Cost-effectiveness of prevention strategies against cervical cancer in women, Vientiane, Lao PDR

Thèse

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Résumé

Introduction: En RDP Lao, le cancer du col de l'utérus est une des causes principales de morbidité et mortalité dues aux cancers. Le cancer du col peut être prévenu par des interventions de prévention primaire (vaccination) et secondaire (dépistage). Afin de réduire le fardeau de cette maladie, nous devrions considérer le coût et efficacité des diverses options de prévention pertinentes compte tenu des spécificités du contexte Lao.

Objectives : l'objectif principal de ce travail est de simuler le coût-efficacité de stratégies préventives contre le cancer du col de l'utérus en RDP Lao. La thèse est basée sur trois études. La première étude a pour but de déterminer la sensibilité et la spécificité de la combinaison test à l'acide acétique (IVA) et frottis du col comme outil de dépistage. Ces paramètres ont été utilisés dans la troisième étude. La deuxième étude a pour but de déterminer le coût-efficacité de modalités de vaccination. La troisième étude a pour but de déterminer le coût-efficacité d'options de dépistage.

Méthodologie : Une revue systématique et une méta-analyse ont été réalisées pour la première étude. Pour la deuxième et troisième étude, un modèle dynamique de la population a été établi pour refléter l'histoire naturelle du cancer du col de l'utérus. Le modèle a été calibré pour tenir compte de la structure d'âge de la population de la Capitale de Vientiane, ainsi que l'incidence du cancer du col de l'utérus et sa mortalité en RDP Lao. La principale issue d'intérêt était le coût incrémental des Années de vie ajustées pour l'incapacité (DALY), dans la perspective du système de santé publique. Le seuil utilisé pour définir si l'investissement requis devrait être considéré comme coût-efficace était celui proposé par l'OMS, soit un ratio coût-efficacité incrémental (ICER) de moins de un PNB per capita par DALY évité.

Résultats : L'estimation moyenne de la sensibilité et de la spécificité de la combinaison des tests pour les cas de positivité (un de deux tests est positive) étaient de 0.87 (95% CI: 0.83-0.90) et 0.79 (95% CI: 0.63-0.89) respectivement. La deuxième étude a montré que la vaccination des jeunes filles âgées de 10 ans est très coût-efficace. Ajouter au programme de vaccination des jeunes filles un rattrapage vaccinal pour les femmes de 11 à 25 ans est plus coût-efficace qu'ajouter les garçons. Cependant, il faut augmenter l'âge maximal du rattrapage vaccinal à 75 si la couverture vaccinale est moins de 50% ou bien si la durée de protection du vaccin ou l'immunité naturelle ne dure pas plus que 10 ans ou si l'incidence de cancer du col de l'utérus est supérieure à 40% de l'estimation de Globocan, soit 17.5 cas pour 100 000 femmes. De plus, ajouter le dépistage à la vaccination des jeunes filles est une option plus coût-efficace que la vaccination seule. Parmi les stratégies de dépistage, l'IVA pour les femmes âgées de 30-65 ans tous les trois ans est l'option la plus coût-efficace. Elle est suivie par le test rapide de détection d'ADN-VPH tous les trois ans et la

combinaison IVA-frottis conventionnel tous les cinq ans. La probabilité d'être coût-efficace pour ces stratégies est de 73%.

Conclusion : Les décideurs devraient considérer d'étendre le programme de vaccination des jeunes filles actuellement mis en place à la capitale de Vientiane à l'ensemble du pays et de considérer l'ajout d'un composant de rattrapage vaccinal et un dépistage par IVA ou un test rapide de détection d'ADN-VPH.

Abstract

Introduction: In Lao PDR, cervical cancer is a leading cause of cancer morbidity and mortality. Cervical cancer can be prevented by primary (vaccination) and secondary (screening) interventions. To reduce the burden of this disease, we need to consider both the cost and effectiveness of the various prevention options that are relevant to the Lao context.

Objectives: The main objective of this thesis is to simulate the cost-effectiveness of prevention strategies against cervical cancer in Lao PDR. The thesis is based on three studies. The first study aimed to determine the average sensitivity and specificity of combined Visual Inspection with Acetic Acid (VIA) and cytology testing. Theses parameters were used for the third study. The second study aimed to determine the cost-effectiveness of various vaccination modalities. The third study aimed to determine the cost-effectiveness of screening strategies.

Methodology: A systematic review and a meta-analysis were conducted for the first study. For the second and third studies, a population-based compartment and dynamic model of the natural history of cervical cancer was built. The model was calibrated to the age structure of the Vientiane capital population, and the incidence and mortality rates of cervical cancer in Lao PDR. The main outcome of interest was the incremental cost per Disability-Adjusted Life Year (DALY) averted, under a public health care system perspective. The threshold for declaring an option very cost-effective was an Incremental cost-effectiveness ratio (ICER) lower than one GDP per capita per DALY averted, based on WHO recommendations.

Results: The pooled estimates of the sensitivity and specificity of the combined VIA and cytology testing (with a positive result in at least one of them) were 0.87 (95% CI: 0.83-0.90) and 0.79 (95% CI: 0.63-0.89), respectively. The second study showed that a 10-year-old girl vaccination program is very cost-effective. Adding a catch-up vaccination element for 11-25 year old women to a girl vaccination program was more cost-effective than adding a boy vaccination component. However, the catch-up should be extended to a higher age if vaccination coverage is lower than 50% or if the duration of the natural immunity or the duration of vaccine protection is no longer than 10 years or if the incidence of cervical cancer is higher than 40% of the Globocan estimates, i.e 17.5 cases per 100 000 women. Additionally, adding a screening strategy to a girl vaccination program is more cost-effective than vaccination alone. Among the screening strategies, a three-yearly VIA screening program for 30-65 year-old women is the most cost-effective strategy, followed by the three-yearly rapid HPV DNA testing option and the five-yearly combined VIA and conventional cytology option, respectively. The probability of cost-effectiveness for these strategies is around 73%.

Conclusion: Decision makers should consider expanding the girl vaccination program currently implemented in Vientiane capital nationwide and adding a catch-up vaccination element and a VIA or rapid HPV DNA testing program as appropriate.

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Preface

This thesis is concerned with a top current public health priority in Lao PDR: the definition of relevant strategies to decrease the number of cervical cancers in the country, notably cervical cancers.

I have acted as principal investigator of the three studies. Since the beginning, I identified the topic I was interested working on, wrote the protocols and conducted the data collection and the analyses under the supervision of my advisors who validated the accuracy of this work.

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This thesis is based on three studies that led to three articles:

1. Accuracy of the combined Visual Inspection with Acetic Acid and cervical cytology testing as a primary screening tool for cervical cancer: a systematic review and meta-analysis. This article is published in the Asian Pacific Journal of Cancer Prevention (Asian Pac J Cancer Prev, 16 (14), 5889-5897 ; DOI:http://dx.doi.org/10.7314/APJCP.2015.16.14.5889). I designed the objective, methodology, I analyzed the data and wrote the manuscript. Lynne Moore and Daniel Reinharz validated the methodology. Mayfong Mayxay, Keokedthong Phongsavan, Donald E Marsden and Lisa Jane White gave comments on the manuscript.

2. Economic evaluation of Human Papillomavirus vaccination strategies against cervical cancer in women in Lao PDR: a mathematical modeling approach. This article is submitted to The Lancet Global Health. I designed, analyzed the data and wrote the article. Lisa Jane White validated the model and the results. Daniel Reinharz and Lynne Moore validated the methodology. Mayfong Mayxay, Donald E Marsden and Keokedthong Phongsavan validated the concepts and the realism of the results according to the Lao context. All authors gave comments and validated the final version.
3. Economic evaluation of screening strategies combined with preadolescent girl HPV vaccination against cervical cancer in Vientiane, Lao PDR. This article is submitted to PLos One. I designed, analyzed the data and wrote the article. Lisa Jane White validated the model and the results. Daniel Reinharz and Lynne Moore validated the methodology and the results. Mayfong Mayxay, Donald E Marsden and Keokedthong Phongsavan validated the concept and the realism of the results according to the Lao context. All authors gave comments and validated the final version.

Chapter 1 : Introduction

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1.1 Research rationale

Cervical cancer is the third cause of cancer morbidity and mortality in Lao women(1). Cervical cancer occurs at a relatively young age (15-44 years old) (1). Human Papillomavirus (HPV), a major risk factor of cervical cancer, is responsible for more than 99% of cervical cancers worldwide (2). In Lao PDR, the prevalence of HPV in women is still unknown (1). Around 2 million Lao women aged 15 years or older are estimated to be vulnerable to HPV infection (1). However, no national screening program or cancer management program exists in the country. Diagnostic approaches, such as precancerous screening (Visual Inspection with Acetic acid (VIA) and Papanicolaou (PAP) test) are available only in central and some provincial hospitals, and the coverage of such screening every three years is low, estimated at 5% among 18-69 year old women in urban areas and 1% in rural areas (1).

Risky sexual behavior, including early onset of sexual intercourse, multiple sex partners, high-risk sex partners and a history of sexually transmitted infections (STIs), have been shown to be associated with invasive cervical cancer through HPV infection (3). A survey indicated that sexual behavior of Lao young people has dramatically changed recently. People engage in sexual activities at an earlier age, and with multiple partners. Condom use with partners is low in both women and men (49% and 42% respectively). In addition, many married men have sexual activity with other partners than their spouse (4, 5).

HPV vaccination has been shown to be effective, providing nearly 100% protection against moderate and severe cervical intraepithelial neoplasia (CIN) related to HPV types 16 and 18 (6). In addition, cytology-based screening programs for cervical cancer have been shown to be effective for decreasing invasive cervical cancer by as much as 80% for a coverage rate of more than 80% (7). Even though cervical cytology screening is particularly effective in developed countries, its effectiveness faces challenges in low resource settings mainly because of quality issues with the procedure and the interpretation of the cytology results (8, 9). Public education and sociocultural norms also have an impact on screening coverage as they affect the contacts between at risk women and the health care system (10, 11).

Most cervical cancer cases are diagnosed at a late stage, but effective treatment for late-stage

cervical cancers, chemoradiation (10), is unavailable in Lao PDR. This underlines the importance of putting in place an effective screening strategy (12, 13). However, a screening strategy should take into account the sustainability, feasibility and accessibility relevant to the Lao context.

It is therefore relevant to establish the best screening strategy for cervical cancer in women in Lao PDR. To answer this crucial question, we need to consider not only the demonstrated effectiveness of a program, but also the capacity to implement the program and expected sustainability considering the Lao context. However, few data are available on the effectiveness and cost/effectiveness of the different available options considering implementation and sustainability issues specific to the Lao context. Decision makers in Lao PDR are therefore lacking information regarding which program should be implemented. Due to the difficulty of implementing a clinical trial on the subject, simulations should be considered to provide the necessary data to support the decision making process.

1.2 Objectives of the study

Our overarching goal is to determine the cost/effectiveness of prevention strategies against cervical cancer from the perspective of the public health care system in Lao PDR.

Specific objectives

1. To estimate the sensitivity and specificity of the combined VIA and conventional cytology testing using a systematic review and a meta-analysis;
2. To determine the cost-effectiveness of various HPV vaccination strategies against cervical cancer.
3. To determine the cost-effectiveness of screening strategies against cervical cancer in addition to a girl vaccination program.

Research hypothesis

The hypothesis underlying this thesis is that a preadolescent girl vaccination program is cost-effective but the cost-effectiveness can be increased by the addition of a catch-up or a screening component.

1.3 Literature review

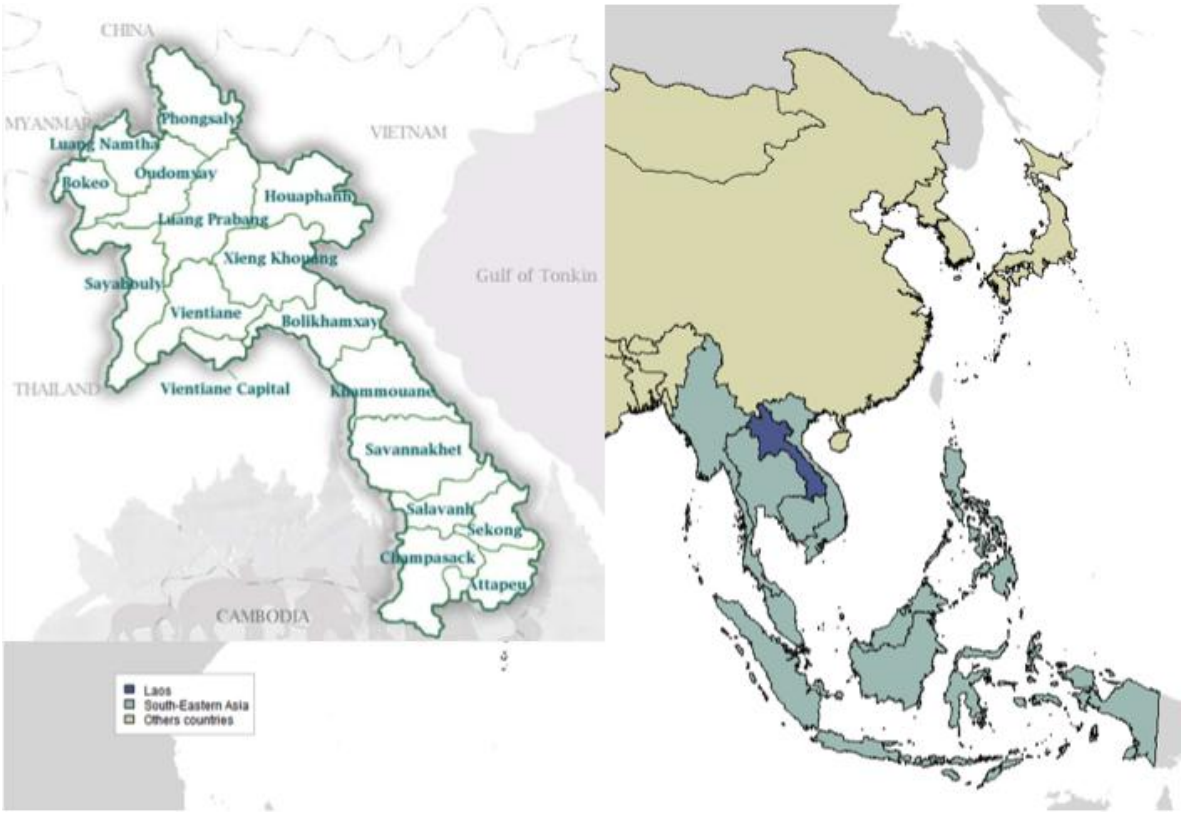
1.3.1 The burden of cervical cancer

Cervical cancer is an avoidable cause of death in women. Based on crude incidence rates, cervical cancer is the fourth most commonly diagnosed cancer, the seventh overall, and the fourth leading cause of cancer-related death in women worldwide (14). In developing countries, it ranks as the second most common cancer, following breast cancer(14). The last worldwide estimated number of annual new cases of cervical cancers was 528 000, accounting for 7.9% of all new cancer cases and 7.5% (275 100) of total cancer deaths among women. More than 85% of these cases and deaths occur in developing countries, where cervical cancers account for 12% of all female cancers(14). Based on the age-standardized rates (ASR), cervical cancer ranks as the third most common cancer in women worldwide for the incidence (ASIR= 43.3; 14.3 and 14/100 000 for breast, colorectum and cervix of uterus, respectively) and fourth for mortality (ASMR=12.9; 11.1; 6.9 and 6.8/100 000 for breast, lung, colorectum and cervical cancers, respectively) (14). Moreover, cervical cancer is an important contributor to the burden of disease of a country, as it is an early-onset cancer that occurs mostly in 15-44 year old women, resulting in proportionally more life-years lost compared to other major cancers (14).

1.3.2 Lao PDR and cervical cancer

1.3.2.1 General information on Lao PDR

Lao PDR is a tropical country located in South-East Asia and landlocked by Thailand, Myanmar, China, Vietnam and Cambodia. It has a population of approximately 7 million people with more than 67% living in rural areas and 37% under 15 years of age (15). There are officially 49 ethnicities, with the majority being ethnic Lao people (52.5%). Estimated life expectancy was higher in women (68.4 years) than men (65.3 years) in 2010-2015 (16). The country is currently categorized as a lower middle-income country. Yet, the remarkable economic development over the last decade (Gross Domestic Product “GDP” growth was 8% in 2011) hasn't been accompanied by an increase in well-being for the entire population. Poverty remains prevalent, particularly in rural regions where most of the population lives (17, 18). Vientiane Capital is the capital of Lao PDR. It is situated in the center of the country. The total estimated population was about 797 130 in 2012 including 304 600 women aged 10-65 years (19).



Source: The Institut Catala d'Oncologia (ICO) Information Centre on HPV and Cancer (1)

1.3.2.2 Health policy and system of Lao PDR

The public health care system is the main health care provider and consists of four levels: primary health care (village health volunteers, health centers), district hospitals, provincial hospitals and the central hospitals, where specialists are based (20). Disease prevention and health promotion as well as improvement in the quality of health care services have been documented as important issues for the government (21). Nevertheless, the Lao health care system is characterized by some disadvantages, due to a lack of competent staff and poor financial support, which leads to poor offer and utilization of health services (22). The major source of funding and technical support is external, coming from a range of international non-governmental sectors and bilateral cooperation. Primary health care, maternal-child health, health system development, and aid effectiveness and coordination have been identified as priority areas by the government for the health care sector. Nevertheless, communicable diseases remain the main cause of morbidity and mortality due to the lack of proper sanitation and water supply, malnutrition, poor health awareness, poor hygiene habits and inadequate access to quality health care. Furthermore, tobacco consumption, boosted by changing lifestyle has become a major preoccupation (23).

In Lao PDR, a country with low-resources, facilities and medical human resources remain a challenge. Currently, there is no medical oncologist or oncology nurse in Lao PDR, and there is only one gynecology pathologist. Additionally, there are no anti-cancer drugs for cervical cancer registered at the Lao Food and Drug Department (personal communication with Keokedthong Phongsavan).

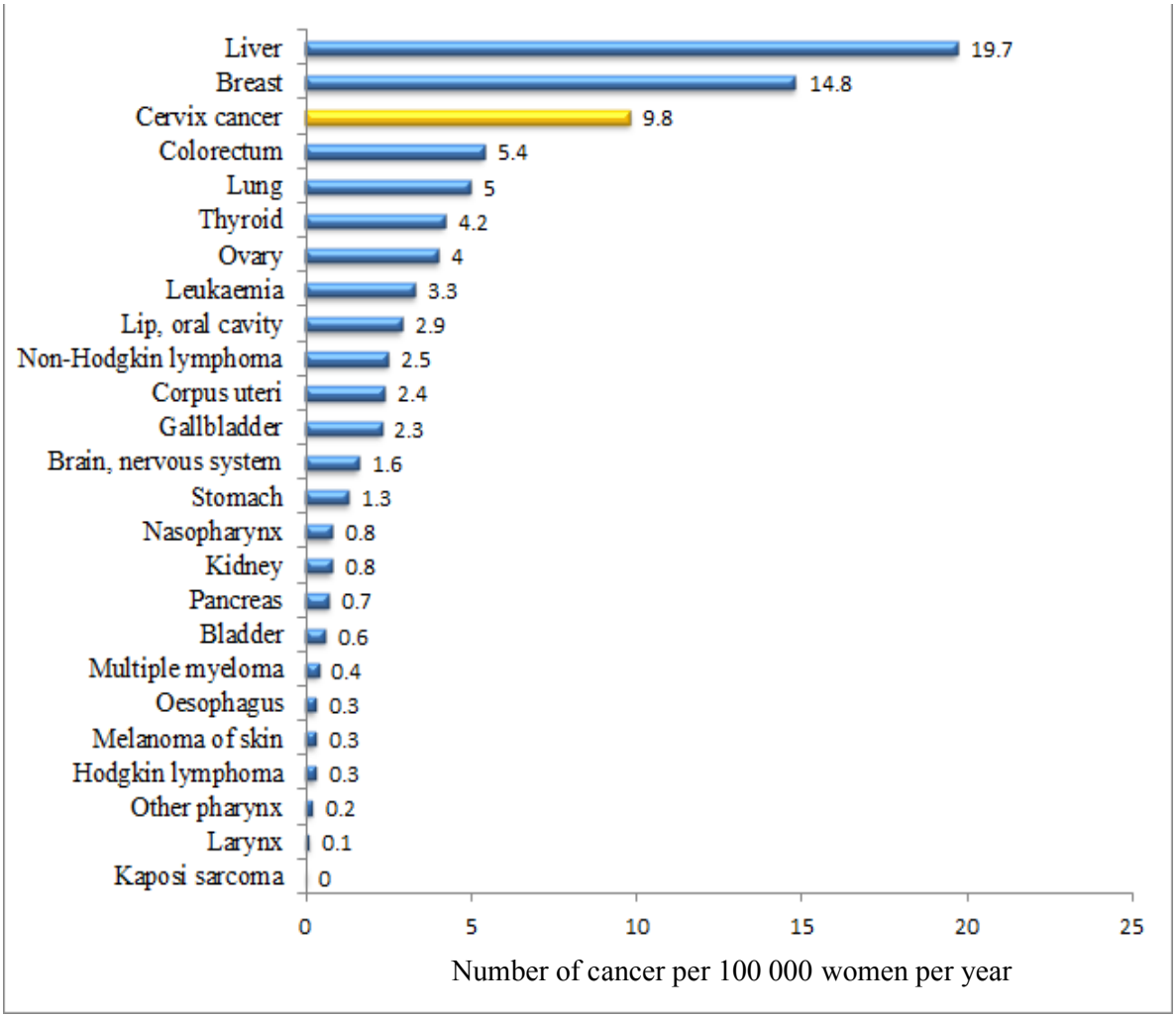
1.3.2.3 Cervical cancer in Lao PDR

Presently, there is no cancer registry in Lao PDR. Cervical cancer screening services (VIA and cytology) are only available at central hospitals. Nevertheless, a recent estimate (2012) from the International Agency for Research on Cancer (IARC) or Globocan (Global Burden of Cancer Study) indicated that cervical cancer was the third most frequent cancer among Lao women, based on annual crude incidence rates (Figure 1), and it had the second incidence among cancers and cancer-related deaths in women aged between 15 and 44 years(1). The incidence is highest in women aged between 50 and 60 years (Figure 2). It is estimated that 314 cases and 168 deaths of cervical cancer occur annually. The age-standardized incidence and mortality rates are 12.5 and 7.4 cases per 100 000 per year (Figure 3). Among eleven countries of South-East Asia, annual incidence rate and mortality of cervical cancer in Lao PDR ranked ninth and seventh, respectively (Figure 4) (1).

Compared to an estimate in 2008, the annual incidence rate decreased in 2012 (22.1 vs 12.5 cases per 100 000 women) (24). However, the lower annual incidence rate of cervical cancer found in 2012 might be explained by different data sources used to produce the estimates in 2008 and 2012. In 2008, IARC used the cancer registry from North-East and North of Thailand (Khon Kaen and Chiang Mai provinces) (24). In contrast, only the registry from North-East of Thailand (Udon Thani (2004-2006) and Khon Kaen (2003-2007) provinces) was used in 2012 (1). Indeed, the annual incidence rate of cervical cancer is higher in Chiang Mai than in Khon Kaen (25).

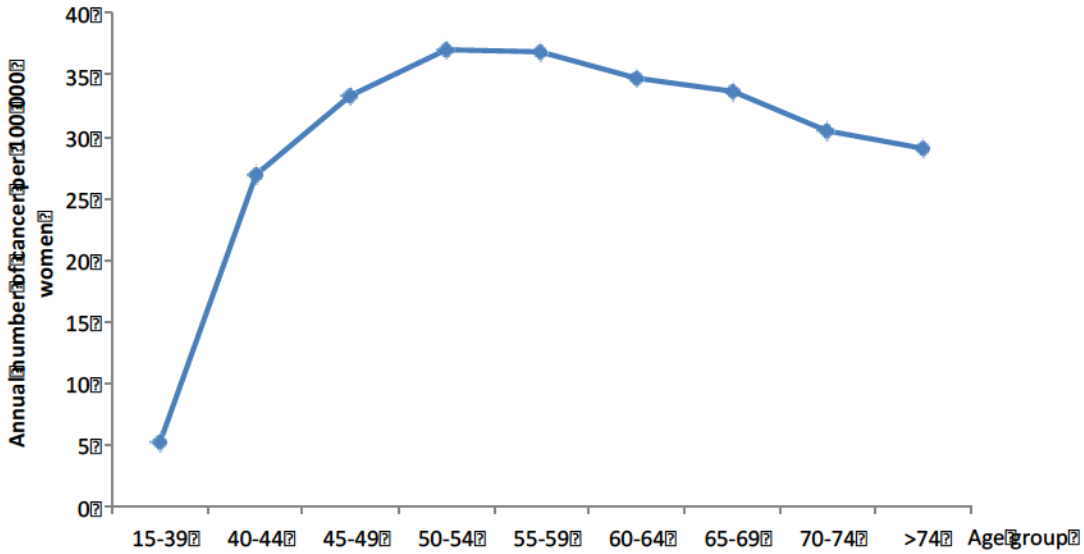
The most recent data on cancer mortality in Lao PDR showed that liver cancer ranked first in both males and females(1). Cervical cancer came third with a rate of 7.4 per 100 000 predominantly in women 75 years old and older (39.4 cases per 100 000 women) (figure 5) (1). Due to limited facilities for the management of cancer in Lao PDR, when they can afford it, people tend to seek care in neighboring countries particularly in Vietnam and Thailand (26). A recent retrospective study in Thai hospitals showed that among Lao women consulting in Thai hospitals for cancer, cervical cancer ranked first. In 45 to 64 year old women, this cancer constituted of 32% of all cases(27). Yet, most of them were already late stage cancers (22% stage III and 41% stage IV) (27).

