WORKING PAPER

Costing of Cervix Uteri Carcinoma in Cambodia: Budget-impact and cost-effectiveness analysis

Summary

Cervix uteri carcinoma (CUC) is a malignant neoplasm that is almost exclusively caused by a persistent infection of the human papilloma virus (HPV). This disease is the second most common cancer in women worldwide, with around 500,000 new cases and 270,000 death cases annually. In Cambodia, it is estimated that around 800 death cases per year are caused by CUC. The number of deaths due to cervical cancer has grown faster than the population. Each year, around 5,000 years of life are lost due to CUC.

Combining treatment, screening and vaccination scenarios has a greater impact on the number of death cases than individual interventions, but the budget required to implement combined interventions is also much higher. Based on the results of the model presented in this paper, the 'see-and-treat' approach combined with a vaccination programme would be most cost-effective.

The results of the simulations in this paper indicate that there are cost-effective interventions to prevent and treat CUC that could be financed with limited budgets. Based on these simulations, the Royal Government of Cambodia should include a 'see-and-treat' approach to CUC care in the basic package of health care services, and begin a HPV vaccination programme as soon as possible.

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Abstract

Background: Cervix uteri carcinoma (CUC) is a malignant neoplasm that is almost exclusively caused by a persistent infection of the human papilloma virus (HPV). This disease is the second most common cancer in women worldwide, with around 500,000 new cases and 270,000 death cases annually. In Cambodia, it is estimated that around 800 death cases per year are caused by CUC. About 1% of the total population (or 3% of women over 15 years old) are expected to have pre-malignant lesions, and approximately 0.01% of the population (or 0.03% of women over 15 years old) will have invasive cervical cancer. This is a humanitarian, social, medical and economic challenge. In particular, prevention and treatment of CUC requires significant health care resources.

Objective: This paper intends to estimate the number of cases and resources required for the prevention and treatment of CUC in Cambodia. Furthermore, the cost effectiveness of possible scenarios (treatment, screening and vaccination) will be assessed.

Methodology: The projections are based on a multi-compartment system dynamics model specifically developed to estimate CUC in Cambodia. This model simulates the demographic system and CUC infections from sexual intercourse for 100 years. Data was taken from existing literature and interviews with public health experts in Cambodia.

Burden of disease: CUC is an increasing problem in Cambodia, and the number of deaths due to cervical cancer has grown faster than the population. Each year, around 5,000 years of life are lost in Cambodia due to CUC.

Treatment: Treatment has a strong impact on the number of death cases caused by CUC. If treatment is able to reduce the mortality rate sufficiently (under 10% mortality), then it is considered cost-effective. If treatment merely increases the survival time, then it is not cost-effective. However, the fact that an intervention is cost-effective does not mean it is feasible, as the health care budget may be seriously limited. In 2025, Cambodia would have to spend between USD 1 million and USD 1.5 million for the treatment of CUC, if patients are able to be completely healed. If treatment only doubles the survival time of CUC patients, the cost is much higher (USD 3.3 million). Until now, no budget allocations have been made for the treatment of CUC.

Screening: Screening for cervical cancer by visual inspection with acetic acid (VIA) once every three years for women 30-49 years old is a cost-effective way to identify CUC. Other scenarios (e.g., screening once a lifetime) might be more cost-effective, but will identify less patients. For almost all scenarios, the cost per VIA screening must be less than USD 5.00 in order to be cost-effective.

Vaccination: This costing model assumes that the CUC vaccine has an efficacy of 90% against the virus types responsible for 70% of CUC cases worldwide, and allows for different vaccination scenarios. However, for almost all scenarios vaccination is only cost-effective if the timeline is long enough; i.e., if policy-makers expect significant results within 20 years, vaccination should not be a priority. If we assume a 100-year timeline, the costs for full vaccination must be lower than USD 30 per person to be cost-effective.

Comprehensive Intervention: This costing model incorporates combining treatment, screening and vaccination scenarios in one simulation. Combined interventions have a greater impact on the number of death cases than individual interventions, but the budget required to implement combined interventions is also much higher. Based on the results of the model, the 'see-and-treat' approach combined with a vaccination programme would be the most cost-effective scenario.

Discussion: The results of the simulation indicate that there are cost-effective interventions to prevent and treat CUC that could be financed with limited budgets. Compared with costings for other countries found in international literature, the incremental cost-effectiveness ratios (ICERs) for Cambodia are quite low, as prevention and treatment are comparably cheap. Based on these simulations, the Royal Government of Cambodia should include a 'see-and-treat' approach to CUC care in the basic package of health care services, and begin a HPV vaccination programme as soon as possible.

1. Introduction

The population of Cambodia is facing a serious threat to its economic development and welfare of its people – noncommunicable diseases (NCDs). While the health care system has been primarily engaged in fighting infectious diseases such as malaria, dengue and diarrhoeal diseases, NCDs have recently become the cause of nearly half (46%) of all death cases [1], and over one-third (34%) of lost quality of life in Cambodia [2].[1] In addition, the prevalence of NCDs is expected to increase steadily with the overall ageing of the population. The Royal Government of Cambodia has responded to this challenge by endorsing the National Strategic Plan for the Prevention and Control of Noncommunicable Diseases [3] as the foundation for its efforts to control these diseases in the country.

As Table 1 and Table 2 show, cancer is a particularly concerning public health issue for the Cambodian population. According to WHO statistics, cancer causes 11,000 death cases and a loss of 169,000 DALYs in Cambodia annually. The four most concerning forms of cancer in Cambodia are cervix uteri carcinoma (CUC), [2] breast cancer, lung and liver cancer. Globocan estimates that over 1,500 Cambodians develop CUC and nearly 800 die every year from this disease (age-standardised incidences of 23.8 and 13.4 per 100,000 people, respectively) [4]. This makes CUC the most prominent cancer in Cambodia. Consequently, the national NCD strategy places considerable emphasis on the prevention and treatment of CUC [3].

The Royal Government of Cambodia needs a budget-impact analysis of selected NCDs in order to know how much the appropriate care of patients with these diseases will cost. Currently, this budgeting can only be based on estimates, as the actual costs of prevention and treatment of NCDs in Cambodia are not well known. This budget-impact analysis must include estimates of the number of CUC cases annually and the consequences for the national budget. At the same time, we need to conduct a scientific analysis of the cost-effectiveness of the prevention efforts stated in the national NCD strategy, in order to prioritise the limited resources on the interventions that can save the most lives.

Condition	Death Cases	Lost DALYs
Communicable, maternal, perinatal and nutritional conditions	83	2,903
Noncommunicable diseases	58	1,724
Malignant neoplasms	11	169
Diabetes mellitus	3	39
Neuropsychiatric conditions	3	451
Cardiovascular disease	24	361
Respiratory diseases	6	132
Digestive diseases	5	122
Other	9	376
Total	**150**	**5,003**

Table 1: Burden of disease in Cambodia, in thousands of cases. (Source: [2])

	Male	Female	Both sexes
Population	7,117,000	7,444,000	14,561,000
Number of new cancer cases	5,900	7,000	12,900
Age-standardised rate (per 100,000 people)	152.9	123.0	133.1
Risk of getting cancer before age 75	16.5%	13.1%	14.3%
Number of cancer death cases	4,600	4,300	8,900
Age-standardised rate (per 100,000 people)	127.5	80.1	98.2
Risk of dying from cancer before age 75	13.6%	8.9%	10.8%

Table 2: Cancer rates in Cambodia (2008). (Source: [4])

1 Measured in disability-adjusted life years (DALYs).

2 It is obvious that there is not a clear distinction between communicable and noncommunicable diseases. CUC, for instance, is caused by an infection which causes cancer after many years. However, WHO classifies CUC as a noncommunicable disease.

This paper intends to provide evidence on the budgetary impact and cost-effectiveness of cervical cancer prevention and treatment efforts in Cambodia. Consequently, the next section provides some background on existing CUC interventions. The next sections present some forecasts of the development of the disease. This includes the development of a forecasting model (section 3) and basic results (section 4). We will also present some estimates on the cost-effectiveness of selected interventions. The paper ends with a discussion of the lessons learned on the Cambodian health sector.

2. Cervix Uteri Carcinoma

2.1. Relevance

Cervix uteri carcinoma (CUC) is a malignant neoplasm (cancer) that is primarily caused by a persistent infection of the human papilloma virus (HPV). This disease is the second most common cancer in women worldwide, with around 500,000 new cases and 270,000 attributed death cases annually [5]. The burden of this disease is highest in low-income countries, where eight out of every ten (80%) cervical cancer cases occur [6]. The mortality rate from CUC in these countries is even higher, as cancer screening and treatment are not generally available.

The prevalence and incidence of HPV infections in the general population can only be estimated for Cambodia. Estimates are based on the national WHO STEPwise approach to Surveillance (STEPS) Noncommunicable Disease Risk Factor Survey conducted in 2010 [7], and a 2012 study by Couture focusing on sex workers [8]. In the Couture study, nearly one-quarter (24%) of female sex workers were found to be infected with the high-risk type of HPV. A study in neighbouring Laos found a high-risk HPV infection rate of 11% among examined women in the general population, with 7%-8% of women having pre-cancerous lesions [9]. Based on these studies, we estimate that about 1% of the adult female population (3% of women over 15 years old) have pre-malignant lesions, and around 0.01% of the population (0.03% of women over 15 years old) have invasive cervical cancer. We also attribute around 800 death cases to CUC annually.

Information on the costs and cost-effectiveness of CUC-related interventions in resource-poor countries is limited. In 2013, Fesenfeld, Hutubessy and Jit compiled a literature review on the cost-effectiveness of HPV vaccinations in low- and middle-income countries. They found 25 related articles, but no single-country studies focusing on low-income countries [9]. In another study, Goldie et al. calculated the life-years saved (LYS), lifetime costs and incremental cost-effectiveness ratios of a 'hypothetical cohort of previously unscreened 30-year-old black South African women' [10]. Other authors have assessed the cost-effectiveness of HPV screening in India and Thailand [11-14]. However, it is very difficult to compare these results between regions, and even between neighbouring countries. National health systems, unit costs (e.g., costs for individual treatment, screening and HPV vaccinations), intervention standards and HPV types and prevalence rates are all different between countries. Thus, it is almost impossible to transfer a model developed for a particular area to another region or country, or to take the results calculated for one region as the standard for another. The greater the differences between health care resources, the less likely the models and results can be applied. Combining disparate South-East Asian countries such as Thailand, Malaysia, Singapore, Laos and Cambodia into one dataset [15] can be misleading, and can only provide an initial insight into Cambodia. There is a strong need for individually made models for specific countries.

In Cambodia, the treatment possibilities for CUC are limited. Cryotherapy is the recommended therapy for pre-invasive forms of CUC (i.e., lesions) in Cambodia, and these lesions could be easily treated at the health centre level if staff were appropriately trained in screening and treatment procedures, and facilities were properly equipped. In reality, health facility staff are not trained in this area, and no screenings are performed. In addition, cryotherapy equipment only exists in a very limited number of private, for-profit facilities. For invasive cancers, there are only three institutions that can provide treatment services, and they are located in the capital city of Phnom Penh. Both surgical oncology and radiotherapy services are only available in the Khmer-Soviet Friendship Hospital. Calmette Hospital currently performs surgical oncology, with radiotherapy services expected to start as soon as the proper equipment is obtained. Some surgical services for CUC patients are also available at the National Maternal Newborn and Child Health Centre. Currently, these services are inaccessible for the majority of Cambodian women suffering from CUC.

2.2. Intervention

Primary and secondary prevention of CUC is possible. Secondary prevention refers to the early detection of CUC and pre-invasive lesions. Cervical screening once every three

years is recommended for all women between 30 and 49 years old [3], which is the standard practice recommended by WHO [12, 16]. Screening can be performed using different methods, such as pap smears and HPV DNA tests. In developing countries, screening by trained midwives or nurses using a visual inspection with acetic acid (VIA) has been proposed [17, 18]. This approach includes the recommendation that any lesions be removed right after screening, as this 'see-and-treat' approach [19, 20] reduces the need for follow-up appointments and the risk of poor compliance with the treatment.

Cryotherapy [3] is the recommended treatment for removing cervical lesions in Cambodia [16, 18]. This method requires a reliable supply of materials, but has low initial costs. The results are quite impressive, and the risk of developing CUC after successful cryotherapy is very low [16, 18]. The Ministry of Health (MOH) of the Royal Government of Cambodia, as well as several partners, plan to launch pilot programmes to screen for cervical cancer. For instance, MOH has already trained midwives in health centres in Prey Chhor Operational Health District, Kampong Cham province, in screening for pre-invasive lesions, but screening has not yet started due to the unavailability of funds.

Primary prevention for CUC is based on a vaccination against high-risk HPV types [21]; particularly HPV types 16 and 18, which are responsible for approximately 70% of all CUC [22, 23]. The HPV vaccines Gardasil and Cervarix were introduced in 2006 and 2009, respectively. Both are effective against HPV types 16 and 18; Gardasil also protects against HPV types 6 and 11 (which are usually not oncogenic) [24]. Three doses of the chosen vaccine should be given before a woman has any sexual intercourse, so that the vaccines can protect against the possibility of sexually transmitted HPV infections [14]. Both vaccines are expected to provide lifelong protection, but because these vaccines are so new this is not yet well understood. Several studies in other countries have proven the cost-effectiveness of HPV vaccination [25], if compliance is sufficiently high.

