, we used the sensitivity and specificity to generate a test probability matrix (TPM). The TPM describes the relationship between each health state (normal, HPV positive, CIN1, CIN2, CIN3 and cancer) and test results. VIA: Visual Inspection with Acetic Acid; VAT: Visual Assessment for Treatment; Given VAT is usually used following a primary test, we used sensitivity and specificity of VIA triage test to generate the TPM for VAT.

(*) Cost of vaccine delivery was excluded program start-up costs (including costs occur in micro-planning, training, and social mobilization, etc.) and was inflated to 2022 price

~ Costs were calculated in US$, 2022.

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TABLE A2. DEATHS AVERTED, AND LIFE YEARS SAVED COMPARED TO STATUS-QUO (NO VACCINATION, SCREENING OR CANCER TREATMENT SCALE-UP)

Scenario	Scenario name	Incidence ASR* (% reduction)	Mortality ASR* (% reduction)	Cumulative cervical cancer cases averted 2023-2100	Cumulative cervical cancer deaths averted 2023-2100	Life years saved
0	Current screening and treatment (status quo)	7.9	5.7	-	-	
1	HPV4 vaccination for girls (90%) at current screening and treatment	2.7 (65.7%)	1.9 (66.5%)	149,342	108,926	3,265,297
2	HPV4 vaccination for girls (50%) at current screening and treatment	4.8 (39.5%)	3.4 (39.5%)	91,997	67,017	2,082,637
3	HPV4 vaccination for girls (90%) and boys (60%) at current screening and treatment	2.6 (67.5%)	1.8 (67.9%)	154,335	112,439	3,360,983
4	HPV4 vaccination for girls (50%) and boys (20%) at current screening and treatment	4.5 (43.4%)	3.3 (42.8%)	101,274	73,598	2,264,590
5	10-yearly HPV screening and treatment scale up only	3.3	1.1	226,724	282,403	7,206,818
6	HPV4 vaccination for girls (90%), at 10-yearly HPV screening and treatment scale up	1.3 (83.2%)	0.4 (92.5%)	286,006	301,846	7,754,213

7	HPV4 vaccination for girls (50%), at 10-yearly HPV screening and treatment scale up	2.1 (73.5%)	0.7 (87.9%)	263,511	294,551	7,546,952
8	HPV4 vaccination for girls (90%) & boys (60%), at 10-yearly HPV screening and treatment scale up	1.3 (83.2%)	0.4 (92.5%)	288,946	302,548	7,769,401
9	HPV4 vaccination for girls (50%) and boys (20%), at 10-yearly HPV screening and treatment scale up	2.0 (74.8%)	0.7 (88.6%)	267,761	296,076	7,584,703
10	HPV4 vaccination for girls (90%), at 3-yearly VIA screening and treatment scale up	1.4 (82.2%)	0.4 (92.8%)	276,094	300,382	7,784,000
11	HPV4 vaccination for girls (90%), at 5-yearly Cytology screening and treatment scale up	1.3 (83.1%)	0.4 (92.8%)	288,201	305,285	7,884,609
12	3-yearly VIA screening and treatment scale up only	3.4 (56.7%)	1.0 (81.9%)	209,945	279,849	7,211,110
13	5-yearly Cytology screening and treatment scale up only	3.2 (58.7%)	1.0 (82.2%)	226,699	287,074	7,377,805

** Age-standardised rate in this table used the Segi World Standard Population to be comparable to previously reported data*