Figure 1: Annual incidence rate of cervical cancer compared to other cancers in women from all ages in 2012, Lao PDR



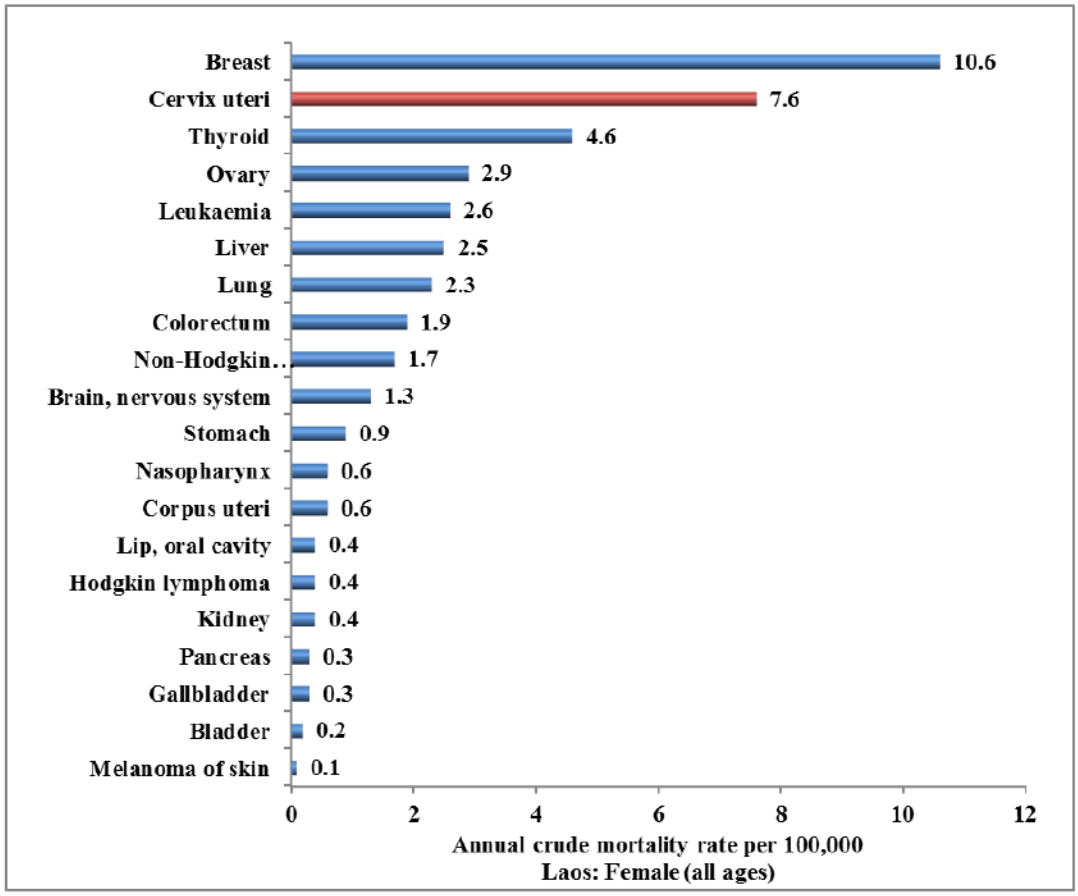
Source: ICO Information Centre on HPV and Cancer (1)

Figure 2: Estimate age-specific incidence of cervical cancer in women in 2012, Lao PDR



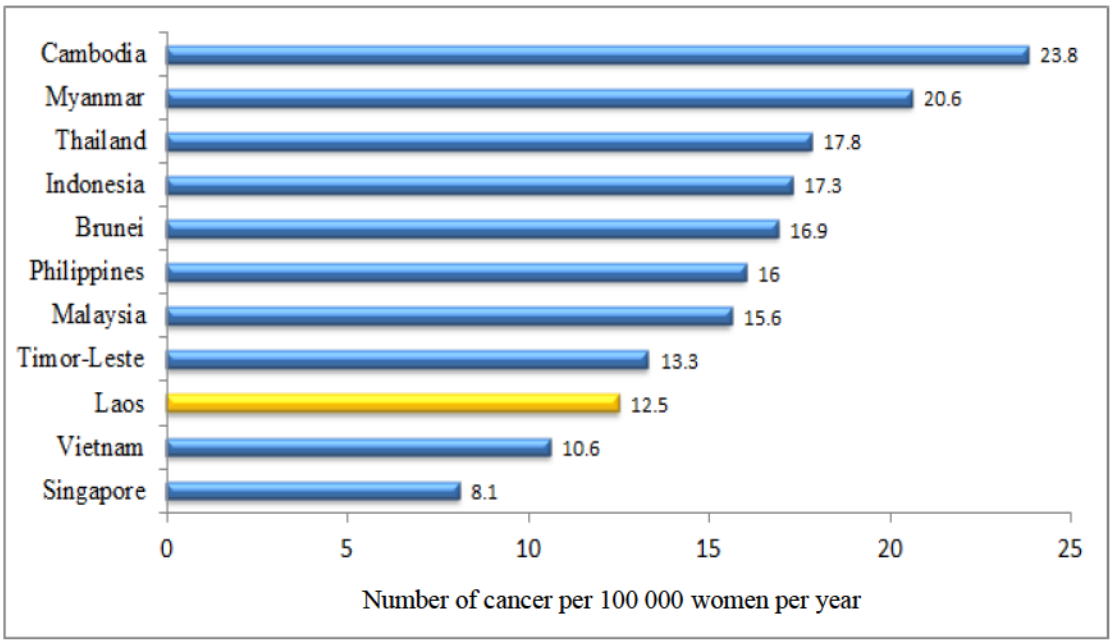
Source: ICO Information Centre on HPV and Cancer (1)

Figure 3: Age-specific incidence rate of cervical cancer compared to age-specific incidence rate of other cancers among women aged 15-44 years in 2012, Lao PDR



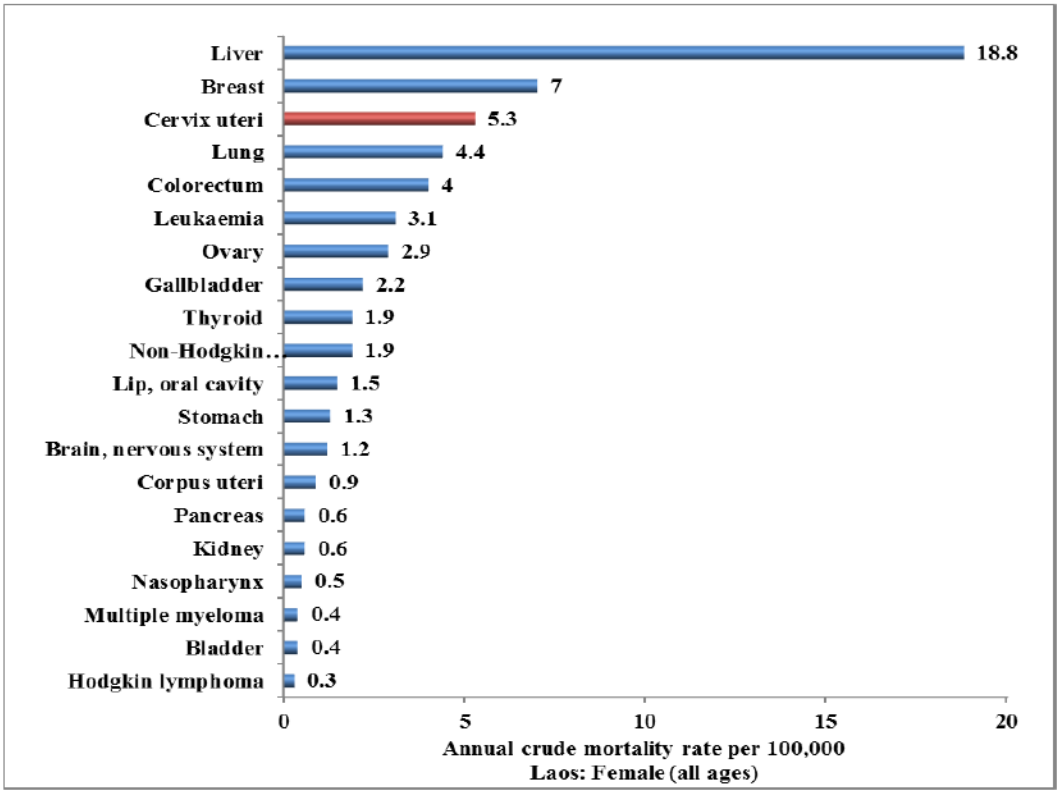
Source: ICO Information Centre on HPV and Cancer (1)

Figure 4: Age-standardized incidence rate of cervical cancer in 2012 in Lao PDR compared to other countries from the South-East Asia region



Source: ICO Information Centre on HPV and Cancer (1)

Figure 5: Cervical cancer mortality compared to other cancer mortalities in women of all ages in 2012, Lao PDR



Source: ICO Information Centre on HPV and Cancer (1)

1.3.3 Natural history of cervical cancer

HPV infection, the cause of almost all cases of cervical cancer, is predominant in young women. Generally, the infection clears up spontaneously within 1-2 years and induces acquired immunity with an estimated duration of at least 10 years (28). However, in 20% of women, HPV infection persists and might lead, over the time, to precancerous lesions (29, 30). These lesions are called Cervical Intraepithelial Neoplasia (CIN). CINs are divided into two categories, low grade (CIN1) and high grade (CIN2/3). CIN1 and CIN2/3 are not cancers (28).

The progression from HPV infection to low-grade or high-grade CIN is associated with the type of HPV infection; CIN1 is commonly caused by a concomitant infection with multiple HPV types while CIN2/3 is associated with a relatively homogenous infection, very few cases being associated with a concomitant infection with multiple HPV types (31). The disease can progress to a higher stage or regress, depending on the severity of precancerous lesions. Most (60%) low-grade CIN1 regress to normal, 30% will persist and 10-15% will progress to CIN2/3 (30, 32, 33). In one year, only 1% of CIN1 progresses to CIN2/3 (34). A meta-analysis showed that the risk of progression of low-grade CIN at 24 months to an invasive cervical cancer was 0.15% while it was 1.44% for a high-grade CIN (35).

1.3.4 Risk factors of cervical cancer

Human Papillomavirus, a sexually transmitted pathogen, is the most common risk factor of cervical cancer. There are also various factors that contribute to the development of cervical cancer following a HPV infection, notably cigarette smoking, immunosuppression (caused by certain diseases, medications, or HIV/AIDS), extended use of oral contraceptives, multiparity (3 or more full term births), younger age at first full-term pregnancy (younger than 20 year old), co-infection with *Chlamydia trachomatis and Herpes simplex virus,* a diet low in fruits and vegetables, low socioeconomic status, low age, diethylstilbestrol (DES) administered to the woman's mother and a family history of cervical cancer (3, 6, 36, 37).

Sexual activity-related determinants include:

- Early initiation of sexual activity: compared to women aged 21 years or older at first intercourse, 18-20 year old women have a 1.5-fold higher risk and women younger than 18 years of age have a two-fold higher risk of invasive cervical cancer (3).

- Multiple sexual partners: compared with women who have one partner, the risk is approximately two-fold higher for women who have two partners and three-fold higher for those who have 6 or more partners (3).
- Partners with high-risk sexual behavior (such as a partner with multiple sexual partners or known HPV infection).

Male circumcision is likely to indirectly protect current partners from cervical cancer. A case-control study performed in five countries showed that women whose sexual partners were circumcised had a lower risk of cervical cancer than those whose partners were uncircumcised (adjusted OR, 0.42; 95% CI, 0.23 to 0.79) (38).

Human Papillomavirus infection and cervical cancer

HPV infection is transmitted through direct skin-to-skin contact, including sexual intercourse, oral sex, anal sex, or any other contact involving the genital area, for instance, hand to genital contact (39). More than 200 genotypes have been identified, causing benign (low-risk, LR-HPV) or malignant (high-risk, HR-HPV) cutaneous or mucosal lesions (36, 40). The common types of HR-HPV are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82 and those of LR-HPV are 6, 11, 40, 42, 43, 44, 54, 61, 72, 81 (41). Among females, global HPV prevalence is estimated to be 11.7% (95% confidence interval, 11.6%-11.7%). Sub-Saharan Africa has the highest prevalence (24.0%), followed by Eastern Europe (21.4%), and Latin America (16.1%). In Asia, the prevalence is 8% (39).

In Lao PDR, according to the last study among Lao women living three province in Central and South (Vientiane capital, Vientiane province and Champassak province), the prevalence of HR-HPV is 11%, and the most common type is the group HPV33/52/58 (3%), followed by the single type 16 (2%) and the group 18/45 (1%) (42). The high prevalence of HR-HPV in Lao PDR compared to HPV prevalence in Asia (8%) might be due to the fact that the study was conducted only in women aged 25-48 years old, which are a mostly high-risk population of HPV persistence.

HPV is the most common cause (99%) of cervical cancer worldwide (2). Types 16 and 18 are responsible for 70% of cervical cancer (43, 44) and types 6 and 11 are the most common cause of warts (40, 45, 46). Indeed, different genotypes cause different histological anomalies. For instance, HPV type 16 causes squamous cell carcinoma and type 18, adenocarcinoma (47).

1.3.5 Prevention strategies against cervical cancer in Lao PDR

Primary prevention

A pilot project consisting of a WHO-supported and GAVI-funded vaccination program using the quadrivalent HPV vaccine for grade 5th schoolgirls was started in October 2013 in Vientiane Capital and Vientiane province. It is estimated that about 13 000 girls will be vaccinated each year. An evaluation will assess the effectiveness of the program after its second year. However, the sustainability of this HPV vaccination program is not guaranteed as it relies on international funding (48).

Routine screening of cervical cancer

In Lao PDR, there is no national treatment guideline for cervical cancer. However, cytology examination and VIA have been implemented as opportunistic screening strategies. Cytology screening is available only in teaching hospitals in Vientiane capital, but with various interpretation systems, some hospitals not using the Bethesda system. In 2013, VIA screening was introduced as a pilot-project in one district hospital (Phon Hong district) and at a provincial hospital (Maria Teresa Hospital) in Vientiane province (personal communication).

The estimated coverage of cervical cancer screening practice, either by cytology or VIA, for 2001-2002 is very low: 5.2% and 1.4% every three years in urban areas and rural areas, respectively (1). The highest coverage rate is found among 30-39 year old women (4%) and the lowest in 60-69 year old women (0.8%) (1). There is no evidence regarding if the screened women belong predominantly to a high economic status. A study has shown that the lack of subjective symptoms was the main reason of not having a gynecological examination (49). Moreover, the initial age of screening and its frequency remains controversial in Lao PDR (personal communication with experts).

There are four teaching hospitals in the Vientiane capital called: Setthathirath, Mahosot, Friendship, and Mother and Child. According to experts (personal communication), colposcopy is available at these hospitals, but very few gynecologists are trained to use them. Cryotherapy and LEEP are available for precancerous lesion treatment, while only hysterectomy is offered for invasive cervical cancer. However, some patients with invasive cervical cancer might be able to afford a chemoradiation in neighboring countries, such as Thailand, Vietnam and China.

1.3.6 The efficacy of preventive strategies of cervical cancer

Preventive strategies for cervical cancer consist of primary and secondary prevention interventions. Primary prevention consists of HPV vaccination and prevention of sexually transmitted infections, while secondary prevention consists of early diagnosis through precancerous lesion screening and early treatment. There are currently three types of effective HPV vaccines available, the bivalent (HVP types 16 and 18), the quadrivalent (HPV types 16, 18, 6 and 11) and nine-valent (HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58) vaccines. The efficacy of these vaccines is nearly 100% in preventing the development of persistent infections and cervical precancerous lesions, once three doses have been administrated prior to the initiation of sexual activity, or to women without prior infection with these HPV types (50).

Screening strategies include HPV DNA testing, VIA and cytology exam or cytology. A recent systematic review and meta-analysis on screening for cervical cancer showed that a cytology program had a protective effect on invasive cervical cancer with an odds ratio of 0.35 (95% CI: 0.30-0.41), compared to the absence of a screening program. The meta-analysis included 12 case-control studies that targeted different age group, ranging from 16 to 80 years old. Moreover, a large study performed in India showed that there is a protective effect of a single lifetime screening program (51).

Yet, screening guidelines vary from one country to another (52, 53). For instance, the American guidelines propose a cytological examination at the age of 21, then every 3 years with an optional combination with HPV DNA testing at the age of 30. Screening should stop when a woman is 65 years old except in cases where abnormal results have been found (54). In developing countries, WHO recommends a cytological examination starting at the age of 30 although other modalities are of course also acceptable, in particularly VIA, as it is an easy and cheap method (52). In Lao PDR, as there is currently no national preventive program for cervical cancer, practices vary according to the availability of equipment and human resources in the different hospitals of the country. VIA and cytology tests are currently available, but limited to the central hospitals of Vientiane Capital (24).

Overall, among screening programs, VIA and cytology testing are the most efficient and effective strategies for detecting and treating the cervical cancer precursors in low-resource settings, as those countries usually lack facilities for performing HPV DNA testing followed by cryotherapy which shows a greater reduction in the incidence of cervical cancer precursors than the use of other screen-

and-treat approaches (55).

1.3.6.1 HPV vaccination

Three types of effective vaccines are currently available (50). According to a worldwide review, the quadrivalent and bivalent vaccines currently administrated prevent 70% of cervical cancers (43, 44). The efficacy of the bivalent and quadrivalent HPV vaccines is nearly 100% in preventing CIN2/3 and adenocarcinoma in situ (AIS) associated with HPV types 16 and 18 in women with no evidence of oncogenic HPV infection prior to the vaccination (56-58). The duration of protection remains unknown, but it is thought that the protection is at least of 5-8 years for the bivalent and quadrivalent vaccines respectively (59). The bivalent vaccine is likely to be more effective than the quadrivalent in terms of cross-protection against non-vaccine types particularly HPV 31, 33, and 45, AIS and cervical cancer, resulting in a broader cancer-related death reduction (59, 60). Both vaccines have been proved to be safe and with acceptable adverse events (56, 61, 62).

HPV vaccination has been included in national vaccination programs of developed countries and some developing countries. The vaccine could be used at the ages of 9 to 26 years (63-65).

1.3.6.2 Cervical cancer screening

1.3.6.2.1 Cytology screening

The Papanicolaou (Pap) smear or Pap test is a screening test to detect precancerous lesions of the cervix. To perform the test, a speculum is used to open the vaginal canal and then a brush is used to collect cells from the outer opening of the cervix of the uterus and the endocervix. Smears are spread on a glass slide, fixed with a preservative, stained and then examined under a microscope for abnormalities by cytologist (66). Another approach, using liquid-based cytology has been proposed. A systematic review showed that liquid-based cytology has equivalent sensitivity and specificity to conventional thin layer cytology (67, 68). Abnormal results, according to the Bethesda System, are classified into: 1) atypical squamous cell (ASC); 2) low-grade squamous intraepithelial lesion (LSIL) which is a low-grade cervical intraepithelial neoplasia (CIN) or very mild dysplasia and mild dysplasia; 3) high-grade squamous intraepithelial lesion (HSIL) which is a high-grade CIN and cancer in situ; 4) squamous cell carcinoma (66, 69-71).

The performance of cervical cytology varies a lot. According to a systematic review on 12 studies of high methodological quality, sensitivity ranged from 30% to 87%, and specificity from 86% to

100% (72). It is likely that the sensitivity is lower for detecting endocervical glandular dysplasia and adenocarcinoma than for detecting squamous malignancy (72-74).

An evaluation of screening programs in eight countries indicated that centrally organized screening programs were more effective than uncoordinated screening programs and suggested that screening programs should be aimed principally at women aged 35-60 but should start some years before the age of 35, and that the intervals between screenings should be three years or less (75).

The cytology screening process, combined with the delays between screening, provision of test results and ultimate treatment (including necessary repeat visits), are major barriers to the success of cytology-based programs in low-resource settings. Indeed, the success of screening depends on the strict compliance with the calendar from 25 to 65 years of age (8, 76).

1.3.6.2.2 Visual Inspection with Acetic Acid (VIA)

VIA, a non-cytological test, is a simple and inexpensive test which can be applied by paramedical personnel shortly trained. VIA can be applied in low-resource countries for the screening of cervical cancer as an alternative to cytology that requires a level of expertise and resources that might be lacking in deprived settings (77). The test consists in applying acetic acid to the cervix with a cotton swab. After 30-60 seconds, the provider examines the cervix with the naked eye. Pre-cancerous lesions turn white when acetic acid is applied, while no change in color appears in cervix without precancerous lesions. Two meta-analyses supported the interest of implementing VIA in low-resource settings. The estimates of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of VIA were 72% to 80%, 79% to 92%, 10% to 17% and 99% respectively. Yet, a low PPV could lead to unnecessary treatment and some psychological impact (78, 79). Nevertheless, VIA has interesting characteristics particularly regarding its sensitivity and NPV compared to conventional cytology. Indeed, the sensitivity of VIA is commonly higher than the sensitivity of the cytology test, but its specificity for the detection of cervical cancer precursor is lower for the detection of cervical cancer precursors (80-83).

1.3.6.2.3 HPV DNA testing

HPV DNA testing currently comes as the first screening approach in high-income countries (55). Specimens for HPV testing can be collected from the endocervix using a Dacron swab or cervical brush, which is then placed in a HPV test transport medium (8). Four methods have been approved by the US Food and Drug Administration (FDA): 1) Hybrid Capture 2, which allows the

identification of the presence of any of 13 high-risk HPV types; 2) Cervista HPV HR test, which allows the identification of the presence of any of 14 high-risk HPV types; 3) Cobas HPV test, which allows the identification of HPV16 and 18 as well as a pooled result for an additional 12 high-risk subtypes and 4) Aptima mRNA test, which allows the identification of 14 high-risk subtypes (84). It might be used to monitor the outcomes of HPV infections particularly in case of a negative cytology (85).

A systematic review showed that primary screening with HPV DNA testing, compared to a cytology exam, has a sensitivity of 25% (95% CI: 15–36%) for the detection of atypical squamous cell, and of 6% (95% CI: 4–7%) for the detection of low-grade squamous intraepithelial lesion, although with a lower specificity, a combined cytological exam with HPV DNA testing increases the test sensitivity. In comparison with screening by cytology alone, double testing resulted in a 35% (95% CI = 15% to 60%) increase in sensitivity to detect high-grade CINs or a cancer. Primary screening with HPV DNA testing followed by cytological triage and repeated HPV DNA testing of HPV DNA positive women with a normal cytology, increase the high-grade CIN or cancer detection sensitivity by 30% (95% CI = 9% to 54%) and maintains a high positive predictive value (relative PPV = 0.87, 95% CI = 0.60 to 1.26) (86).

Care-HPV, a rapid HPV DNA testing approach, has become a new alternative for primary screening of precancerous lesions of the cervix in developing countries, as it provides a simple, rapid (only 2.5 hours), accurate, reproducible and acceptable screening test (87, 88). Overall, Care-HPV efficacy is similar to the efficacy of HPV DNA testing for the detection of high-grade CINs. A study in a rural area of China demonstrated that Care-HP, rapid HPV DNA testing, had a lower sensitivity and specificity than other HPV DNA testing, but it was not statistically significant 84.2% and 85.6% and 90.0% and 97.1%, respectively (89). The feasibility and acceptability of Care-HPV implementation have been shown to be high at the community level in low-resource settings (90).

The main barriers of cervical cancer prevention programs include a broad lack of awareness regarding cervical cancer and limited resources, as well as an absence or poor quality of cytology, low accessibility of populations in need to services, and an under-prioritization of cervical cancer control among health care priorities. Moreover, the fact that the disease has a symptom-free pre-invasive stage may delay the presentation to care (11, 91).

To overcome the barriers of access to screening facilities, a self-collection approach has been discussed. A study performed in Thailand showed that a self-collection device for cytology tests by the Kato method, a specific instrument that is inserted into the vaginal canal, might be considered as an alternative choice for women who are too shy to undergo pelvic examination (92). A study in Lao women also showed that this technique is acceptable (93). However, self-collected sampling needs advises by a knowledgeable practitioner to insure an adequate quality (94).

1.3.7 Treatment of precancerous lesions

The treatment of precancerous lesions is clinically and ethically required. There are generally two approaches to treat CIN: ablative methods (freezing, cryotherapy or laser ablation) and excision methods (loop electrosurgical excision procedure (LEEP) or cold knife or laser conization) (71). The choice of treatment depends on the severity of the disease, the morbidity, the risk of adverse effects, the availability of the method and the expertise with its use, and, ideally, consideration for its cost-effectiveness. A systematic review showed that these techniques were equally effective when applied to approximately 90% of precancerous lesions (95). Cryotherapy is a safe way of treating precancerous cervical lesions and results in cure rates of at least 85 percent, with minimal complications (55, 96, 97). In Lao women, there are some evidences that show that VIA combined with cryotherapy is feasible, acceptable and safe (98). However, cryotherapy is likely to be less effective than LEEP in treating high grade squamous intra-epithelial lesions (99).

1.3.8 Invasive cervical cancer treatment

An invasive cervical cancer is expected to be treated according to its stage, in accordance with recommendations by the International Federation of Gynecology and Obstetrics (FIGO). A localized cervical cancer is staged from IA1 to IIA2. The standard treatment is a simple hysterectomy for IA and a radical hysterectomy for IB to IIA2. A regional cervical cancer (also called early advanced cancer) is staged from IIB to IVA (100, 101). These stages are treated by chemoradiation. However, radiotherapy is commonly used as an alternative treatment. Meanwhile, a distant cervical cancer is staged IVB and is treated by palliative chemotherapy (102). Early stage can be treated more effectively than late stages. For instance: the five-year survival rate after hysterectomy in localized cancer ranges from 50% to 95%, while the rate after chemoradiation for regional cancer is 40 to 80%. When a patient reaches the metastatic stage, her survival is about 7 months with a cisplatin-based regimen (103).

Table 1: Cervical cancer staging according to the International Federation of Gynecology and Obstetrics

Staging	Classification	Standard treatment
IA1	Local	Simple hysterectomy
IA2	Local	Simple hysterectomy
IB1	Local	Radical hysterectomy
IB2	Local	Radical hysterectomy
II A1 or 2	Local	Radical hysterectomy
II B	Regional	Chemoradiation
III A	Regional	Chemoradiation
III B	Regional	Chemoradiation
IV A	Regional	Chemoradiation
IV B	Distant	Palliative chemotherapy

1.3.9 Economic evaluation in health care

Economic evaluation is a comparative analysis of alternative courses of action, aiming at providing information to decision makers in terms of both cost and consequences of relevant interventions. There are three main types of economic evaluation, depending on how outcome is measured: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA) (104).

1.3.9.1 Cost-effectiveness and cost-utility analysis

Cost-effectiveness analysis is a method for assessing the gains in health relative to the costs of different health interventions. The outcome of interest can be measured by various indicators, such as the number of cases, life-year saved and DALYs, which express the quality of life. Quality-adjusted life year (QALY) is the indicator used in a cost-utility analysis, using utility as the health outcome, which encounters both quantity and quality of life. The measurement of utility could be done by various methods, which include a visual analogue scale (VAS), the time trade-off (TTO) and the standard gamble (SG) (105). Most economic evaluations on cervical cancer prevention done in developing countries are cost-effectiveness analyses with DALYs averted as main denominator (106), while studies done in developed countries are usually cost-utility analyses (107).

Incremental cost effectiveness ratio (ICER) is an indicator used in cost-effectiveness studies to express the incremental cost per unit of health benefit gained compared to an alternative. This

alternative is generally the next more costly AND more effective option. When the alternative is more costly and less effective, it is considered as dominated.

$$ICER = \frac{(Cost\ of\ intervention\ A - Cost\ of\ interventon\ B)}{(Effect\ of\ intervention\ A - Effect\ of\ intervention\ B)}$$

The suggested threshold to define an option as being cost-effective varies from one country to another. For instance, it is 3340 International dollars (I$) per QALY in Thailand (108), £20 000-£30 000 per QALY in the UK, and $50 000-$100 000 per QALY in the USA (109). WHO recommends for developing countries the use of GDP per capita per DALY averted. Less than a 1 GDP per capita per DALY averted is considered as "very cost-effective", 1-3 GDP per capital per DALY averted is considered as "cost-effective". A GDP per capita per DALY averted more than 3 is considered as non-cost-effective (110). However, using GDP per capita to define cost-effectiveness thresholds might not fully reflect the national budget availability in developing countries. This threshold remains therefore controversial.

1.3.9.2 Cost-benefit analysis (CBA)

Cost-benefit analysis is another method of economic evaluation in health care in which both elements of an economic evaluation; the outcomes and the costs are measured in monetary units. The research question is commonly stated to find out whether the intervention program is worthwhile, based on the net social benefit of the program, i.e. the difference between the costs (investment) and the outcomes (benefits). This type of economic evaluation faces the challenge of how to value the consequences in terms of money (104). It is not surprising that cost-benefit analyses have not been often conducted in studies on cervical cancer control. A recent systematic review of model-based cervical cancer screening evaluations was unable to retrieve a single cost-benefit analysis study (111).

1.3.9.3 Uncertainty and sensitivity analysis

Uni-way or multi-way sensitivity analyses are recommended to handle the uncertainties of data used in economic evaluations. The WHO recommends to conduct probabilistic sensitivity analyses (PSA) in order to take into account the joint variation of key parameters (112). The advantage of uni-way sensitivity analyses is that they enable to determine key parameters influencing the outcome of interest. The results of uni-way sensitivity analyses are commonly presented on Tornado diagrams. Results of PSA analyses commonly use cost-effectiveness acceptability curves (CEACs) over willingness-to-pay threshold ratios (113).

Table 2: Methods for measuring the cost and consequence in economic evaluation

Type	Measurement of cost	Consequence	Measurement of consequence
Cost-effectiveness analysis	Monetary	Single effect of interest	Natural units (life-years gained, DALY averted, number of cancer reduction, etc.)
Cost-utility analysis	Monetary	Single or multiple effect of interest	Quality-adjusted life-years
Cost-benefit analysis	Monetary	Single or multiple effect of interest	Monetary

Source: Methods for the economic evaluation of health care programs (104)

1.3.9.4 Models used for economic evaluation of cervical cancer prevention

Modeling is well adapted to addressing policy questions thanks to their capacity to explore the complex factors and uncertainties of epidemiological, clinical and economic data. Economic evaluation is conducted using either patient-level data or decision analytic modeling (DAM) (104).

Patient-level data modeling is an economic evaluation conducted along with clinical trials. The effectiveness and cost collected from clinical trial faces to the limitation of external validity. Meanwhile, decision-analytic models (DAMs) are commonly used for economic evaluation of cervical cancer control. The models used for DAMs include dynamic models, decision tree, Markov model, Patient level simulation (or microsimulation), and discrete event simulations (114). The type of model used for economic evaluation of cervical cancer control depends on 1) the question of the study, 2) the availability of parameters, of data needed to calibrate and validate the model, 3) the competence in using different modeling techniques, 4) the time requirement for developing the model and 5) programming skills (115). However, microsimulation and Markov models are both commonly used in economic evaluations on cervical cancer control.

The static versus dynamic model

Dynamic models take into account the effect of herd immunity, indirect protection of HPV vaccination, by allowing the interaction between populations, sexual contact, and considering the probability of a new partner to becoming infected and HPV transmissibility (116). In contrast, the static model uses constant probabilities of HPV infection regardless of changes over time. In this case, herd immunity is not considered in the model. HPV incidence reduces along with the

susceptible population reduction. However, static and dynamic models provide similar results when the vaccination coverage is suboptimal in which the benefit of herd immunity considered in dynamic models can be ignored (117). Static models, using Markov cohort model, are largely used in studies conducted in either developed (107) or developing countries (106). Static models are particularly used when the research question focuses on screening programs (111). Dynamic models are preferred for questions that address catch-up vaccination, including boys, or the combination of girl vaccination with screening strategies (116).