Recently, the Royal Government of Cambodia decided to include four more vaccines in the package of basic health care services: rubella; Japanese encephalitis; pneumococcus; and, rotavirus These vaccines have been given national priority before the HPV vaccine. Thus, a pilot testing of the HPV vaccine might not happen until 2017, or later. Nevertheless, the Royal Government of Cambodia has already approached Gavi, the Vaccine Alliance, to support a pilot study on HPV vaccination in Cambodia.

The pilot screening programmes for cervical cancer will deliver important data on the prevalence of early-stage and invasive cervical cancer in Cambodia. However, the current set-up of the pilots does not allow a budget-impact analysis or an assessment of the cost-effectiveness of the interventions. Thus, we developed a model to forecast the expected budgetary impact of CUC, and assess the efficiency of preventive measures.

3 Cold coagulation [21, 22] has proven to be a reliable alternative to cryotherapy, with reasonable costs. However, a discussion on the pros and cons of cryotherapy versus cold coagulation is beyond the scope of this paper.

3. Model

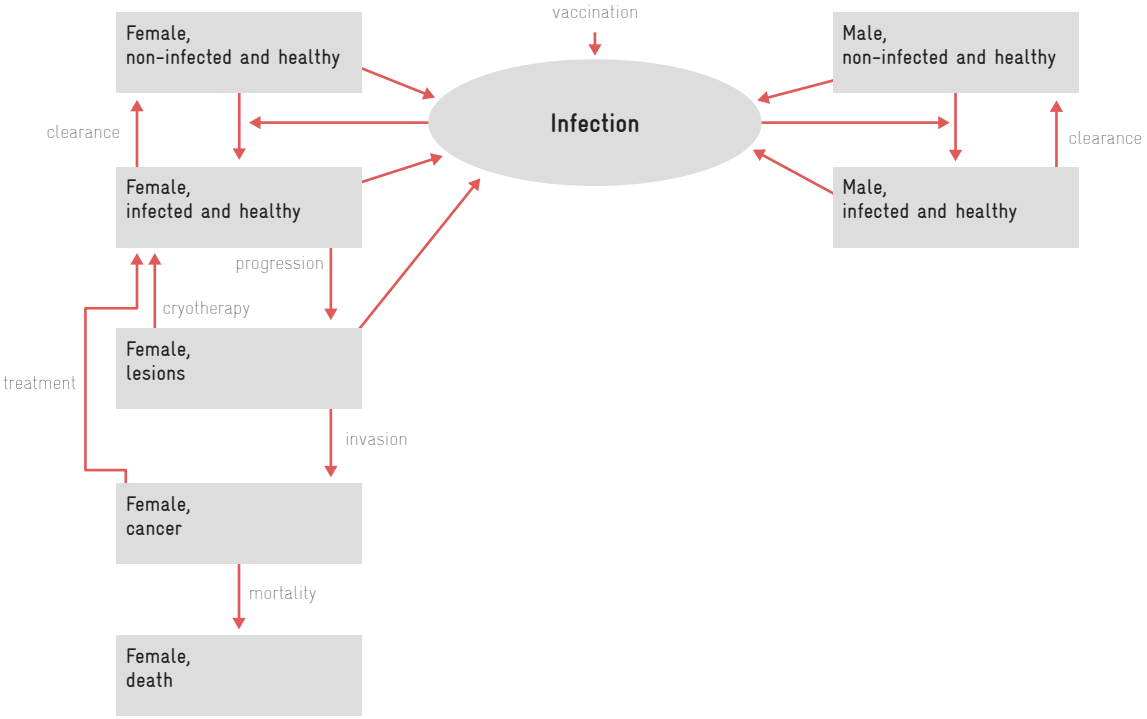
Based on the categorisations of Kim et al., the forecasting model presented here is dynamic (i.e., 'the population within the model can interact'), open ('populations are allowed to enter the model'), deterministic ('transition rates are fixed') and aggregate ('using values reflecting population averages') [26]. It simulates the natural history of CUC, from initial infection to death. The model assumes that HPV is exclusively transferred by sexual intercourse. Males are considered to be infected along with their female sex partners are, but the potential effect of cancer in males due to HPV infection (especially oropharyngeal cancer) is beyond the scope of this analysis. [27].

Figure 1 shows the basic structure of the system dynamics model employed in this analysis. The population is stratified according to age (0-99 years old), sex (male, female) and disease stage (healthy; HPV infected and healthy; HPV infected with a pre-malignant lesion; and, invasive cervical cancer).

Based on discrete time steps of one day, the model calculates difference equations and adjusts the compartments accordingly, which is standard for system dynamics models [28]. As this model attempts to predict CUC prevalence in the long-term, it incorporates a complete demographic model of fertility and mortality for the Cambodian population. Furthermore, the model assumes two modes of HPV transmission, using descriptions for other sexually transmitted diseases: within monogamous partnerships; and through single sexual contacts [29].

The mathematical model is presented in the appendix. The necessary information was taken from the literature review or interviews with Cambodian health specialists (Table 3). The cost estimates reflect the latest costing study of Cambodian health services, and the expected rebates of the National Social Security Fund (NSSF) [30]. The cost of vaccination includes three doses (at USD 5.00 each), plus the respective costs of three outpatient visits in a health centre (at USD 2.50 each). Some uncertainty remains, which will be addressed through sensitivity analysis.

Figure 1: Diagram of the basic system dynamics model for cervical cancer in Cambodia. (Source: [26]).



System	Source	Parameter	Value
Demography	[16, 31, 32]	Population, fertility, mortality, prevalence	Diverse
Transition	[10, 16, 21, 33]	'Healthy, infected' to 'lesion'	16 years
		'Lesion' to 'cancer'	8 years
		'Cancer' to 'death'	2 years
Medical	[33-36]	Infectivity	50%
Intervention parameters	[16, 37-39]	Effectiveness of vaccine	63%
		Compliance with vaccine	75%
		Age at VIA screening	30-49
		Compliance with VIA	50%
		Compliance with cryotherapy	75%
		Screening interval	3 years
		Treatment effectiveness	25%
Cost parameters	Expert interviews in Cambodia, [14, 30, 37, 40, 41]	VIA	USD 2.50
		Cryotherapy	USD 7.50
		Treatment at national hospital	USD 800
		Vaccination	USD 22.50
Sexual activity	Expert interviews in Cambodia, [42]	Median age at first intercourse (women/men)	20.8/22.1 years
		Median age at marriage (women/men)	20.3/22.6 years

Table 3: Basic data for the system dynamics model of HPV infection in Cambodia.

The simulation model was implemented in Delphi XE. Based on this model, an initial prediction of the number of CUC cases can be simulated. Although a forecast for 100 years is highly uncertain, a thorough analysis of interventions has to consider a very long timeline because the impact of these interventions is lifelong. Thus, the following simulations were made with a 100-year timeline. However, as this paper is targeted to support the Royal Government of Cambodia's current efforts to control NCDs, the cost-effectiveness of interventions is focused on the period from 2010 to 2030. All gains and costs are discounted at a rate of 5%, per NSSF standards.

4. Burden of disease

The analysis follows international standards for health economic evaluations [43-45]. The basic simulation assumes that no CUC interventions (including treatment, screening, and vaccinations) are currently implemented in Cambodia. This is generally the reality for the vast majority of the Cambodian population.

The following figures show the results of the basic simulation. Figure 2 shows the incidence of pre-invasive and invasive cervical cancer cases in Cambodia, as well as the number of death cases. It is obvious that CUC is an increasing problem. From 2010 to 2110, the incidence of pre-invasive and invasive CUC will grow at an annual rate of around 1.65% and 1.73%, respectively. Death cases due to cervical cancer in this timeframe will also grow at a rate of 1.71% per year. The growth rate of CUC is slightly above the annual population growth rate of 1.66%. Thus, about 1% of the adult female

Figure 2: CUC incidence and attributed death cases in Cambodia, 2010-2110 (basic simulation).

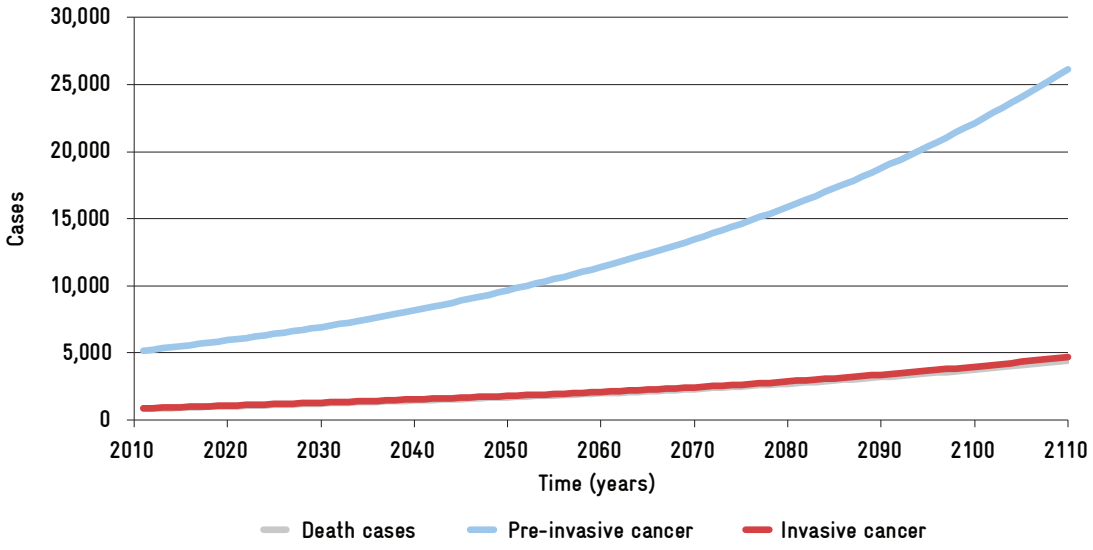


Figure 3: Population growth in Cambodia (basic simulation), 2010-2110.

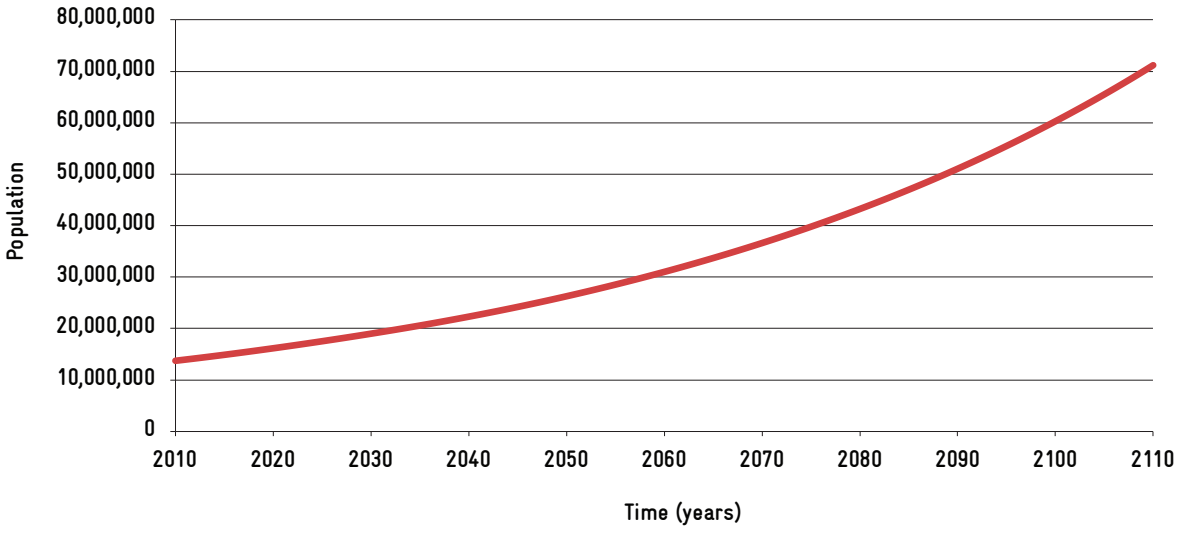
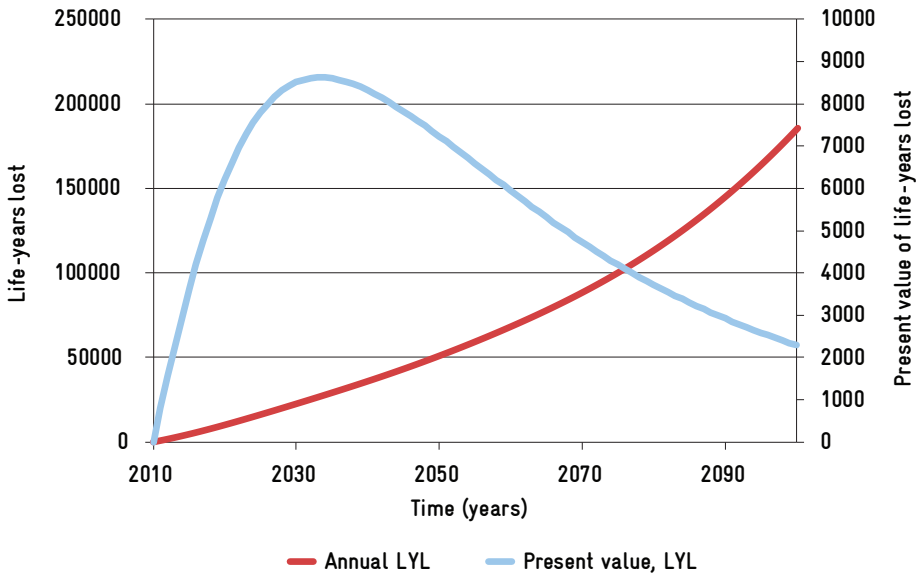


Figure 4: Life-years lost annually in Cambodia due to CUC, 2010-2110.



population (3% of women over 15 years old) have pre-invasive lesions and 0.01% of the population (0.03% of women over 15 years old) have invasive cervical cancer.