TABLE A3. BENEFITS AND HARMS OF DIFFERENT SCREENING STRATEGIES

Scenarios	Incidence ASR* (% reduction)	Mortality ASR* (% reduction)	Cumulative cervical cancer deaths (% reduction)	Pre-cancer treatments/100,000 women	NNT to prevent a cervical cancer death	Discounted lifetime costs (US$, 2021)
S0. Current screening and treatment - comparator	7.9	5.7	424,345	-	-	7
I. Offering cervical screening for unvaccinated women (e.g. women were ineligible for HPV vaccination)						
S5. 10-yearly HPV screening (30-50 years) and treatment scale-up	3.3 (58.1%)	1.1 (81%)	282,403 (67%)	10,127	15	28
S12. 3-yearly VIA screening (30-50 years) and treatment scale-up	3.4 (56.7%)	1 (81.9%)	279,849 (66%)	128,108	197	37
S13. 5-yearly cytology screening (30-50 years) and treatment scale-up	3.2 (58.7%)	1 (82.2%)	287,074 (68%)	7,497	11	40
II. Offering cervical screening for vaccinated women (e.g. women were eligible for HPV vaccination)						
S6. Two-dose female-only HPV4 (90%), 10-yearly HPV screening (30-50 years) and treatment scale-up	1.3 (83.1%)	0.4 (92.5%)	301,846 (71%)	7,897	11	57
S10. Two-dose female-only HPV4 (90%), 3-yearly VIA screening (30-50 years) and treatment scale-up	1.4 (82.2%)	0.4 (92.8%)	300,382 (71%)	127,001	169	67
S11. Two-dose female-only HPV4 (90%), 5-yearly cytology screening (30-50 years) and treatment scale-up	1.3 (83.1%)	0.4 (92.8%)	305,285 (72%)	5,792	8	69

** Age-standardised rate in this table used the Segi World Standard Population to be comparable to previously reported data*

TABLE A4. EFFECTIVENESS AND COST-EFFECTIVENESS OF DIFFERENT SCREENING STRATEGIES (0% DISCOUNT RATE FOR EFFECT)

Scenarios	Incidence ASR*(% reduction)	Mortality ASR* (% reduction)	Cumulative cervical cancer cases averted (% reduction)	ICER US$	
				$6.5/dose	$6.5, then $15/dose
I. Offering cervical screening for unvaccinated women (e.g. women were ineligible for HPV vaccination)					
S0: Current screening and treatment (status quo)	7.9	5.7	553,775		
I. Offering cervical screening for unvaccinated women					
S5. 10-yearly HPV screening (30-50 years) and treatment scale-up	3.3 (58.1%)	1.1 (81%)	327,051 (41%)	164#	
S12. 3-yearly VIA screening (30-50 years) and treatment scale-up	3.4 (56.7%)	1 (81.9%)	343,830 (38%)	Extended dominated	
S13. 5-yearly Cytology screening (30-50 years) and treatment scale-up	3.2 (58.7%)	1 (82.2%)	327,075 (41%)	6,226#	
II. Offering cervical screening for vaccinated women (e.g. women were eligible for HPV vaccination)					
S6. Two-dose female-only HPV4 (90%), 10-yearly HPV screening (30-50 years) and treatment scale-up	1.3 (83.1%)	0.4 (92.5%)	267,769 (52%)	731	1106
S10. Two-dose female-only HPV4 (90%), 3-yearly VIA screening (30-50 years) and treatment scale-up	1.4 (82.2%)	0.4 (92.8%)	277,681 (50%)	22,686	22,686
S11. Two-dose female-only HPV4 (90%), 5-yearly cytology screening (30-50 years) and treatment scale-up	1.3 (83.1%)	0.4 (92.8%)	265,574 (52%)	Extended dominated	Extended dominated

** Age-standardised rate (ASR) in this table used the Segi World Standard Population to be comparable to previously reported data*

 # These strategies considered screening only.

ICER: Incremental cost-effectiveness ratio.

Willingness-to-pay threshold: 1GDP per capita: US$ 3,640 (2022)

TABLE A5. EFFECTIVENESS AND COST-EFFECTIVENESS OF EXPLORATORY STRATEGIES CONSIDERING SWITCHING FROM ONE-DOSE HPV4 VACCINE TO ONE-DOSE HPV9 VACCINE AND 5-YEARLY HPV SCREENING STRATEGIES (0% DISCOUNTED RATE FOR EFFECTS AND 3% FOR COSTS)