Individual and population-based model

Individual-based model or microsimulation is commonly stochastic. They track the costs and the consequences individually and also memorize the previous event. However, this method requires advanced computer skills (115). In contrast, the population-based model, aggregated population moves from one to another health state according to their relevant status. Most dynamic models used for cervical cancer are population-based model.

The model is run either deterministically or stochastically. In contrast to deterministic models, stochastic model allow for events to occur randomly. Most dynamic models are deterministic; meanwhile the microsimulation models are naturally stochastic (116).

Experts have developed a simple model specifically for countries where data are unavailable, a companion Excel-based model. This model is a population-based model, and constructed as a static cohort simulation, which has been created to examine the cost-effectiveness of preadolescent girl HPV vaccination in 72-eligible countries for GAVI (118).

1.3.10 Cost-effectiveness studies on cervical cancer prevention strategies

HPV model

HPV model evolution

A HPV model structure reflects the natural history of HPV infection and its progression to invasive cervical cancer. A simple or complex model structure is created according to the research questions and available data. For instance, Goldie et al (118) created a simple excel-based simulation for 72 GAVI-eligible countries, while Jit et al (119) created a global model. Both models do not reflect fully the natural history of HPV infection and cancer. The model by Goldie et al (118) consists of only stage distribution of cancer, duration of disease, proportion of incident cases resulting in death. The model by Jit et al (119) which is called Papillomavirus Rapid Interface for Modelling and

Economics (PRIME), is simpler than Goldie's model and considers only the incidence of mortality of cervical cancer related to HPV types 16/18. Both models aimed to simply determine the cost-effectiveness of girl HPV vaccination, compared to no intervention.

A static model is a first generation of HPV model to answer the question regarding the effectiveness and the cost-effectiveness of screening and/or HPV vaccination intervention as summarized in table 3 and 4. A static model is simple and mostly conducted through a Markov model (106, 115). Most studies used the Myer et al. parameters of natural history of HPV infection (120). These parameters consist of age-specific transition probabilities from one state to another. This type of model provides conservative benefits for HPV vaccination due to the absence of consideration for the herd immunity effect and the small number of HPV groups. This might result in biasing the estimate of the benefit of HPV vaccination.

Transmission dynamic models have been developed to study the effectiveness and cost-effectiveness of HPV vaccination strategies. Dynamic models can provide more accurate estimation of HPV vaccination benefit because these models take into account the herd immunity effect (115). Dynamic models were firstly developed for population in high-income countries, and then used in low-resource settings are presented in tables 3 and 4. The models are quite complex (age and genotype-specific probabilities), and tend to reflect fully the natural history of HPV infection. Individual or population-based models are applied, depending on the capacity of the software used for the analyses. A matrix of sexual contacts was different from one to another study. Jit et al. (121) considered the number of sexual partners by age and by sexual activity. The recent model of Van de Velde et al (122) considered sexual acts rather than the number of sexual partners. The model compartment differs from one study to another, depending on the available data and research question. Most models, generally called SIRS models, assume that there is a wane of natural immunity (tables 3 and 4).

In developed countries, such a model was created to study HPV vaccination (table 4) (115, 116). Another model allowed to study the combined HPV vaccination and screening strategies but for developing countries (table 3) (106). This might be because the effective screening strategy is already available in developed countries where infrastructure for screening is adequately available.

Results

HPV vaccination in conjunction with cervical pre-cancer screening is an efficient option against cervical cancer (123). However, one should keep in mind that different modalities and frequencies of screening might be required according to the context to be effective and efficient (25, 124). Among HPV vaccination models, preadolescent girl vaccination is cost-effective. This cost-effectiveness was found in country-level (106, 115), regional (125-127) and global studies (119). Meanwhile, systematic reviews conducted in either developing or developed countries have shown that preadolescent girl vaccination programs are more cost-effective than an option with vaccination to which a boy vaccination element has been added, despite better outcomes when all HPV-related diseases were considered or when the girls vaccination coverage was suboptimal (128, 129). It is more cost-effective to increase the coverage of a girl vaccination program rather than vaccinating boys (130). A study in Mexico showed that adding a boy vaccination component to girl vaccination program can be cost-effective (131). However, the result must be cautiously interpreted because the study considered three GDP per capita per DALY averted as a threshold of cost-effectiveness, which is a relatively high threshold.

Adding a catch-up component to a girl vaccination program is another interesting option. This strategy is cost-effective compared to a girl vaccination program alone in some high-income (121, 132) and upper middle-income countries (106). However, the considered age of catch-up was different from one study to another: 24 years old in Elbasha et al., (132) and 18 years old in Jit et al., (121).

The disparities found among various cost-effectiveness studies might be explained firstly by differences in willingness-to-pay thresholds, secondly by the purchasing cost of the vaccine, thirdly by different characteristics in terms of epidemiology in the local context and finally by different assumptions in term of model structure (dynamic or static), coverage and perspective used in the cost analyses. For instance, a study showed that HPV vaccination and an expansion of the treatment were both most cost-effective in settings with a high mortality rate and a low screening coverage (133). It is therefore difficult to generalize results to another setting

A systematic review of cost-effectiveness studies revealed that the most cost-effective screening techniques in low-resource countries include visual inspection with acetic acid and HPV DNA testing in cervical cell samples, particularly in case of two clinical visits (8, 134). However, the modality of screening might be different from one setting to another. In China, rapid HPV-DNA

testing has been found to be more cost-effective than cytology, particularly when based on two visits with screening and diagnosis at the first visit, and treatment at the second visit. In Thailand, screening with VIA for women aged 30-45 years followed by cytology for women aged 50-60 years every five years was found to be cost-effective (135). Sharma et al., (25) demonstrated that a combination of girl vaccination and HPV DNA testing five times in a lifetime, starting at 35 years was cost-effective (taking I$8100 as a threshold of cost-effectiveness). Nevertheless, none of the models stated above had similar model structure. They also differed in their economic component. As consequence, evidences brought by a study might not be applicable to another depending on their disease burden and infrastructure to implement the appropriate intervention of cervical cancer control characteristics.

Table 3: Different models used for analyzing the cost-effectiveness of HPV vaccination and/or screening programs against cervical cancer

Article	Type of model	Country	Type of model population	Natural immunity	Contact	HPV types	Strategies	Outcomes	Sensitivity analyses
Developed countries									
Goldhaber-Fiebert, 2007	Static	USA	Individual	SIR	Transition probability	16,18, other HR and LR	Girl vaccination + screening	CIN, ICC	Multi-way
Goldie, 2004	Static	USA	Aggregate	SIR	Transition probability	HPV	Screening	LYS	Multi-way
Developing countries									
Praditsitthikorn, 2011	Static	Thailand	Aggregate	SIRS	Transition probability	All HPV types	Girl vaccination + screening	QALY	Multi-ways and PSA
Sharma, 2012	Dynamic	Thailand	Individual	SIRS	Heterosexual with sexual contact matrix	16 and 18	Girl vaccination + screening	LYS	One-way and multi-way
Gutierrez-Delgado, 2008	Static	Mexico	Aggregate	SIS	Transition probability	Not specify	Girl vaccination alone; vaccination + screening	DALY	One-way
Campos, 2012	Dynamic	Multiple countries	Individual	SIRS	Heterosexual with sexual contact matrix	16,18, other HR, possible HR and LR	Girl vaccination + screening	LYS	One-way
Canfell, 2012	Dynamic	China	Aggregate	SIRS	Heterosexual with sexual contact matrix	16,18, other HR and LR	Girl vaccination + screening	LYS	One-way and PSA
Demarteau, 2012	Static	UK and Brazil	Aggregate	SIS	Transition probability	HR	Girl vaccination + screening	ICC	One-way

Diaz, 2008	Dynamic	India	Individual	SIRS	Heterosexual with sexual contact matrix	16,18, other HR and LR	Girl vaccination + screening	LYS	One-way
Ezat, 2010	Static	Malaysia	Aggregate	SIS	Transition probability	HR	Girl vaccination + screening	ICC and QALY	One-way
Ginsberg, 2009	Static	Global	Aggregate	SC	Transition probability	HR	Girl vaccination + screening	DALY and QALY	One-way
Kim, 2008	Dynamic	Vietnam	Individual	SIRS	Heterosexual with sexual contact matrix	16,18, other HR and LR	Girl vaccination + screening	ICC and LYS	One-way
Levin, 2010	Hybrid	China	Aggregate	SIS	Transition probability	HR	Screening	LYS	One-way

Note :
SIS; Susceptible-Infection-Susceptible; SIR; Susceptible-Infection-Recovery; SIRS; Susceptible-Infection-Recovery-Susceptible; SC: Susceptible-cancer.
HR; high-risk HPV; LR: slow-risk HPV
CIN: cervical intraepithelial neoplasia; ICC: invasive cervical cancer; LYS: life year saved; DALY: disability adjusted life year; QALY: quality adjusted life year.

Table 4: Different models used for analyzing the cost-effectiveness of HPV vaccination strategies against cervical cancer

Article	Type of model	Country	Type of model population	Natural immunity	Contact	HPV types	Strategies	Outcomes	Sensitivity analyses
Developed countries									
Kim, 2008	Dynamic	USA	Individual	SIRS	Heterosexual with sexual contact matrix	16 and 18	Bivalent girl vaccination and catch-up component	QALY	One-way
Jit, 2008	Dynamic	UK	Aggregate	SIRS	Heterosexual with sexual	6,11, 16,18 and other	Quadrivalent Girl	Warts and QALY	One-way and multi-

					contact matrix	HR	vaccination		way
Kulasingam, 2007	Static and hybrid	Australia	Aggregate	SIRS	Transition probability	16,18, other HR and LR	Bivalent girl and boy vaccination	Warts and QALY	One-way
Brisson, 2007	Static	Canada	Aggregate	SIRS	Transition probability	6,11, 16,18 and other HR	Bivalent girl and boy vaccination	Warts and QALY	One-way and multi-way
Elbasha, 2007	Dynamic	USA	Aggregate	SIRS	Heterosexual with sexual contact matrix	6,11, 16 and 18	Quadrivalent Girl and vaccination and catch-up component	Warts and QALY	One-way
Taira, 2004	Hybrid	USA	Aggregate	SIRS	Heterosexual with sexual contact matrix	16 and 18	Bivalent girl and boy vaccination	QALY	One-way
Goldie, 2004	Static	USA	Aggregate	SIRS	Transition probability	16, 18, other HR and LR	Bivalent girl and boy vaccination	QALY	One-way
Sanders, 2003	Static	USA	Aggregated	SIR	Transition probability	HR and LR	Bivalent girl vaccination	LYS and QALY	One-way
Developing countries									
Termrungruanglert, 2012	Static	Thailand	Aggregate	SIS	Transition probability	6,11, 16 and18	Quadrivalent Girl vaccination	QALY	Multi-way
Colantonio, 2009	Static	Latin America	Aggregate	SIRS	Transition probability	HR	Bivalent girl vaccination	QALY	One-way
Goldie, 2008	Static	72 GAVI eligible countries	Aggregate	Partial	Transition probability	HR	Bivalent girl vaccination	ICC and DALY	One-way
Goldie, 2008	Static	Latin America	Aggregate	Partial	Transition probability	HR	Bivalent girl vaccination	ICC and DALY	One-way
Goldie, 2008	Static	Asia	Aggregate	Partial	Transition	HR	Bivalent girl	ICC and	One-way

		pacific			probability		vaccination	DALY	
Kim, 2007	Dynamic	Brazil	Individual	SIRS	Heterosexual with sexual contact matrix	16 and 18	Bivalent girl and boy vaccination	ICC and LYS	One-way
Insinga, 2007	Dynamic	Mexico	Individual	SIRS	Heterosexual with sexual contact matrix	6,11,16 and 18	Quadrivalent girl vaccination and catch-up component	High-grade CIN, genital warts and QALY	One-way and multi-way
Reynales-Shigematsu, 2009	Static	Mexico	Aggregate	SIS	Transition probability	HR and LR	Bivalent girl vaccination	LYS	One-way
Sinanovic, 2009	Static	South Africa	Aggregate	SIS	Transition probability	HR and LR	Bivalent girl vaccination	QALY	One-way
Suares, 2008	Static	Multi-region	Aggregate	SIS	Transition probability	HR	Bivalent girl vaccination	LYS and QALY	One-way
Vanagas, 2010	Static	Lithuania	Aggregate	SIS	Transition probability	HR	Bivalent girl vaccination	Life year saved	One-way

Note :
SIS: Susceptible-Infection-Susceptible; SIR: Susceptible-Infection-Recovery; SIRS: Susceptible-Infection-Recovery-Susceptible; SC: Susceptible-cancer.
HR: high-risk HPV; LR: slow-risk HPV.
CIN; cervical intraepithelial neoplasia; ICC: invasive cervical cancer; LYS: life year saved; DALY: disability adjusted life year; QALY: quality adjusted life year.

1.3.11 Summary

Only a comprehensive approach can provide an effective way to reduce the morbidity and mortality of cervical cancer. This includes both expanding and improving the quality of services in the fields of prevention, treatment and monitoring. Failing to emphasize the importance of all components reduces the effectiveness of any program implemented to fight the disease. For instance, HPV vaccination without screening can prevent cancer in the youngest generation but not for those who are older. Also, screening without treating is not ethically acceptable (136). Moreover, opportunistic screening are less effective than organized programs (75), and different modalities of screening strategies show different levels of efficacy in terms of sensitivity and specificity as well as the frequency of screening. For instance, cytology probably requires too much expertise and material resources to be feasible in many low-resource settings (11). Meanwhile, VIA has a low specificity and a low PPV, leading to unnecessary treatment (78). Yet, particularly in poor countries, a realistic approach has to take into consideration the scarcity of resources, not only financial, but also material and human, as well as their accessibility. Any decision regarding which screening programs are implementable should consider the social and political context at hand.

Options are numerous. A clinical trial is poorly adapted for identifying which strategy should be promoted. Simulations are an elegant solution to tackle the question. Simulations would allow us to define which strategy is expected to be optimal considering the specificity of the setting. They would also allow more accurate estimation of the investments that are required in a specific context in order to improve the epidemiologic situation of a preventable disease that represents an important burden in terms of morbidity, mortality and resource use. For these reasons, simulation is a relevant tool to handle the question of the choice among HPV-related cancer prevention options in Lao PDR.

1.4 Research structure (Cost-effectiveness of prevention strategies against cervical cancer in women, Vientiane, Lao PDR)

The thesis is composed of three articles aiming at identifying the most relevant option of HPV cancer prevention in the context of Lao PDR. It aims at exploring the value of adding other strategies to the only preventive one implemented in the country: vaccinating girls (in two provinces only).

To answer this question, we conducted three studies 1) a meta-analysis to estimate the average sensitivity and specificity of the combined VIA and conventional cytology testing and 2) two health

economic evaluations, using a mathematical approach to predict the cost and the consequences of various interventions of cervical cancer control.

To estimate the summary sensitivity and specificity of the combined VIA and conventional cytology testing, a systematic review and a meta-analysis were conducted. A meta-analysis is a powerful instrument to explore the significant conflicting study results by identifying if the differences found are statistically true, i.e. if they occur by chance, or if the differences can be explained by different study characteristics. We followed the standard Cochrane guidelines for systematic reviews of diagnostic test accuracy in order to minimize the bias of analyzing data and reporting the result (137). We expected that this would provide meaningful information regarding the pooled estimates of sensitivity and specificity of this combined test. Original articles were searched throughout up to June 2014 without language restriction. The average estimation not only provided useful information for clinical practice, but also required further examination on its effectiveness and cost-effectiveness. That is why we examined this strategy in terms of cost-effectiveness. Results are reported in article 3. The article on the meta-analysis was published in the Asian Pacific Journal of Cancer Prevention. Details on the methodology and the results are described in chapter 2.

To answer whether the girl vaccination is cost-effective and whether there is an interest for a catch-up component or a boy vaccination component, we built up a compartmental dynamic model to reflect the natural history of HPV infection and cervical cancer. The dynamic model took into account the herd immunity, which is more appropriate than a static model (115, 138). Indeed, previous studies showed that static models tend to underestimate the effectiveness of HPV vaccination. This becomes relevant when the research question is focusing on examining an inclusion of the catch-up component and the boy vaccination element (138). Differential equations related to various HPV vaccination strategies were created and run in Berkeley Madonna version 8.3.18 (139). A cost-effectiveness analysis was then performed. A cost-utility analysis was not performed because utility values relevant to the Lao context are not available.

Only cervical cancers and DALYs related to HPV type 16/18 were considered as outcomes. If we consider all cases, we might underestimate the benefit of HPV vaccine because of the possible replacement of 16/18 types by other high-risk HPV types (140-142). The article has been submitted to The Lancet Global Health. It is described in chapter 3. Details on the methodology and additional results are presented in Appendix 1.

Finally, we considered that in the future, it might be possible to implement a screening program. We therefore constructed further differential equations for various screening compartments (VIA, rapid HPV DNA testing, combined VIA and conventional cytology, liquid-based cytology and conventional cytology) in order to examine whether this component with/without girl vaccination can be cost-effective in the Lao context. In this case, cervical cancers related to all high-risk HPV types were considered. This outcome was considered as more appropriate because screening can reduce cervical cancer cases related to all HPV types. Considering only cases related to HPV types 16/18 would underestimate the effectiveness of the screening program, particularly when comparing this option to a girl vaccination only program. This article has been submitted to Plos One. It is described in Chapter 4. Details on the methodology and additional findings are presented in Appendix 2.

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Chapter 2

Accuracy of the combined Visual Inspection with Acetic Acid and cervical cytology testing as a primary screening tool for cervical cancer: a systematic review and meta-analysis

Chapter 2: Accuracy of the combined Visual Inspection with Acetic Acid and cervical cytology testing as a primary screening tool for cervical cancer: a systematic review and meta-analysis

2.1 Résumé

Introduction: La combinaison test à l'acide acétique (IVA) et frottis du col pour le dépistage du cancer du col, est une option particulièrement pertinente pour les pays en développement. La performance de chacun de ces tests individuellement est connue, mais aucune étude n'a porté sur leur combinaison.

Objectif : L'objectif de cette étude était d'estimer la sensibilité et la spécificité de la combinaison IVA-frottis pour la détection des lésions précancéreuses du col de l'utérus.

Méthodologie : Une revue systématique et une méta-analyse ont été réalisées. Nous avons considéré deux cas : 1) positivité faible, un résultat étant alors dit positif si au moins un des deux tests est positif, et négatif si les deux tests sont négatifs; 2) positivité forte, le résultat positif impliquant alors une positivité aux deux tests. Les études éligibles ont été identifiées dans les bases de données Pubmed, Embase, Website of Science, CINHAL et COCRANE databases. La moyenne des sensibilité et spécificité, la vraisemblance positive et négative et les Odds ratios diagnostiques (DOR) ont été mis en commun en utilisant un modèle à effet aléatoire hiérarchique. Un récepteur hiérarchique d'exploitation résumant les caractéristiques (HSROC) a été généré. L'hétérogénéité a été explorée à travers les covariants qui, potentiellement, pouvaient influencer le DOR.

Résultats : Neuf articles ont été inclus dans l'analyse. L'estimation moyenne de la sensibilité de la combinaison des tests pour les cas de positivité faible et forte étaient de 0.87 (95% CI: 0.83-0.90) et 0.38 (95% CI: 0.29-0.48), respectivement. L'estimation des spécificités était de 0.79 (95% CI: 0.63-0.89) et 0.98 (95% CI: 0.96-0.99) respectivement. Les DORs de la combinaison des tests dans le cas de positivité faible et forte étaient de 27.7 (95% CI: 12.5-61.5) et 52 (95% CI: 22.1-122.2), respectivement. Lorsque seuls les articles sans biais de vérification et avec des cas ayant une néoplasie cervicale intra-épithéliale (CIN) de haut niveau comme seuil de positivité ont été considérés, le DOR pour le cas de positivité forte est toujours plus élevé. Cependant, ses DORs diminuent à 27.6 (95% CI : 8.54-89.2) et 37.3 (95% CI : 12.3-113.1), respectivement. Lorsqu'on ne considère que les articles ayant un CIN de haut niveau comme seuil de positivité, il apparait que le type du professionnel du dépistage, le lieu d'étude et la taille de la population influencent significativement le DOR de la combinaison des tests dans le cas de positivité forte.

Conclusion : La combinaison des tests dans le cas de positivité forte a une haute sensibilité, mais une basse spécificité. Tester les cas positifs de VIA par cytologie serait probablement une autre solution pour diminuer les cas faux positifs dans les pays en voie de développement.
Mots clés : performance du test de dépistage, combinaison des tests, frottis du col de l'utérus, IVA, pays en voie de développement, méta-analyse.

2.2 Abstract

Background: The performance of combined testing visual inspection with acetic acid (VIA) and cervical cytology tests might differ from one setting to another. The average estimate of the testing accuracy across studies is informative, but no meta-analysis has been carried out to assess this combined method.

Objective: The objective of this study was to estimate the average sensitivity and specificity of the combined VIA and cervical cytology tests for the detection of cervical precancerous lesions.

Methodology: We conducted a systematic review and a meta-analysis, according to the Cochrane Handbook for Systematic Review of Diagnostic Test Accuracy. We considered two cases. In the either-positive result case, a positive result implies positivity in at least one of the tests. A negative result implies negativity in both tests. In the both-positive case, a positive result implies having both tests positive. Eligible studies were identified using Pubmed, Embase, Website of Science, CINHAL and COCRANE databases. True positive, false positive, false negative and true negative values were extracted. Estimates of sensitivity and specificity, positive and negative likelihood (LR) and diagnostic odds ratios (DOR) were pooled using a hierarchical random effect model. Hierarchical summary receiver operating characteristics (HSROC) were generated and heterogeneity was verified through covariates potentially influencing the diagnostic odds ratio.

Findings: Nine studies fulfilled inclusion criteria and were included in the analysis. Pooled estimates of the sensitivities of the combined tests in either-positive and both-positive cases were 0.87 (95% CI: 0.83-0.90) and 0.38 (95% CI: 0.29-0.48), respectively. Corresponding specificities were 0.79 (95% CI: 0.63-0.89) and 0.98 (95% CI: 0.96-0.99) respectively. The DORs of the combined tests in either-positive or both-positive result cases were 27.7 (95% CI: 12.5-61.5) and 52 (95% CI: 22.1-122.2), respectively. When including only articles without partial verification bias and also a high-grade cervical intraepithelial neoplasia as a threshold of the disease, DOR of combined test in both-positive result cases remained the highest. However, their DORs decreased to 27.6 (95% CI: 8.54-89.2) and 37.3 (95% CI: 12.3-113.1), respectively. The screener, the place of study and the size of the population significantly influenced the DOR of combined tests in the both-

positive result case in restriction analyses that considered only articles with CIN2+ as disease threshold.

Conclusion: The combined test in the either-positive result case has a high sensitivity, but a low specificity. Sequentially testing cytology for positive cases of VIA might be another solution to minimize the number of false positive cases in developing countries.

Key words: screening test performance, combined test, cervical cytology, VIA, developing countries, and meta-analysis.

2.3 Introduction

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide, and is amenable to both primary and secondary preventative strategies (1). More than 85% of the cases and deaths occur in developing countries, where cervical cancers account for 12% of all female cancers (1). In Asia, 6.4 per 100 000 women die each year because of the disease, but the rates vary largely among different sub-regions. The highest rate is found in South Asia (2). Cervical cancer could be prevented through Human Papillomavirus (HPV) vaccination and screening as primary and secondary prevention strategies, respectively (3, 4). Several approaches are available for the screening of precancerous cervical lesions. In developing countries, because of resources issues, the main options are cervical cytology and visual Inspection with Acetic Acid (VIA) (5).

Yet, the accuracy of both cervical cytology and VIA tests for detecting cervical precancerous lesions varies from one setting to another. According to a systematic review on 12 studies, cervical cytology sensitivity ranged from 30% to 87% and its specificity from 86% to 100% (6). Meanwhile, sensitivity and specificity estimates for VIA were 72% to 80% and 79% to 92%, respectively (7). In India, for instance, screening with VIA could prevent 22 000 deaths due to a cervical cancer each year (8). Nevertheless, VIA, besides its easiness of use and its low cost (5), has interesting characteristics, particularly regarding its sensitivity and its negative predictive value compared to conventional cytology. The sensitivity of VIA is commonly higher than the sensitivity of Cervical cytology, but its specificity for the detection of precancerous cervical lesions is lower, leading to more false positive results (9).

There is evidence that in comparison with screening by cytology alone, double testing with HPV DNA and cervical cytology results in a 35% (95% CI = 15% to 60%) increase in sensitivity to detect high-grade cervical intraepithelial neoplasia (CIN) or a cancer, compared to testing with

cervical cytology alone (10). Co-testing with these screening techniques is now currently practiced in the USA (11). However, HPV DNA testing is limited in low-resource settings. Another potential combined method for the detection of cervical precancerous lesions would be cervical cytology and VIA as the latter is readily available in low-income countries. A few studies have been published on the topic. However, results diverge (12-14). A systematic review and a meta-analysis are still required to evaluate the accuracy and the potential usefulness of this combined test.

2.4 Methods

Search strategy

We conducted a systematic review and meta-analysis in compliance with the guidelines of the Cochrane Handbook for Systematic Review of Diagnostic Test Accuracy (15) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (16). Articles were searched up to June 2014 in Pubmed, Embase, Website of Science, CINHAL and COCRANE databases using the following key-words: cytology; VIA and sensitivity and their synonyms based on CisMef, without language or publication type restrictions. After removing duplicated records, all citations were included in the citation screening process using EndNote Software, version X6 (Thomson Reuters, 2012). Two reviewers independently screened titles, abstracts and full articles to establish eligibility and extract the data from included studies. A third reviewer was consulted in case of disagreement.

Eligibility criteria

To be eligible, articles had to report data on the sensitivity and specificity of combined VIA and cytology testing. Both VIA and cervical cytology had to be performed in the same women with asymptomatic or symptomatic conditions. Colposcopy and/or biopsy on at least a positive VIA or cervical cytology result had to be selected as a goal standard. Review articles were excluded.

Outcome of interest

The primary outcome was the sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR-) and diagnostic odds ratio (DOR) of combined VIA and cytology testing. A secondary outcome was the difference in sensitivity and specificity ratios between the combined test and the single tests.

Two situations were examined: either-positive result cases and both-positive result cases. In the either-positive result case, positivity in at least one of the tests implies a positive result. Negativity in both tests implies a negative result. In the both-positive case, a positive result implies having both tests positive. A negative result implies negativity in one of them.

The definition of a positive result on cervical cytology was low-grade squamous intraepithelial lesion (LSIL) or higher, according to the Bethesda System. The positive result of Visual Inspection with Acetic acid (VIA) was the color of the cervix turning to white when acetic acid is applied. These definitions were used in all included studies.

Quality assessment

Two authors independently examined the risk of bias and applicability using the Quality Assessment of Diagnostic Accuracy Study 2 (DUADAS-2) tool (17). A third author was consulted to solve discrepancies. Items examined included: 1) patient selection, 2) index test, 3) reference standard and 4) flow and timing. Meanwhile, the items examining applicability concerns were 1) patient selection, 2) index test, and 3) reference standard. Each item was rated as high, low or unclear risk or concern.

A study was considered to be of appropriate quality in the following cases: it avoided a case-control study design, it used a randomized recruitment strategy and more than 80% of patients were included in the analysis, the reference standard was performed within two weeks of the combined test, the interpretation of cervical cytology was blinded to VIA result and all patients underwent the same reference standard test.

The study was considered of low quality when it referred to symptomatic patients, patients with high HPV prevalence such as HIV patients, patients with precancerous lesions and invasive cancer. Partial verification bias was considered possible if only some of the included patients underwent the reference standard test.

Data collection

Two authors independently extracted the data from eligible studies. When results were discordant, a third author was consulted. We extracted information on the characteristics of the study; authors, year of publication, year the study was conducted, setting, study population and design, screener, threshold of cervical cytology positive results, and gold standard. The threshold for a positive result case of cervical cytology was either Atypical Cells of Undetermined Significance (ASCUS) or LSIL. When both ASCUS and LSIL thresholds were reported, we defined LSIL as a positive result because this was the threshold considered in most studies that were included in the analysis.

The true positive (TP), false positive (FP), true negative (TN) and false negative (FN) rates of both combined test and single tests were extracted from individual studies (18).

Data analysis

We used a bivariate hierarchical random-effects model, as recommended in Cochrane guidelines (18), using Stata program version 12 (StataCorp LP, College Station, TX, USA) with the metandi command (19). The meta-analytical random-effects model was used to pool and compare the relative ratios of sensitivity and specificity to detect precancerous lesions or cancers, using the combined test as numerator and single tests as denominators. Forest plots were produced to present pooled and individual estimates of sensitivity and specificity and their 95% confidence intervals using Cochrane Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2012).