However, it must be noted that this growth rate is lower than for some other chronic-degenerative diseases, such as diabetes. This is because the majority of HPV infections occur in people under the age of 35 (while lesions and CUC manifest much later). Thus, Cambodia's ageing population will be more affected by diseases like stroke, diabetes and heart attack, which are more common in older people. Nevertheless, this model clearly indicates that the absolute burden of CUC is steadily growing, and will have a tremendous impact on human suffering, the national health system and economic productivity.

Figure 4 shows the life-years lost (LYL) due to cervical cancer within the 100-year timeframe of the forecasting model. The upward curve shows the absolute LYL, and the other curve shows the present LYL value, with a discount rate of 5%. It is obvious that the burden of CUC is steadily increasing, and that the worst consequences of CUC are still to come. The present value of LYL over 100 years is 516 (r=5%); i.e., half a million life-years will be lost due to CUC within a century. The large amount of life-years lost reflects the fact that CUC affects patients relatively early in life, in comparison to some other frequent cancers. In Cambodia, most cervical cancers are diagnosed in patients when they are around 50 years old.

In summary, CUC is a serious and increasing public health problem in Cambodia, with considerable impact on human life and suffering, economic development and the social stability of the nation. The Royal Government of Cambodia and its partners should focus on the planning and implementation of cost-effective interventions to reduce the long-term impact of CUC.

5. Cost-Effectiveness Analysis

This cost-effectiveness model provides for three different interventions: treatment, screening and vaccination. We consider an intervention to be cost-effective if the costs per life-year saved (LYS) are lower than the average annual gross national product per person; i.e., if the incremental cost-effectiveness ratio (ICER) is less than 1,000 (USD/LYS) [46].

5.1. Treatment

This model is based on the assumption that treatment of invasive cancers in Cambodia can only be done in national hospitals [16].[4] In the standard simulation, we assumed that proper treatment would be 25% effective at healing CUC; i.e., one-quarter of patients with CUC would return to the infected but otherwise healthy population after treatment. This assumption is based on the estimates of public health experts in Cambodia, as evidence-based research is hardly available for this country. The chances for successful treatment depend greatly on the severity of CUC. Whereas early-stage cervical cancer (FIGO stage 1) has a five-year survival rate of around 90% (under optimal circumstances), the survival rate for late-stage CUC (FIGO stage 4) is only 5%-10% [16]. [5]

We have made simulations for treatment effectiveness rates of 10% (eff=10%), 25% (eff=25%) and 50% (eff=50%), as well as a basic scenario assuming no treatment (described in section 4). In addition, we analysed one scenario where treatment only impacts survival time, but does not heal the cancer. In this case, we assumed that the survival time has been increased from two to four years (l=4 yrs.).

Figure 5 shows the impact of treatment on the number of death cases for the four scenarios. It is obvious that the more effective a treatment is, the more it will reduce CUC death cases. Without discounting, a treatment that is 10% effective would save around 1.2 million life-years, one that is 25% effective would save around 2.5 million life-years, and one that is 50% effective would save around 3.9 million life-years in the next 100 years. With a discounting rate of 5%, the respective figures are approximately 74,000, 152,000, and 235,000 LYS.

4 The simulation programme allows for treatment at health centres and lower level hospitals, but currently this seems be to unrealistic in Cambodia.

5 Using the International Federation of Gynecology and Obstetrics (FIGO) system for staging cervical cancer.

Figure 5: Impact of CUC treatment scenarios on attributed death cases, 2010-2110.

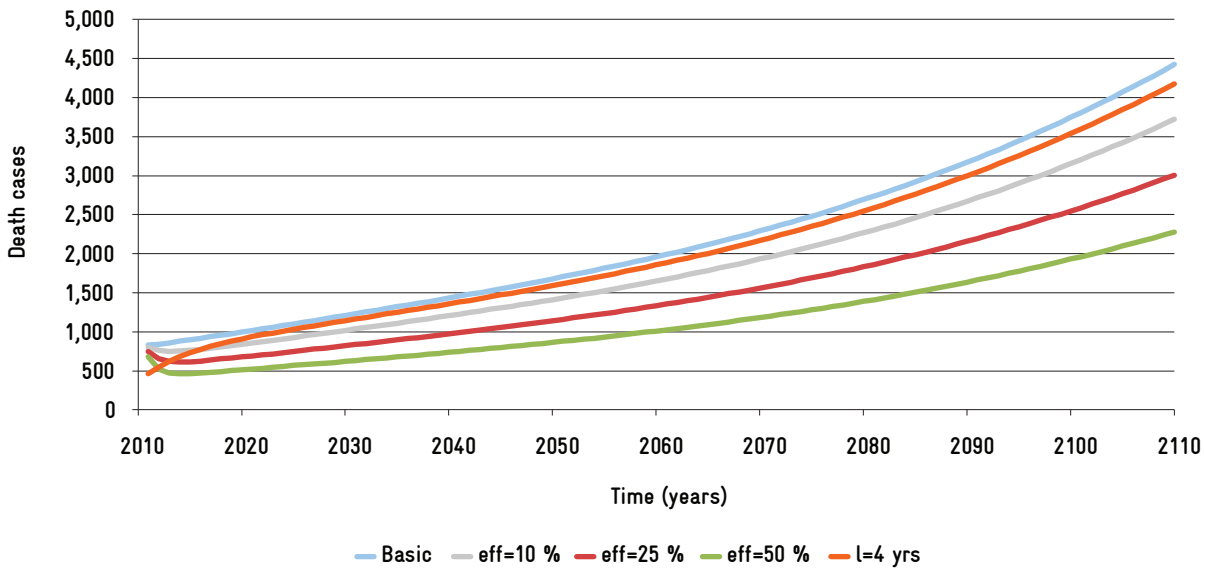


Figure 6: Impact of CUC treatment scenarios on attributed death cases, 2011-2020.

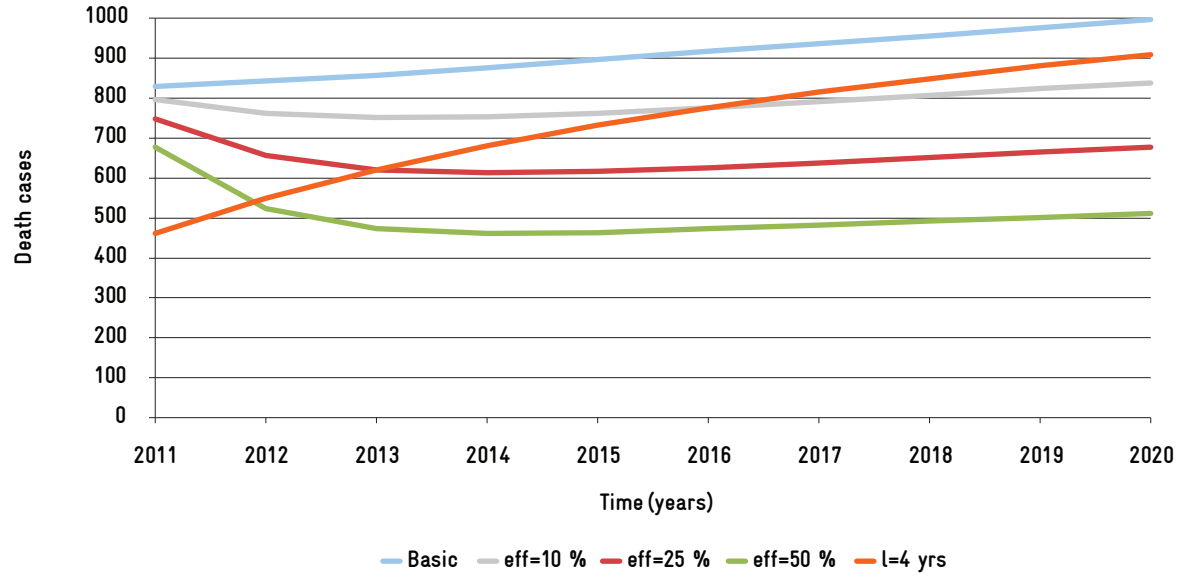
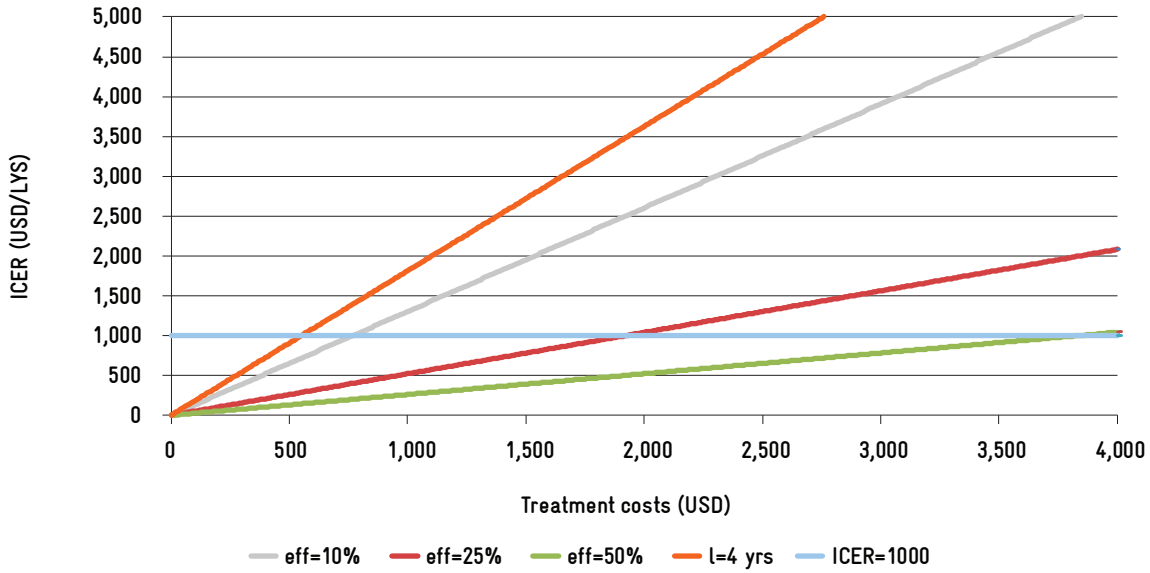


Figure 7: Incremental cost-effectiveness ratios (ICER) for CUC treatment scenarios and annual costs per patient.

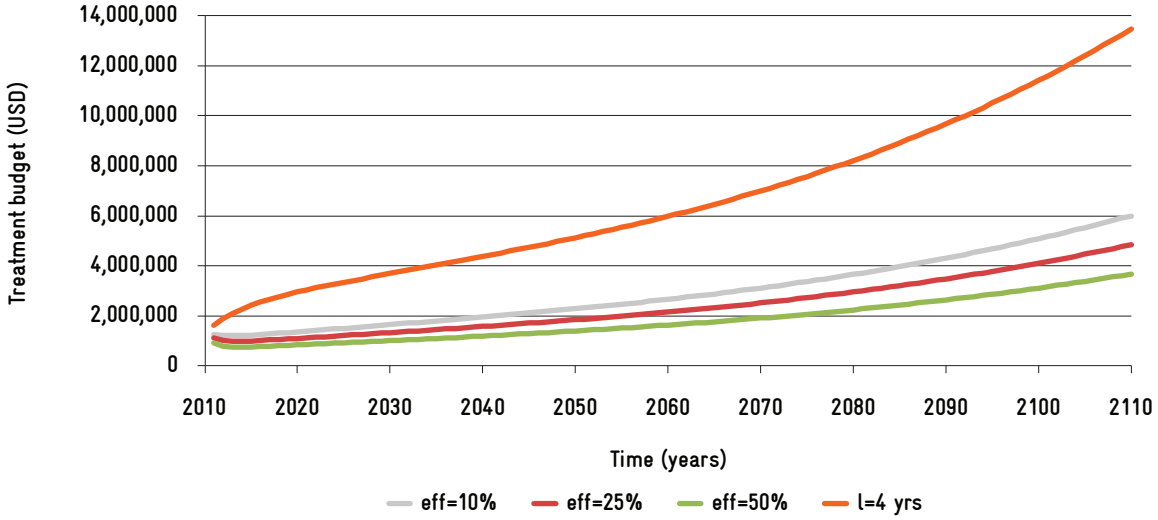


However, if treatment only has an impact on a patient's survival time, the number of death cases is almost as high as for the basic simulation without any treatment. Without discounting, non-curative treatment will save around 1.1 million life-years (67,000 LYS, at r=5%).

An extract of Figure 5, Figure 6 shows the progression of CUC-attributed death cases in the first 10 years after introducing treatment scenarios. Even in this initial period, treatment has a strong impact on death cases. In the first four years of all treatment programmes simulated, the number of death cases declines if treatment heals the cervical cancer. Afterwards, death cases start to rise again as the population changes. If treatment only results in increased patient survival time, the number of death cases will start low, but increase after the first year; i.e., CUC death cases are only deferred, not reduced in this scenario (l=4 yrs.).