Scenarios	Incidence ASR * (% reduction)	Mortality ASR* (% reduction)	Incremental Cost-effectiveness ratio (ICER) CE threshold 1 GDPpc (2021) = US$ 3640	
			HPV9 = US$15/dose	HPV9 =US$122.8/dose
Investment case 1: Investing on HPV4, HPV9 with current screening and treatment				
Current screening and treatment (status quo)	7.9	5.7	-	-
HPV4, HPV9 vaccination for girls (90%) at current screening and treatment	1.4 (82.8%)	1 (82.7%)	29	776
HPV4, HPV9 vaccination for girls (90%) and boys (60%) at current screening and treatment	1.3 (84%)	0.9 (84%)	5,652	38,454
HPV4, HPV9 vaccination for girls (50%) at current screening and treatment	3.9 (50.3%)	2.8 (50.2%)	18	705
HPV4, HPV9 vaccination for girls (50%) and boys (20%) at current screening and treatment	3.7 (53.3%)	2.7 (53.1%)	717	5,430
Investment case 2: Investing on HPV4, HPV9 with 5-yearly HPV screening and treatment scale up				
5-yearly HPV screening and treatment scale up	3	1	-	-
HPV4, HPV9 vaccination for girls (90%) at 5-yearly HPV screening and treatment scale up	0.5 (80.7%)	0.2 (80.8%)	498	5,261
HPV4, HPV9 vaccination for girls (90%) and boys (60%) 5-yearly HPV screening and treatment scale up	0.5 (81.7%)	0.2 (81.5%)	67,020	452,376
HPV4, HPV9 vaccination for girls (50%) 5-yearly HPV screening and treatment scale up	1.4 (49.8%)	0.4 (49.6%)	174	547
HPV4, HPV9 vaccination for girls (50%) and boys (20%) 5-yearly HPV screening and treatment scale up	1.4 (51.1%)	0.4 (50.8%)	3,620	26,577

** Age-standardised rate (ASR) in this table used the Segi World Standard Population to be comparable to previously reported data*
ICER: Incremental cost-effectiveness ratio; Willingness-to-pay threshold: 1GDP per capita: US$ 3,640 (2022)

TABLE A6. ESTIMATED ANNUAL AND 5-YEARLY FINANCIAL COSTS (UNDISCOUNTED) OF DIFFERENT STRATEGIES IN VIET NAM, US$

Scenario	Scenario name	Incidence ASR* (% reduction)	Mortality ASR* (% reduction)	Annual undiscounted financial costs (20% added indirect costs)	5-yearly undiscounted financial costs (20% added indirect costs)
0	**Current screening and treatment (status quo)**	7.9	5.7	$152,301,839 ($182,762,206)	$795,317,189 ($954,380,627)
1	**HPV4 vaccination for girls (90%) at current screening and treatment**	2.7 (65.7%)	1.9 (66.5%)	$217,875,943 ($261,451,132)	$1,089,379,716 ($1,307,255,659)
2	**HPV4 vaccination for girls (50%) at current screening and treatment**	4.8 (39.5%)	3.4 (39.5%)	$192,158,524 ($230,590,228)	$960,792,618 ($1,552,264,568)
3	**HPV4 vaccination for girls (90%) and boys (60%) at current screening and treatment**	2.6 (67.5%)	1.8 (67.9%)	$258,710,761 ($310,452,914)	$1,293,553,807 ($1,552,264,568)
4	**HPV4 vaccination for girls (50%) and boys (20%) at current screening and treatment**	4.5 (43.4%)	3.3 (42.8%)	$205,096,469 ($246,115,763)	$1,025,482,345 ($1,230,578,814)
5	**10-yearly HPV screening and treatment scale up only**	3.3	1.1	$252,070,208 ($302,484,249)	$1,260,351,038 ($1,512,421,245)
6	**HPV4 vaccination for girls (90%), at 10-yearly HPV screening and treatment scale up**	1.3 (83.2%)	0.4 (92.5%)	$311,222,548 ($373,467,058)	$1,556,112,741 ($1,867,335,289)
7	**HPV4 vaccination for girls (50%), at 10-yearly HPV screening and treatment scale up**	2.1 (73.5%)	0.7 (87.9%)	$285,373,172 ($342,467,806)	$1,426,865,860 (1,712,239,031)
8	**HPV4 vaccination for girls (90%) & boys (60%), at 10-yearly HPV screening and treatment scale up**	1.3 (83.2%)	0.4 (92.5%)	$351,953,892 ($422,344,670)	$1,759,769,460 ($2,111,723,352)
9	**HPV4 vaccination for girls (50%) and boys (20%), at 10-yearly HPV screening and treatment scale up**	2.0 (74.8%)	0.7 (88.6%)	$298,506,938 ($358,208,326)	$1,492,534,692 ($1,791,041,630)
10	**HPV4 vaccination for girls (90%), at 3-yearly VIA screening and treatment scale up**	1.4 (82.2%)	0.4 (92.8%)	$307,893,528 ($369,472,234)	$1,539,467,642 ($1,847,361,171)
11	**HPV4 vaccination for girls (90%), at 5-yearly cytology screening and treatment scale up**	1.3 (83.1%)	0.4 (92.8%)	$341,841,456 ($411,409,747)	$2,013,620,097 ($2,416,344,116)
12	**3-yearly VIA screening and treatment scale up only**	3.4 (56.7%)	1.0 (81.9%)	$246,552,348 ($295,862,818)	$1,232,761,740 ($1,479,314,088)
13	**5-yearly cytology screening and treatment scale up only**	3.2 (58.7%)	1.0 (82.2%)	$341,841,456 ($411,409,747)	$1,714,207,283 ($2,057,048,739)