Hierarchical summary receiver operating characteristics (HSROC) curves were generated. Heterogeneity was assessed by evaluating the influence of pre-established variables (site of study "lower-middle-income countries or other", the sample size "more or less than 900" and the screener "Physician or other") on the DOR using a meta-regression model. The I^2 statistic was calculated to quantify heterogeneity (18). Lower-middle-income countries were defined, according to the World Bank, as countries with a gross national income (GNI) per capita from $1,046 to $4,125 (20). Statistically significance was set at $p<0.05$ (18).

Sensitivity analyses

Sensitivity analyses on verification bias and disease positivity criteria were conducted to evaluate the robustness of the results. We restricted the analyses to the five studies without partial verification bias and to five studies with only CIN2+ as a definition of positivity for the disease.

2.5 Results

Study characteristics

353 citations were identified based on article titles (figure 1). After removing duplicates, 233 abstracts were examined. Forty-three were retained for full-text screening. Nine articles were retained. Among excluded articles, 29 did not provide data on the performance of combined VIA and cervical cytology testing and five were duplicates of the same study.

All included articles were based on cross-sectional studies (Table 1). Three were conducted in India and the others in Iran, Pakistan, Sudan, Brazil, Zimbabwe and Kenya. Five studies were conducted

in asymptomatic healthy women; one in HIV-positive women, one in symptomatic women and two in women having an unknown clinical condition. The study with the highest sample size, 10,138 women, was a multiple setting study performed in Brazil and Argentina. Most screeners of VIA were trained nurses (55.6%). Most studies used LSIL as a cut-off point for a positive cervical cytology test (seven studies). Meanwhile, high-grade CIN was considered as a threshold for the disease in six studies. The gold standard test for confirming the cervical precancerous lesions was a colposcopy/direct biopsy (Table 1).

Quality assessment of studies

Overall, two of nine studies met the criteria of high quality according to the QUADAS-2 tool. First, there was no risk of bias in terms of patient selection as all studies were cross-sectional, and all subjects were included in the analysis. However, there were some concerns as 4 of 9 included studies did not clearly specify whether participants were asymptomatic or not. The risk of bias in terms of the index test was low; all studies had a clear definition of a positive result for VIA and cervical cytology tests (low risk of bias in terms of index test). Only one study did not specify the occupation of the screeners. Some studies did not specify whether the histology interpretation was blind from the result of the cervical cytology test, leading to a potential concern on risk of bias in terms of the reference standard. Among the nine studies, four had a high risk of partial verification biases, because only some positive results were referred to a reference standard examination (data not shown).

Summary estimates of test performance

Figure 2 presents the summary estimates of the sensitivities and specificities of the combined VIA and cervical cytology tests and of the single tests in detecting cervical precancerous lesions in each study included in the analysis. The range of sensitivity and specificity was large for all tests.

The pooled estimates of sensitivity and specificity of the combined test in the either-positive result case for detecting cervical precancerous lesions were 0.87 (95% confidence interval: 0.83-0.90) and 0.79 (95% CI: 0.63-0.89), respectively. The corresponding values for the combined test in the both-positive result case were 0.38 (95% CI: 0.29-0.48) and 0.98 (95% CI: 0.96-0.99), respectively. The pooled estimates of the positive and negative likelihood ratio and diagnostic odds ratio (DOR) of the combined tests were lower in the either-positive cases compared to the both-positive result cases in all included studies. Details are presented in Table 2.

There was a significant difference in performance between the combined test and the single tests. Compared to the combined test in the both-positive result case, the combined test in the either-positive result case had a significantly higher pooled estimated relative sensitivity, even in the sensitivity analyses restricted to studies without partial verification bias and in the CIN2+ study. Compared to the VIA and cervical cytology tests alone, the combined test in the either-positive result case also had a higher sensitivity. However, its pooled estimated relative specificity was significantly lower than that of the combined test in the both-positive result case or the VIA and cervical cytology tests alone. Meanwhile, the combined test in the both-positive result case had a significant higher pooled estimated relative specificity than the VIA and cervical cytology tests alone in both non-restriction and restriction analyses (results not shown).

Figure 3 shows the hierarchical summary receiver operating characteristics (HSROC) curves of the combined test in the either-positive result case and in the both-positive result case under different scenarios i.e. all included studies, articles without partial verification bias and CIN2+ disease positive threshold analyses. The curves display the joint sensitivity and specificity in each study, showing the individual estimates, the summary estimates, their 95% confidence and the prediction region. Compared to the combined test in the both-positive result case, the summary point of the combined test in the either-positive result case was on the upper-right side, indicating a higher sensitivity and a lower specificity. Additionally, the 95% prediction region for the combined test in the either-positive result case was larger than the combined test in the both-positive result case.

Heterogeneity of diagnostic performance

Heterogeneity between studies was tested with the I^2 statistic in addition to the influence of covariates on DOR. Results show that the combined test in the either-positive result case and in the both-positive result case presented a large heterogeneity between studies, with an I^2 statistic higher than 75% (Figure 2).

Table 3 shows that there was no significant association between any covariates and DOR for the combined test in the either-positive result or the both-positive result cases if all studies were included in the meta-regression model. When the analysis was restricted to include only studies with CIN2+ as a threshold of the disease, we found that the place of the study had a significant influence on the DOR of the combined test in the either-positive result as well as in the both-positive result cases. Additionally, other covariates, including the screener and the size of study had a significant influence on DOR of the combined test in the both-positive results case.

Sensitivity analyses

In analyses restricted to articles without partial verification bias and high-grade CIN or worse (CIN2+) as a threshold for the diagnosis of the disease, the same pattern was produced. DORs rank did not change; the DOR of the combined test in the both-positive results case remained the highest. However, the DORs in the restricted analyses were lower than those calculated on all studies. In addition, the specificity of the combined test in the either-positive result case was lower when analyses were restricted to studies without partial verification bias and high-grade CIN as a threshold of positive disease (Table 2).

2.6 Discussion

To the best of our knowledge, this is the first meta-analysis aiming to determine the accuracy of combined VIA and cervical cytology testing in detecting cervical precancerous and cancerous lesions. The main findings in this meta-analysis are: 1) under the either-positive result case the combined VIA and cervical cytology test has a higher sensitivity but a lower specificity than under the both-positive result case for detecting cervical precancerous lesions; 2) the sensitivity of the combined test in the either-positive result case was significantly higher than the sensitivities of the VIA or cervical cytology tests alone; 3) specificity of the combined test in the either-positive result case decreased in analyses restricted to articles without partial verification bias and CIN2+ disease positive threshold; and 4) restriction analyses showed that the screener, the place of study and the size of the population are covariates that significantly influence the diagnostic accuracy of the combined test in the both-positive result case.

The low specificity of the combined test in the either-positive result case, compared to VIA or cervical cytology tests alone, is probably due to the fact that a true negative result required negativity of both VIA and cervical cytology. Similarly, low sensitivity of the combined test in the both-positive result case, compared to VIA or cervical cytology tests alone, required positivity of both VIA and cervical cytology. In contrast, the combination of HPV DNA and cervical cytology increases test sensitivity and maintains an adequate specificity (21). Effectively, maintaining the performance of the test requires a high consistence of diagnostic accuracy in both tests to detect and rule out the disease. This might not be the case of VIA and cervical cytology. Result interpretation of these tests is subjective. VIA commonly has a high sensitivity, but a low specificity compared to cervical cytology (9, 22). The positive result of VIA could be related not just only to cervical precancerous lesions, but also to inflammation and infections other than HPV infection (23). Meanwhile, the quality of cervical cytology depends on the quality of the sample collection and the

competence of the cytologist in interpreting the result (24). As a result, there is a large variation in the performance of the test, with both VIA and cytology, not only between countries, but also inside countries. For instance, it has been shown that the sensitivity of cytology varied from 28.9 to 76.9% at LSIL threshold in India (25).

A low specificity of the combined tests in the either positive results case leads to high false positive cases. This might increase the total cost as a result of complementary exams and/or unnecessary treatments, and also have a negative psychological impact on a patient. Sequentially testing cytology in VIA positive result cases might reduce the number of false positive cases. However, a recent study demonstrated that the combination of rapid HPV DNA testing and VIA in parallel had the highest sensitivity (72%) compared to other combinations (VIA plus cytology or rapid HPV DAN testing plus cytology) regarding the detection of high-grade CIN or worse. It might become another solution for developing countries where cytology is not available (26).

DOR results lead to the same conclusion as LR+, indicating that the combined test in the both-positive case is the most accurate diagnostic test. The increase of DOR indicates an increase in the discriminating power of the tests (27). The highest DOR in the combined test in the both-positive case might be explained by its highest specificity, which was nearly 1 despite its lowest sensitivity.

The combined test in both, the either-positive result and in both-positive result cases had advantages and limits to detect and rule out the disease. Our meta-analysis found a high probability of false positive results (1- specificity) in the either-positive result case, and of high false negative results in the both-positive result case (1-sensitiviy). The false positive result could lead to anxiety and further unnecessary invasive investigation or treatment, which are harmful in terms of physical, psychological and economic burden. In contrast, false negative results yield to considerable delay in diagnostic and treatment particularly when screening interval spreads over several years. This delay might lead to more complicated and advanced stages of the disease, requiring more advanced diagnostic investigations, and consequently delayed treatment and a higher risk of death as found in countries with high incidence and mortality rates of invasive cervical cancer (27).

The performance of the combined test varied across studies. This variability might occur as a result of the variability of the performance of both VIA and cervical cytology tests. The result of I^2 statistic found consistently large variations between studies in meta-regression analysis. Indeed,

meta-regression analysis confirmed this significant variability by exploring the influence of covariates on DOR in restriction analyses, which consisted in including only studies with CIN2+ as the threshold of disease. Our finding is consistent with the study by Chen *et al* (28) that shows that the setting and the size of the population were significantly associated with DOR of VIA in restriction analyses. These covariates did not significantly influence the DOR in non-restriction analyses. This indicated that the influence of covariates depended on study characteristics, particularly the threshold of the disease. To better clarify and rule out the variability of the diagnostic test accuracy, more restriction is probably needed, for instance: restricting the analyses to articles with similar characteristics of test performance (setting, capacity of interpreter and etc.). However, we could not conduct this restriction analysis in our meta-analysis due to the limited number of relevant studies. Further individual studies on the performance of VIA and cervical cytology combined test are apparently required.

The specificity of the combined test in the either-positive result case decreased when analyses were restricted to studies without partial verification bias. This indicates an overestimate of specificity for the combined test in the either-positive result case. Evidently, a partial verification bias can lead to an overestimate of the sensitivities and specificities as a result of a lower proportion of false negatives. The verification bias could be corrected using a Bayesian approach, multiple imputation and the conventional correction method proposed by Begg and Greenes (29).

As noted, the performance of colposcopy exam is not a perfect test for diagnosing cervical precancerous lesions. Meta-analyses showed that colposcopy had sensitivities ranging from 64% to 99% and specificities from 30% to 93% in the detection of high-grade CIN (30). In none of the included studies did all women receive a biopsy. The subjectivity of the colposcopy-directed biopsy exam could have affected the pooled estimated sensitivity and specificity found in our meta-analysis due to a low number of false negative result cases (31). Due to the limited number of included studies, the restriction analysis could not be done for this case.

Limitations

This meta-analysis does have some limitations, which could affect the interpretation of results. First, due to the limited number of studies included, we could not assess the change of sensitivity and specificity among women with ASCUS as positive result of cervical cytology, a low-grade CIN as a disease, the geographical region and symptomatic women. However, the performance of the

combined test did not change when the analyses were restricted to articles without partial verification bias and CIN2+, with the exception of the specificity of the combined test in the either-positive result case, which was high compared to non-restriction analysis. This might reflect an overestimation of the specificity of this test.

Second, VIA is recommended only for women aged of 30-45 years. But we could not conduct the analysis in this subgroup due to lack of information on test performance according to the age. This could underestimate the sensitivity due to a greater number of false negative results (32).

Third, due to the limited number of studies focusing on the diagnostic accuracy of the combination VIA and cervical cytology tests for the detection of cervical precancerous and cancerous lesions, we could not explore the performance of sequential testing cervical cytology in positive VIA cases. This strategy might diminish the false positive rate of VIA, particularly in settings where VIA screening is implemented. Further individual and meta-analytic studies are therefore needed to answer this question.

2.7 Conclusion

The combination of VIA and cervical cytology in the either-positive result case gained sensitivity compared to the use of a single approach, but lost specificity, contrary to combination in the both-positive result case. Our results suggest that the combined test should be considered in developing countries as a primary screening test if facilities exist to confirm, through colposcopy and biopsy a positive result in order to diminish the number of false positive cases and its consequence, unnecessary treatment.

Conflict of interest

The authors have no conflict of interest to declare

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Figure 1: Flowchart of procedure performed in systematic review

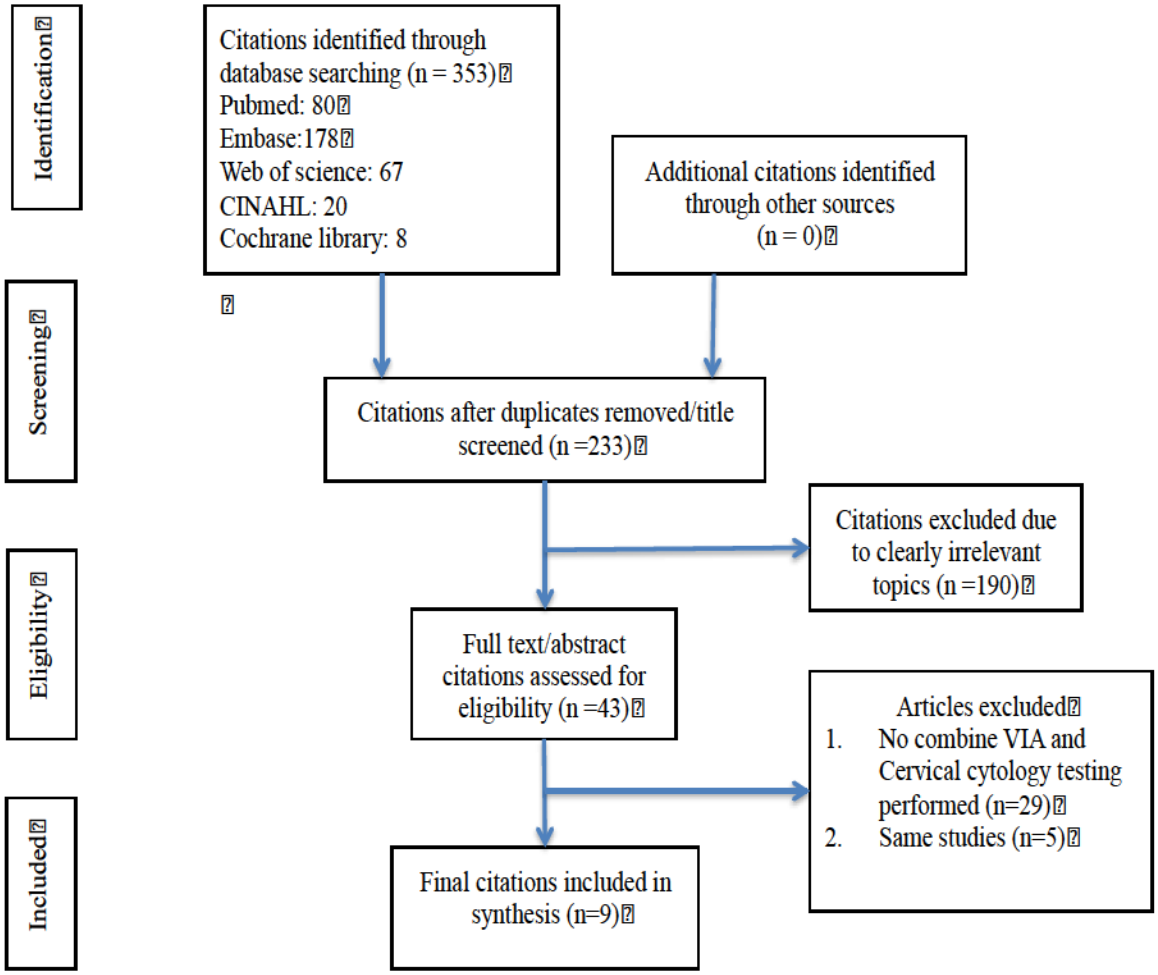


Table 1: Characteristics of included articles in the analysis

Authors	Study design	Study site	Clinical condition	Sample size	Screener	Threshold of cervical cytology ¶	Goal standard	Criteria for goal standard performance
Blumenthal *et al.*,[33] (2001)	Cross-sectional study from 1995-1997	Peri-urban primary care clinics in Zimbabwe	Unspecified clinical condition women aged between 25 and 55years,	2073	Trained nurse-midwife	LSIL+	Colposcopy and biopsy in positive colposcopy (CIN2+)	All participants underwent to colposcopy
Shastri *et al.*,(34) (2005)	Cross-sectional study from 2001-2003	Mobile field clinics in India	Asymptomatic women aged 30–65 years	3749	Trained health worker	LSIL+	Colposcopy and biopsy in positive colposcopy (HG-CIN)	All participants underwent to colposcopy
Bhatla *et al.*,(12) (2007)	Cross-sectional study in 2003	Gynecology out-patient department in India	Symptomatic women aged 30-74 years #	100	Trained-nurse and gynecologist for cervical cytology	LSIL+	Colposcopy and biopsy in positive colposcopy (CIN2+)	All participants underwent to colposcopy
Chung et al.,(13) (2013)	Cross-sectional study in 2009	OPD during clinical follow-up in Kenya	HIV-positive aged 18-55 years	453	Trained-nurse and gynecologist for cervical cytology	LSIL+	Colposcopy and biopsy in positive colposcopy (HG-CIN)	All participants underwent to colposcopy
Sahasrabuddhe et al.,(14) (2012)	Cross-sectional study from 2006-2007	Out-patient department in India	Non-pregnant and previously unscreened HIV-positive	266	Trained nurses	LSIL+	Colposcopy and biopsy in positive colposcopy (CIN2+)	All participants underwent to colposcopy
Ibrahim *et al.*,(35) (2012)	Cross-sectional study from	Primary health care in Khartoum	Asymptomatic married women aged 25-50 years	934	Trained physician	ASCUS+	Colposcopy and biopsy in positive	At least one positive test underwent to

	2009-2010						colposcopy (CIN1+)	colposcopy
Longatto-Filho et al.,(36) (2012)	Cross-sectional study from 2002-2003	Clinics in Brazil and Argentina	Asymptomatic women aged 18–60 years	10138	Trained nurse	LSIL+	Colposcopy and biopsy in positive colposcopy (CIN2+)	At least one positive test underwent to colposcopy
Mahmud *et al.*,(37) (2013)	Cross-sectional study in 2010	Out-patient department in Pakistan	Asymptomatic and symptomatic married women sexually active aged 19-51 years	519	Unknown	LSIL+	Colposcopy and biopsy in positive colposcopy (CIN1+)	At least one positive test underwent to colposcopy
Ghaemmaghami et al.,(38) (2004)	Cross-sectional study from 1999-2001	Gynecology out-patient department in Iran	Unspecified, women aged 15-70 years	1190	Trained midwife and gynecologist	ASCUS+	Colposcopy and biopsy in positive colposcopy (CIN1+)	All positive tests, and 25% randomly of negative results underwent to colposcopy

Symptomatic consisted of persistent vaginal discharge, intermenstrual bleeding, post coital bleeding, unhealthy cervix on examination

LSIL+ consisted of low grade squamous intraepithelial lesion or worse

ASCUS+ consisted of atypical Squamous Cells of Undetermined Significance and worse

¶ Cervical cytology was Conventional cytology with Ayre's spatula and cytobrush

HG-CIN consisted of high-grade cervical intraepithelial neoplasia only

CIN2+ consisted of high-grade cervical intraepithelial neoplasia and invasive cervical cancer

CIN1+ consisted of low-grade and high-grade cervical intraepithelial neoplasia and invasive cervical cancer

Table 2: Pooled estimates of combined VIA and cervical cytology testing: Meta-analysis results in all studies included, verification unbiased articles and CIN2+

Test/ Category	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	DOR
Either positive result						
All studies	9	0.87 (0.83-0.91)	0.79 (0.63-0.89)	4.29 (2.26-8.13)	0.15 (0.11-0.21)	27.66 (12.48-61.28)
Unbiased†	5	0.88 (0.80-0.92)	0.61 (0.45-0.76)	2.31 (1.56-3.43)	0.19 (.12-0.31)	12.07 (6.05-24.1)
CIN2+¶	6	0.86 (0.82-0.90)	0.67 (0.50-0.80)	2.67 (1.70-4.17)	0.19 (0.15-0.24)	13.77 (7.92-23.95)
Both positive result						
All studies	9	0.38 (0.29-0.48)	0.98 (0.96-0.99)	32.32 (13.27-78.73)	0.62 (0.54-0.72)	51.97 (22.1-122.19)
Unbiased†	5	0.41 (0.31-0.52)	0.97 (0.90-0.99)	16.59 (4.85-56.83)	0.61 (0.52-0.7)	27.59 (8.54-89.17)
CIN2+¶	6	0.37 (0.28-0.47)	0.98 (0.93-0.99)	23.65 (7.11-78.67)	0.63 (0.55-0.73)	37.31 (12.31-113.1)
VIA alone						
All studies	9	0.67(0.59-0.74)	0.81 (0.66-0.91)	3.74 (1.92-7.32)	0.39 (0.31-0.51)	9.42 (4.17-21.29)
Unbiased†	5	0.73 (0.62-0.82)	0.72 (0.59-0.83)	2.71 (1.82-4.01)	0.37 (0.26-0.51)	7.36 (4.12-13.17)
CIN2+¶	6	0.69 (0.57-0.79)	0.76 (0.63-0.85)	2.94 (2.04-4.24)	0.39 (0.29-0.53)	7.41 (4.68-11.72)
Cervical cytology alone						
All studies	9	0.60 (0.50-0.70)	0.91 (0.80-0.96)	7.4 (3.03-18.08)	0.43 (0.33-0.55)	17.35 (6.31-47.75)
Unbiased†	5	0.63 (0.47-0.76)	0.88 (0.72-0.96)	5.73 (2.28-14.39)	0.41 (0.29-0.58)	13.94 (5.19-37.48)
CIN2+¶	5	0.62 (0.49-0.73)	0.92 (0.78-0.97)	7.95 (2.97-21.31)	0.41 (0.3-0.54)	19.64 (7.13-54.09)

† Unbiased articles refer to studies that all women with positive result on index test were referred to colposcopy/direct biopsy.

¶ CIN2+: Cervical Intraepithelial Neoplasia or worse

Hierarchical bivariate random effect model was used to analyze the pooled estimate

Table 3: Sources of heterogeneity assessment through the analysis of covariates influencing DORs in all included studies, CIN2+ and asymptomatic women

Variable	Combined test in either-positive result				Combined test in both-positive result			
	All included studies		CIN2+ ¶		All included studies		CIN2+ ¶	
	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
Place of study:								
Lower-middle income countries	89.8	0.32	35.7	0.001	15.1	0.69	146.6	<0.0001
Otherwise	(Ref)		(Ref)		(Ref)		(Ref)	
Size of population								
≥ 900	- 124.7	0.14	5.3	0.51	59.7	0.09	152.1	<0.0001
< 900	(Ref)		(Ref)		(Ref)		(Ref)	
Screener								
Physician	- 44.2	0.63	13.8	0.19	8.86	0.82	154.9	<0.0001
Otherwise	(Ref)		(Ref)		(Ref)		(Ref)	

¶ CIN2+: Cervical Intraepithelial Neoplasia or worse

The meta-regression was used to assess the heterogeneity. The influence of covariate on DOR could not done in articles with verification bias through this analysis due to limited number of included studies.

Figure 2: Forest plot of the VIA and cervical cytology combined test and single test.

The forest plot displays the sensitivity and specificity and their interval confidence of VIA alone, cytology alone and the combined VIA and cytology testing in either positive result and both positive result in the nine articles included in the analyses.

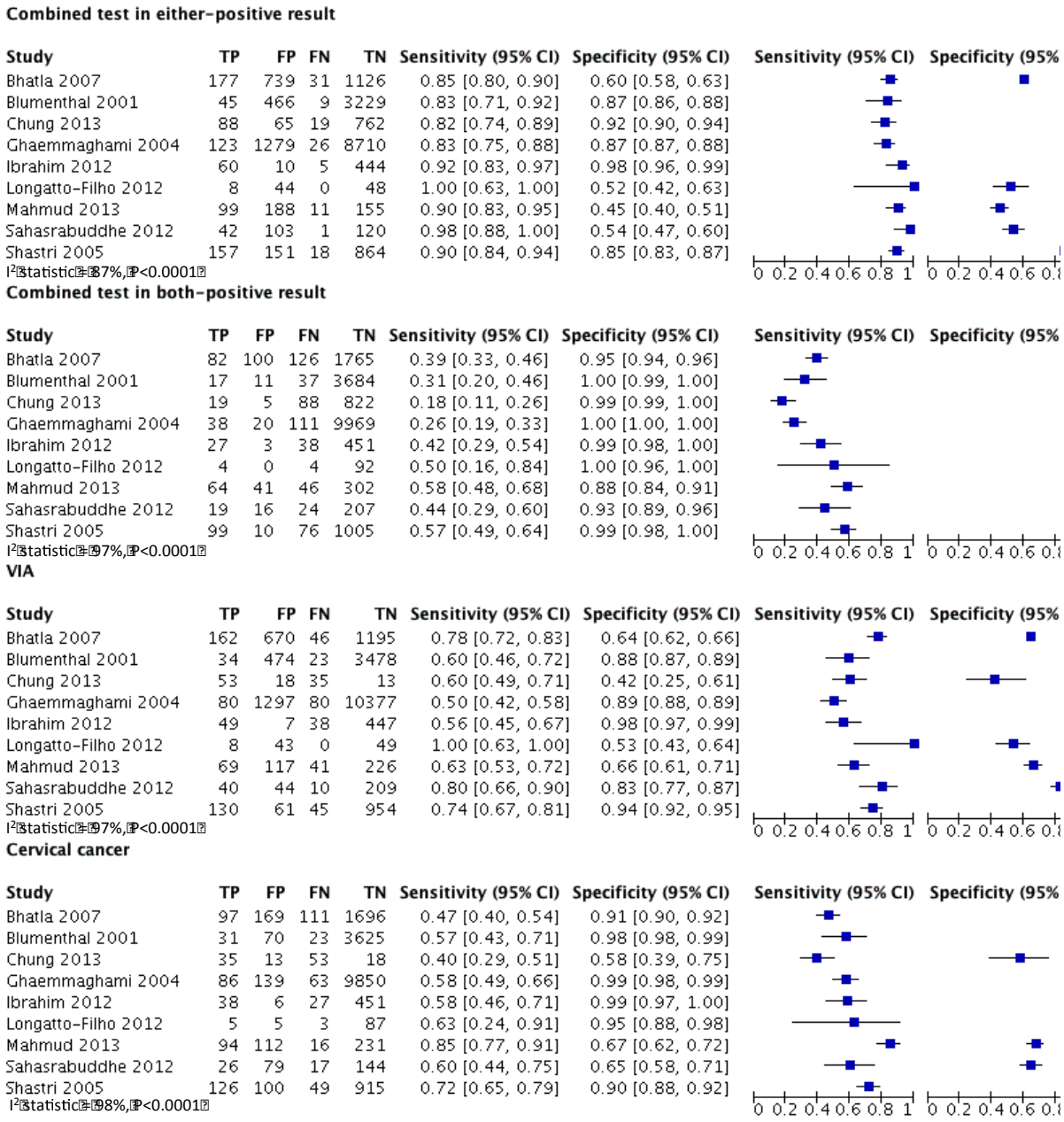
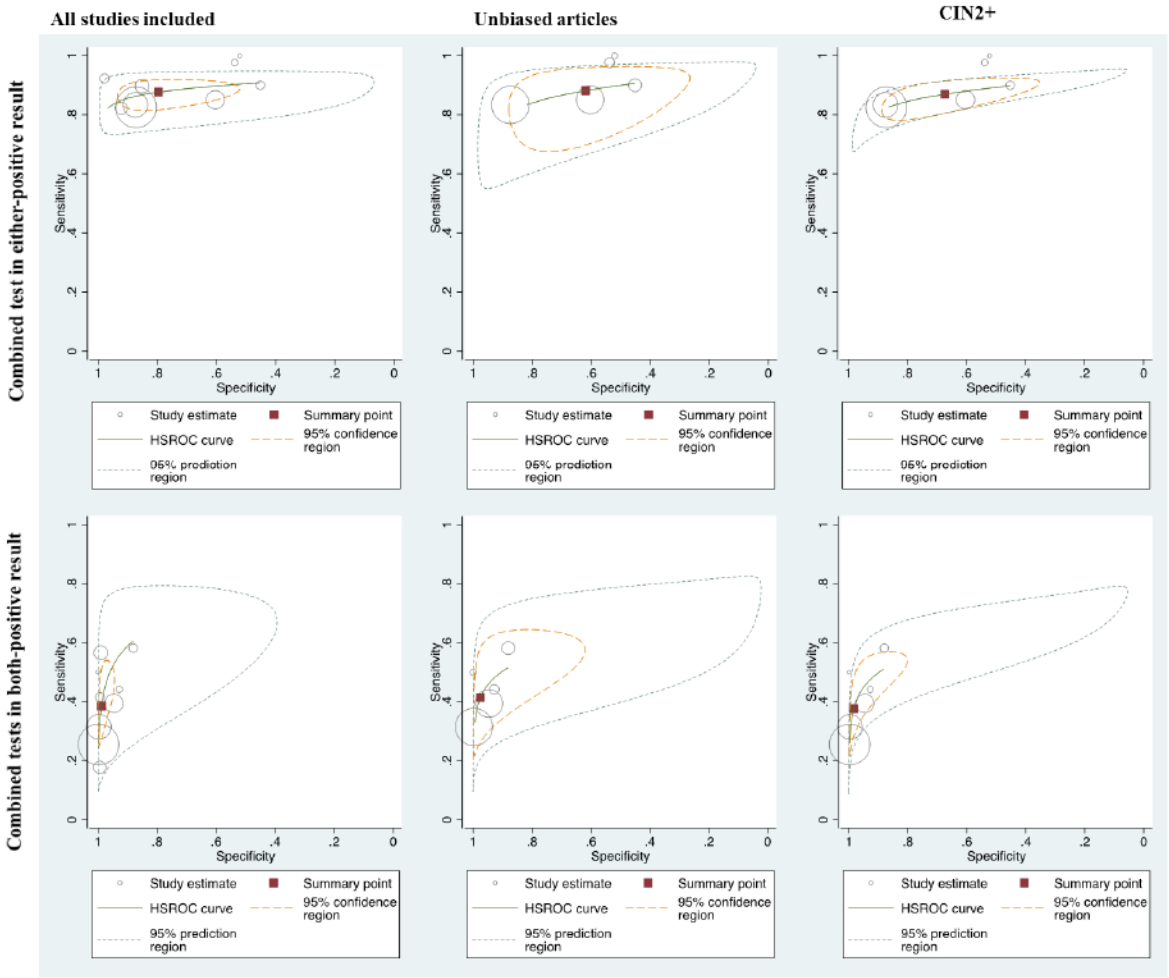


Figure 3: Hierarchical summary receiver operating characteristics (HSROC) curves for the VIA and cervical cytology combined test in either-positive result and in both-positive result: restriction and non-restriction analyses.