The average treatment costs for CUC are assumed to be USD 800 per patient per year. If treatments are 25% or 50% effective, then these interventions are cost-effective,

Figure 8: Impact of CUC treatment scenarios on annual health care budget, 2010-2110 (in USD).



with an ICER (costs per life-year saved) of around USD 431 and USD 210, respectively. If the effectiveness is only 10%, then the treatment is not cost-effective (with an ICER of USD 1,096). If survival time is doubled (l=4 yrs.) the ICER is around USD 1,541, which is also not cost-effective for Cambodia.

More effective treatment at a certain cost also increases cost-effectiveness. As Figure 7 shows, Cambodia can spend up to USD 3,830 per patient annually for treatment that is 50% effective without passing the ICER limit of USD 1,000. For less effective treatments, the cost thresholds are USD 1,920 (eff=25%) and USD 770 (eff=10%). For non-curative treatment (l=4 yrs.), the threshold is USD 550.

However, just because an intervention is cost-effective does not mean that it is feasible, given the limited national health care budget. Figure 8 shows the impact of the treatment scenarios on the national budget. As expected, the more effective a treatment is, the less it will cost to implement nationally. Except for the first few years after the treatments are introduced nationwide, the budget required for all treatments will increase steadily. For instance, in 2025 Cambodia would have to spend between USD 900,000 and USD 1.5 million for the curative treatment of cervical cancer. If treatment only leads to a doubling of survival times, the costs are much higher (USD 3.3 million in 2025). Until now, no budget allocations have been made for CUC.

5.2. Screening

The forecasting model also allows us to simulate different screening scenarios. The standard screening model assumes that all women between 30 and 49 years old are invited to visit a health centre, where a cervical screening is done by visual inspection with acetic acid (VIA) [12, 17, 38]. This model also assumes that VIA are performed every three years, starting with the first year of the simulation, and that 50% of women in the target age range comply and are screened. If a lesion is found, cryotherapy [16] is immediately performed at the health centre level (the 'see-and-treat' approach) [19, 20]. We assume that when a pre-invasive lesion is found, 75% of women will accept treatment. We also assume that a patient with lesions who underwent cryotherapy can be reclassified as part of the healthy infected population. Table 4 shows the parameters of different screening scenarios used in the model. In order to isolate the impact of screening, all screening simulations assume that no treatment is included in the programme. A comprehensive package of services will be discussed in section 5.4.

Scenario	Age (years)	Frequency	VIA Compliance	Cryotherapy Compliance
Stand-ard	30-49	Every 3 years	50%	75%
Long	30-60	Every 3 years	50%	75%
Once	30-49	Once in lifetime	50%	75%
VIA20	30-49	Every 3 years	20%	75%
VIA80	30-49	Every 3 years	80%	75%

Table 4: Parameters for CUC screening scenarios.

As Figure 9 shows the effects of different screening programmes on death cases attributable to CUC, including a basic scenario with no screening intervention (which is currently the reality in Cambodia). Screening for CUC has a strong impact on the number of death cases. The greatest reduction in mortality would be achieved by offering screening to all females 30-60 years old, but this scenario is also quite expensive, with an ICER of around USD 617. If 80% of women 30-49 years old received VIA once every three years, the impact on death cases is also quite high. However, this scenario has an ICER of USD 768, making it only marginally cost-effective. The best ICER is achieved if VIA screening is offered only once a lifetime (USD 523), but the impact on the number of death cases is lower than

Figure 9: Impact of CUC screening scenarios on attributed death cases annually, 2010-2110.

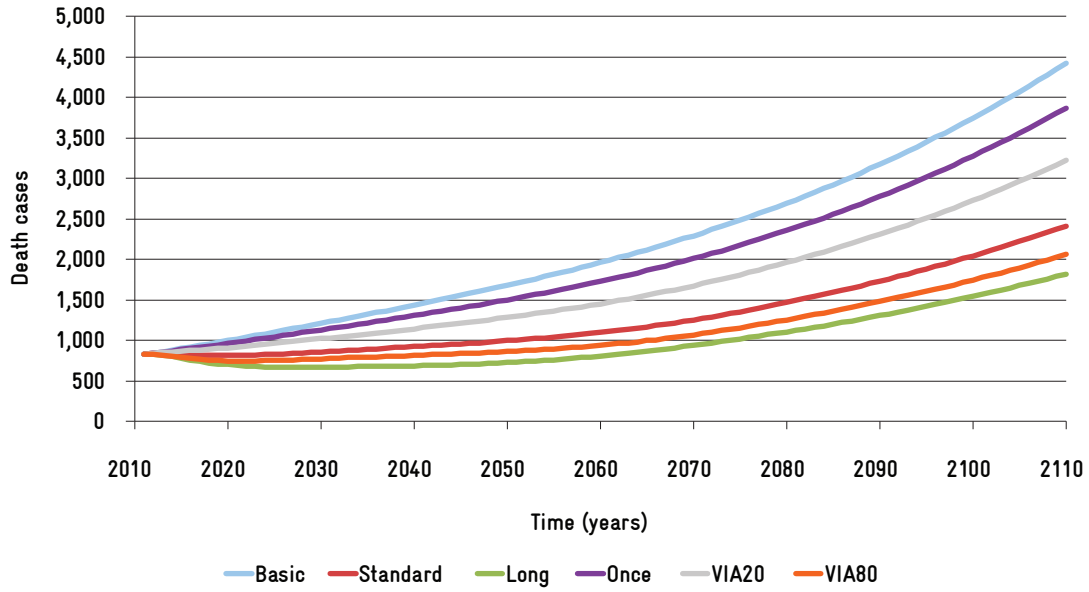


Figure 10: Annual budgets for CUC screening scenarios, 2010-2110 (in USD).

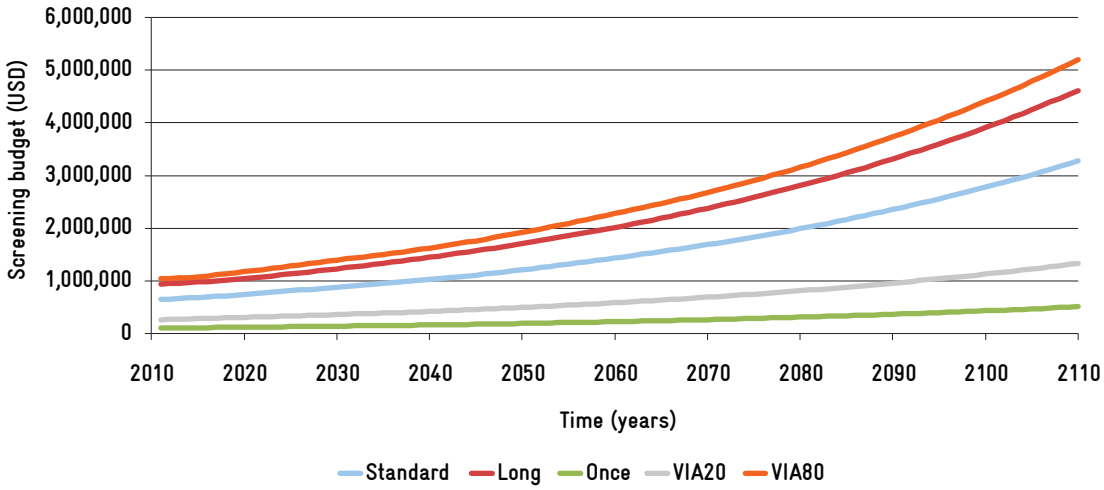
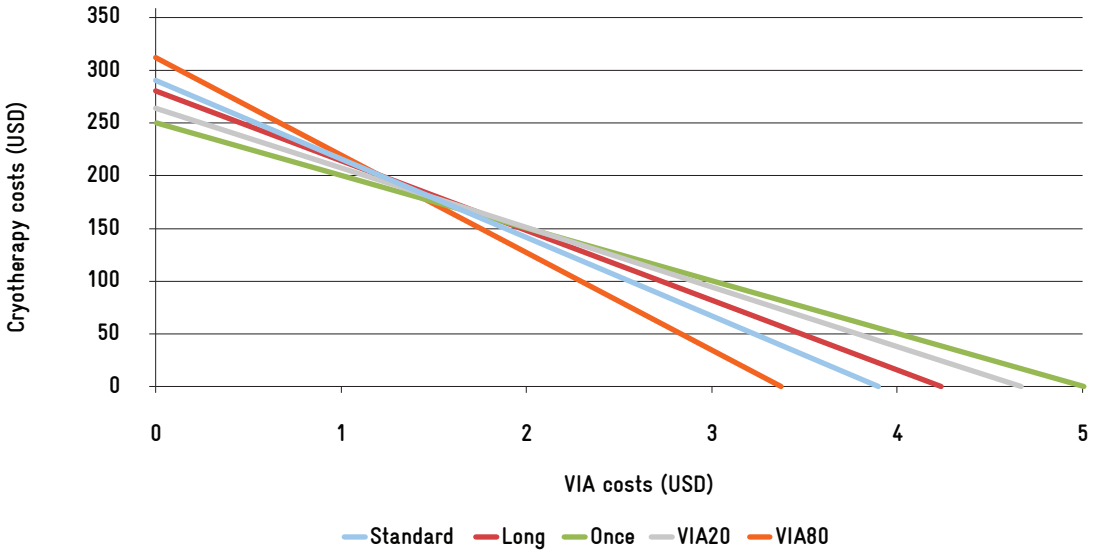


Figure 11: Cost-effectiveness thresholds for CUC screening scenarios (VIA and cryotherapy costs, in USD).



for other scenarios. For the Standard scenario the ICER is USD 661, and for the 20% compliance with VIA scenario (VIA20) it is USD 561.

Figure 9 also shows that the Standard, Long and VIA80 scenarios result in an absolute decline in the number of death cases for many years. Afterwards, population growth will reduce the impact of screenings, so the number of death cases will increase again.

Figure 10 shows the budget necessary for VIA screening and cryotherapy scenarios. It is obvious that screening once in a lifetime is the cheapest option, whereas higher compliance (VIA80) and an expanded screening population (all females 30-60 years old, as in the 'Long' scenario) require higher budgets. These calculations assume that one VIA costs USD 2.50, and one cryotherapy treatment costs USD 7.50. These figures represent the minimum actual costs in Cambodia calculated by NSSF for preventive outpatient services and minor surgical procedures, respectively. To allow for different cost structures, Figure 11 shows the cost-effectiveness thresholds for different combinations of VIA and cryotherapy costs across the simulated screening approaches. All combinations of VIA and cryotherapy costs to the left of each screening scenario threshold are cost-effective; all combinations to the right are ineffective. Under no circumstances should the cost per VIA be above USD 5.07. At the same time, the cost per cryotherapy can increase considerably, as only a small percentage of screenings will result in cryotherapy treatment.

In summary, VIA screening for cervical cancer is highly cost-effective at the assumed prices for Cambodia. Screening all women once in a lifetime seems to provide the best ICER, but the Standard scenario (screening all women 30-49 years old every three years) provides a much greater effect on death cases while still being highly cost-effective.

5.3. Vaccination

The forecasting model allows for initiation of an HPV vaccination programme [20, 47]. We designed multiple models for compliance and vaccine efficacy, all of which we assumed would start in 2015. Table 5 shows the parameters of the different vaccination scenarios analysed. In the Standard model, 75% of eligible girls comply with the full vaccination schedule (three doses of the vaccine) before their first sexual experience. We also assumed that the vaccine has a 63% efficacy, meaning it is 90% effective against the HPV virus types responsible for 70% of cervical cancer cases worldwide (HPV 16 and 18). This is a standard efficacy rate for existing HPV vaccines [48]. The E100C100 scenario describes the ideal situation, where all eligible girls receive full vaccination, and the vaccine protects perfectly against all cancerous HPV types. E90C75 is a scenario where the vaccine protects against 90% of high-risk HPV types, but only 75% of girls receive full vaccination. E63C100 assumes the efficacy of existing vaccines, but with a very high compliance. The Short scenario assumes the same efficacy and compliance as the Standard scenario, but limits the vaccine's effectiveness to 20 years.

Scenario	Start Date	Efficacy	Compliance	Protection
Standard	2015	63%	75%	Lifelong
E100C100	2015	100%	100%	Lifelong
E90C75	2015	90%	75%	Lifelong
E63C100	2015	63%	100%	Lifelong
Short	2015	63%	75%	20 years

Table 5: Parameters for model HPV vaccination scenarios.

As Figure 12 shows, vaccination has a major impact on the number of death cases attributed to CUC, compared with the Basic scenario which assumes no vaccinations (the current situation). Even the Standard scenario, with the current vaccine efficacy rate and an expected compliance of 75%, would strongly reduce the number of deaths caused by cervical cancer in the next 100 years. However, HPV vaccination does not necessarily lead to the elimination of cervical cancer. Only by increasing compliance and efficacy of the vaccines will we finally be able to eliminate CUC completely. Some vaccination scenarios (E90C75 and E63C100) it might look as if the number of death cases declines after about 50 years of the vaccination programme, but this may only happen for a few years. Afterward, the number of insufficiently protected women (either because of noncompliance or ineffective vaccination) increases again, raising the number of infections and related death cases. Close to the infectivity threshold, infections can occur in long-term cycles, called Lotka-Volterra cycles [49].

