Cervical Cancer in Cambodia: Can we afford not to address it?

**KEY MESSAGES**

- Cervical cancer is the second most common cancer among women worldwide, and the most severe cancer among women in Cambodia.

- There are an estimated 10,000 women living with cervical cancer in Cambodia now. Every year, approximately 1,500 women will develop cervical cancer, and 800 will die from it.

- Cervical cancer kills almost half as many women every year as maternity-related conditions.

- Cervical cancer is primarily caused by the human papilloma virus (HPV) which is sexually transmitted.

- Cost-effective and affordable preventive and therapeutic interventions exist for Cambodia.

- However, cost-effectiveness depends on the quality and efficacy of interventions:
  - Treatment at national referral hospitals is currently cost-effective, but there is room for improvement.
  - A ‘see-and-treat’ approach, combining screenings for all women between 30 and 49 years old every three years and cryotherapy, is the most cost-effective intervention as long as costs for screening can be maintained under USD 5.
  - Vaccination programmes would only have an impact on cervical cancer rates after 25 years, and would only be cost-effective if a long-term perspective is considered.

- For the vaccine to be effective, women need to be inoculated against HPV before first sexual intercourse.

- Cambodia should start implementing a screening and treatment programme as soon as possible, complemented with an HPV vaccination programme, with the support of its health partners. This comprehensive intervention would cost around USD 4 million a year, but avert 750 deaths a year by 2030.

- Compliance with screening and treatments could be promoted through already proven strategies, such as vouchers.
Introduction – Noncommunicable diseases: a priority for Cambodia

Noncommunicable diseases (NCDs) are on the rise, worldwide and in Cambodia, with an immense negative impact on societies and health systems. NCDs threaten to exacerbate poverty and exert an enormous cost on the Cambodian economy. The World Health Organization estimates that the four most severe NCDs (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes) cause about 50% of adult deaths in Cambodia, and this figure is projected to rise further as a consequence of changes in lifestyle and environment. Fighting NCDs requires a mix of interventions, combining preventive and therapeutic strategies. Implementing such a disease-based approach is a complex endeavour and demands a well-structured health system. This paper gives an overview of the disease burden of cervical cancer in Cambodia, and the rationale for preventive and therapeutic actions against it, arguing that such actions can be cost-effective, as also technically and financially feasible.

Rationale – Why address cervical cancer

Cervical cancer, or cervix uteri carcinoma (CUC) is a malignant neoplasm (cancerous tumour) that is almost exclusively caused by a persistent infection of the human papilloma virus (HPV) that is sexually transmitted. CUC is the second most common type of cancer in women worldwide, with more than 85% of attributed deaths in low- and middle-income countries. CUC has tremendous social and economic costs, which hamper economic development. Most cases are diagnosed in women when they are about 50 years old. Despite its prevalence, most cases of CUC are preventable. In high-income countries, prevention programmes have led to a massive reduction of cases and deaths by combining primary prevention (vaccination) and secondary prevention (screening and early removal of precancerous lesions). Such strategies can prevent up to 80% of cervical cancers.

About 3% of all adult women in Cambodia may have pre-malignant cervical lesions – small wounds on the cervix that can become cancerous if not treated. This represents as many as 165,000 women, or 1% of the total population. Of these women, approximately 1,500 women will develop CUC, and 800 will die every year if the current situation is not averted, making it the most severe cancer among the female Cambodian population. This makes CUC a national issue at the same level as maternity-related deaths, which have continuously declined in Cambodia but still account for 1,700 deaths every year.