HSROC curves display the variation of sensitivity and specificity of combined VIA and cytology in either positive result and in both positive result, which were reported in three different scenarios: all studies included unbiased articles and CIN2+. The large curve reflects large variation of test performance across included studies.



Chapter 3 :

The economic evaluation of Human Papillomavirus vaccination strategies against cervical cancer in women in Lao PDR: a mathematical modeling approach

Chapter 3: The economic evaluation of Human Papillomavirus vaccination strategies against cervical cancer in women in Lao PDR: a mathematical modeling approach

3.1 Résumé

Introduction: Le cancer du col de l'utérus est la troisième cause de la morbidité et mortalité liées au cancer en RDP Lao. Aucune étude n'a comparé les stratégies de vaccination du Virus de Papillome Humain (VPH) d'un point de vue du coût-efficacité à RDP Lao.

Méthodologie : Un modèle dynamique et de la population a été établi. En plus du dépistage, les interventions considérées ont inclus la vaccination des jeunes filles âgées de 10 ans seule ou bien combinée avec la vaccination des garçons et ou un rattrapage. La simulation a porté sur une durée de 100 ans. Dans les analyses de base, nous avons émis les hypothèses d'une couverture vaccinale de 70% avec une durée de protection à vie, une efficacité de 100% contre le VPH type 16/18. Les issues d'intérêt étaient le coût incrémental (ICER) des Années de vie ajustées pour l'incapacité (DALY).

Résultats : Selon l'analyse de base, en tenant compte du seuil proposé par l'OMS pour définir quel investissement devrait être considéré comme coût-efficace, il apparait que la vaccination des jeunes filles est très coût-efficaces. Ajouter au programme de la vaccination des jeunes filles un rattrapage vaccinal pour les femmes de 11 à 25 ans est très coût-efficace (1 559 I$ par DALY évité). Augmenter l'âge maximal du rattrapage vaccinal à 75 ans est coût-efficace (5 840 I$ par DALY évité). Ajouter une composante vaccination des garçons n'est pas coût-efficace à moins de ne considérer qu'une période de 30 ans et si le rattrapage vaccinal implique les femmes et les hommes.

Interprétation: Ajouter un rattrapage vaccinal à un programme de vaccination du VPH chez les jeunes filles de 10 ans est plus intéressant que d'ajouter une composante vaccination des garçons.

Subvention: Agence Universitaire de la Francophonie et Programme interuniversitaire de formation en recherche en santé mondiale (Santé-Cap). LJW est subventionnée par le Wellcome-Trust du programme d'outre-mer majeure en Asie du Sud-est (Numéro de subvention 106698/Z/14/Z).

3.2 Abstract

Background: Cervical cancer, a preventable disease, is the third leading cause of cancer morbidity and mortality in Lao PDR. No study has compared the cost-effectiveness of various Human Papillomavirus (HPV) vaccination options in Lao PDR.

Methodology: A dynamic compartment model was created. In addition to the routine screening activities in place, the interventions include a 10-year girl vaccination only program combined

with/without a boy vaccination and/or a catch-up component. The simulation was run over 100 years. In base case analyses, we assumed 70% of vaccination coverage with lifelong protection and 100% efficacy against HPV type 16/18. The outcomes of interest were the incremental cost per Disability-Adjusted Life Year (DALY) averted.

Findings: In base case analyses, according to the WHO definition of cost-effectiveness thresholds, vaccinating 10-year-old girls was very cost-effective. Adding a catch-up vaccination element for 11-25 year-old women was very cost-effective, costing 1 559 I$ per DALY averted. Increasing the age limit of the catch-up vaccination component to 75 years made the addition still a cost-effective option (5 840 I$ per DALY averted). Adding a boy vaccination is not cost-effective unless if we consider short time simulation, 30 years or less and if a catch-up vaccination component for both women and men is added.

Interpretation: Adding a catch-up vaccination component is more attractive than adding a boy vaccination component.

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3.3 Introduction

Cervical cancer is the leading cause of cancer deaths among women in Lao PDR with an estimated number of 320 cases and 170 deaths annually (1). The high fatality rate of cervical cancer is probably due to lack of national Human Papillomavirus (HPV) vaccination program, lack of effective chemo-radiation treatment in the country and delay in diagnosis (1). The delay in diagnosis is in great part due to the fact that there is no national cervical cancer screening program in the country. In Lao PDR, it has been estimated that only 5% of 18-69 year old women in urban areas and 1% in rural areas are screened every 3 years (1).

A systematic screening program could reduce the disease burden, but might be not possible in Lao PDR due to many reasons such as financial and sociocultural barriers, poor health care infrastructure (2), poor performance of the laboratory test (3). Given these problems, HPV vaccination might be a more suitable approach for the country. It has been shown to be effective, with the bivalent and quadrivalent vaccines providing extremely high rates of protection against high grade cervical intraepithelial neoplasia (CIN 2/3) related to HPV types 16 and 18 (4). Moreover, Goldie et al (5) showed that preadolescent girl HPV vaccination is very cost-effective in 72 GAVI-eligible countries including Lao PDR, and Jit et al., (6) found similar outcome in global

scale. However, no nationwide vaccination strategy has so far been implemented in the country.

A HPV vaccination pilot project consisting in vaccinating 5th grade schoolgirls in the capital and in the neighbouring Vientiane Province is currently taking place. It is likely that such a HPV vaccination program will become routine practice in the future. However, coverage might be low. Considering this eventuality, it might be interesting to evaluate the benefit of complementing such vaccination program with additional interventions, as adding a catch up vaccination campaign and/or a boy vaccination element. In order to examine this question, we used a mathematical modeling study to estimate the cost-effectiveness of various HPV vaccination strategies in the Lao context.

3.4 Methodology

Model structure

This economic evaluation study complied with the recommendations of WHO for cost-effectiveness analyses (7). Inspired by previous economic models of HPV vaccination (8), a compartmental dynamic population-based model was created to reflect the expected effect of HPV vaccination programs, both in females and males. The model considered that the HPV genotypes were a 16, 18 or other high-risk type, or a low-risk type.

For females, the model considers that an infection regresses due to natural immunity, while remaining susceptible for other HPV types. An infection can persist or progress into a Cervical Intraepithelial Neoplasia (low-grade CIN or high-grade CIN). A low-grade CIN might regress to an immunity state or an infection state, or progress into a high-grade CIN. A high-grade CIN regresses to an immunity state or an infection state or low-grade CIN, or might progress into an invasive cervical cancer (local, regional and distant, respectively). Women diagnosed with high-grade CIN are treated. Women with invasive cervical cancer might be symptomatically detected. Diagnosed cancer cases are treated, with a probability of recovery, treatment failure or death (Figure 1).

For males, only the susceptibility, infection and recovery states were considered. Vaccinated people remained susceptible for non-vaccine HPV types or they could become susceptible to 16/18 types HPV infections in case of vaccine-induced immunity waning.

Parameters

Monthly transition age-specific probabilities from one lesion state to another and regression rates presented in Table 2 were taken from Kim et al (9) with the exception of the infection rate. Infection rates were given by the sexual relationship matrix multiplied by HPV genotype-specific transmissibility and age-specific HPV prevalence in the opposite sex. To simplify the model, we considered all members of the population as heterosexual. The sexual relationship matrix consists of the monthly age-specific probability of having new sexual partner in which each age group has the probabilities of having a sexual intercourse with someone of the same and a different age group of 0.6 and 0.4 respectively (10) (Appendix 1). The initial age of sexual intercourse is 15 years old or more in both girls and boys (11). The screening and treatment parameters are described in the appendix 1.

Model calibration

The population was stratified by gender and age. The model is in the form of a realistic age structured (RAS) model. The equations were numerically solved in Berkeley Madonna version 8.3.18 (12). The model was calibrated using maximum likelihood. The details are described in the Appendix 1. Briefly, the model was first calibrated in order to produce a demographic structure similar to the 2014 distribution of the Vientiane capital population (in one-year intervals) (13). Thereafter, the model was calibrated for the age-specific incidences and mortalities of cervical cancer, according to the Globocan estimates (1).

Scenarios

In the baseline model, the model considered that in Lao PDR there is no vaccination program, and that the coverage of routine cytology screening is 5.2% among 18-68 year old women (1). We assumed that screening coverage would remain the same over time. The HPV vaccination program consisted of a 10-year-old girl vaccination program combined or not with a catch-up component and/or a boy vaccination element. The details of the strategies are described in Table 1. The population of 10-year-old girls was chosen because the current HPV vaccination demonstration project targets 5th grade girl students who are mostly 10 years old. The first selected age group for a catch-up vaccination was 11-25 year old women, as this age group represents the age of undergraduate students who are reachable through school and university-based interventions. The 11-75 year old age group represents the population at risk of HPV infection in our model.

The coverage of HPV vaccination was assumed to be about 70% (range: 30-80% for sensitivity analysis), with 100% (range: 30-100% for sensitivity analysis) effectiveness against HPV type 16 and 18 and a lifelong protection (10 years to lifelong).

Costing

The perspective considered was essentially the perspective of the public health care system. Only direct medical costs and the programmatic cost of the vaccination program were considered. The costing methodology is detailed in the Appendix 1. Briefly, the cost of delivering HPV vaccines consisted of the price of the vaccine and the programmatic cost of vaccination delivery. The programmatic cost of 3-dose HPV vaccine per girl was retrieved from evaluation on HPV vaccination performed in Vientiane capital by WHO (personal communication, 2015). The Global Alliance for Vaccines and Immunization (GAVI) vaccine cost per dose was used (14). Medical consumption was estimated based on data cost study done at the Ministry of Health (personal communication, 2014). This includes cytology screening visits and laboratory exams, precancerous lesions and cervical cancer treatments. The cost of treatment for stage-specific invasive cervical cancer was retrieved from Goldie et al (5).

Analyses

The simulation process deterministically ran over a 100 year-span to capture the long-term benefits of vaccination. For each option, the output consisted of the cumulative number of cervical cancers per 1 000 women, the DALYs per 1 000 women and the cost of screening and treatment per 1 000 women. The strategies were ranked based on the cost, from the lowest to the highest. In case of a non-dominant situation, strong or extended dominance, the incremental cost/effective ratio was calculated using the reduction of HPV-16 and 18 related cervical cancer cases and DALYs averted as denominators. DALYs were calculated based on the WHO table without age weighting. The disability weight for cancer treatment was retrieved from the current literature (15). All costs and DALYs were discounted at a rate of 3% in base case simulations (7). The cost-effectiveness results were categorized into three categories: 1) very cost-effective (ICER< Lao GDP per capita; 2) cost-effective (ICER between 1-3 times the GDP per capita); and 3) not cost-effective (ICER > 3 times the GDP per capita) (16).

One-way sensitivity analyses were conducted to identify the parameters that might influence the incremental cost-effectiveness ratio per DALY averted. The parameters varied included the values of the incidence of cervical cancer, vaccination coverage, vaccine efficacy, duration of vaccine protection, duration of natural immunity, cost of vaccine per dose, cost of cancer treatment, and discount rate. Other sensitivity analyses were conducted to explore various factors, such as the initial age of vaccination in girls (11, 12 and 13 years old), the effect of 10 consecutive cohorts vaccination only and a time horizon of 30 and 50 years.

Role of the funding source

The sponsor had no role in the design, collection and analysis of the data or the writing of the manuscript. The corresponding author had full access to all the data in the study and assumed the final responsibility for the decisions regarding the submission of the manuscript.

3.5 Results

Model calibration

The model was able to reproduce the 2014-Vientiane Capital expected values regarding demographic data, both for female and male populations (Appendix 1). However the number of individuals was high for 10 to 25 year old individuals compared to expected values, while it was low for 25-35 year old individuals. The model reproduces results that are consistent with the estimated incidence of cervical cancer and its mortality due to any high-risk HPV type according to the estimates of Globocan 2012 (Figure 2). The proportion of cervical cancers related to HPV type 16 and 18 was about 75%.

Clinical impact and cost-effectiveness

Table 3 shows that vaccinating 10-year-old girls has the potential to reduce the number of cervical cancers due to HPV type 16/18 by 78% and provides a potential diminution of 31 DALYs per 1 000 women. These benefits increase when a catch-up vaccination and/or a boy vaccination component are added. The reduction of cancer in adding catch-up vaccination was in earlier stage compared to adding boy vaccination (Figure 3).

In terms of cost, the baseline strategy (no vaccination with 5.2% of conventional cytology) is the cheapest option, followed by a 10-year-old girl vaccination program and a catch-up vaccination component for 11-25 year-old females, respectively. In terms of ICER per cancer prevented, the girl vaccination option is cost-effective with an ICER of 6 334 I$ per cancer prevented, which is between 1 and 3 GDP per capita. Adding a catch-up vaccination component for 11-25 years old women or a boy vaccination component to the girl vaccination program does not appear to be cost-effective since their ICERs are higher than 3 GDP per capita. Other strategies are dominated. In terms of ICER per DALY averted, compared to the baseline, the girl vaccination option is very cost-effective. Adding a catch-up vaccination component for 11-25 year old women is very cost-effective compared to the girl vaccination option alone. Moreover, extending the age limit of the catch-up component up to 75 years is cost-effective. In contrast, adding a boy vaccination

component to the girl vaccination option alone or along with a catch-up component does not appear to be cost-effective (Table 3).

Table 4 shows the different upper ages of the catch-up component in women. The addition of a catch-up component remains very cost-effective until an upper age of 40 years. Vaccinating older women than this age is considered cost-effective.

Sensitivity analyses

Sensitivity analyses show that the parameters that have the greatest impact on ICERs per DALY averted are vaccination coverage, cost of vaccine, discount rate, incidence of cervical cancer, duration of vaccine protection and of natural immunity, and efficacy of the vaccine. The cost of cancer treatment and the disability weight had no impact on ICERs.

The girl vaccination program is robust to changes in vaccination costs. But the ICER for a catch-up component for 11-25 year old is higher than one GDP per capita when the cost of the vaccine is 50 I$ or higher per dose. Meanwhile, adding a catch-up vaccination component for 11-75 years old women becomes very cost-effective compared to a catch-up for 11-25 years old women in following situation: 1) vaccination coverage is 50% or lower, or 2) the vaccine effectiveness is 30% or lower, or 3) the incidence of cervical cancer increases to 40%, 4) the duration of natural immunity and of vaccine protection is no longer than 10 years, 5) DALYs are not discounted and 6) the discount rate is 5% for DALY and 6% for the costs.

Moreover, the time horizon also influenced the cost-effectiveness. In 50 years simulation, the ICERs are slightly higher than in the 100 years simulation cases. In contrast, in 30 years simulation, adding boy vaccination and catch-up component for both women and men becomes cost-effective (Appendix 1).

The cost-effectiveness of HPV vaccination is not affected by different initial ages of girl vaccination. When taking into account all cervical cancer cases, we find that the number of cancers due to other high-risk HPV increases by about 2% from the baseline. However, this does not change the cost-effectiveness results (Appendix 1).

To evaluate the generalizability of results, we calibrated the model to different populations in terms of population size and demographic structure, i.e. Vientiane province. Results were robust to these changes (appendix 1).

3.6 Discussion

Vaccinating 10-year-old girls is very cost-effective even if the vaccine is expensive (100 I$ per dose). Adding a boy vaccination component produces little additional benefit, with only a further reduction of 3.4% of the number cancers. As a result, adding this component is not superior to a girl vaccination along with a catch-up vaccination component for 11-25 year-old women, which produces a further reduction of 8.9% in the number of cancers and an additional diminution of 5 DALYs per 1,000 women. This catch-up vaccination component becomes the most attractive strategy with a cost per DALY below one GDP per capita. This result is similar to what was found in a previous review (17).

Moreover, adding a catch-up component for 11-25 years old women was more attractive than adding a catch-up component for an older group, if GDP per capita is considered. This age group was also cost-effective in the study of Elbasha et *al.,* (18) and Dasbach et *al.,* (19). However, to provide more comprehensive information regarding the appropriate maximum limit age in the catch-up component, which was not reported in previous studies (19), we compared further maximum ages, from 18 to 75, using 5-year intervals. Our study found that a catch-up component for women up to 40 years was the most attractive option, costing less than one GDP per capita per DALYs averted. Several reasons can be proposed. First, the ideal age for a catch-up component might depend on sexual behavior. Second, the prevalence of HPV infection in our model simultaneously decreases after 40 years of age. Finally, one should consider that the incidence of cervical cancer increases after 40 years of age. However, our results should be cautiously interpreted because our model was not calibrated to age-specific HPV prevalence, although the trend of HPV prevalence in Lao PDR seems to be similar to what is found worldwide (20). Also, a clinical trial showed that the vaccine was safe and that it conferred a high-level immunogenicity in women up to the age of 45 years (21).

Nevertheless, in the case of a higher burden of the disease, or wane of natural immunity or a suboptimal protection from the vaccine in terms of duration, effectiveness or vaccination coverage, implementing a catch-up component for 11-75 years-old women is the most attractive option. The impact of these parameters on outcome was also reported by Jit *et al* (8) and by Van de Velde *et al.,*

(22). Indeed, the effectiveness of the vaccination increases when 1) the incidence of cervical cancer is high or when 2) the natural immunity wanes; contrarily, this effectiveness decreases in other cases. However, both directions come with the same conclusion that it is efficient to vaccinate larger female population. The lower effectiveness of vaccine might be true in developing countries due to the fact that HPV vaccine also requires an appropriate maintenance and delivery process (23). In Lao PDR, a low optimal efficacy of vaccination was reported for hepatitis B vaccine, only around 65%. The rate is even much lower in rural areas (24). Moreover, a low vaccination coverage might be found in rural settings where fewer girls are likely to attend school, 83% of girls in rural areas attend primary school with small proportion of regular attendance (10).

Furthermore, it is more cost-effective to include a boy vaccination component in addition to the catch-up component to the girl vaccination program if the time covered by the simulation is shorter, 30 years for instance. This reflects the insufficient level of vaccination protection in the population in early stage. However, to our best knowledge, no study considered the cost-effectiveness of HPV vaccination in early stage.

Our study had some limitations. First, our model did not take into account cross-protection provided by the vaccine or other HPV-related diseases, such as warts and other cancers. This might underestimate the total DALYs averted related to all HPV types. However, this might not significantly bias the conclusion because of slight benefit of the cross-protection (25). Second, we have ignored some costing items related to screening and treatment. These include the cost of specimen delivery and the cost of treatment complications. This might lead to an underestimation of the total cost per person. However, according to Goldhaber-Fiebert and Goldie (26), these cost components are small relative to the cost of screening and treatment. Finally, it is likely that newer vaccines, active against multiple HPV types, will provide even greater levels of protection (27), and also an equivalent effectiveness of two doses instead of three doses HPV vaccination (28) might reduce the cost, subsequently increase the cost-effectiveness of the vaccination as demonstrated in a cost-effectiveness study in UK (29). However, our study did not take into account these aspects, future study might be necessary for Lao PDR.

Finally, one should stress that the study does not reflect the financial affordability of the health care system in Lao PDR. The threshold ratio used to measure the cost-effectiveness is the GDP per capita, which is controversial (30). Moreover, the limited resources in the country lead to a strong

competition among interventions in health care programs. The cervical cancer prevention program might compete with programs for other diseases in the areas of mother and child health and tropical diseases. Accurate data on the burden of the disease in Lao PDR might provide useful elements for decision maker. Nevertheless, preadolescent girl vaccination should be considered to implement nationwide at least in Lao PDR in the combination of catch-up component.

Panel: Research in context

Systematic review

We did not conduct the systematic search in our work for HPV vaccination. However, following the experts' consultation and literature review, there is a concern of cervical cancer control particularly in low and middle-income countries due to lack of effective prevention strategies relevant to the local context. Lao PDR, for instance, the precancerous lesions screening is very limited, and the preadolescent girl vaccination program, implemented as a pilot project in Vientiane capital and Vientiane province, does not fully protect the vaccinated and unvaccinated population against the cervical cancer. This means that precancerous lesions screening remains necessary. However, improving the screening quality or increasing the screening coverage is unlikely possible in next decades. Vaccinating larger population might be the better alternative option such as adding catch-up component and/or boy vaccination to the girl vaccination. Nevertheless, the evidence of cost-effectiveness of these options is limited. Most studies have been conducted in high-income countries. No evidence is available for low or lower meddle-income countries like Lao PDR where the budget and infrastructure resources for cervical cancer prevention are scarce.

Interpretation

Our study uses the most available data deemed relevant to the local context in terms of costing and current practice related to cervical cancer. With model calibration to Globocan estimated incidence and mortality related to cervical cancer, our conclusion is not different from the literature where more data are available to calibrate more other compartments such as the prevalence of HPV and precancerous lesions. We found that the preadolescent girl vaccination is very cost-effective. Including boy vaccination is dominated by a temporary catch-up component for 11-25 years old women, which is considered the most attractive strategy. However, adding catch-up component for 11-75 years old women could be very cost-effective if the effectiveness of vaccination is lower or higher than optimal assumption. Moreover, including boy vaccination to catch-up component and girl vaccination would become interesting in early 30 years of the program. Nevertheless, our study suggests that the catch-up vaccination should at least be included to girl vaccination in Lao PDR and other lower middle-income countries. Moreover, a multicountry model to study the cost-effectiveness of including catch-up vaccination will be valuable for global cervical cancer control.

Contributors

PC designed, analyzed and wrote the article. LJW validated the model and result. DR and LM validated the methodology. MM, DEM and KP validated the concept and result realistically to Lao context. All authors gave comments and validated the final version.

Conflict of interest

Authors declare no conflict of interest for this study

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Figure 1: Model structure for natural history of Human Papillomavirus infection and cervical cancer.

The model structure reflects the natural history of HPV infection towards cervical cancer. Women can be infected by HPV and progress to low-grade CIN or high-grade CIN, or regress with natural immunity. Low-grade CIN progress to high-grade CIN, or regress thanks to the natural immunity. High-grade CIN progress to invasive cervical cancer (local, regional and distant cancer), or regress thanks to the natural immunity. In the male model, there are three compartments considered: susceptibility to infection, infection and recovery with natural immunity. Female can be protected by HPV vaccine.

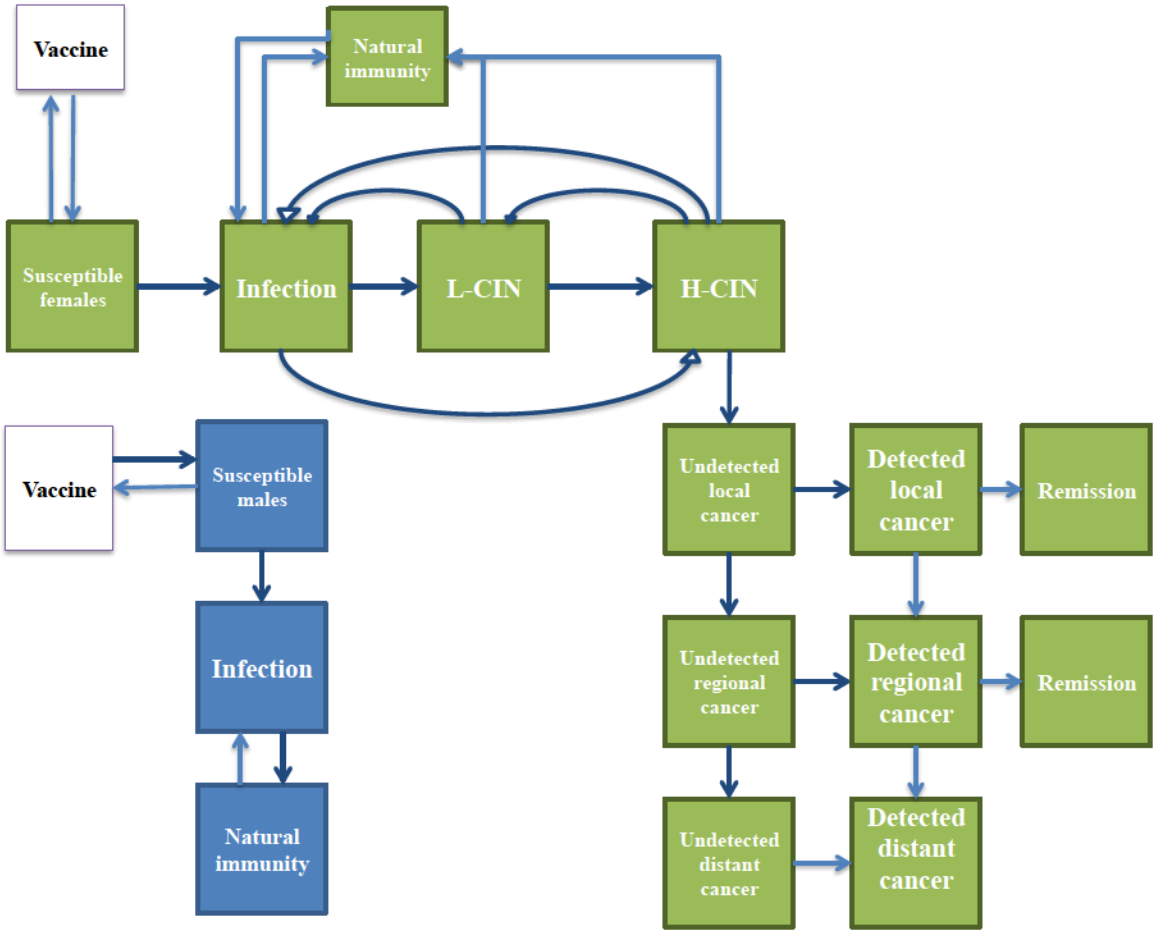

Figure 2: Model calibration to age-specific incidence and mortality of cervical cancer

Predicted incidence of cervical cancer and predicted mortality related to cervical cancer follow the age specific-distribution of observed data in Lao PDR, as estimated by Glocoban.