Even if compliance is very high and the vaccines are highly effective, CUC will not be automatically eliminated. First, the vaccination programme must be financed and implemented for almost 100 years. As the figures indicate, vaccination programmes have very little impact within the first 40-50 years. Afterwards, there is a decline in the number of death cases. However, the experiences of other vaccination programmes have shown that there is a risk that vaccination coverage will decline the first 40-50 years, so complete elimination of the disease cannot be achieved.

Second, the selected vaccine must provide lifelong protection. As Figure 12 shows, a vaccine that only protects for 20 years has the same impact as a lifelong vaccine for the first 20 years, and almost the same impact for another 10-15 years. Afterwards, there will be an increase in CUC death cases unless there is a re-vaccination programme. The model accounts for lower sexual activity among women 20 years after they were initially vaccinated, but still there is an increase in death cases if vaccination is not permanent.

Figure 12 seems to show that these vaccination programmes have no impact for the first 25 years. However, Figure 13 demonstrates the relative decline of pre-invasive cancer (lesions), invasive cancer (cancer) and CUC-related death cases (death cases) from 2015-2040 as a result of the HPV vaccine. All figures correspond to the Standard vaccination scenario (with 75% compliance and 63% efficiency) and show the relation between the burden of disease compared to the respective numbers in the Basic scenario (without vaccination). As expected, the reduction in lesions happens earlier than declines in invasive cancer and death cases, but there is a reduction across all three disease stages relative to the current situation. Whether this change could be recorded by the existing documentation system in Cambodia is questionable.

Figure 12: Impact of HPV vaccination scenarios on annual death cases attributed to CUC, 2010-2110.

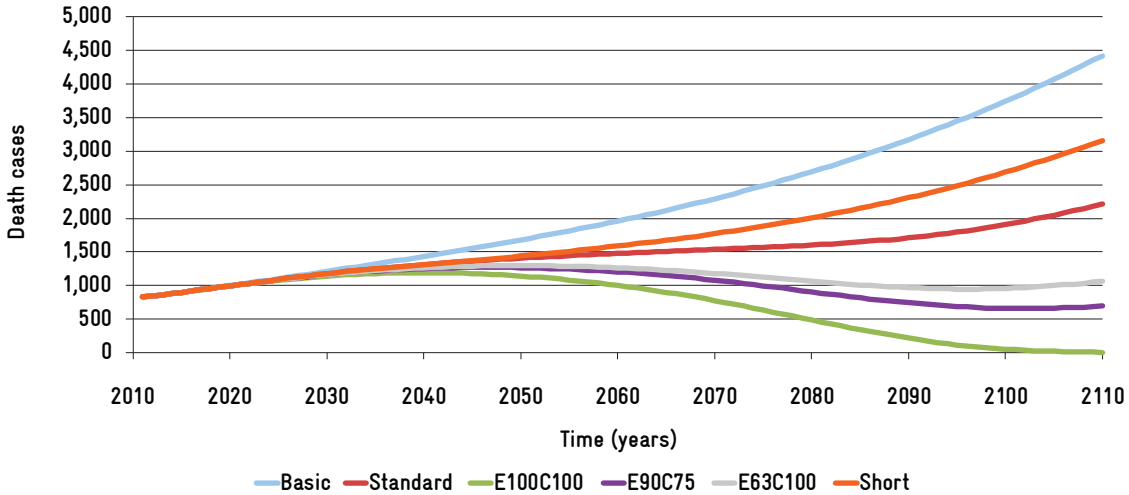
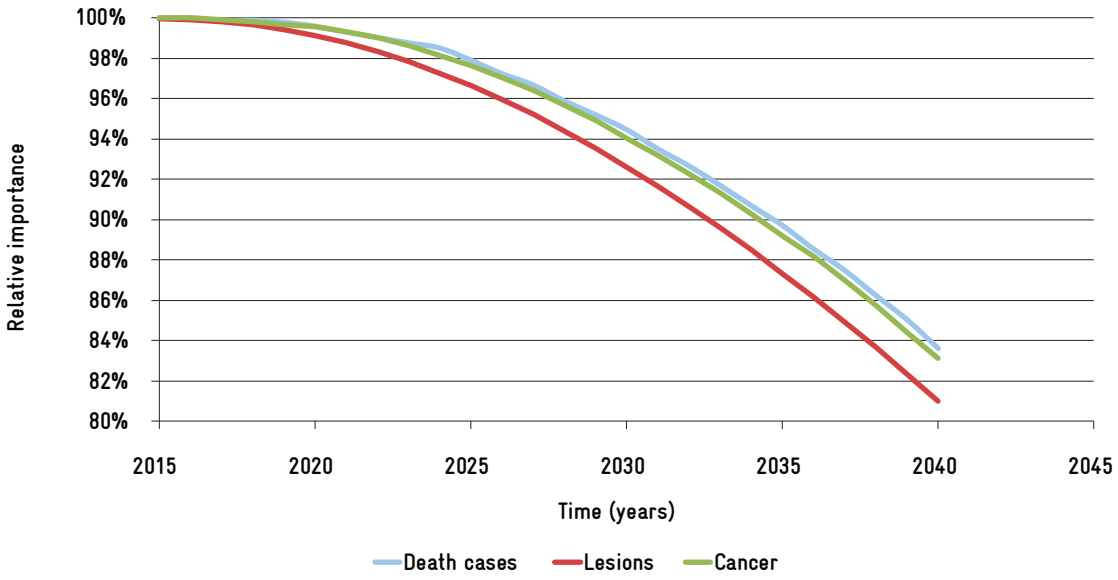


Figure 13: The relative impact of HPV vaccination on cervical cancer disease burden in Cambodia, 2015-2040.



The cost-effectiveness analysis of an HPV vaccine largely depends on the timeframe examined. For most scenarios, the HPV vaccine has a long-term (lifelong) impact, so major improvements in mortality are only seen after decades. If we analyse the ICER for the five vaccination scenarios across the 100-year timeframe, they are all cost-effective (Table 6). Even a vaccine that only provides 20 years of protection would be cost-effective across this timeframe. The higher the effectiveness of the vaccine, the lower the ICER.

Scenario	ICER (2035)	ICER (2110)
Standard	57,196	625
E100C100	35,642	443
E90C75	40,011	411
E63C100	58,232	590
Short	57,196	712

Table 6: ICER values for HPV vaccination scenarios after 20 years (2035) and 100 years (2110), in USD per LYS.

However, if we only analyse a 20-year timeframe (corresponding to MOH's current strategy), the ICER values increase dramatically. In section 5.5 we will address this issue more, but here it is worthwhile stating that a vaccination programme only makes sense if we have a long-term perspective, whereas treatment and screening also provide short-term benefits. Even if a full vaccination programme was established, a screening programme would still be required for unvaccinated women and those with lesions/CUC caused by HPV types not covered by the vaccine). On the other hand, a vaccination programme is the only intervention that has at least a small chance to eventually eliminate cervical cancer.

Figure 14 shows the annual costs of financing HPV vaccination interventions nationwide. This analysis assumes that full vaccination costs USD 22.50 per person; i.e., three vaccine shots at USD 5.00 each, and USD 2.50 each visit for health service delivery. As expected, the costs of the Standard, E90C75 and Short scenarios are the same, as are the costs of the E100C100 and E63C100 scenarios, so the graph shows only two curves. Compared with treatment and screening activities, a vaccination programme is quite expensive – up to USD 13 million annually. But this is the cost for 100% vaccine compliance in 2110. An initial HPV vaccination programme could be started in 2015 with an annual budget between USD 2 million and USD 2.7 million.

As Figure 15 shows, the cost-effectiveness of a vaccination programme depends on the scenario and the cost of vaccination. The vaccination costs per woman could be higher than our estimate of USD 22.50 as long as the vaccine remains effective. For the Standard scenario, full vaccination can cost up to USD 36 and still be cost-effective (ICER below USD 1,000). For the other scenarios, the respective cost thresholds are USD 51 (E100C100), USD 55 (E90C75), USD 38 (E63C100), and USD 32 (Short). However, as stated before, vaccination programmes are only cost-effective over very long timeframes. For short time periods, vaccination programmes will never be cost-effective.

Figure 14: Annual costs for HPV vaccination scenarios implemented nationwide, 2010-2110.

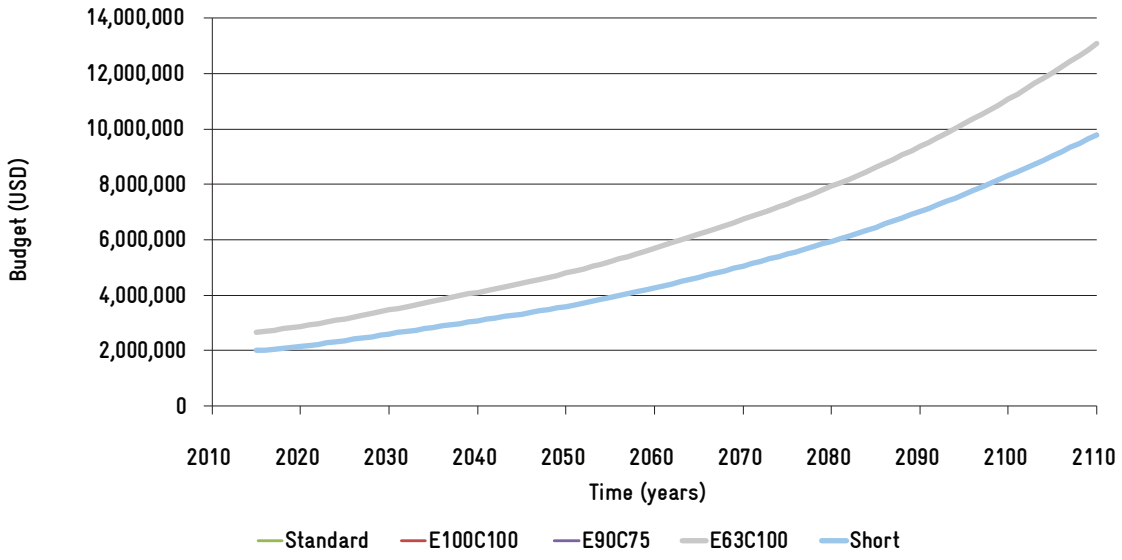
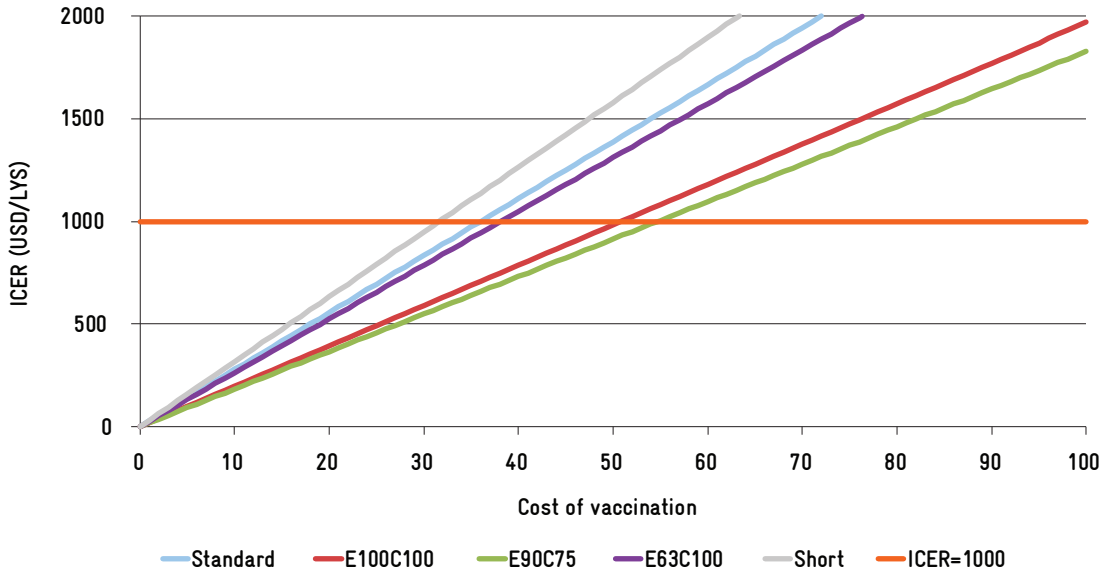


Figure 15: Cost-effectiveness of HPV vaccination scenarios, in USD per patient.



This analysis clearly shows that HPV vaccination programmes are cost-effective for Cambodia. However, the primary impact of vaccination will only be seen after decades. It seems that screening programmes are more cost-effective, while providing better results in the short term.

5.4. Comprehensive Intervention

Sections 5.1, 5.2 and 5.3 assume that the screening, treatment and vaccination interventions are implemented separately. This is quite unrealistic, as the availability of successful treatment options is one of the central criteria for initiation of a screening programme; it would be unethical to implement a screening programme without the ability to offer some care for patients found to have lesions or invasive cancer. At the same time, vaccination programmes are most likely to be introduced into Cambodia after a screening programme is already in place. Thus, in this section we will design comprehensive intervention scenarios and analyse their cost-effectiveness.

Figure 16 clearly shows that combined interventions have a higher impact on the number of death cases than

Figure 16: Impact of CUC intervention scenarios on attributed death cases in Cambodia, 2010-2110.