** Age-standardised rate (ASR) in this table used the Segi World Standard Population to be comparable to previously reported data*
ICER: Incremental cost-effectiveness ratio; Willingness-to-pay threshold: 1GDP per capita: US$ 3,640 (2022)

TABLE A7. DEATHS AVERTED AND LIFE YEARS SAVED, ALTERNATIVE SCENARIOS COMPARED TO BASE SCENARIO

Scenario	Deaths averted	Life years saved
1	140,210	2,492,138
2	89,039	2,490,078
3	145,395	4,083,723
4	97,663	2,733,112
5	302,464	7,779,832
6	321,608	8,294,868
7	314,185	8,092,718
8	322,015	8,297,541
9	315,080	8,120,320

TABLE A8. RETURN ON INVESTMENT ANALYSIS, HPV4 AND HPV9 (US$ 15.00)

Scenario	Economic benefit (US$ million)	Social benefit (US$ million)	Cost (US$ million)	Economic benefit BCR	Economic and social benefit BCR
1	3,257	2,449	341	9.5	16.7
2	3,250	2,445	199	16.3	28.6
3	5,291	3,946	594	8.9	15.5
4	3,564	2,673	285	12.5	21.9
5	10,891	9,981	1,258	8.7	16.6
6	11,646	10,493	1,511	7.7	14.6
7	11,336	10,285	1,395	8.1	15.5
8	11,629	10,487	1,835	6.3	12.1
9	11,390	10,318	1,486	7.7	14.6

TABLE A9. RETURN ON INVESTMENT ANALYSIS, HPV4 (US$ 15.00) AND HPV9 (US$ 122.80)

Scenario	Economic benefit (US$ million)	Social benefit (US$ million)	Cost (US$ million)	Economic benefit BCR	Economic and social benefit BCR
1	3,257	2,449	2,704	1.2	2.1
2	3,250	2,445	1,534	2.1	3.7
3	5,291	3,946	4,782	1.1	1.9
4	3,564	2,673	2,202	1.6	2.8
5	10,891	9,981	1,258	8.7	16.6
6	11,646	10,493	4,162	2.8	5.3
7	11,336	10,285	2,868	4.0	7.5
8	11,629	10,487	6,254	1.9	3.5
9	11,390	10,318	3,548	3.2	6.1

TABLE A10. TIMELINES FOR CERVICAL CANCER ELIMINATION - SELECTED MAIN SCENARIOS

Scenario	Scenario name	ASR# incidence rate per 100,000 women at year reached elimination	Year reached elimination	Cost-effectiveness
0	**Current screening and treatment (status quo)**	10.8	2100 – Cannot reach elimination	NA
1	**HPV4 vaccination for girls (90%) at current screening and treatment**	4.0	2083	Yes, up to 3 doses and vaccine price per dose up to $15
2	**HPV4 vaccination for girls (50%) at current screening and treatment**	6.2	2100 – Cannot reach elimination	Yes, up to 3 doses and vaccine price per dose up to $15
3	**HPV4 vaccination for girls (90%) and boys (60%) at current screening and treatment**	3.8	2083	No, only marginally CE at one-dose at vaccine price of $6.5 per dose and 0% discount for effects only.
4	**HPV4 vaccination for girls (50%) and boys (20%) at current screening and treatment**	5.7	2100 – Cannot reach elimination	Only marginally CE up to three-dose and at vaccine price of $6.5 per dose and 0% discount for effects only.
5	**10-yearly HPV screening and treatment scale up only**	4.4	2100 – Cannot reach elimination	Cost-effective
6	**HPV4 vaccination for girls (90%), at 10-yearly HPV screening and treatment scale up**	4.0	2055	Yes, up to 2 doses and vaccine price per dose up to $6.5
7	**HPV4 vaccination for girls (50%), at 10-yearly HPV screening and treatment scale up**	NA	NA	Yes, up to 2 doses and vaccine price per dose up to $6.5