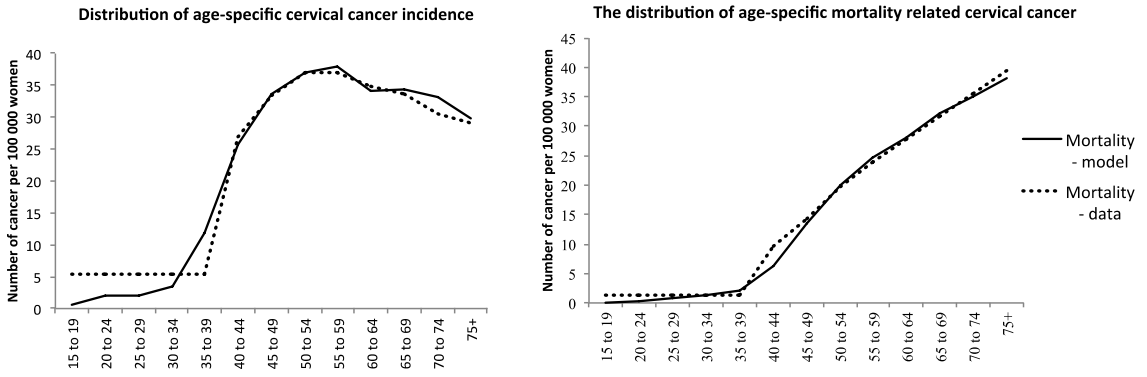

Figure 3: The effectiveness of various HPV vaccination strategies in term of cervical cancer reduction

The number of cervical cancer decreases over time in the strategies to, either adding boy or adding a catch-up vaccination component to the girl vaccination. Adding a catch-up component decreases cervical cancer in earlier stage compared to adding a boy vaccination component.

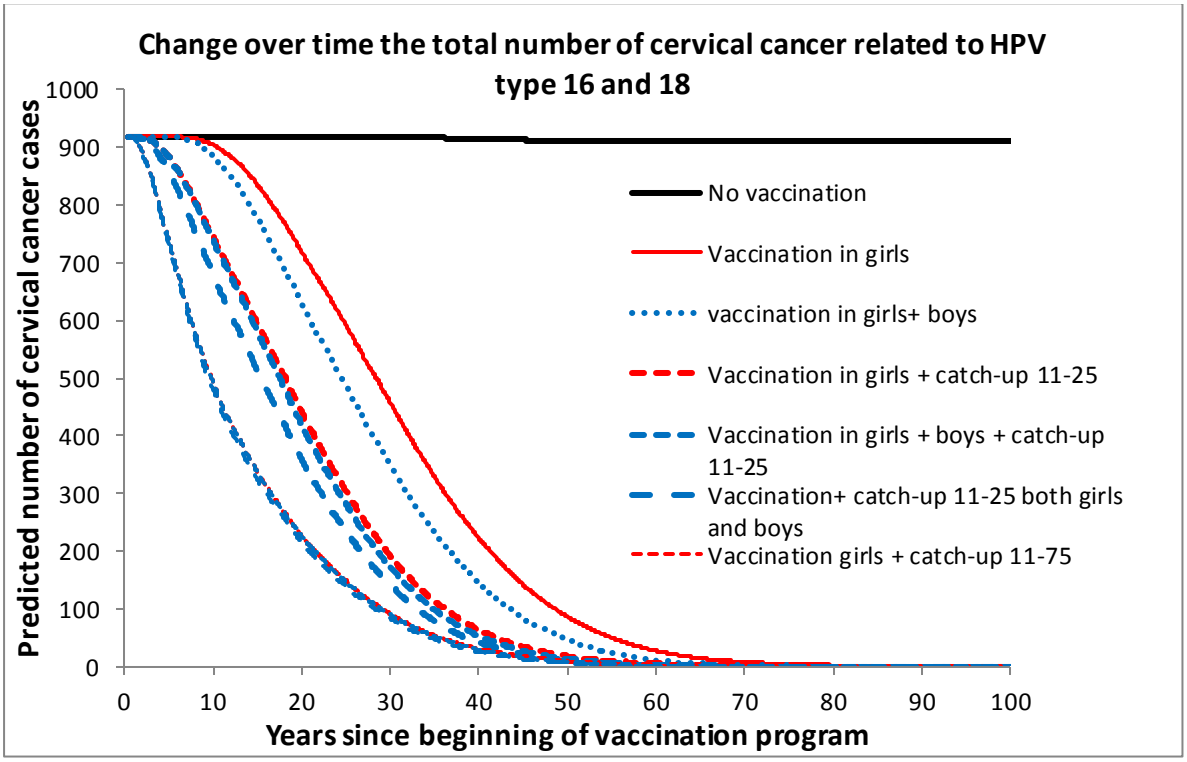

Table 1: Summary of the vaccination strategies evaluated

	Female			Male		
	Routine vaccination	Catch up campaign		Routine vaccination	Catch up campaign	
	10 years	**11-25 years**	**11-75 years**	**10 years**	**11-25 years**	**11-75 years**
1	X					
2	X			X		
3	X	X				
4	X	X		X		
5	X	X		X	X	
6	X		X			
7	X		X	X		
8	X		X	X		X

Table 2.1: Summary of input parameters for the model

Parameters		Baseline values*	Range ¶	Source
Progression				
Healthy to infection †	HPV-16	0.000175-0.003148	0.0001426-0.00761	Calibrated
	HPV-18	0.0004-0.000789	0.000102-0.00168	
	Other HR HPV	0.000206-0.004038	0.0001703-0.00911	
	LR HPV	0.000958-0.018412	0.00069-0.0537	
HPV DNA to CIN1‡	HR-16 HPV	0.005194-0.00901		(9)
	HR-18 HPV	0.002793-0.004845		
	HR-other HPV	0.007693-0.013345		
	LR-HPV	0.002397-0.001222		
Proportion (%) of women who transition directly from HPV DNA to CIN2,3	HR-16 HPV	0.64		(9)
	HR-18 HPV	0.975		
	HR-other HPV	0.966		
	LR-HPV	0.98		
CIN 1 to CIN 2,3 ‡	HR-16 HPV	0.00951-0.012363		(9)
	HR-18 HPV	0.0051-0.00663		
	HR-other HPV	0.00747-0.009711		
	LR-HPV	0.000149-0.000222		
CIN 2,3 to local cancer	HR-16 HPV	0.000151-0.00906		(9)
	HR-18 HPV	0.000264-0.01584		
	HR-other HPV	0.000199-0.01194		
Local to regional invasive cancer		0.0200		
Regional to distant invasive cancer		0.0250		
Regression				
HPV DNA to Normal	HR-16 HPV	0.09089		(9)
	HR-18 HPV	0.09089		
	HR-other HPV	0.09272		
	LR-HPV	0.09699		
CIN 1 to normal ‡‡	HR-16 HPV	0.03782		(9)
	HR-18 HPV	0.03782		
	HR-other HPV	0.04575		
	LR-HPV	0.01708		
CIN 2,3 to Normal §§	HR-16 HPV	0.000798-0.000455		(9)
	HR-18 HPV	0.003556-0.011938		
	HR-other HPV	0.002926-0.009823		
	LR-HPV	0.001904-0.006392		
Other				
Immunity (%) (HR-HPV types only) ¶¶	HR-16 HPV	0.66		(9)
	HR-18 HPV	0.86		
	HR-other HPV	0.59		
Annual probability of symptom detection #	Local invasive cancer	0.33		(9)
	Regional invasive cancer	0.60		
	Distant cancer	0.9		
Proportion of cancer patient receiving the treatment	Local cancer	100%		Calibrated
	Regional cancer	80%		
	Distant cancer	70%		

Table 2.2: Summary of input parameters for the model (continued)

Parameters		Baseline values*	Range ¶	Source
Age-specific 5-year survival proportion after diagnosis and treatment (%) £	Local cancer	0.29-71%		Calibrated
	Regional cancer	0.24-78%		
Age-specific monthly probability of death	Complication of local cancer treatment	0.012-0.037		Calibrated
	Complication of regional cancer treatment	0.0098-0.028		
	Distant cancer	0.28-0.83		

Note:

* Baseline values are monthly age-specific rates, unless otherwise noted

¶ Range is age-specific rate calibrated with the assumption of unchanged natural progression and regression of HPV infection and cervical cancer.

† The transition from healthy state to infection is a force of infection derived from the number of sexual partner change, HPV type-specific transmissibility (range: 0.353-0.41)

‡ HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; HR, high risk; LR, low risk

‡‡ 70% of women with CIN 1 regress to normal, 30% to HPV.

§§ 70% of women with CIN2,3 regress to normal, 15% to HPV, 15% to CIN 1.

¶¶ Immunity represents the degree to protection each woman faces against future type-specific infection after infection after first infection and clearance. The immunity was assumed to be lifelong protection.

The annual probability of symptom detection corresponds to 15% for local cancer and 85% for advanced cancer

£ Age-specific survival proportion was calibrate, based on a mortality rate by Globocan (1).

Table 3: The effectiveness, the total cost and the incremental cost-effectiveness by vaccination strategy against cervical cancer due to HPV type 16 and 18

Number	Options	Total cost per 1000 women	Cancer per 1000 women	Cancer Reduction (%)	DALY averted per 1000 women	Cost-effective ratio (cancer reduction)	Cost-effective ratio (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
1.	No vaccination with current screening	4497	3.4	Ref	Ref	Ref	Ref	Ref	Ref
2.	10 years old girls	21599	0.7	77.9	31.1	8000	695	6334	550
3.	10 years old girls+catch-up girls aged 11-25 years old	27807	0.4	86.8	35.1	9269	792	20693	1559
4.	10 years old girls+boys	38030	0.6	81.3	32.6	13582	1167	D	D
5.	10 years old girls+catch-up girls aged 11-75 years old	39059	0.3	91.4	37.0	12600	1056	112520	5840
6.	10 years old girls+boys+catch-up girls aged 11-25 years old	44263	0.4	87.4	35.3	14754	1254	D	D
7.	10 years old girls+boys+catch-up girls and boys aged 11-25 years old	50210	0.4	88.7	35.9	16737	1399	D	D
8.	10 years old girls+boys+catch-up girls aged 11-75 years old	55520	0.3	91.4	37.0	17910	1501	D	D
9.	10 years old girls+boys+catch-up girls and boys aged 11-75 years old	72723	0.3	91.8	37.2	23459	1955	D	168320

Note: The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. The D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.
The GDP per capita in 2013 was about 4,822 international dollars (31).

Table 4: The cost-effectiveness of catch-up vaccination by upper age limit

Number	Options	Total cost per 1000 women	DALY averted per 1000 women	ICER (DALY)
1.	No vaccination with current screening	4497	-	-
2.	Catch-up 11-18	24680	34.1	592
3.	Catch-up 11-20	25548	34.4	2373
4.	Catch-up 11-22	26446	34.7	3476
5.	Catch-up 11-25	27807	35.1	3420
6.	Catch-up 11-30	29983	35.7	3880
7.	Catch-up 11-35	31919	36.2	3882
8.	Catch-up 11-40	33584	36.5	4662
9.	Catch-up 11-45	34991	36.7	7012
10.	Catch-up 11-50	36159	36.9	8408
11.	Catch-up 11-55	37109	36.9	D
12.	Catch-up 11-60	37857	37	15750
13.	Catch-up 11-65	38418	37	D
14.	Catch-up 11-70	38812	37	D
15.	Catch-up 11-75	39059	37	D

Note: The incremental cost of the effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategies, the ICER was calculated by devising different costs by different effectiveness. The intervention was compared to the next more effective and more costly option. The D refers to strong dominance, which is expressed as a higher cost and a lower effectiveness compared to the alternative options.
The GDP per capita in 2013 was about 4,822 international dollars (30).

Chapter 4

Economic evaluation of screening strategies combined with preadolescent girl HPV vaccination against cervical cancer in Vientiane, Lao PDR

Chapter 4: Economic evaluation of screening strategies combined with preadolescent girl HPV vaccination against cervical cancer in Vientiane, Lao PDR.

4.1 Résumé

Introduction: Plusieurs approches pour réduire l'incidence de cancer invasif du col de l'utérus sont possibles. Le choix de l'intervention à implanter devrait tenir compte des facteurs contextuels qui influencent le coût-efficacité des options.

Objectif : Déterminer le coût-efficacité des stratégies du dépistage combiné avec un programme de vaccination contre le virus du papillome humain (VPH) chez les jeunes filles âgées de 10 ans en RDP Lao.

Méthodologie : Un modèle dynamique de la population a été établi. Les interventions considérées ont inclues le programme de vaccination du VPH seul ou combiné avec un dépistage. Plusieurs options étaient possibles : Inspection visuelle après application d'acide acétique (IVA), frottis de dépistage, test rapide de détection d'ADN-VPH et combinaison l'IVA et frottis. La simulation a porté sur une durée de 100 ans. A l'analyse de base, nous avons émis l'hypothèse d'une couverture vaccinale de 70% avec une durée de protection à vie et une couverture du dépistage de 50%. Les issues d'intérêt étaient le coût incrémental (ICER) par Années de vie ajustées pour l'incapacité (DALY).

Résultats : Selon l'analyse de base, comparé à l'option la plus efficace suivante, un programme de dépistage par IVA pour les femmes âgées de 30-65 ans tous les trois ans combiné à la vaccination est l'option la plus intéressante avec un coût de 2 544 dollars internationaux (I$) par DALY évité. Le test rapide de détection d'ADN-VPH est plus coût/efficace que le frottis de dépistage. Parmi les options de frottis, la combinaison IVA-frottis conventionnel est l'option la plus intéressante, suivie par l'option frottis sur couche mince puis frottis conventionnel. Les analyses de sensibilité multivariées n'ont pas montré de changement du résultat à la variation de paramètres-clefs. Comparé au test rapide ADN-VPH, l'IVA a une probabilité d'être coût-efficace de 73%. Comparé à la vaccination seule, la probabilité qu'un dépistage tous les 5 ans soit coût-efficace est 60% et de 80% si le seuil de coût/efficacité est de 1et de 3 produit intérieur brut (PIB) per capita per DALY évité, respectivement.

Conclusion : Le programme du dépistage par IVA en plus de la vaccination des jeunes filles sont des options coût/efficaces dans le contexte Lao. Dans ce pays tout au moins, cette stratégie devrait être prioritairement considérée pour le dépistage primaire.

Mots clés : évaluation économique, vaccination du VPH, dépistage, cancer du col de l'utérus, RDP Lao, modèle mathématique.

4.2 Abstract

Background: Several approaches to reduce the incidence of invasive cervical cancers exist. The choice should take into account context factors that influence the cost/effectiveness of the available options.

Objective: determine the cost-effectiveness of screening strategies combined with a 10-year old girl vaccination program in women in Vientiane, Lao PDR.

Methodology: A population-based dynamic compartment model was constructed. The interventions consisted of a 10-year old girl vaccination program only or this program combined with screening strategies, i.e. Visual Inspection with Acetic Acid (VIA), cytology-based screening, rapid Human Papillomavirus (HPV) DNA testing or combined VIA and cytology testing. Simulations were run over 100 years. In base case scenario analyses, we assumed a 70% vaccination coverage with lifelong protection and a 50% screening coverage. The outcome of interest was the incremental cost per Disability-Adjusted Life Year averted.

Findings: In base case scenarios, compared to the next best strategy, 30-65 year old VIA screening every three years combined with vaccination is the most attractive option, costing 2544 International dollars (I$) per DALY averted. Meanwhile, rapid HPV DNA testing is more attractive than cytology-based screening or its combination with VIA. Among cytology-based screening options, combined VIA with conventional cytology testing is the most attractive option. Multi-way sensitivity analyses did not change the results. Compared to rapid HPV DNA testing, VIA has a probability of cost-effectiveness of 73%. Compared to the vaccination alone option, the probability that a program consisting of screening women every five years is cost-effective is around 60% and 80% if the willingness-to-pay threshold is fixed at one and three GDP per capita, respectively.

Conclusion: VIA screening program in addition to a girl vaccination program is the most attractive option in the health care context of Lao PDR. In this country at least, this strategy should be considered as primary screening intervention.

Key words: economic evaluation, HPV vaccination, screening, cervical cancer, Lao PDR and mathematical model.

4.3 Introduction

While there is little accurate data regarding the incidence or mortality of cervical cancer (or any cancer, in fact) in the Lao PDR, health professionals believe it constitutes a major public health

burden with a high rate of morbidity and mortality in women of both reproductive age and older women. One often-quoted source suggests that it is the third commonest cancer in Lao women and the third leading cause of cancer deaths. (1). The Lao PDR is one of 72 Global Alliance for Vaccines and Immunisation GAVI-eligible countries for Human Papillomavirus (HPV) vaccination programs. A demonstration project of HPV vaccination program targeting fifth grade girls was launched in Vientiane capital and Vientiane province in 2014. However, the number of girls vaccinated was very small. Vaccination can be expected to reduce the number of cervical cancers by about 70-75% as it confers protection against HPV type 16 and 18 related cancers. Moreover, only once high levels of coverage of the female population are achieved, after a few decades of girl vaccination, might unvaccinated women benefit from herd immunity. Therefore, large scale community screening programs are needed to significantly affect the incidence and mortality of the disease among the population as a whole (2). A screening program that targets women who are not covered by the usual vaccination program might be an effective complement to vaccination of schoolgirls.

Despite the availability of cytology screening facilities in the country, at least in Vientiane Capital, only 5.2% of women aged 18-69 years in urban areas and 1.4% in rural areas have ever had cytological screening, either as part of a community screening program, or opportunistically when visiting a health care facility for some other reason (1). Opportunistic screening is less effective than organized programs (3), and there are a range of screening strategies which show different levels of efficacy in terms of sensitivity and specificity. Several screening approaches can be implemented. Visual Inspection with Acetic Acid (VIA) and cytology show low reproducibility. Cytology requires expertise, a healthcare infrastructure and resources and it has a low sensitivity and high cost compared to VIA (4). Meanwhile, VIA has a low specificity and a low positive predictive value (PPV), leading to unnecessary treatment (5). In contrast, a rapid HPV DNA testing approach provides simple, accurate and reproducible results (6, 7). However, its use in developing countries is limited by its high cost and due to the fact that HPV DNA testing only detects HPV infection, but not precursors of cancer so that there is a need to follow up of positive results (8).

Which screening strategy should be implemented in a developing country with scarce resources devoted to health like Lao PDR? To answer this crucial question for the country, we need to consider not only the demonstrated effectiveness of a screening program, but also its cost. Health

policy decision makers in Lao PDR are lacking key information to decide about the relative value of the diverse screening programs that might be implemented in the country.

The goal of the study was to determine, using mathematical modeling, the cost/effectiveness of various options regarding cervical cancer screening strategies along with a girl HPV vaccination program in the capital of Lao PDR.

4.4 Methodology

The outcome of interest was incremental cost-effectiveness (C/E) ratios (ICERs). The C/E denominator consisted of 1) the reduction in the incidence of cervical cancers and 2) DALYs averted related to all cervical cancer cases. The numerator consisted of the direct cost of the various options compared, from a public health care system perspective. This economic evaluation study complied with the recommendations of WHO for cost-effectiveness analyses (9).

Virtual population

The initial virtual population (at year 1) consisted of the entire population of women with characteristics similar to the Vientiane capital population in terms of age distribution (personal communication, 2014) and estimated age-specific incidence rates of cervical cancer in 2014 (1). The Vientiane capital population was used in the model instead of the whole country due to the fact that the population of the country is predominantly rural (10), and the ethnic mix of the population (11) is likely to be very different in each of the provinces; subsequently the vaccination uptake might be different.

Model structure and parameters of natural history

The details of the model structure have been described in appendix 2. Briefly, a compartmental dynamic population-based model was created to represent the natural history of cervical cancer. The model considers various HPV-related cervical outcomes. Each state might persist or progress to a higher state. Some lesions regress thanks to HPV-type specific natural immunity but women remain susceptible for other HPV types (12-15). Women with an invasive cervical cancer may be symptomatically detected. A diagnosed invasive cervical cancer is treated appropriately according to stage, with a defined stage-probability of recovery or treatment failure or death due to treatment complications.

For screening model, true high-grade Cervical Intraepithelial Neoplasia (CIN) cases at a cytology exam or rapid HPV DNA testing receive Loop Electrosurgical Excision Procedure (LEEP) or hysterectomy treatment. When VIA is used, a see-and-treat approach is adopted. True positive and

false positive high-grade CIN cases receive cryotherapy treatment. Cured cases regress to a recovery state with specific-type natural immunity. Unscreened or undetected cases or treatment failure follow the natural history of HPV infection, which may lead to cervical cancer.

For males, only the susceptibility, infection and recovery states were considered. Vaccinated people remained susceptible for non-vaccine HPV types or they could become susceptible to 16/18 types HPV infections in case of vaccine-induced immunity waning.

The progression and regression rates from one state to another one were based on the literature (16). However, we calibrated infection rates and cancer stage-remission rates. The sensitivity and specificity of screening and diagnostic tests and remission rate of precancerous lesions treatment are retrieved from meta-analysis and systematic reviews. Meanwhile, the remission rate of stage-specific invasive cervical cancer was calibrated, based on estimates of the mortality related to cervical cancer in Lao PDR. The details and summary tables are presented in appendix 2.

Model calibration

The population was stratified by gender and age. The model is in the form of a realistic age structured (RAS) model. The equations were numerically solved in Berkeley Madonna version 8.3.18 (17). The model was calibrated using maximum likelihood. The details are described in the appendix 2. Briefly, the model was first calibrated in order to produce a demographic structure similar to the 2014 distribution of the Vientiane capital population (in one-year intervals) (10). Thereafter, the model was calibrated for the age-specific incidences and mortalities of cervical cancer, according to the Globocan estimates.

Scenarios

Scenarios included the baseline option and the prevention programs options. The baseline considered that no vaccination program existed and that, based on WHO estimates, the coverage of a cytology screening program where screening was repeated every three years was 5.2% (1).

The scenarios were built on the following options: 1) girls vaccination alone, 2) girls vaccination combined with screening: VIA, rapid HPV DNA testing, combined VIA and conventional cytology testing, Liquid-Based Cytology (LBC) and conventional cytology, and 3) screening alone. Screening strategies were selected based on feasibility and accessibility considerations relevant to the Lao context. Screening is done by a gynecologist during gynecological outpatient visits.

In each screening scenario, different initial ages for screening were considered: 20, 25 and 30 years old. The maximum age was fixed at 65 years. Moreover, the frequency of screening was fixed at either yearly, three-year or five-year intervals. Yearly interval screening reflects the current practice in Vientiane Capital. Three-year intervals follow WHO recommendations (18) and five-year intervals are current practice in the USA (19).

In all options, base case analyses are performed with a screening coverage assumed to be 50% (range: 10%-80%). Loss to follow-up was assumed to be 15% per visit (range: 0%-50%). The proportion of women receiving cancer treatment among diagnosed patients was calibrated to the mortality rate of cervical cancer. The age and stage-specific monthly remission rates for cancer treatment were calibrated based on the estimated mortality rates of cervical cancer (summary table in appendix 2) (1).

The coverage of HPV vaccination both in girls and boys was assumed to be about 70% (30-80% for sensitivity analyses), with 100% (30-100% for sensitivity analyses) effectiveness against HPV type 16 and 18 and a lifelong protection (10 years to lifelong).

Costing

For the costs estimation, the perspective considered was essentially the perspective of the public health care system. Only direct medical and programmatic costs were considered. Details on the approach used to calculate consumption of items are described in appendix 2. Briefly, we used data from the Ministry of Health (personal communication, 2014) collected in central hospitals for a study aiming at determining costs per patient for each hospital. This data was used to estimate the screening visit and treatment cost. The cytology alone or combined with VIA options requires three visits. The first visit is for screening, the second for receiving the result and making an appointment for positive cases. The third is for a colposcopy with a direct biopsy. Meanwhile, rapid HPV DNA testing requires two visits. The first is for primary screening, the second for a colposcopy with direct biopsy in case of a positive result. VIA requires only one “see-and-treat approach” visit.

The cost of invasive cervical cancer treatment was retrieved from a study done in 72-Alliance for Vaccines and Immunization (GAVI) eligible countries (20). The items of the screening programmatic cost included quality control, training, administration and recruitment costs.

The base case per dose cost of the vaccine was based on the purchasing cost from the GAVI (4.5 I$ per dose) (21). The full programmatic cost of 3-dose HPV vaccine per girl is 29.1 international dollars (I$) according to the previous survey on the demonstration project of girl vaccination in Vientiane capital (personal communication, 2015). Unit prices are reported as 2013 international dollars, using the purchasing power parity (PPP) exchange rate (1 International dollar I$ = 2,694.27 kips) (22).

Simulation analyses

The simulation process deterministically ran over a 100 years span to capture the short and long term benefits of vaccination. For each option, the output consisted of the cumulative number of cervical cancers per 1 000 women, the DALYs per 1 000 women and the cost of screening and treatment per 1 000 women. The strategies were ranked based on the cost, from the lowest to the highest. In case of a non-dominant situation, strong (more effective and higher cost) or extended dominance (ICER of prior comparison is higher than the next one), the incremental cost/effective ratio was calculated using the reduction of cervical cancer cases and DALYs averted as denominators. DALYs were calculated based on the WHO table without age weighting. The disability weight for cancer treatment was retrieved from the current literature (23). For each strategy, C/E was calculated using the reduction number of cervical cancer and DALY averted as denominators.

All costs and DALYs were discounted at a rate of 3% in base case simulations to convert future costs and life expectancies and duration of disability to their present value (9). However, other discount rates of 0% to 5% for DALYs and 6% for costs were also explored. The results were interpreted taking into account the recommendations of the UN Commission on Macroeconomics and Health which proposes classifying cost-effectiveness studies into three categories: 1) highly cost-effective (ICER< Lao GDP per capita); 2) cost-effective (ICER between 1-3 times the GDP per capita); and 3) not cost-effective (ICER > 3 times the GDP per capita) based on the willingness-to-pay threshold (24). The GDP per capita in 2013 was about 4,822 international dollars using the Purchasing Power Parity (PPP) exchange rate (25).

Sensitivity analyses

One-way sensitivity analyses were conducted on the cost of vaccine, screening and vaccination coverage, loss to follow-up and sensitivity of VIA and conventional cytology, which were expected to significantly influence the incremental cost-effectiveness ratios.

In order to take into account uncertainties and joint effects, multi-way sensitivity analyses on parameters were conducted using probability sensitivity analyses. Each parameter was randomly drawn from its distribution (summary table in appendix 2). As stated above, the parameters that were varied include: natural history progression of HPV infection, the proportion of people receiving treatment, monthly remission rates of precancerous lesions and cancer treatment, screening sensitivity and specificity, screening coverage, vaccination coverage, wane of natural and vaccine immunity, effectiveness of the vaccine, disability weight and discount rate. The costing parameters with the exception of cancer treatment were varied by 75% in the sensitivity analyses (summary table in appendix 2) by using gamma distributions. A lognormal distribution was used for the multipliers of natural history of cervical cancer and a beta distribution for other parameters.

The Monte Carlo simulation was run for 1 000 iterations with Berkeley Donna. The program computes means and standard deviations for each option. Acceptability curves were produced according to the probability of the ICERs to be cost-effective, taking into account the recommendation of the UN Commission on Macroeconomics and Health on various ceiling ratios. Acceptability curves were produced to take into account various willingness-to-pay thresholds as recommended by the UN Commission on Macroeconomics and Health (24). The acceptability curve was based on the results of probabilistic sensitivity analyses (26). Additionally, the acceptability curve was analyzed in clusters, including vaccination and screening coverage and the cost of the vaccine, which were expected to have a major impact on the difference of cost-effectiveness among screening strategies. This could answer the effect of heterogeneity on the probability of cost-effectiveness and better provide concise information to decision makers.

4.5 Results

Impact of prevention strategies

The model output of demographic data shows that the virtual population is similar to the general population in terms of age distribution and trends over time. After the equilibrium state has been reached, the age-specific incidence of cervical cancer and the mortality rate are similar to expected values, and are consistent over the time span of the simulation (appendix 2).

In base case analyses, the most effective strategy was a program consisting of annual VIA screening for 20-65 year old women in addition to a vaccination program for 10-year-old girls. This strategy can prevent 87% of cervical cancers and produces a gain of 50 DALYs per 1000 women, about 32% less cancer and 11 additional averted DALYs compared to a program consisting of only vaccination

in girls. In the case that implementing a VIA program is not realistic, rapid HPV DNA testing in addition to a vaccination program becomes the most effective option, with 85.7% cancer reduction and 49.3 DALYs averted per 1000 women. Among cytology-based screening strategies, LBC and combined VIA and cytology testing in addition to a vaccination program are equally the most effective options, with 84% cancer reduction and 49 DALYs averted per 1 000 women (figure 1).