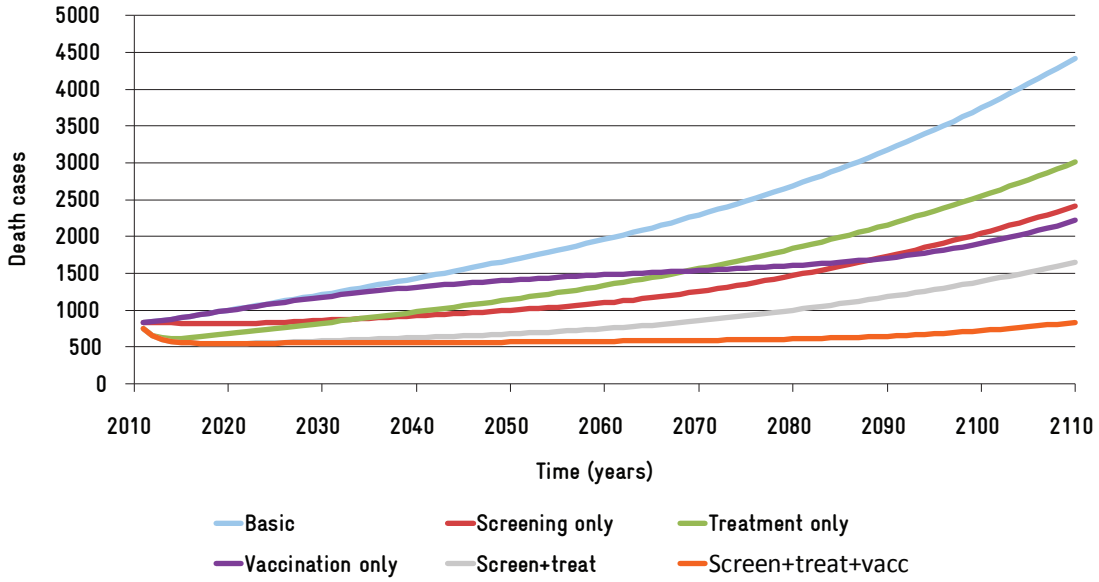
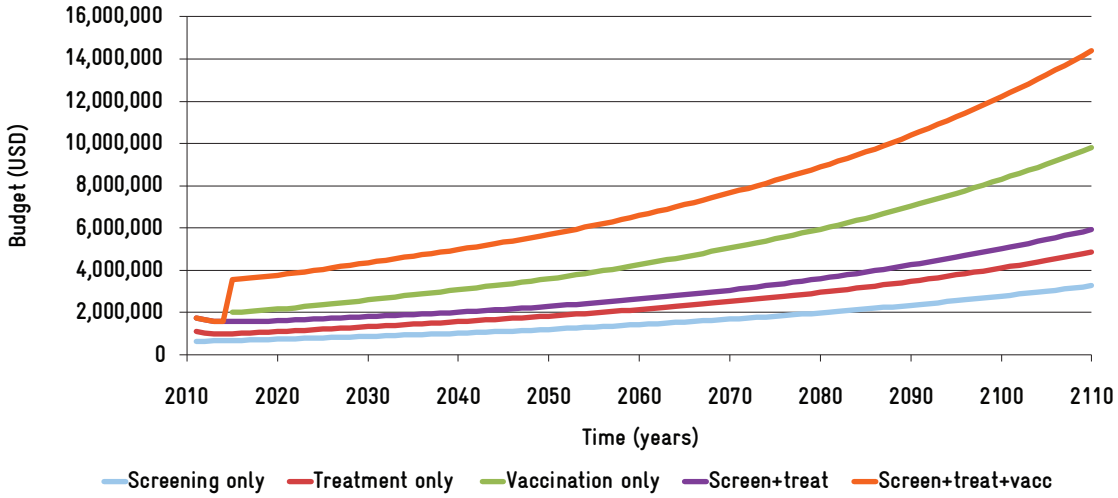


Figure 17: Budget for CUC intervention scenarios in Cambodia, 2010-2110 (in USD).



single interventions. At the same time, the budget required to finance these combined interventions is also much higher than for individual scenarios (Figure 17). These figures also indicate that screening and treatment alone will not eliminate CUC from Cambodia. Even existing vaccines will not completely remove cervical cancer from the country. Cambodia should start a comprehensive intervention, including an effective and professionally managed vaccination programme, but this will not have a significant effect on death cases for decades, and will require high compliance and an increase in vaccine efficacy. Vaccination programmes need patience and a long-term timeframe. To start a vaccination programme without treatment and screening components would be futile in the short-term. Until 2065, even a basic approach with only treatment services has a higher impact on the number of death cases than a vaccination programme.

If we assume a 20-year timeframe, the cost-effectiveness of the scenarios are quite different. The treatment only scenario is most cost-effective, with an ICER of USD 431 per LYS, followed by the screening and treatment scenario (USD 489) and the screening only scenario (USD 661). With an ICER of USD 954, the screening, treatment and vaccination scenario is still cost-effective in this reference period. However, the approach to only vaccinate young women without offering treatment or screening services to women is not cost-effective, with an ICER of USD

Interest Rate	Timeframe (years)	Screening Only	Treatment Only	Vaccination Only	Screening and Treatment	Screening, Treatment and Vaccination
0%	20	518	362	43,996	398	1,116
	40	165	191	2,059	169	728
	60	96	139	580	109	646
	80	74	113	272	84	625
	100	64	96	168	71	620
5%	20	661	431	57,196	489	954
	40	258	260	3,666	252	508
	60	178	212	1,346	191	377
	80	152	192	816	168	323
	100	142	182	623	157	296
10%	20	866	521	76,024	611	824
	40	436	369	7,351	390	363
	60	367	341	3,889	349	225
	80	353	334	3,185	340	163
	100	350	333	3,005	338	128

Table 7: Impact of timeframe and interest rate variations on the cost-effectiveness of CUC intervention scenarios, in ICER (USD/YLS).

57,196. However, as we stated before, the cost-effectiveness of these interventions depends on the timeframe. This issue is critical, and will be discussed again in the next section.

In summary, Cambodia has a choice between a number of scenarios which are cost-effective in both the short- and long-term. However, cost-effective does not necessarily mean affordable with the limited national health care resources. The screening, treatment and vaccination scenario may provide the best public health outcomes, but it is also the most expensive programme to finance. In this case, Cambodia should begin implementing a screening and treatment scenario while looking for additional funds (such as support from Gavi) for a vaccination programme in the near future.

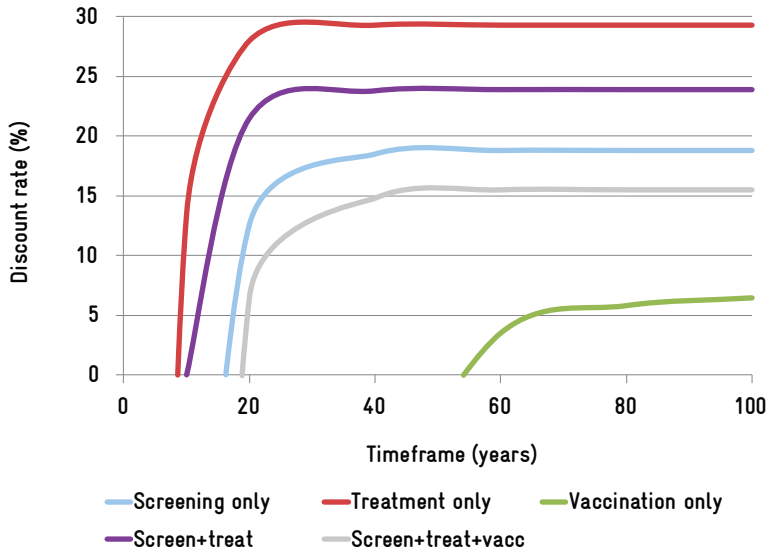
5.5. Sensitivity

The results shown above include intervention scenarios based on alternate constants (e.g., effectiveness of treatment and vaccines). Figure 7, Figure 11 and Figure 15 also include some sensitivity analysis, which will not be repeated here. The timeframe and discount/interest rate are important parameters to consider for the economic analysis of a disease such as CUC, with a delay of several decades between infection and death. Thus, we would like to stress this aspect more.

Table 7 examines the cost-effectiveness of the intervention scenarios described previously, with varying interest rates and timeframes. As the benefits of all interventions are only seen after many years, a higher interest rate generally leads to a lower cost-effectiveness (i.e. higher ICER). Thus, the systematic disregard of future benefits discredits intervention programmes. This is most impressive for the vaccination only scenario; even with a 100-year timeframe, the ICER is greater than USD 1,000 for all interest rates greater than 6.5%. Thus, the systematic disregard of future benefits discredits vaccination programmes.

Figure 18 shows the cost-effectiveness of different combinations of timeframes and discount rates for the CUC intervention scenarios. All combinations of longer timeframes and lower interest rates (i.e., the area below each curve) would be considered cost-effective, with an annual ICER of less than USD 1,000 per LYS. For realistic discount rates, the screening only, treatment only, screening and treatment, and screening, treatment and vaccination scenarios are cost-effective if the timeframe is longer than 40 years. These results are highly sensitive to changes in interest rates in timeframes of less than 40 years. For the vaccination only scenario, the timeframe must be at least 55 years for it to be cost-effective.

Figure 18: Cost-effectiveness of CUC intervention scenarios by discount rates, over a 100-year timeframe (ICER threshold of 1000 USD/LYS).



	Year	Treatment	Screening	Vaccination	Total
Screening, Treatment and Vaccination	2015	887,635	677,939	1,998,793	3,564,367
	2016	879,037	688,570	2,027,056	3,594,663
	2017	874,383	699,988	2,056,980	3,631,351
	2018	872,185	712,064	2,088,673	3,672,922
	2019	872,561	724,671	2,122,209	3,719,441
	2020	872,496	737,700	2,157,630	3,767,826
Screening and Treatment	2015	887,634	677,939	0	1,565,573
	2016	879,214	688,570	0	1,567,784
	2017	874,834	699,989	0	1,574,823
	2018	873,474	712,065	0	1,585,539
	2019	874,578	724,673	0	1,599,251
	2020	875,840	737,705	0	1,613,545

Table 8: Estimated annual budgets for comprehensive CUC intervention scenarios, 2015-2020 (in USD).

This is also reflected in the impact of the timeframe on ICER. Scenarios with shorter timeframes are less cost-effective. However, the impact of the timeframe also depends on the scenario selected. For instance, the ICER of the screening only scenario with a 100-year timeframe is only around one-fifth (21%) of the ICER of the same scenario with a 20-year timeframe (r=5% in both cases). This ratio for the treatment only scenario is 42%, 1% for the vaccination only scenario, 32% for the screening and treatment scenario, and 31% for the screening, treatment and vaccination intervention. The more impact an intervention has in the first years after initiation, the lower the difference between the ICER after 20 and 100 years. Therefore, the cost-effectiveness of treatment is not as dependent on the timeframe as the ICER for screening. The cost-effectiveness of vaccination programmes, with their emphasis on long-term results, depends largely on the timeframe examined.

In summary, the leadership of Cambodia has to decide on an appropriate discount rate and timeframe for whichever intervention scenario they select. A short-term approach, with priority on early benefits, may not provide any long-term benefits to the population. At the same time, the Royal Government of Cambodia should include the fight against CUC in its annual operational plans (AOP). Table 7 shows the estimated annual costs for the initiation of comprehensive CUC intervention scenarios from 2015-

2020. A screening and treatment programme would cost around USD 0.11 per person (USD 0.06 for screening and USD 0.05 for treatment), with total costs of around USD 1.6 million if implemented nationwide. If limited to pilot programmes in selected operational districts, the unit costs might be higher as pilot programmes are more expensive (per service unit) than nationwide implementation.

6. Discussion

These simulations show the considerable burden of cervical cancer on the Cambodian population. This burden will only increase as the country develops, and more women will suffer from cervical cancer unless interventions are planned and implemented now. Our analysis clearly indicates that cost-effective interventions can be financed with limited budgets. For instance, screening for lesions and treatment of invasive cancer are cost-effective interventions in Cambodia under almost all realistic assumptions. Vaccination against HPV is also cost-effective if the timeframe is long and the interest rate is low. In the following discussion, we will examine the assumptions and consequences of these statements.

6.1. Treatment

The simulations assume that treatment of invasive cancer is only feasible in national hospitals in Cambodia, with health centres and lower level hospitals having only a small role in the treatment of invasive CUC. Currently, only three hospitals have the medical capability of treating cervical cancer, and all have very limited capacity. Assuming that effective treatment for 25% of the cases, we estimate that around 1,200 patients will require treatment for CUC in 2014. This is far beyond the current capacity. Thus, proper treatment will require hospitals to expand their services for oncological patients.

The respective requirements for appropriate CUC treatment are clearly stated by the World Health Organization [16]. The Royal Government of Cambodia will have to discuss whether it is more effective and efficient to expand existing services centralized in Phnom Penh, or strengthen the capacity of regional hospitals; especially the highest level hospitals in Cambodia (CPA-3). Because transportation difficulties and distance limit people's access to currently available oncological services, improving regional service would be appropriate, but these services may take years to develop. Meanwhile, the government has to ensure that existing oncological services in Phnom Penh are of sufficiently high quality and quantity to provide for at least some CUC patients.