8	**HPV4 vaccination for girls (90%) & boys (60%), at 10-yearly HPV screening and treatment scale up**	4.0	2055	Not cost-effective
9	**HPV4 vaccination for girls (50%) and boys (20%), at 10-yearly HPV screening and treatment scale up**	NA	NA	Only marginally CE up to two-dose at vaccine price of $6.5 per dose and 0% discount rate for effects only
10	**HPV4 vaccination for girls (90%), at 3-yearly VIA screening and treatment scale up**	4.0	2057	Not cost-effective
11	**HPV4 vaccination for girls (90%), at 5-yearly Cytology screening and treatment scale up**	3.8	2055	Not cost-effective
12	**3-yearly VIA screening and treatment scale up only**	4.8	2100 – Cannot reach elimination	Not cost-effective
13	**5-yearly Cytology screening and treatment scale up only**	4.6	2100 – Cannot reach elimination	Not cost-effective

** Age-standardised rate (ASR) in this table used the 2015 World Standard Population as recommended for the measurement of cervical cancer elimination*

TABLE A11. TIMELINES FOR CERVICAL CANCER ELIMINATION - SELECTED ALTERNATIVE SCENARIOS

Scenario	Scenario name	ASR# incidence rate per 100,000 women at year reached elimination	Year reached elimination	Cost-effectiveness
0	**Current screening and treatment (status quo)**	10.8	2100 - Cannot reach elimination	
1A	**HPV4, switching to HPV9 vaccination for girls (90%) at current screening and treatment**	4.0	2073	Yes, at one-dose HPV9 vaccination at the vaccine price per dose up to US$122.8 per dose
2A	**HPV4, switching HPV9 vaccination for girls (50%) at current screening and treatment**	5.0	2100 - Cannot reach elimination	Yes, at one-dose HPV9 vaccination at the vaccine price per dose up to US$122.8 per dose
3A	**HPV4, switching HPV9 vaccination for girls (90%) and boys (60%) at current screening and treatment**	3.9	2072	Not cost-effective
4A	**HPV4, switching HPV9 vaccination for girls (50%) and boys (20%) at current screening and treatment**	4.4	2100 – Cannot reach elimination	Only CE at one-dose HPV9 vaccination at the vaccine price per dose of US$15
5A	**5-yearly HPV screening and treatment scale up only**	4.0	2054	
6A	**HPV4, switching to HPV9 vaccination for girls (90%), at 5-yearly HPV screening and treatment scale up**	4.0	2047	Yes, at one-dose HPV9 vaccination at the vaccine price per dose of US$15
7A	**HPV4, switching to HPV9 vaccination for girls (50%), at 5-yearly HPV screening and treatment scale up**	3.8	2050	Yes, at one-dose HPV9 vaccination at the vaccine price per dose of US$15
8A	**HPV4, switching to HPV9 vaccination for girls (90%) & boys (60%), at 5-yearly HPV screening and treatment scale up**	4.0	2047	Not cost-effective
9A	**HPV4, switching to HPV9 vaccination for girls (50%) and boys (20%), at 5-yearly HPV screening and treatment scale up**	3.8	2050	Marginally cost-effective at one-dose HPV9 vaccination at the vaccine price per dose of US$15.