When we compared different initial ages for a screening program and frequencies of screening within the same screening strategy, we found that screening at an early age of 20 or 25 years old, adds a slight reduction in the number of cancers compared to a program starting at the age of 30. In contrast, the reduction in the number of cancers increases with the frequency of the screening intervals, i.e. screening with VIA for 30-65 year old women alone reduces the number of cancers by 80%, 58% and 44% if screening is performed every year, every three years or every five years, respectively (figure 1).

In terms of costs, LBC is the most expensive option followed by the combined VIA and cytology testing, rapid HPV DNA testing and VIA options, respectively. The annual LBC for 20-65 year old women in addition to a girl vaccination program costs 280 353 I$ per 1 000 women (appendix 2).

Cost-effectiveness

Table 1 shows the comparison of all available screening strategies. In base case scenarios, the girl vaccination only program is dominated by a program consisting of annual VIA screening for 30-65 year old women. VIA screening also dominates other screening strategies. Therefore, comparisons were conducted only among VIA screening options. Two strategies, based on the GDP per capita threshold ratios, are considered very cost-effective in terms of cancer reduction compared to the next best strategy: a program consisting of VIA screening for 30-65 year old women every five years alone or an every-three-year program combined with vaccination. These cost 4 468 I$ and 4166 per case cancer reduction and 2 544 I$ and 351 I$ per DALY averted, respectively. In addition to these strategies, others are also considered very cost-effective in terms of DALYs averted. These include a VIA screening program targeting 25-65 year old women every five years, a VIA screening program targeting 30-65 year old women every three years alone and a VIA screening program targeting 30-65 year old women every five years to which is added a girl vaccination component. These cost 856; 1 064; and 1 362 I$ per DALYs averted, respectively.

If VIA alone is not realistic, rapid HPV DNA testing is more cost-effective than cytology-based screening. Among these options, compared to the next best strategy, a screening program for 30-65 year old women every 3 and 5 years in addition to a girl vaccination component are considered to be very cost-effective. They cost 4 391 and 2 102 I$ per DALYs averted. An annual screening strategy is cost-effective, costing 10 983 I$ per DALYs averted.

If cytology and the combined VIA and conventional cytology testing strategies are realistic, the combined VIA with conventional cytology testing option is more cost-effective than the cytology-based screening option. Among these, a program consisting of screening 30-65 year old women every five years is the most attractive option, costing 2 836 I$ per DALY averted compared to program consisting of only girl vaccination. Regarding the cytology-based screening options, we find that a girl vaccination program dominates screening alone options. LBC is more cost-effective than conventional cytology. Among these, a program consisting of screening 30-65 year old women every five years in addition to a girl vaccination program is the most attractive option, costing 3 455 I$ per DALY averted compared to the vaccination alone option. Also, conventional cytology-based screening option using five-year interval is more cost-effective than using other frequency intervals (Table 2).

Sensitivity analyses

One-way sensitivity analyses show that it is still more cost-effective to combine the screening strategy with vaccination than either component alone when the vaccination coverage is suboptimal. The same result is found when screening coverage is suboptimal, compared to vaccination alone. However, the combination of screening and vaccination provides ICER higher than one GDP per capita when the cost of vaccine is higher than 50 I$ per dose. Meanwhile, rapid HPV DNA testing becomes more attractive when the sensitivity of VIA is 30% less than the one in base case or when there is no loss of follow-up for rapid HPV DNA testing screening. Also, LBC is not more cost-effective than conventional cytology if the sensitivity of conventional cytology is 70% or higher (Appendix 2).

Multi-way sensitivity analyses did not change the range of cost-effectiveness in base case analyses. Combined vaccination and VIA screening remained dominant, but screening 30-65 years old women with VIA every year becomes more attractive than every three years, with an average cost of 4 202 I$ per DALY averted. Meanwhile, the ICER for a combined vaccination and VIA screening every three years is 1 567 I$ per DALY averted compared to screening every five years.

Figure 2 shows the probability of cost-effectiveness for combined vaccination and screening strategies compared to vaccination alone or different screening intervals. Among these, the probability of cost-effectiveness for the three-yearly VIA screening program for 30-65 years old women is about 67% compared to a five-yearly VIA screening. When this strategy is compared to rapid HPV DNA testing, the probability of cost-effectiveness becomes 73%. Meanwhile, compared to vaccination alone, the probability of cost-effectiveness for a five-yearly rapid HPV DNA testing is similar to a five-yearly combined VIA and cytology testing and LBC, about 60%. When willingness-to-pay increases to 3 times GDP per capita, probability increases to around 80%, with the exception of the conventional cytology-based screening option, which is about 60%.

In clustering PSA, we compared the combined vaccination and screening strategy to vaccination alone under different cost of vaccine and different coverage of vaccination scenarios, and compared the combined strategy to screening alone under different screening coverage scenarios. We found that the probability of cost-effectiveness for the combined vaccination and screening strategy options depends on the cost of the vaccine, as well as screening and vaccination coverages. The probability of cost-effectiveness for these strategies is less than 50% when the cost of the vaccine is higher than 50 I$ per dose. Moreover, their probability drops when the screening coverage is lower than 30% or when vaccination coverage is lower than 50% (Appendix 2).

4.6 Discussion

Four main findings can be retained from our results: 1) the combined vaccination and screening option is more cost-effective than either strategy alone; 2) screening 30-65 year old women with VIA every three years along with girl vaccination is the most attractive strategy; 3) Excluding VIA screening, rapid HPV DNA testing in addition to a girl vaccination program is the most attractive option, followed by combined VIA and cytology testing, the LBC option and the conventional cytology in addition to a girl vaccination program option, respectively; 4) the probability of cost-effectiveness is around 60-67% for screening strategies.

In base case analyses, the combined girl vaccination and screening option dominates a program consisting of one of these two components alone. However, their cost-effectiveness varies considerably according the cost of the vaccine, the screening and the vaccination coverage, when the threshold ratio used is one GDP per capita. To maintain the cost-effectiveness, the cost of

vaccine has to be lower than 50 I$ per dose. With optimal vaccination coverage, screening coverage could be lower than 50%; otherwise, it should be at least 50% if vaccination coverage is less than 70%. However, maintaining high vaccination coverage might better maintain the reduction of morbidity and mortality-related cervical cancer in a low resource setting like Lao PDR, where screening is challenging due to a lack of infrastructure and human resources (27). Lack of knowledge and awareness toward cervical cancer control among Lao women both in urban (28) and rural areas (29) are key factors of current low screening coverage in Lao PDR.

Among screening strategies, VIA screening is the most attractive option. This result is similar to that of other studies conducted in developing countries (30-32). This might be explained by the combination of its advantages. First, VIA screening has higher sensitivity, in base case scenarios, than a conventional cervical cytology option and only slightly lower than other screening options considered in this study. Second, VIA can be used as a single-visit approach; subsequently there is no loss to follow-up among positive cases that require treatment. Third, although the treatment for VIA positive patients, who may have either low-grade or high-grade precancerous lesions, cryotherapy, has a slightly lower remission rate (33) compared to LEEP. The difference is so small that it would not be expected to impact the overall effectiveness of treatment for precancerous lesions. Nevertheless, VIA is controversial due to its limitations; a positive VIA does not systematically reflect precancerous or cancerous stages. Furthermore, invasive cervical cancer cases might not be adequately treated (34). VIA has a low positive predictive value, which could lead to unnecessary treatment and psychological repercussions (5, 35). A positive VIA result can be due to polyps, inflammatory conditions, or squamous metaplasia (36). Also, VIA is subjective. Its interpretation requires careful training and supervision. It is also not appropriate for postmenopausal women due to lesions within the endocervical canal, which cannot be visualized. That is why WHO recommends using VIA only for women who are less than 50 years old (37).

As demonstrated in the sensitivity analyses, the VIA screening option with a 30% suboptimal sensitivity is not cost-effective compared to the rapid HPV DNA testing options. In the case where VIA is not realistic, rapid HPV DNA testing becomes the most attractive option. The dominance of rapid HPV DNA testing option over the cytology-based screening option was also reported in China (38). The use of HPV DNA testing needs to take into consideration its benefits and disadvantages. The advantage of HPV DNA testing is its high sensitivity and specificity, its reproducibility and the fact that the sample can be collected by the patients (37). However, the test requires appropriate

storage and accessibility. Moreover, a positive case does not necessarily mean an abnormal cervix or a cervical cancer, and does not automatically require a treatment. The infection mostly clears up spontaneously within 1-2 years and induces acquired immunity with an estimated duration of at least 10 years (39, 40). Also, a psychological burden has been reported among HPV-positive women (41).

With cytology-based screening, cervical cancer incidence could be reduced by 80% (42) if the sensitivity of cytology and screening coverage are high. LBC has a higher sensitivity than conventional cytology, but its cost is relatively high (37). Compared to VIA and rapid HPV DNA testing, a cytology-based screening option is more costly and less effective as a result of lower sensitivity and specificity (43) and a higher number of losses to follow-up. Only 55% of true positive cases receive treatment. In this case, the combined VIA and conventional cytology testing option becomes attractive. The use of both tests as primary screening options might improve the detection of precancerous cases in spite of the important number of false positive cases, which leads to a high rate of unnecessary colposcopies and biopsies.

The elements stated above, i.e. affordability, feasibility, accessibility and acceptability, must be carefully examined before a screening strategy is nationally implemented. There is therefore a need to further step-up the analyses of these factors in the Lao context prior the making a decision about which option to propose.

Limitations

Our model has several limitations: it assumed that the natural progression and regression of the cervix state did not depend on the setting. This assumption might under or overestimate progression and regression rates due to the fact that the epidemiological burden of disease is considerably different between countries. Subsequently, this might under or overestimate the cost of precancerous lesion treatment. However, because of the lack of available data on variables such as HPV prevalence, prevalence of CIN and HPV type distribution for lesions and cervical cancers, defining these parameters in the calibration process is difficult. We addressed this problem by conducting probabilistic sensitivity analyses, using the range of values found in the literature.

To simplify model assumptions, we had to assume that only women with high-grade CIN were treated despite the fact that women with low-grade CIN were followed every three to six months and were treated if the result remained positive on the second or third test. This might underestimate

the cost of screening and treatment as well as the effect of cervical cytology and rapid HPV testing. However, to our best knowledge, this should not impact much the effectiveness or the total cost because some of the positive low-grade CIN cases will be lost to follow-up, and the cost of precancerous lesions for positive cases is marginal compared to screening cost.

Our study assumed that all women participated equally in the screening program even in subsequent screenings. This might overestimate screening coverage that could change over time among screened and unscreened women. Screened women with normal test results might not return to the next cycle and vice-versa.

The sensitivities and specificities used in our model were derived from the meta-analysis of worldwide available articles. However, both VIA and cytology-based screenings approaches are subjective, and could vary across settings (37). Future evidence on test performance relevant to the local context might better guide decision processes.

We ignored some costs related to screening and precancerous lesion treatment. These include the cost of specimen delivery and the cost of complications following a treatment. This might underestimate the total cost per person. However, according to Goldhaber-Fiebert (44), these cost components are small relative to the cost of administration and equipment. Therefore, this is unlikely to have a big impact on ICER and should not bias our conclusions.

4.7 Conclusions

The combined girl vaccination and screening is more cost-effective than either component alone. Besides VIA, the rapid HPV DNA testing option is more cost-effective than a cytology-based screening option or its combination with VIA. Therefore, VIA or rapid HPV DNA should be considered for primary screening of precancerous lesions in Lao PDR.

Supporting information

Appendix file provides detail of model structure, input and calibration as well as the methodology of costing and additional result.

Contributors

PC designed, analyzed and wrote the article. LJW validated the model and result. DR and LM validated the methodology. MM, DEM and KP validated the concept and result realistically to Lao context. All authors gave comments and validated the final version.

Conflict of interest

Authors declare no conflict of interest for this study

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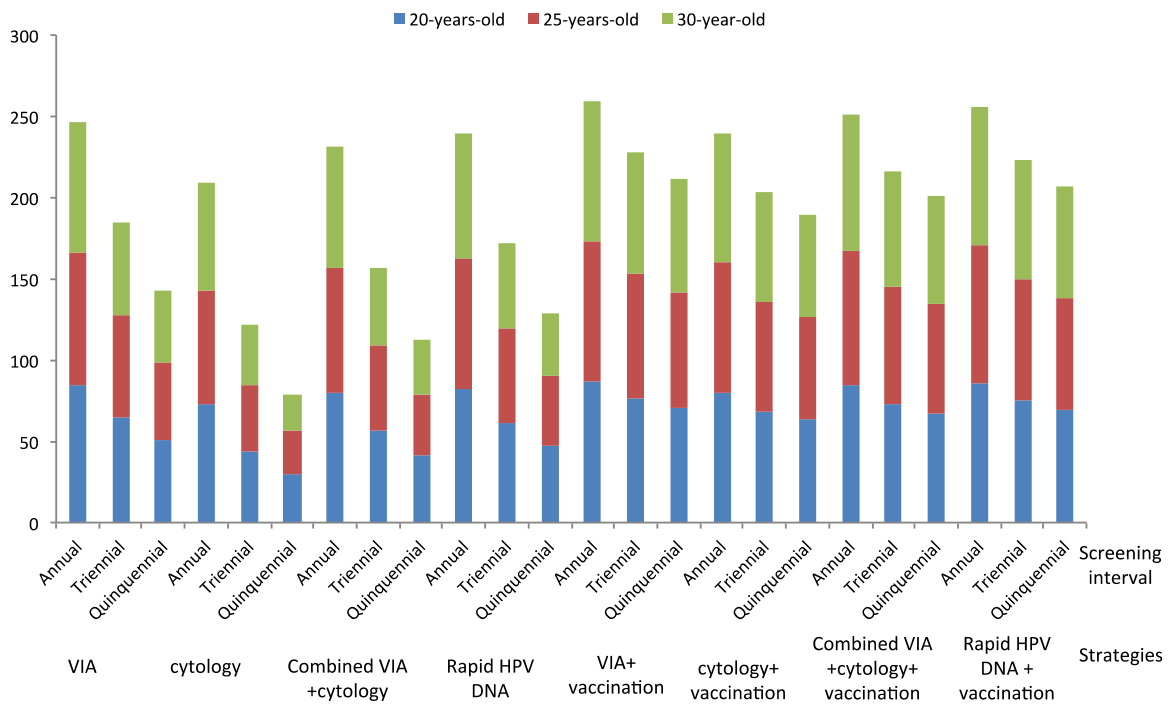
Figure 1: The cancer reduction by prevention strategies according to screening age initiation and frequency



Note:

The figure displays the comparison of cervical cancer reduction in different targeted age screening and screening intervals (yearly, three-yearly and five-yearly). The cancer reduction is higher when screening is more frequently done, but the reduction is relatively similar in early and late initiation ages.

Table 1: cost-effectiveness of screening strategies combined with 10-years-old girl vaccination

Option	Total cost per 1000 women	Cancers per 1000 women	Cancer reduction (%)	DALYs averted per 1000 women	ICER (cancer reduction)	ICER (DALYs averted)
All screenings are realistic						
Baseline	4716	4.8	Ref	Ref	-	-
Vaccination	21824	2.1	54.9	30.7	D	D
Five-yearly VIA_25-65	15598	2.5	47.7	27.0	11302	895
Yearly VIA_30-65	64261	1.0	79.9	45.7	ED	ED
Three-yearly VIA_30-65	21766	2.0	57.9	32.8	12771	1064
Five-yearly VIA_30-65	13325	2.7	43.5	24.5	4166	351
Yearly cytology_30-65	109312	1.6	66.5	39.3	D	D
Three-yearly cytology_30-65	37199	3.0	36.6	21.8	D	D
Yearly LBC_30-65	147137	1.2	74.7	44.1	D	D
Three-yearly LBC_30-65	49868	2.4	48.6	28.9	D	D
Yearly VIA+cytology_30-65	123124	1.2	74.5	44.0	D	D
Three-yearly VIA+cytology_30-65	41858	2.5	48.3	28.7	D	D
Yearly HPV testing_30-65	109208	1.1	77.5	45.7	D	D
Three-yearly HPV testing_30-65	37242	2.2	53.5	31.8	D	D
Yearly VIA_20-65 + vaccination	104683	0.6	87.0	49.8	422480	30462
Three-yearly VIA_20-65 + vaccination	46763	1.1	76.7	43.6	D	ED
Five-yearly VIA_20-65 + vaccination	35202	1.4	71.0	40.2	ED	ED
Yearly VIA_25-65 + vaccination	93002	0.6	86.5	49.4	D	24136
Three-yearly VIA_25-65 + vaccination	42862	1.1	76.1	43.2	D	ED
Five-yearly VIA_25-65 + vaccination	32862	1.4	70.5	39.8	D	ED
Yearly VIA_30-65 + vaccination	81575	0.7	85.7	49.0	85116	6733
Three-yearly VIA_30-65 + vaccination	39051	1.2	75.2	42.6	4468	2544
Five-yearly VIA_30-65 + vaccination	30577	1.4	69.7	39.3	15718	1362
Yearly cytology_30-65 + vaccination	126424	1.0	78.8	45.8	D	D
Three-yearly cytology_30-65 + vaccination	54264	1.6	67.1	38.5	D	D
Yearly LBC_30-65 + vaccination	164287	0.8	82.9	48.2	D	D
Three-yearly LBC_30-65 + vaccination	66944	1.3	71.6	41.4	D	D
Yearly VIA+cytology_30-65 + vaccination	140273	0.8	82.8	48.2	D	D
Three-yearly VIA+cytology_30-65 + vaccination	58935	1.4	71.5	41.3	D	D
Yearly HPV testing_20-65 + vaccination	165588	0.7	85.7	49.6	D	D
Three-yearly HPV testing_20-65 + vaccination	67411	1.2	75.0	43.5	D	D
Five-yearly HPV testing_20-65 + vaccination	47694	1.4	69.6	40.2	ED	ED
Yearly HPV testing_25-65 + vaccination	145701	0.7	85.1	49.6	D	D
Three-yearly HPV testing_25-65 + vaccination	60775	1.2	74.4	43.1	ED	ED
Yearly HPV testing_30-65 + vaccination	126370	0.7	84.4	49.2	D	D
Three-yearly HPV testing_30-65 + vaccination	54327	1.3	73.5	42.6	D	D

Note:

All screening strategies with different initial age "20, 25, and 30 years old" and screening interval "every year, and" were analyzed, but only some are presented here in this table. The detail is described in appendix 2 2.

Baseline refers to no vaccination with 5.2% cytology screening for women aged 18-68 years old.

Vaccination is for 10-years-old girls. Cytology refers to conventional cervical cytology; LBC refers to liquid-based cervical cytology; HPV testing refers to rapid HPV DNA testing; VIA+cytology refers to the combined testing VIA and cytology.

The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness.

D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

ED refers to extendedly dominance, which has higher ICER than the next ICER.

Table 2: The incremental cost effectiveness ratio (ICER) of screening strategies and 10-years-old girl vaccination by realistic assumption

VIA is not realistic	ICER (cancer reduction)	ICER (DALY averted)	**When cytology or combined with VIA is realistic**	ICER (cancer reduction)	ICER (DALY averted)
Baseline	-	-	Baseline	-	-
Vaccination	6555	557	Vaccination	6555	557
Yearly cytology_30-65	D	D	Yearly cytology_30-65	D	D
Three-yearly cytology_30-65	D	D	Three-yearly cytology_30-65	D	D
Five-yearly cytology_30-65	D	D	Five-yearly cytology_30-65	D	D
Yearly LBC_30-65	D	D	Yearly LBC_30-65	D	D
Three-yearly LBC_30-65	D	D	Three-yearly LBC_30-65	D	D
Five-yearly LBC_30-65	D	D	Five-yearly LBC_30-65	D	D
Yearly VIA+cytology_30-65	D	D	Yearly VIA+cytology_30-65	ED	ED
Three-yearly VIA+cytology_30-65	D	D	Three-yearly VIA+cytology_30-65	D	D
Five-yearly VIA+cytology_30-65	D	D	Five-yearly VIA+cytology_30-65	D	D
Yearly HPV testing_30-65	ED	ED	Yearly cytology_30-65 + vaccination	ED	ED
Three-yearly HPV testing_30-65	ED	ED	Three-yearly cytology_30-65 + vaccination	D	D
Five-yearly HPV testing_30-65	D	D	Five-yearly cytology_30-65 + vaccination	ED	ED
Yearly cytology_30-65 + vaccination	D	D	Yearly LBC_30-65 + vaccination	D	D
Three-yearly cytology_30-65 + vaccination	D	D	Three-yearly LBC_30-65 + vaccination	D	D
Five-yearly cytology_30-65 + vaccination	ED	ED	Five-yearly LBC_30-65 + vaccination	D	D
Yearly LBC_30-65 + vaccination	D	D	Yearly VIA+cytology_20-65 + vaccination	786975	61537
Three-yearly LBC_30-65 + vaccination	D	D	Three-yearly VIA+cytology_20-65 + vaccination	ED	ED
Five-yearly LBC_30-65 + vaccination	D	D	Five-yearly VIA+cytology_20-65 + vaccination	ED	ED
Yearly VIA+cytology_30-65 + vaccination	D	D	Yearly VIA+cytology_25-65 + vaccination	608081	44987
Three-yearly VIA+cytology_30-65 + vaccination	D	D	Three-yearly VIA+cytology_25-65 + vaccination	ED	ED
Five-yearly VIA+cytology_30-65 + vaccination	D	D	Five-yearly VIA+cytology_25-65 + vaccination	ED	ED
Yearly HPV testing_30-65 + vaccination	139597	10983	Yearly VIA+cytology_30-65 + vaccination	151018	11771
Three-yearly HPV testing_30-65 + vaccination	57639	4391	Three-yearly VIA+cytology_30-65 + vaccination	66830	5068
Five-yearly HPV testing_30-65 + vaccination	28397	2102	Five-yearly VIA+cytology_30-65 + vaccination	38253	2836

Note: All screening strategies with different initial age "20, 25, and 30 years old" and screening interval "every year, and" were analyzed, but only some are presented here in this table. Baseline refers to no vaccination with 5.2% cytology screening for women aged 18-68 years old.

Vaccination is for 10-years-old girls. Cytology refers to conventional cervical cytology; LBC refers to liquid-based cervical cytology; HPV testing refers to rapid HPV DNA testing; VIA+cytology refers to the combined testing VIA and cytology.

The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. **D** refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options. **ED** refers to extendedly dominance, which has higher ICER than the next ICER.

Table 2: The incremental cost effectiveness ratio (ICER) of screening strategies and 10-years-old girl vaccination according to realistic assumption (continued)

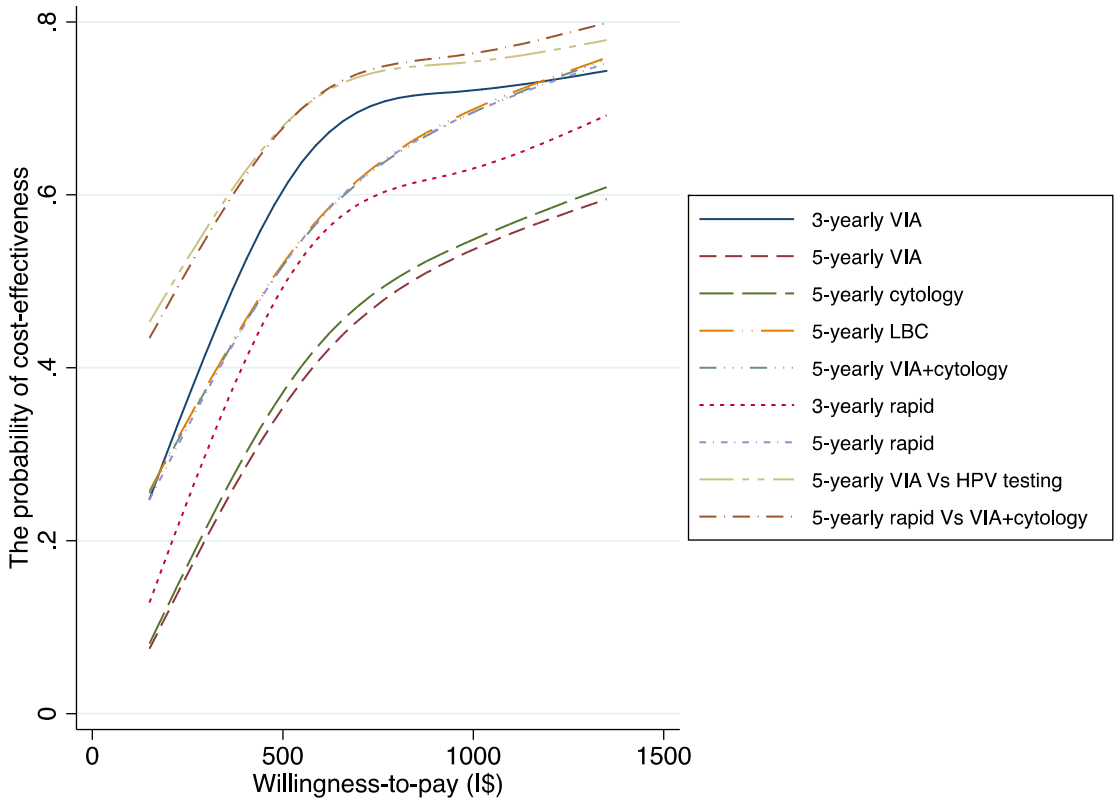
When only cytology is realistic			**When only conventional cytology is realistic**		
Baseline	-	-	Baseline	-	-
Vaccination	6555	557	Vaccination	6555	557
Yearly cytology_30-65	D	D	Yearly cytology_20-65	D	D
Three-yearly cytology_30-65	D	D	Three-yearly cytology_20-65	D	D
Five-yearly cytology_30-65	D	D	Five-yearly cytology_20-65	D	D
Yearly LBC_30-65	D	D	Yearly cytology_25-65	D	D
Three-yearly LBC_30-65	D	D	Three-yearly cytology_25-65	D	D
Five-yearly LBC_30-65	D	D	Five-yearly cytology_25-65	D	D
Yearly cytology_30-65 + vaccination	172755	13544	Yearly cytology_30-65	D	D
Three-yearly cytology_30-65 + vaccination	D	D	Three-yearly cytology_30-65	D	D
Five-yearly cytology_30-65 + vaccination	ED	ED	Five-yearly cytology_30-65	D	D
Yearly LBC_20-65 + vaccination	6611733	73818	Yearly cytology_20-65 + vaccination	D	51006
Three-yearly LBC_20-65 + vaccination	ED	ED	Three-yearly cytology_20-65 + vaccination	ED	ED
Five-yearly LBC_20-65 + vaccination	D	ED	Five-yearly cytology_20-65 + vaccination	D	ED
Yearly LBC_25-65 + vaccination	730436	54053	Yearly cytology_25-65 + vaccination	490402	35960
Three-yearly LBC_25-65 + vaccination	D	D	Three-yearly cytology_25-65 + vaccination	D	ED
Five-yearly LBC_25-65 + vaccination	D	ED	Five-yearly cytology_25-65 + vaccination	D	ED
Yearly LBC_30-65 + vaccination	196119	15155	Yearly cytology_30-65 + vaccination	128937	9888
Three-yearly LBC_30-65 + vaccination	79743	6048	Three-yearly cytology_30-65 + vaccination	66648	5017
Five-yearly LBC_30-65 + vaccination	46610	3455	Five-yearly cytology_30-65 + vaccination	49716	3709

Note: All screening strategies with different initial age "20, 25, and 30 years old" and screening interval "every year, and" were analyzed, but only some are presented here in this table. Baseline refers to no vaccination with 5.2% cytology screening for women aged 18-68 years old.

Vaccination is for 10-years-old girls. Cytology refers to conventional cervical cytology; LBC refers to liquid-based cervical cytology; HPV testing refers to rapid HPV DNA testing; VIA+cytology refers to the combined testing VIA and cytology.

The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. **D** refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options. **ED** refers to extendedly dominance, which has higher ICER than the next ICER.

Figure 2: The probability of cost-effectiveness of combined vaccination and screening by willingness-to pay



Note:
All screenings stated above are combined with girl vaccination
Excepted where is noted, the five-yearly screenings are compared to vaccination alone. For three-yearly screening is compared to five-yearly one in the same screening technique.
LBC refers to liquid-based cytology
HPV testing refers to rapid HPV DNA testing

Chapter 5

Discussion and conclusions

Chapter 5: Discussion and Conclusion

5.1 Study framework

Cervical cancer is one of the most prevalent cancers worldwide, particularly in low-resource settings that lack infrastructure and human resources (1). The implementation of a prevention program against cervical cancer might contribute to reduce the burden of this disease. However, options are numerous. The choice between them should, ideally, lie on the comparison of the cost and the effectiveness of each of them, taking into account the specificity of the country.

This thesis had two goals: 1) evaluate the performance of the cervical cancer screening combined test: Visual Inspection with Acetic Acid (VIA) and conventional cytology; 2) providing to health policy decision makers best evidence-based information on the cost-effectiveness of Human Papillomavirus (HPV) vaccination strategies combined or not with a screening program in the Lao PDR context.