Our model assumes annual treatment costs of USD 800 per CUC patient. This includes the cost of laboratory tests, surgery, radiation therapy, hospital care and palliative care. These cost estimates are lower than estimates given in other research. For instance, Goldie et al. [37, 41] conducted cost estimates for India, Kenya, Peru, South Africa and Thailand that range from 1,263 international dollars (PPP$) for treatment of cancer in India to PPP$ 2,749 for treatment of cancer in Peru. The costs estimated for Thailand are rather high, ranging from PPP$ 2,210 for local cancer to PPP$ 2,552 for distant cancer. However, we should note that the costs of medical treatment in Cambodia are much lower than in neighbouring Thailand or India. In a costing study of Cambodian hospitals, Martin [30] found that the average costs of a major surgical intervention in a CPA-3 hospital in Cambodia are USD 340, which is only a fraction of the costs for a similar intervention in Thailand. USD 350 is also the maximum amount NSSF will to refund for a major operation. Thus, treatment costs of USD 800 per patient annually seem to be a fair estimate for Cambodia.

As Figure 7 shows, the cost-effectiveness of treatment is more dependent on the effectiveness of treatment than the costs. To our knowledge, no research on CUC patient survival times, and the effect of treatment on survival, exists for Cambodia. Survival times differ considerably between countries with different levels of economic development, so estimates from countries with higher health care budgets cannot be used as a standard for Cambodia [50, 51]. The vast majority of women suffering from cervical cancer in Cambodia do not receive any treatment. Those patients who can afford hospital services and are able to access a treatment provider will frequently receive low-quality services. As our simulations show, a treatment effectiveness of only 10% is unlikely to be cost-effective. Thus, providing cost-effective treatment, which is at least 25% effective (as assumed in our Standard simulation), will require additional effort from MOH. This includes additional staff training, procurement of appropriate, modern equipment, ensuring availability of patient transport, purchasing of drugs and radioactive materials, and early detection of cervical cancer cases.

6.2. Screening

The simulations clearly show that the 'see-and-treat' strategy (screening with VIA, with follow-up cryotherapy treatment for lesions) at the health centre level is cost-effective under all realistic scenarios. For the Standard scenario, the ICER is USD 661 (with screening of all women 30-49 years old every three years). Offering screening only once in a lifetime would be more cost-effective (ICER of USD 523), but would not be as effective at reducing death cases.

These findings for Cambodia confirm the results of a number of other studies in developing countries. Goldie et al. showed that in India, Kenya, Peru, South Africa and Thailand, one CUC screening in a lifetime 'reduced the lifetime risk of cancer by approximately 25 to 36 percent, and cost less than USD 500 per year of life saved' [37]. Screening more often was less cost-effective, but in all cases the cost per life-year saved (ICER) was below the annual gross national product per person. In India, Legood et al. found average costs for VIA screening of USD 3.92, and concluded that VIA was the least expensive option for CUC screening [38]. Research on the costs and effectiveness of similar interventions in developed countries cannot be compared with Cambodia, as the cost per service unit, the epidemiological data and the resulting ICER are quite different (see, for example, Mandelblatt [39]).

Our analysis provides evidence to support the WHO recommendations and the national NCD strategy of Cambodia, which state that a see-and-treat approach using VIA screening and cryotherapy treatment are cost-effective and feasible within the national budget [46, 52]. Cold coagulation appears to be a sufficient alternative to cryotherapy, but an examination of the relative merits of each technique is beyond the scope of this analysis.

As Figure 11 shows, these results are highly dependent on the costs of screening. If the costs per VIA screening are higher than USD 5.00, screening would probably not be cost-effective in Cambodia. Thus, we have to examine our estimated screening costs, to ensure they are realistic. In 2002, Mandelblatt et al. calculated the cost of VIA screening and cryotherapy treatment for Thailand. They found costs of around USD 1 per VIA screening and USD 7.50 for cryotherapy. These cost estimates for Thailand are more than a decade old, but may be relevant to the current situation in Cambodia (given Cambodia's lower cost and income levels). Goldie et al. attached a detailed calculation of the costs of VIA screening and cryotherapy for Thailand [37, 41]. They calculated the cost per VIA as PPP$ 1.62 (using purchasing power parity in 2000). Their estimates for the cost of cryotherapy were much higher than Mandelblatt et al. (PPP$ 40.50), but this is still within the cost-effective range for Cambodia (Figure 11).

For the basic simulation, we assumed costs of USD 2.50 per VIA screening and USD 7.50 per cryotherapy treatment. These are the full costs of preventive outpatient services, including minor outpatient surgery [30], per MOH and will also be the NSSF reimbursement fees for these services (once NSSF is initiated). A further micro-costing of these services should be performed in the future, especially as these costs include both fixed and overhead costs, and variable costs. Variable costs, such as for consumable supplies, will increase with the number of women screened, whereas the overhead costs per screening will decline as the number of patients increases. However, these figures seem to be good estimates for the current situation in Cambodia.

Another important parameter of the simulation is compliance with the intervention activities. The Standard model assumes that 50% of all eligible women will have VIA screenings and 75% of those with lesions will receive cryotherapy treatment at the health centre, if a see-and-treat approach is implemented. Our simulations show that higher compliance will further reduce the number of death cases, but we are not sure whether this is feasible in Cambodia. Seeing that barriers to health centre access (such as distance, transportation availability and cost, etc.) still exist in some regions, it is unlikely that Cambodia will achieve the 80% compliance rate stipulated by WHO [16]. Fortunately, even interventions with lower compliance rates are still cost-effective and reduce CUC-related mortality.

But, even reaching 50% compliance may be a challenge. Gakidou et al. analysed compliance with cervical cancer screenings in 57 countries and concluded that 'coverage of cervical cancer screening in developing countries is on average 19%, compared to 63% in developed countries, and ranges from 1% in Bangladesh to 73% in Brazil'. They also show that compliance is lowest for the poorest women; the effective compliance with screening interventions among women in the poorest 10% of the population was only around 10%, compared with more than 60% compliance for women in the richest 10% (across all countries in the study). Our forecasting model does not allow us to examine women by wealth group,

but when formulating the national intervention for CUC we must remember that prevention of cervical cancer is also a social and economic problem.

Furthermore, we assume that 75% of women with lesions will have follow-up cryotherapy treatment. This assumption is based on a see-and-treat approach, as recommended for Cambodia. The compliance rate of 75% seems quite high, but using this approach, women with pre-cancerous lesions will receive treatment at the same place and on the same day. Thus, a rate of 75% should be feasible, but compliance will also depend on the availability of equipment, trained personnel and appropriate counselling. We also recommend that confirmation screenings should not be conducted in Cambodia, as this would only increase costs and reduce compliance with cryotherapy.

Other important parameters for screening interventions are the target age group and the screening interval. Our analysis shows that all screening scenarios are cost-effective, but have different impacts on the number of death cases and the national budget. The Standard scenario assumes VIA screening of all women between 30 and 49 years old, as recommended by the national NCD strategy [52]. MOH considers this an initial target group, with other age groups to be added later. WHO stipulates that the 'priority age group for initial screening are women age 35–54 years' [53]. We also simulated a screening scenario for this age group, and found that it is also cost-effective or Cambodia (ICER of around USD 602). Thus, Cambodia could reconsider the age groups for initial VIA screenings. However, increasing the age of women eligible for screening may require another screening method, as VIA is not recommended for women after menopause. The current WHO guidelines only recommend VIA screening for women less than 50 years old [21].

We also analysed a screening intervention for women 30-49 years with a screening interval of five years, instead of three years. Delayed screening would result in an increase in death cases from 128,000 to 150,000 (an increase of 16%) relative to the Standard model during the 100-year timeframe. However, a five-year screening interval is more cost-effectiveness, with an ICER of USD 580 compared to USD 661 for the Standard screening procedure. This comparison indicates that the most effective scenario overall (the three-year screening interval) is not necessarily the most cost-effective option.

Furthermore, our model assumes that VIA screening and cryotherapy have no negative effects. This seems to reasonable as only minimal complications of cryotherapy have been reported [54]. However, this assumption depends on the qualifications, training and motivation of staff. MOH will have to invest in increasing the capacity of health care workers to ensure that cryotherapy is not harmful for patients. This is especially important because VIA can produce false positive results, although these results should be reduced through standard quality assurance measures.

Finally, there is the issue of where screenings should be performed. There seems to be general agreement that screenings should be performed in areas that are accessible to as much of the population as possible, to ensure high compliance with the intervention [16, 52]. Health care workers, especially nurses and midwives, can be trained in VIA screening and cryotherapy within weeks [12]. As Jacob et al. note:

"Cryotherapy, in use for the past 40 years, is relatively simple, safe, effective, acceptable, and [studies] conducted in more than a dozen developing countries show that cryotherapy for pre-cancer can be performed safely and effectively as an outpatient procedure at all levels of health facilities by trained and competent midlevel providers, thus increasing availability and accessibility to pre-cancer treatment services [55]."

The equipment to perform cryotherapy treatment is not expensive (estimates range from USD 1,500 to USD 2,000 per unit), and depreciation of equipment is included in the estimated costs of cryotherapy (USD 7.50 per patient). However, cryotherapy requires a steady supply of frozen carbon dioxide and a functional logistical system to transport and store it. Preventing and treating cervical cancer in Cambodia requires more than just good medicine; it also requires a health care system that safeguards and provides necessary equipment and consumables to all health centres in the country. Consolidating cryotherapy treatments at the district hospital level (CPA-1) may solve some logistical problems and reduce unit costs, but it would probably reduce compliance significantly. Cold coagulation might be a suitable alternative to cryotherapy, as it does not require a supply of frozen carbon dioxide.

In summary, the Royal Government of Cambodia should start a nationwide screening programme based at the health centre level. Furthermore, they should examine whether all or only certain health centres should be equipped and trained on VIA screening and cryotherapy, based on regional accessibility.

6.3. HPV Vaccination

The findings of this simulation confirm the results of previous research on the economic impact of HPV vaccination programmes. For both high-income [36, 56-58] and low- and middle income countries, the majority of studies show that vaccination of girls is cost-effective, and can even be cost-saving, meaning that total costs (including intervention costs) may decrease after the start of the programme. Fesenfeld at al. analysed 25 articles on the cost-effectiveness of HPV vaccination in low- and middle-income countries, and concluded that 'vaccination is cost saving at low vaccine prices. Indeed, across all studies, if the cost per vaccinated girl was below PPP$ 25, then the ICER of vaccination compared to no prevention was consistently below PPP$ 200' [59].

However, the parameters and results differ widely between studies. For instance, Goldie et al. analysed the impact of vaccination in 72 Gavi-eligible countries [47]. They assumed costs of PPP$ 10 per vaccinated girl, and showed that in 49 of 72 countries the cost per DALY saved was less than PPP$ 100, and it was more than PPP$ 200 in only 13 countries. However, PPP$ 10 seems to be very inexpensive, as these costs should cover three doses of the vaccine, as well as logistics, waste management, health service delivery and administration costs.

The main factor influencing cost-effectiveness for vaccination programmes appears to be the price of the vaccine. For instance, Termrungruanglert et al. [60], Praditsitthikorn et al. [61] and Sharma et al. [20] analysed the cost-effectiveness of HPV vaccination in Thailand. Termrungruanglert et al. concluded that HPV vaccination was cost-effective, Praditsitthikorn et al. determined HPV vaccination was not cost-effective, and Sharma et al. concluded that HPV vaccination was cost-saving. These contradictory findings are the result of the first research group estimating vaccine costs (for three doses) at USD 200 per girl, the second group estimating costs of USD 470 per girl, and the last group estimating costs of USD 10 per girl (with some sensitivity analysis). This reinforces the fact that the values of parameters in our simulations have to be accurately calculated.

Figure 15 provides us with relevant information on this issue. For Cambodia, vaccination will be cost-effective in the long-term if the costs per fully vaccinated girl are less than USD 32. For some effectiveness and compliance scenarios, the costs can be much higher. Our forecasting model assumes full vaccination costs of USD 22.50, based on three vaccine doses per girl to achieve full efficacy. Recently, the WHO announced that two doses of HPV vaccine would be sufficient to provide full efficacy, if it was absolutely certain that the second dose was given before first sexual intercourse [62]. As we assume stable prices for the vaccine, this change in implementation would result in a one-third increase in the cost-effectiveness (ICER) of vaccination scenarios. However, the principle findings of section 5.3 remain unchanged; all vaccination scenarios are cost-effective over a 100-year period, and none are cost-effective over a 20-year period. Whether Cambodia chooses to implement a vaccination programme consisting of two or three doses, it should follow the appropriate WHO guidelines to ensure maximum efficiency.