** Age-standardised rate (ASR) in this table used the 2015 World Standard Population as recommended for the measurement of cervical cancer elimination*

CERVICAL CANCER ELIMINATION CHECKLIST, UNFPA AND CANCER COUNCIL NSW (2020)

1	**Develop a comprehensive costed National Cervical Cancer Elimination Strategy and seek endorsement among government, country leaders, policymakers, and communities**
2	Communication and public outreach
2.1	Develop a comprehensive communications strategy to accompany each component of the elimination strategy engaging health workers, community leaders, parents, teachers, and young people to maintain confidence in the programme and address stigma and misconceptions.
3	**National HPV vaccination programme**
3.1	Introduce the HPV vaccine for girls aged 9-14 years into national immunization programme.
3.2	Secure sufficient and affordable HPV vaccine and ensure an adequate cold-chain system for vaccine storage and delivery is in place.
3.3	Achieve and maintain high coverage of HPV vaccination by identifying appropriate multi-sectoral vaccination delivery platforms.
3.4	Establish or improve monitoring systems or vaccination registers to enable measurement of coverage and vaccine schedule adherence.
4	**National cervical cancer screening and precancerous treatment programme**
4.1	Develop a national cervical cancer screening programme with clinical protocols for primary HPV testing and precancer treatment, involving relevant stakeholders when appropriate.
4.2	Integrate screening and precancer treatment into existing primary care and Universal Health Care (UHC) packages, including sexual and reproductive health services, HIV clinics, antenatal care.
4.3	Establish continuing professional development in-service programmes to build capacity of providers in cervical cancer screening and precancer treatment.
4.4	Understand social, financial, cultural, societal, and structural barriers to accessing services and create an enabling environment for cervical cancer screening and precancer treatment.
4.5	Strengthen laboratory capacity and quality assurance (QA) programmes and develop data systems that link laboratory information, screening registry data and other data systems (such as medical records and cancer registries).
5	**Invasive cancer treatment and palliative care**
5.1	Develop and implement cervical cancer management guidelines and clinical protocols.
5.2	Establish effective referral pathways for women at all stages of care.
5.3	Strengthen pathology services, particularly at regional pathology centres and, if appropriate, make use of telepathology platforms to improve the capacity to interpret samples.
5.4	Expand surgical capacity through training programmes and expand access to radiotherapy and chemotherapy services and strengthen oncology services.
5.5	Strengthen and integrate palliative care services by developing treatment plans that incorporate not only end-of-life care and pain relief, but also psychological and family support.

5.6	Optimize health workforce competencies throughout the continuum of care by establishing a long-term continuous training and education strategy for a multidisciplinary workforce.
5.7	Reduce cancer stigma by providing comprehensive support to enhance quality of life and address mental and sexual and reproductive health challenges faced by cancer survivors.
6	**Monitoring and evaluation**
6.1	Strengthen governance and accountability of cervical cancer related programmes (HPV vaccination, cervical cancer screening, cancer treatment) and conduct regular reviews to ensure that national strategies, plans, and resource allocations reflect actual country needs.
6.2	Set country-specific targets, milestones, and indicators for monitoring and evaluating implementation of the National Cervical Cancer Elimination Strategy.
6.3	Improve current population-based cancer registries and develop new population-based cancer registries as needed to track the progress of the elimination targets.
6.4	Track patients throughout the continuum of services (screening, diagnosis and treatment).

CONTRIBUTION

For this study, the Daffodil Centre has contributed the cost-effectiveness analysis for a range of different scenarios of vaccine coverage, screening and cervical cancer treatment. The Daffodil Centre is a leading research centre on cancer control and policy and has expertise in epidemiology and population health research, predictive statistical forecasting and microsimulation modelling, large-scale linked data analysis, systematic review and meta-analysis, biostatistical methods, health economic evaluation, health services research and behavioural and implementation science. The Daffodil Centre has contributed its significant expertise in epidemiology and population health research for modelling the effectiveness and cost-effectiveness of HPV vaccination and cervical cancer screening strategies.

The Victoria Institute of Strategic Economic Studies at Victoria University has undertaken the return on investment analyses.

This report has been prepared by Dr Kim Sweeny, Victoria University, Melbourne and Dr Diep Thi Ngoc Nguyen, Dr Kate Simms, Dr Adam Keane, Professor Deborah Bateson, and Professor Karen Canfell, Daffodil Centre, Sydney in Australia.

DISCLAIMER:

The views and opinions expressed in this report are those of the researchers and do not necessarily reflect the views and policies of the Ministry of Health and UNFPA.

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