Analysis – Addressing cervical cancer in a cost-effective way

Possible Interventions

Cervical cancer is one of the diseases already prioritised for action in the National Strategic Plan for the Prevention and Control of Noncommunicable Diseases. Primary prevention through HPV vaccination is the most effective way to avert CUC, but the cost of vaccination needs to be compared to other alternative or complementary strategies. Vaccination is also most effective only if women are inoculated before their first sexual intercourse. Thus, complementary prevention strategies such as screening and early treatment are needed to reduce the burden of CUC in the medium-term.
Cost-effectiveness analysis

Selecting and combining public health interventions should be based on their comparative cost-effectiveness. Common measures to assess cost-effectiveness try to capture 'value-for-money' of an intervention or combination of interventions. This can be expressed by comparing the cost of the intervention by the number of deaths averted, or the years of life saved. Interventions can then be compared on their cost-effectiveness in order to be prioritised by decision-makers. Assessing if individual interventions are cost-effective requires a threshold to be set – a value for each life-year saved which is high enough to be worth investing in by public authorities. A commonly used threshold is the average gross national product (GNP) per capita, which is the value each individual in a country adds annually. An intervention is considered cost-effective as long as the cost of saving one year of life is less than what that life would have potentially contributed to the country's economy of a country. Such an assessment raises ethical and social concerns on its appropriateness, but is unavoidable as rational decisions on allocation of resources are needed.

Another advantage of cost-effectiveness analysis is that it assesses assumptions about prices and average expenditures per case. They allow efficiency targets to be set, by determining the threshold unit costs per life-year saved of each intervention. This means that such studies can help set maximum costs that a health system can accept before an intervention stops being cost-effective.

There are three different CUC screening methods that are proven effective:

- Visual inspection using acetic acid (VIA) – visual inspection of the lower uterus, the cervix, using chemically pure vinegar to spot lesions;
- Pap-smear – an examination of scraped cervical cells under a microscope;
- HPV-DNA-test – a blood test in which the presence of HPV is confirmed by testing for the genetic code of HPV.

VIA has the advantage that it can be directly combined in a 'see-and-treat' strategy by immediately removing the potentially precancerous lesions using cryotherapy, a relatively simple intervention. In cryotherapy, a very cold chemical is used to freeze, kill and subsequently remove the suspected lesions.

In the absence of prevention, CUC may develop, and invasive cancer treatments will be required such as radiation therapy, chemotherapy and, often, surgical removal of the uterus. Currently, only the national referral hospitals in Phnom Penh provide such advanced interventions.

Cost-effectiveness, prioritising and setting expenditure targets

The National Strategic Plan for the Prevention and Control of Noncommunicable Diseases already identifies the priority interventions to address CUC. These recommendations are based on international evidence. Unfortunately, the strategy lacked costing and country-specific data to support its implementation. Evidence from a costing and modelling study which addressed this information gap is briefly presented here.¹

This study assesses the cost-effectiveness of invasive cancer treatment, 'see-and-treat' and HPV vaccination in the Cambodian context under set assumptions, termed 'scenarios'. It also presents estimates of the budgetary needs for a national implementation of the most cost-effective scenarios.

The next paragraphs present the cost-effectiveness figures for independent and combined intervention scenarios.

**Invasive cancer treatment**

Measuring the effectiveness of a treatment that may only extend life expectancy, in cases such as cancer, is delicate. However, survival rates are usually used to assess the effectiveness of cancer treatments. These measure the percentage of patients that are still alive five years after diagnosis/prognosis – usually 90% for early stage CUC but less than 10% for the most advanced stage.

Currently, treatment of CUC at national referral hospitals only costs about USD 800 per patient per year. This low cost is partially explained by the technologies available, but also the relatively low labour costs in Cambodia. However, CUC treatment that costs up to USD 1,900 per patient annually would still be considered cost-effective as long as 25% of patients were effectively healed. Investing in effective treatment also has medium- and long-term saving effects. A treatment protocol that would only extend patient survival from two to four years, could cost up to USD 3.3 million by 2025 and still be cost-effective. By comparison, any effective treatment which would heal over 10% of patients would reduce the direct annual costs for the health system by more than half.

**See-and-treat**

An obvious driver of cost in this intervention is the frequency at which screening is proposed to women and their rate of compliance, which means the rates at which women are screened using the VIA protocol and potentially cancerous tissues are removed through cryotherapy.

Assuming 50% compliance with VIA screening and 75% compliance with cryotherapy treatment, the study suggests that even offering screenings every five years to all women between 30 and 60 years old would still be cost-effective, and a maximum number of deaths could be averted. However, the study recommends first proposing screenings only every three years to women between 30 and 49 years of age to limit the financial needs of a national programme. Such limitation would result in a programme that would cost less than USD 800,000 a year by 2025 and be highly cost-effective, as long as the average unit costs for VIA could be maintained under USD 5.