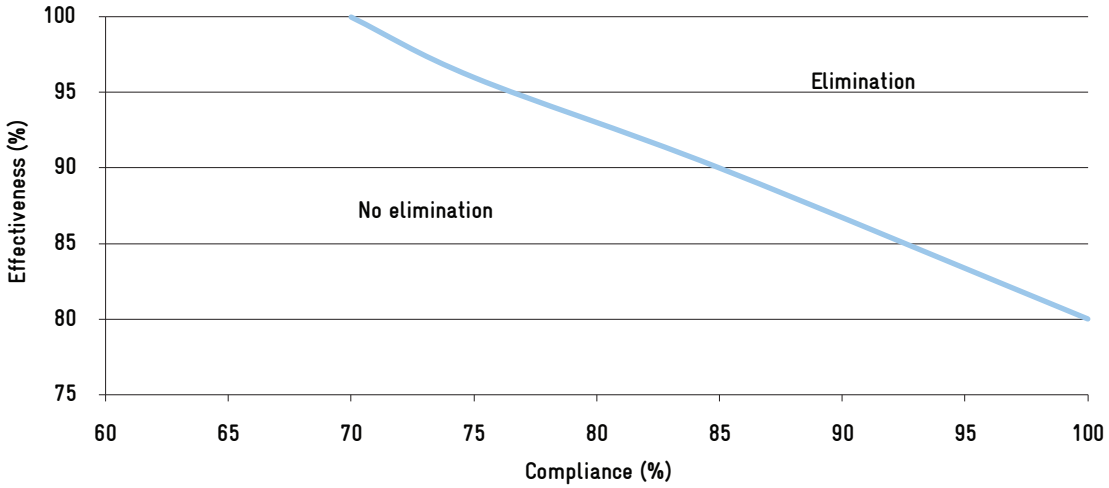
A price of USD 5.00 per vaccine dose is seen as an international standard [25]. In addition, we assumed that administration of each dose would incur service delivery costs of USD 2.50, which are the full costs for other preventive outpatient services in Cambodia (including administration of other vaccinations) calculated by Martin [30].

In the Standard model, the effectiveness of vaccination was estimated at 90%, with 70% coverage of all HPV types; i.e., the medical infectivity of HPV was reduced by 63% among vaccinated girls. 70% seems to be standard for a bivalent vaccine [48]. A minimum efficacy of 90% is also standard, assuming proper logistics and handling [56]. Thus, MOH has to ensure that HPV vaccines are not only available, but also in good condition. This may be a challenge in parts of the country.

Most scientists agree that elimination of HPV is theoretically possible [63-66]. Our model predicts that cervical cancer can be eliminated in Cambodia if compliance with the vaccination schedule is very high, and if the vaccine is highly effective. Figure 19 shows the combinations of compliance and effectiveness for a vaccination programme that will lead to elimination of CUC in Cambodia within 100 years. All combinations to the right of the curve will result in eradication of the disease in Cambodia. This simulation is in agreement with other biomedical models which state that the critical vaccination threshold is generally below 100% [67].

Most models of vaccination programmes only forecast effects over a lifetime; i.e., 30-50 years [59]. However, as shown in Figure 12, hardly any impact can be seen in this

Figure 19: HPV vaccination effectiveness and compliance thresholds to eliminate CUC within 100 years.



timeframe. Our model analyses the effects of a vaccination programme over 100 years, but any prediction of impact over such a long timeframe is highly uncertain. This model also supports the thesis that cervical cancer can be eliminated in Cambodia, but this will require more effective vaccines (covering other oncogenic HPV types) and very high compliance. Most importantly, eliminating CUC will require prioritising the financing and implementation of cancer control in Cambodia for many decades [63, 65, 66]. Although theoretically feasible, there are significant barriers to nationwide elimination of cervical cancer [64].

A major problem with the vaccination programme model is whether Cambodia can achieve 75% compliance with the vaccination schedule among all girls before their first sexual intercourse. To address this concern, WHO recommends 'prioritising high coverage in the primary target population of girls who are 9 to 13 years old' [68]. However, there are many ways to distribute the HPV vaccine, including through school-based programmes and local health centres [68]. An analysis of this issue is beyond the scope of this paper, but our simulations show that high compliance is crucial for the success of a vaccination programme. Because there are some remote areas of Cambodia that have limited access to health centres, distribution of the vaccine through schools might be more appropriate. However, this requires close cooperation between MOH and the Ministry of Education, Youth and Sports (MOEYS).

Finally, the start of the HPV vaccination programme has to be determined. The comprehensive model (screening, treatment and vaccination) assumes that HPV vaccination is initiated five years after the start of nationwide screening. This is based on the fact that screening is more cost-effective than HPV vaccination, and is aligned with the national NCD strategy [3], which initially focuses on nationwide screening. HPV vaccination is scheduled to be introduced only after other vaccination programmes (rubella, Japanese encephalitis, pneumococcus and rotavirus) have been successfully implemented. However, it seems that Cambodia has applied for funds from Gavi to begin a pilot HPV vaccination. The results of our simulations clearly show that this approach will be cost-effective if the time horizon is long enough, but also indicate that the 'see-and-treat' approach should be the initial priority for the prevention and treatment of CUC in Cambodia.

This forecasting model can only address some of the issues regarding CUC prevention and treatment in Cambodia. Other aspects, such as HPV vaccinations for boys [36], were seem as a lower priority for Cambodia right now. Some results have to be interpreted with caution, as they are based on general estimates of parameters due to a lack of available evidence. For instance, there is a 'need for better micro-costing data on HPV vaccine delivery and programmatic cost' [69]. Where possible, we developed different scenarios and cost-effectiveness ranges to control for the uncertainty of various parameters. Finally, system dynamics models are the best predictors of population dynamics, but they become unreliable with small populations. Thus, our simulations are not very accurate in the last few years before the elimination of CUC. Discrete event simulations would be more appropriate for these simulations.

Even with all our precautions and conservative assumptions, the results of this model clearly show that preventing and treating cervical cancer in Cambodia is both effective and cost-effective. The first priority should be a nationwide screening programme based on VIA screening and cryotherapy (or similar methods to remove pre-invasive lesions). For ethical reasons, this programme should be accompanied by an increase in the capacity of the public health system to treat cervical cancer. Many aspects of this system still have to be addressed, such as the coverage of transport and treatment costs by health equity funds, NSSF and other organisations. But, the results of these simulations clearly indicate to the Royal Government of Cambodia and the donor community that it is time to start addressing cervical cancer in Cambodia.

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Annex 1: System Dynamics Model

Variables:

$P_{t,s,a,h}$	Population in time *t* of sex *s* in age *a* in health status *h* with $s = \begin{cases} 1 & \text{male} \\ 2 & \text{female} \end{cases}$ a =Age [years], a=0..99 $h = \begin{cases} 1 & \text{not infected} \\ 2 & \text{infected, healthy} \\ 3 & \text{infected, lesion} \\ 4 & \text{cancer} \end{cases}$
$I\_P_{t,s,a}$	Newly infected through stable partnership in time *t* of sex *s* in age *a*; s=1,2; a=0..99
$I\_S_{t,s,a}$	Newly infected through short-term relationship in time *t* of sex *s* in age *a*; ; s=1,2; a=0..99

Constants:

$f_{t,a}$	Fertility of age *a* in time *t*, a=0..99
$m_{t,a,s}$	Mortality of age *a* of sex *s* in time *t*, s=1,2; a=0..99
$i\_l_{s,a}$	Average transition period from health status 2 (infected, healthy) to health status 3 (infected, lesion) in sex *s* and age *a*, s=1,2; a=0..99
$i\_c_{s,a}$	Average transition period from health status 3 (infected, lesion) to health status 4 (cancer) in sex *s* and age *a*, s=1,2; a=0..99
$i\_d_{s,a}$	Average survival period of cancer in sex *s* and age *a*, s=1,2; a=0..99
l_r	Average period of spontaneous recovery
$q_{t,s,a}$	Medical infectivity for a person of sex *s* and age *a* in year *t*, s=1,2; a=0..99
d_p	Average lengths of a stable partnership [years]
$k\_p_{s,a}$	Coitus frequency in stable partnership of a person of sex *s* in age *a*, s=1,2; a=0..99
$s\_p_{s,a,u,v,}$	Selection wish of stable partnership of person of sex *s* with age *a* for a person of sex *u* with age *v*, s=1,2; a=0..99; u=1,2; v=0..99
$s\_i_{s,a,u,v,}$	Number of promiscuous sexual interactions which a person of sex *s* with age *a* wishes with a person of sex *u* with age *v*, s=1,2; a=0..99; u=1,2; v=0..99
$sp_{s,a}$	Maximum inclination of a person of sex *s* in age *a* towards a stable partnership, s=1,2; a=0..99
$si_{s,a}$	Maximum wish of promiscuous partners of a person in sex *s* and age *a*, , s=1,2; a=0..99
scr	Screening programme parameter $scr = \begin{cases} 1 & \text{if screening program exists and screening is done in year t} \\ 0 & \text{else} \end{cases}$
asu	Lowest age-set included in screening programme
aso	Highest age-set included in screening programme
cs	Compliance of screening
$sp_{s,a}$	Maximum inclination of a person of sex *s* in age *a* towards a stable partnership, , s=1,2; a=0..99
$si_{s,a}$	Maximum wish of promiscuous partners of a person in sex *s* and age *a*, s=1,2; a=0..99

t*	Beginning of simulation [year]
Fs	Screening interval [years]
t**	End of simulation [years]
q_normal	Medical infeciosity without vaccination
vs	Start of vaccination programme [years]
ve	Effectiveness of vaccination [%]
vc	Vaccination compliance [%]
$vi_{t,s,a}$	Share of immunized in time *t* of sex *s* in age *a*, s=1,2; a=0..99

1. Demography

1.1. Fertility

$$\Delta P_{t,1,0,1} = 0.5 \cdot \sum_{a=15}^{45} \sum_{h=1}^{3} P_{t,2,a,h} \cdot f_{t,a}$$

$$\Delta P_{t,2,0,1} = 0.5 \cdot \sum_{a=15}^{45} \sum_{h=1}^{3} P_{t,2,a,h} \cdot f_{t,a}$$

1.2. General mortality

$\Delta P_{t,s,a,h} = P_{t,s,a,h} \cdot m_{t,a,s}$ for a=0..99, s=1..2, h=1..4

1.3. Ageing

$\Delta P_{t,s,a,h} = -P_{t,s,a,h}/365$ for a=0..99, s=1..2, h=1..4

$\Delta P_{t,s,a+1,h} = P_{t,s,a,h}/365$ for a=0..98, s=1..2, h=1..4

2. Transition

2.1. Progression from 'infected, healthy' to 'infected, lesions'

$\Delta P_{t,s,a,2} = -P_{t,s,a,2}/i\_l_{s,a}$ for s=1..2, a=0..99

$\Delta P_{t,s,a,3} = P_{t,s,a,2}/i\_l_{s,a}$ for s=1..2, a=0..99

2.2. Clearance

$\Delta P_{t,s,a,2} = -P_{t,s,a,2}/\mathrm{l\_r}$ for s=1..2, a=0..99

$\Delta P_{t,s,a,1} = P_{t,s,a,2}/\mathrm{l\_r}$ for s=1..2, a=0..99

2.3. Invasion

$\Delta P_{t,s,a,3} = -P_{t,s,a,3}/i\_c_{s,a}$ for s=1..2, a=0..99

$\Delta P_{t,s,a,4} = P_{t,s,a,3}/i\_c_{s,a}$ for s=1..2, a=0..99

2.4. Cancer to death

$\Delta P_{t,s,a,4} = -P_{t,s,a,4}/i\_d_{s,a}$ for s=1..2, a=0..99

3. Stable partnership infections

$$I\_P_{t,s,a} = \sum_{u=1}^{2} \sum_{v=14}^{99} \left[\frac{P_{t,s,a,1}}{P_{t,s,a,1}+P_{t,s,a,2}+P_{t,s,a,3}} \cdot \frac{P_{t,u,v,2}+P_{t,u,v,3}}{P_{t,u,v,1}+P_{t,u,v,2}+P_{t,u,v,3}} \cdot \frac{1}{d_p} \cdot \left\{ 1 - \left(1 - q_{t,s,a}\right)^{d_p \cdot Min\left(k p_{s,a}; k p_{u,v}\right)} \right\} \cdot \right.$$

$(1 - vi_{t,s,a}) \cdot MIN\left\{s_{p_{s,a,u,v}} \cdot \left(P_{t,s,a,1} + P_{t,s,a,2} + P_{t,s,a,3}\right); s_{p_{u,v,s,a}} \cdot \left(P_{t,u,v,1} + P_{t,u,v,2} + P_{t,u,v,3}\right)\right\}\Bigg]$ for s=1..2 and a=14..99.

4. Infection during short-term relationship

$$I\_S_{t,s,a} = \sum_{u=1}^{2} \sum_{v=14}^{99} \Bigg[\frac{P_{t,s,a,1}}{P_{t,s,a,1} + P_{t,s,a,2} + P_{t,s,a,3}} \cdot \frac{P_{t,u,v,2} + P_{t,u,v,3}}{P_{t,u,v,1} + P_{t,u,v,2} + P_{t,u,v,3}} \cdot q_{t,s,a} \cdot \left(1 - vi_{t,s,a}\right) \cdot MIN\left\{s\_i_{s,a,u,v} \cdot \left(P_{t,s,a,1} + P_{t,s,a,2} + P_{t,s,a,3}\right);\ s\_i_{u,v,s,a} \cdot \left(P_{t,u,v,1} + P_{t,u,v,2} + P_{t,u,v,3}\right)\right\}\Bigg]$$

for s=1..2 and a=14..99.

5. Adjustment for infections

$\Delta P_{t,s,a,1} = P_{t,s,a,1} - I\_P_{t,s,a} - I\_S_{t,s,a}$ for s=1..2 and a=14..99

$\Delta P_{t,s,a,2} = P_{t,s,a,1} + I\_P_{t,s,a} + I\_S_{t,s,a}$ for s=1..2 and a=14..99

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