**Vaccination**

The efficacy of HPV vaccination is only ensured if full immunisation can be achieved before first potential contact with the sexually transmitted virus HPV – ideally, when girls are between nine and 13 years old. Considering the time between age of first sexual contact and CUC diagnosis, this means that vaccination campaigns will only achieve a maximum return on investment after 40 years. Also, compliance with vaccination is unlikely to be complete for a vaccine that targets teenagers on a voluntary base.

HPV vaccines are relatively recent developments with limited effectiveness – full immunisation is only achieved by 63% of women after three injections of the vaccine, and lifetime immunisation is not yet verified. Each dose of the vaccine costs USD 22.50 but is currently only provided at private clinics for approximately USD 50.

Taking into account the above constraints, the study concludes that a national HPV vaccination campaign would still be cost-effective if a long-
term perspective (of 100 years) is taken into consideration. A HPV vaccination campaign could be initiated for as little as USD 2 million, and would reach USD 3 million by 2025. In the medium-term, the cost of full vaccination would need to be reduced substantially to improve cost-effectiveness. This can only be achieved in the framework of a global movement, as there are only a few companies producing HPV vaccines worldwide. Experience in other low-income countries shows that such campaigns can be initiated with the support of partners such as Gavi, the Vaccine Alliance. However, even most high-income countries still lack national HPV vaccination programmes.

**Combined interventions**

A comprehensive programme to tackle CUC is needed. The above sections illustrate that individual programme components are cost-effective on their own. However, the study also suggests that synergies can be achieved from a comprehensive national programme which would combine decentralised prevention through ‘sea-and-treat’ and vaccination with CUC cancer treatment at a central level. VIA screening is also likely to uncover advanced stages of CUC, for which not providing treatment would be unethical.

The study suggests that a comprehensive nationwide programme combining all interventions could be initiated for less than USD 4 million a year, at around USD 0.26 per capita per year. Such a programme would still be cost-effective due to the combined effects of reduced mortality and life-years saved, but as long as a medium-term perspective of 20 years is considered.

In addition to these combined interventions, appropriate reproductive health education may further prevent the spread of sexually transmitted infections such as HPV. Such information, education and communication strategies were not costed as part of the study but should at least target behavioural change communication for risk reduction, condom use and male circumcision (when culturally appropriate).

**Conclusions**

The results of the costing study summarised in this paper confirm the appropriateness of the interventions identified in the National Strategic Plan for the Prevention and Control of Noncommunicable Diseases. They further underline the financial feasibility of such a comprehensive programme to address an urgent public health issue. However, implementing such a programme will require initial investment of both political and logistical capital. The capacity development costs of such a programme have not been considered. Fortunately, the options considered in this study are also the most feasible for the public health system. VIA and cryotherapy require a low level of investment for both technical skills development and equipment. Over the years, Cambodia has also developed substantial capacities in implementing vaccination programmes, which can be applied to an HPV vaccination campaign.

Another main consideration of policy-makers should be the continuous increase in long-term costs of not addressing CUC. Addressing existing cases will be even more costly as cases increase with population growth. The associated economic and social impacts will be substantial if an intervention programme is not rapidly initiated.
Currently, undiagnosed CUC cases may amount to more than 10,000. Many of these will be diagnosed in the first screening round of the programme, which will result in an initial rapid increase in treatment costs and pressure on existing therapeutic capacities.

Continuous strategic adjustments will therefore be needed in addressing CUC. In particular, complementary demand-generating interventions will be required to ensure uptake of new services. Similar interventions that have proven successful in other low-income countries include voucher programmes in combination with capacity building of health providers and social marketing at the local level. The Cambodian Ministry of Health is currently implementing a similar voucher programme for reproductive health services with the support of the German development cooperation. The lessons learned by implementing this programme will provide valuable evidence on the costs of such a strategy, as well as the most effective strategies to reach women and address a major public health issue.

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