To achieve these goals, we designed three studies. The first study consisted of a systematic review and a meta-analysis to estimate the sensitivity and the specificity of the combined VIA and conventional cytology testing. The results provided data for the 3rd study. The second and third studies consisted of developing a compartmental dynamic model that takes into account the herd immunity to simulate the cost/effectiveness of different preventive options relevant for the Lao context.

5.2 Critical overview

5.2.1 Combined VIA and conventional cytology testing compared to conventional cytology or VIA alone

Consultation with experts in screening techniques in the Lao context led us to propose a new combination that might reduce the limitation of the available screening tests. In developing countries, the available techniques have both advantages and limitations: cytology has a low sensitivity (2), and VIA has low specificity and a high false positive rate, leading to unnecessary treatments (3). Combining both screening techniques might therefore improve the effectiveness of the screening approach.

We found that the combined test in either positive result has a significantly higher pooled estimate of sensitivity but a lower specificity than those of either test alone. However, the heterogeneity is high compared with the results of a meta-analysis that was performed on the combined HPV DNA and cytology testing (4). This might be because our meta-analysis included studies coming from different low and middle-income countries, hence with different characteristics. Effectively, the quality of the screening performance might vary across settings. Moreover, the threshold of true positive case is not always the same across studies, ranging from low-grade Cervical Intraepithelial Neoplasia (CIN) to high-grade CIN.

Nevertheless, the results suggest that the combined test would improve the detection of cervical precancerous or cancerous lesions, but would also increase the number of false positives, which would lead to a higher number of women requiring further diagnostic confirmation test and a treatment. This case is similar to the VIA screening option alone (3). The benefits and losses have to be taken into consideration in terms of both cost and effectiveness. This is the reason why we complemented this first study with a cost/effectiveness study (article 3). On other hand, it might be interesting to study the performance of the sequentially cytology testing in positive cases at the VIA test. This might reduce the screening cost and the number of false positive cases for VIA. Yet, further evidence is needed. However, a recent study demonstrated the interest of combining rapid HPV DNA testing and VIA. The study showed that combining these tests in parallel has a relatively high sensitivity (72%), but a low specificity (5). Thus, sequential VIA testing in positive cases of rapid HPV DNA testing might be relatively interesting particularly in settings where cytology is not available or of poor quality.

5.2.2 Cost-effectiveness of HPV vaccination and screening strategies against cervical cancer in women in Lao PDR

Lao PDR is one of the 72 GAVI-eligible countries for preadolescent girl vaccination. In 2014, a vaccination demonstration project aiming 5th grade schoolgirls has been implemented in two provinces: Vientiane capital and Vientiane province. The project is likely to be expanded nationwide if it is proved to be successful. Along with this project, a costing analysis study was done by WHO to provide estimates on the cost of the vaccination program. However, a comprehensive evidence-based economic evaluation modeling is still lacking. We therefore conducted an economic evaluation study by building a decision analytic model using the most recent and relevant data to the Lao context. We expected that such a study would not only make a contribution to the provision of information to decision makers in Lao PDR, but also demonstrate

the interest of conducting research projects and strengthening the capacity building on this field in this country. Furthermore, we hoped that such a study would convince decision makers of the interest of having national guidelines for health economic evaluation in Lao PDR as a decision-helping tool in the country.

With the current estimate of a low screening coverage of 5% in urban areas (6) and with just one pilot-project on HPV vaccination for girls, it is difficult to predict what the future will be. We therefore assumed two situations along a HPV vaccination program: 1) the current screening situation and 2) a screening program with a moderate screening coverage of 50%. In Lao PDR, there is no national guideline for the conduction of health economic evaluations. We therefore applied the methodology and the recommendations proposed by WHO (7). The studies were conducted under a public health perspective; only direct costs and programmatic cost were taken into account.

Firstly, we aimed at determining the cost-effectiveness of various HPV vaccination strategies (Chapter 3). To our knowledge, this study is the first performed with low and middle-income countries data to examine the addition of a catch-up and/or boy vaccination components. We found that vaccinating 10-years old girls could reduce by 78% the cumulative number of cervical cancers due to HPV type 16/18 and avoid 31 DALYs per 1 000 women over 100 years under the condition of a 70% vaccination coverage rate with a 100% effectiveness of the vaccine and a lifelong protection. A preadolescent girl HPV vaccination program is very cost-effective compared to the absence of a vaccination program. Yet, it might be relevant to consider including a temporary catch-up vaccination component for 11-25 years girls, as this addition makes the program more attractive when we consider a cost/effectiveness threshold of one GDP per capita per DALY averted. In contrast, adding a boy vaccination component to a girl vaccination program brings little additional benefit compared to adding a catch-up component, and it costs more. These results were also reported in previous studies performed in high-income countries (8-12) as well as in middle-income countries (13). Furthermore, a previous study has also demonstrated that increasing the girl vaccination coverage was more cost-effective than adding a boy vaccination element to a baseline coverage rate because vaccinating the entire population of girls would protect not only girls but also boys in contrast to a program where 50% of girls and boys are vaccinated (9). The model predicted that adding both a boy vaccination element and a catch-up component can be cost-effective under a short period time, i.e. 30 years because the reduction of HPV infection and cervical cancer cases in

this strategy occurs at an early stage compared to girl vaccination or adding catch-up component. However, the higher reduction of cervical cancer at an early stage was also found when adding a catch-up component only compared to what is expected in a girl vaccination program only. This is similar to what has been found in previous studies (8, 14, 15).

As demonstrated in previous studies (8, 10, 16, 17), the duration of the vaccine protection, the duration of the natural immunity and the incidence of cervical cancer have an impact on the cost-effectiveness of HPV vaccination. In our study, we found that adding a catch-up component is more cost-effective for 11-75 years old women than for 11-25 year old women when there is a wane natural immunity or higher incidence of cervical cancer. This might be explained by the higher effectiveness of HPV vaccination in this cases, which is also demonstrated with a previous model (8). In contrast, the shorter duration of vaccine protection reduces the effectiveness. Vaccinating a larger group of women might increase the total cost of vaccination, but its benefit in term of health makes this avenue obviously invaluable. However, we did not examine the impact of a higher cost of vaccine in these cases. With a higher cost, vaccinating a larger population might no longer be cost-effective. For instance, if the cost of vaccine is I$ 50 per dose, the Incremental Cost-Effective Ratio (ICER) of the catch-up component for 11-25 years old women will be higher than one GDP per capita per DALY averted.

The last study aimed at determining the cost-effectiveness of a girl vaccination program combined with various screening strategies (Chapter 3). HPV vaccination is effective to reduce the burden of disease. But many women are not targeted by such a program and some of them might already have lesions. Therefore, screening remains necessary particularly in the early stage of a cervical cancer control strategy. We assumed that a girl vaccination program will be implemented and remain along with the screening program whose coverage will be about 50%. To determine whether a combined strategy of the girl vaccination and screening program is cost-effective, we added other differential equations to the HPV vaccination model for various screening strategies which are reasonably implementable in Lao PDR, such as VIA, rapid HPV DNA testing, combined VIA and conventional cytology testing, liquid-based cytology (LBC) and conventional cytology. In this model, instead of cervical cancer related to HPV types 16/18 only, the simulation considered all expected cervical cancers because screening prevents all cervical cancer cases.

In the base case analyses (70% girl vaccination, lifelong protection and 50% screening coverage), it appears that the combination of a screening strategy and a girl vaccination strategy is more cost-effective than either component alone. Among the screening strategies, three-yearly VIA for 30-65 years women appears to be the most cost-effective option, followed by three-yearly rapid HPV DNA testing, five-yearly combined VIA and conventional cytology testing, five-yearly LBC and five-yearly conventional cytology options. Our results are similar to the conclusions of a recent review (18). Most economic analyses concluded that screening should be introduced despite the HPV vaccination, with the VIA option recommended over other screening methods if VIA is realistic (19). Yet, our study added new evidences on the combined VIA and conventional cytology testing that might be an alternative option particularly in settings where there is a lack of rapid HPV DNA testing and a low quality of cytology-based screening.

Our result reflects the fact that the cost-effectiveness of these strategies is dependent on the test performance and the cost of the screening test. VIA is the cheapest method with a relatively high sensitivity in base case analyses (77%) despite higher false positive cases. The treatment cost of false positive cases might not be high enough to affect the total cost, resulting in VIA being the most attractive option. However, the rapid HPV DNA testing could become more interesting if there is no loss to follow-up or if VIA has a sensitivity lower than 52%. The latter assumption might be true as shown in a systematic review which revealed that the sensitivity of VIA could be lower than 40% in some settings due to the subjectivity of the technician who performs the test (20). To sustain a higher efficiency of VIA screening, a process of quality control of the VIA technique has to be implemented. Furthermore, we could not deny the fact that conventional cytology will dominate liquid-based cytology if its sensitivity is at least 70%. This can be true if the quality of the sample collection and the interpretation process are ensured. In previous reviews, the sensitivity of the conventional cytology could be as high as 82% (2), and was not significantly different to LBC in the detection of high-grade Cervical Intraepithelial Neoplasia (CIN) (21, 22). Further study on the performance of conventional cytology and LBC in the Lao context would be necessary in order to implement the appropriate intervention if cytology-based screening is considered to be realistic.

In the screening model, we decided to undertake probabilistic sensitivity analyses (PSA) in addition to one-way sensitivity analyses. PSA allows examining joint parameters uncertainties and reporting the results as probabilities to be cost-effective. This analysis is useful for decision makers who want to have a better vision about the outcome of a budget they are ready to spend (23). We found that

the magnitude of the cost-effectiveness of a girl vaccination program combined with a screening program could be influenced by the cost of vaccine as well as the screening and vaccination coverage. The impact of these parameters was also demonstrated in a previous Thai model (24). For instance, the probability of cost-effectiveness is reduced when the cost of the vaccine is I$ 50 or higher or when the coverage of vaccination or screening is lower than 50%.

5.2.3 Limitations

Inspired by previous complex models (10, 13), we modeled the natural history of HPV infection and cervical cancer on the compartmental dynamic model. The transmission dynamic model predicts more accurately the effectiveness of HPV vaccination than a static model, particularly, when a boy vaccination and a catch-up component are included thanks to a herd immunity effect (8, 25). Nevertheless, we have to be cautious when interpreting the results because of the limitations regarding model calibration. In our model, we lacked data to calibrate the prevalence of HPV infection, low-grade Cervical Intraepithelial Neoplasia (CIN) and high-grade CIN. We therefore used natural progression and regression of HPV infection from a Brazilian model (13) although these rates might be different from one setting to another, particularly where the epidemiology of the disease is different. We might therefore have over or underestimated the effectiveness of HPV vaccination. Further work to explore this element would be desirable to see if a simpler model leads to the same conclusion as a complex one.

Moreover, the incidence and mortality rates estimated by Globocan using neighboring countries data might not accurately reflect the current disease burden in Lao PDR. As demonstrated by Van de Velde *et al.,* (26), an underestimation of the vaccine effectiveness could be brought by uncertainties in the natural history parameters introduced in the model. However, our model provided similar conclusion in term of cost-effectiveness for HPV vaccination program compared to other complex models (8, 10, 13).

Also, our model did not consider some compartments that might have influenced the outcomes. These include: 1) cross-protection, which might underestimates the effectiveness of HPV vaccination, and 2) multiple HPV types infections in a same individual. Previous models taking into account cross-protection and multiple HPV type infections (9, 13) did not bring a different conclusion in term of cost-effectiveness of HPV vaccination. This might be because cross-protection brings a slightly additional benefit (27). Also, a previous model suggested avoiding

grouping the HPV types which could lead to a conservative effectiveness of HPV vaccination (8). Our model minimized this impact by creating four groups of HPV types.

Even though VIA is the most attractive among screening strategies, we have to acknowledge that its use in clinical practice is controversial due to the number of false positive cases. Indeed, this impact might not be trivial. Moreover, our study did not examine the cost-effectiveness of the number of times that someone was screened during her lifetime. A previous model demonstrated that a single lifetime VIA screening was cost-effective in India, Kenya, Peru, and Thailand (28). Another Thai model also demonstrated that HPV screening five times per lifetime was cost-effective (29). However, this component might not fully provide useful information to decision makers because the screening program might not be able to limit the number of screening per lifetime. Instead, a program has to determine the appropriate screening interval as demonstrated in our study.

In our studies, we did not examine the combination of three components: preadolescent girl vaccination, catch-up component and screening program. This combination has been shown to be cost-effective in the Canadian context (30). In addition, our compartment model might not have fully captured the clinical practices, particularly the procedures following treatments. This might underestimate both the cost and the effectiveness of the screening strategies. An individual-based model, which is more flexible and tracks better these procedures, might in that sense be interesting.

With no information on the willingness-to-pay thresholds that would make sense in the local context, we assessed the cost-effectiveness of the options based on WHO's recommendations, despite the fact that it might not reflect national funding affordability (31). We recognize this limitation, but we consider that it is a challenge to move forward in exploring further the willingness-to-pay thresholds that would be acceptable by national governments in order to maximize the efficiency and sustainability of the programs that are evaluated.

5.3 Contribution and further work

This is the first health economic evaluation applying a mathematical modeling approach to predict the costs and the consequences of a preventive intervention relevant to the Lao context. Despite the limitations of the approached used, we could demonstrate evidences of cost-effectiveness of cervical cancer control strategies in Lao PDR, a lower middle-income country. Combining a preadolescent girl vaccination program with a temporary catch-up component or with a screening program is cost-

effective. This combination reduces significantly the incidence of cervical cancer, saves life and improves women health.

Even though the combination strategy is efficient, some key parameters need to be followed-up. First, a sufficient coverage rate of vaccination is required to maintain the maximum benefit of the vaccination program. To maintain a high coverage level, we need to convince people about the benefit and safety of the vaccine. Second, we should not forget that HPV vaccine does not protect against all HPV type-related cervical cancers. Around 30% of vaccinated girls are still at risk of cervical cancer due to other high-risk HPV types not covered by the vaccine. There is therefore a need to undergo further screening at appropriate ages. Third, sex education is still needed to make people understand that the vaccine does not protect against other sexually transmitted infections. Finally, there is a need of more accurate data on costing and epidemiological data on cervical cancer, including the prevalence of HPV infection, low-grade CIN and high-grade CIN and the incidence and mortality of cervical cancer.

In addition, as Lao PDR is predominantly a rural country where there is a lack of standard infrastructure and medical supplies (32), The screening technique that should be implemented in different settings in the country depends on local characteristics. There is also a need of defining what strategies might increase coverage in order to maximize and sustain the efficiency of a cervical cancer control programs. Putting in place panels of discussion that involve policy makers, clinical practitioners and researchers, might be a judicious approach to support an effective implementation and surveillance of the program.

In term of model application, our model might be able to be used for further works on HPV, e.g. on the cost-effectiveness of a two-dose HPV vaccination program, a self-collection sample of rapid HPV DNA testing or the influence of HPV vaccination in future screening. Our model can also be adapted for further research not only on HPV cancer-related diseases but also on other problematic requiring a transmission dynamic model (SIR or SIS or SIRS).

Finally, this work emphasizes the interest of conducting model-based economic evaluations to inform decision makers regarding the efficiency of budget allocation. The method applied here aims at providing decision makers with the best evidences relevant to the local context (18). The use of modeling in a decision analytic framework can identify the factors most likely to influence

outcomes, can guide the design of future clinical studies and operational research, and can provide insight into the cost-effectiveness of different strategies. It can assist in early decision-making while considering different criteria such as public preferences, and political and cultural constraints (33). We therefore propose further work to advance and develop health economic simulations as a standard tool for the decision-making process in developing country public health care system in order to help maximizing the scare resources that these countries, as Lao PDR, have.

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Appendix 1: Methodology and additional findings for HPV vaccination model (Chapter 3)

Appendix 1: Methodology and additional findings for HPV vaccination model (chapter 3)

1. Methodology

A simulation of the cost/effectiveness of cervical cancer prevention strategies was conducted. Two outcomes were considered as denominators 1) the number of cervical cancers related to HPV type 16 and 18 and 2) Disability adjusted life years (DALYs) related to HPV type 16 and 18. The numerator consisted of the direct cost to the public health care system of each strategy. This economic evaluation study complied with the recommendations of WHO for cost-effectiveness analyses (1).

1.1 Simulation overview

Using a mathematical approach, a compartmental dynamic model of the natural history of HPV infection and cervical cancer was constructed and calibrated to reflect the Vientiane capital population in terms of age and sex distribution (2), as well as the age-specific incidence and mortality rates related to cervical cancer in 2014 (3). The model consisted of a dynamic cohort population categorized in one-year age groups. The model considered the occurrence of HPV infection and its progression to precancerous lesions and invasive cervical cancer (4), according to the probabilities of administrating a context-appropriate treatment for cervical precancerous and invasive cancers. Events defined in the model (such as Cervical Intraepithelial Neoplasia (CIN), cervical cancer, death) were probabilistically monthly imputed to the virtual population over the time course of the simulation. The parameters were retrieved from the literature. The vaccination strategies consisted of including a 10-year-old boy vaccination program and/or a catch-up vaccination element for different age groups of the population.

The virtual population was processed over a period of 100 years. This period of time was used to capture the long-term impact of HPV vaccination (5). Incremental cost/effectiveness ratios were computed on the simulation results. Sensitivity analyses were performed on a specific set of parameters expected to be the most influential on the outcomes (6).

1.2 Virtual population

The baseline virtual population (at year 1) consisted of the entire population of women with characteristics similar to the 2014 Vientiane capital population in terms of age and sex distribution (2) and age-specific incidence and mortality rates of cervical cancer (in one-year intervals) (3). The

Vientiane capital population was used in the model instead of the whole country due to the fact that the population of the country is predominantly rural (7), and the ethnic mix of the population (8) is likely to be very different in each of the provinces; subsequently the vaccination uptake might be different.

1.3 Scenarios

The scenarios consisted of 1) a baseline which referred to the situation of no-vaccination and a prevalence of cytology-based screening of 5.2% (3), reflecting the situation before the implementation of a girl vaccination program in Vientiane Capital, 2) a 10 years- old girl vaccination program, 3) a girl and boy vaccination program, 4) a girl vaccination program with a catch-up component for 11-25 years old women, 5) a girl and boy vaccination program with a catch-up component for 11-25 years old women, 6) a girl and boy vaccination program with a catch-up component for 11-25 years old women and men, 7) a girl vaccination program with a catch-up component for 11-75 years old women, 8) a girl and boy vaccination program with a catch-up component for 11-75 years old women, and 9) a girl and boy vaccination program with a catch-up component for 11-75 years old women and men.

The 10-year-old girl vaccination program was chosen because the vaccine ensures maximum benefit if administered to girls before they become sexually active and because this age group is more easily reachable through schools. The first age group for the catch-up vaccination component was selected because the 11-25 year old age group represents the age of undergraduate students who are reachable through school and university-based interventions. The 11-75 year old age group represents the population at risk of HPV infection in our model.

1.4 Model structure

Inspired by previous economic models of HPV vaccination (9-11), a dynamic transmission and compartment population-based model was created to reflect the expected effect of HPV vaccination programs, both in females and males. Susceptible girls and boys were considered to be at risk of being infected based on estimated infection rates between partners. For both males and females, the model considered if the HPV genotype was a 16, 18 or other high-risk types, or if it was of low-risk types.

The model considers that among infected women, some lesions regress thanks to a natural immunity against a specific HPV type, but these women remain susceptible to be infected with other HPV types. The infection might also persist and might then progress to Cervical Intraepithelial Neoplasia

(low-grade CIN “CIN 1” or high-grade CIN "CIN 2/3”, according to the Richard's modified classification) (12). A low-grade CIN might regress to either immunity state, or infection state (13-16) or progress to a high-grade CIN. In case of high-grade CIN, the lesion might regress to immunity state, infection state or low-grade CIN or might progress and become an invasive cervical cancer (local, regional and distant progression) (17, 18). Distant/metastatic cancer can only evolve towards death. Additionally, women may die of another cause than cervical cancer. Women diagnosed with precancerous lesions will be treated by either Loop Electrosurgical Excision procedure (LEEP) or hysterectomy. Women with invasive cervical cancer might be symptomatically detected. Diagnosed invasive cervical cancer is treated accordingly, with a defined probability of recovery or treatment failure or death due to treatment complications (figure 1).
In males, the infection might persist or regress conferring them a natural immunity against a defined HPV genotype. The consequences of HPV infection in males, such as warts, were not included in the model because we were only interested in the impact of HPV vaccination on cervical cancer in women. Males could die from general causes.

The model assumed that vaccinated people who entered into the vaccine protection compartment remained susceptible for HPV genotypes uncovered by the vaccine; consequently, they had a certain probability of being infected with HPV and getting an invasive cancer. Vaccinated people were susceptible to the 16/18 types HPV infection depending on assumptions done regarding the wane of vaccine immunity.

The model was validated by Lao experts in order to ensure that it realistically reflects the possibilities of routine screening and treating patients in the Vientiane capital context.

1.5 Parameters

The infection rate depended on the age-specific number of new sexual partners per month, the HPV genotype-specific transmissibility and the age-specific HPV prevalence in the opposite sex. To simplify the model, we considered all members of the population as heterosexuals. With each sexual partner, the HPV infection is probabilistically transmitted, depending on genotype-specific transmission probabilities and age-specific HPV prevalence in the opposite-sex population. A sexual relationship matrix group was constructed. The matrix consists of the monthly age-specific probability of having new sexual partners. Each age group has a probability of having a sexual intercourse with someone of the same or a different age group of 0.6 and 0.4 respectively, based on a previous national survey (19). The initial age of sexual intercourse is 15 years old or more in both

girls and boys, according to the last survey performed in Vientiane capital city (20). Due to unknown parameters of the number of new sexual partners in Lao PDR, data from the UK (10) were used and calibrated to the age-specific incidence of cervical cancer in Lao PDR. The transmissibility of each HPV type was calibrated to take into account the proportion of genotype specific-HPV prevalence and the proportion of cervical cancers due to HPV type 16/18 (table 2). The proportion of HPV types 16 and 18 among all-type HPV infections was, based on Thai data (21), assumed to be 45-50%. These infections may reasonably be assumed to be responsible for approximately 75% of the total incidence of invasive cervical cancer (22).

Monthly transition probabilities from one lesion state to another and regression rates were taken from Kim et al (23). For instance, the age-specific monthly probability that a HPV type 16 infection evolves to a low-grade CIN is 0.0047-0.0085, while the rate of transition from low to high-grade CIN is 0.0001-0.0039. The annual rate of detecting an invasive cervical cancer through symptoms is 0.19, 0.6 and 0.9 for local, regional and distant cervical cancers, respectively (table 3).

A true positive result of cervical cytology was defined as a high-grade CIN. We assumed that 55% of them would receive the whole treatment regimen, considering 15% loss to follow-up over the three expected visits. The first visit is for screening, the second for receiving the result and making an appointment for positive case. The third is for a colposcopy with direct biopsy. The proportion of treatment with LEEP or cryotherapy was based on experts' opinions. The rate of remission was retrieved from the literature (24, 25). The experts' panel consisted of two gynecologists with a practice focused on cervical cancer in Lao PDR, Dr. Phongsavan K. and Dr. Marsden E.D.

The proportion of women receiving cancer treatment among diagnosed patients and the stage-specific five-year survival rates due to cancer treatment complications were calibrated based on the estimated mortality rates related to cervical cancer according to Globocan, 2012 (table 3) (3).

The sensitivity and specificity of the conventional cervical cytology to detect a high-grade CIN or worse were considered to be 59% (range: 29%-82%) and 94% (range: 88%-99%), respectively (26). The model considers that colposcopy with direct biopsy is used to confirm a positive result from a cervical cytology test. The sensitivity and specificity of colposcopy were considered to be 96% (64 –99%) and 48% (30 –93%), respectively. Biopsy was assumed to have a sensitivity and a specificity of 100% (table 4).

Precancerous lesions and cancer stage treatment

Success rates for LEEP and hysterectomy were supposed to be 96.7% (90-98%) and 99% (90-100%), respectively (25). The proportion of positive women treated with LEEP or hysterectomy depends on their age. For women aged 35 years or less, it was considered that 80% (50-100%) would be treated with LEEP and 20% (0-50%) with a hysterectomy. For those older than 35 year old, the numbers were reversed: 20% (0-50%) with LEEP and 80% (50-100%) with hysterectomy. The remission rate of stage-specific invasive cervical cancer was calibrated, based on the estimate mortality related to cervical cancer in Lao PDR (3) (Table 4).

1.6 Model calibration

The population was stratified by gender and age. The model is in the form of a realistic age structured (RAS) model. The equations were numerically solved in Berkeley Madonna version 8.3.18 (27). The model was calibrated using maximum likelihood for the age-specific distribution of the 2014-estimated incidence of cervical cancer and mortality related to cervical cancer data in Lao PDR. Thai data on the prevalence of HPV infection and the prevalence of low-grade and high-grade CIN were used to guide their age-specific distributions. The demographic distribution followed an exponential distribution using UN data to predict the changing birth and death rates over time for Lao PDR (28). To calibrate the age-specific incidence of cervical cancer, we assumed that only the infection rate was different from the Kim et al. model (23). We consequently calculated an infection rate multiplier to calibrate the incidence of cervical cancer according to the Globocan estimates and used under and over estimates in sensitivity analyses (Table 5).

The calibration of parameters for the age and stage-specific mortality rates of cervical cancer was conducted by varying the proportion of women receiving treatment for local, regional and distant cancer, the monthly death rates due to treatment complications and the age and stage-specific remission rates. The true proportion of women receiving a treatment in Lao PDR is unknown; we therefore estimated its value according to the experts' opinion. The best guess of the proportion of women receiving a treatment for a local, regional or distant cancer was 100%, 80% and 70%, respectively (Table 3).

1.7 Costs

One should stress the fact that no economic evaluation of health interventions has ever been done in Lao PDR. This section refers therefore to a component that required some approximations, as the structure supporting the health care system has not been built to provide the required information for

conducting economic evaluations. We recognized that this is a limit, but also considered that undertaking this component would open doors to the realization of further studies on the value of money spent in the Lao PDR health care sector.

The perspective considered was essentially the perspective of the public health care system. Only direct medical costs and the programmatic cost of vaccination implementation were considered.

Items

Items were related to the consumption of medical resources for the diagnosis and treatment of cervical cancer and HPV (screening facilities, laboratory, diagnostic tests, hospitalizations, and treatment), as well as the vaccination cost (programmatic cost). A preliminary list of items was built with the help of gynecologists and pathologists working in Lao PDR. These items consisted of:

1. Screening related items: include support items, medical administration, and labor costs. The ingredients of support items consisted of the cost of electricity, water and transportation supplies and other office materials and staffs. Medical administration included training support and medical equipment. Labor cost included the time spent by the gynecologist and the nurse for screening activities. The cytology requires three visits. The first visit is for screening, the second for receiving the result and making an appointment for positive case. The third is for a colposcopy with direct biopsy.
2. Laboratory related items: items were listed according to a pathologist's advice. Cervical cytology and histology exams included administration, consumable and labor costs. Consumable items for cervical cytology included cover glass, malinol, Gill hemato, OG-6, EA-50, mask, xytene, etanol, and slide. For histology exams, the ingredients included formaline, hematocyline, eosine, paraphine, 130assette, cyline, obsolute, acetone and malinone. In the Vientiane Capital, four pathology technicians work together and can prepare a total of 50 smear slides for conventional cervical cytology per day. They can also in total prepare 10 histology slides per day. A pathologist needs 20 to 35 minutes for a cytology and histology examination. Other materials used for a cytology examination could not be identified due to lack of information (table 7).
3. Medication and surgery: the items of precancerous lesions treatment included support activities, drugs, and equipment and labor costs. LEEP requires one day of hospitalization and simple hysterectomy 7-days.
4. Vaccination included the vaccine cost and programmatic cost, which included micro-planning, training, social mobilization, procurement, logistics, service delivery, supervision and waste management.

5. Programmatic cost of screening included quality control, training, administration and recruitment costs.

Quantification

There are no national guidelines for cervical cancer control in Lao PDR. Quantities were therefore estimated based on experts' opinion.

1. Time spent for screening is supposed to be about 20 minutes for cervical cytology. Meanwhile, time spent for cervical cytology and histology interpretations is supposed to be about 20 and 35 minutes per case, respectively.
2. The number of visits considered is three.
3. Only consumable items of cytology and histology laboratory were considered. In the Vientiane Capital, four pathology technicians work together and spent a day to prepare 50 to 80 smear lames for conventional and liquid-based cervical cytology, respectively. They also prepare in total 10 histology lames per day. A pathologist needs 20 to 35 minutes per cytology and histology case, respectively.
4. Other quantities were approximated, for instance: hospitalization, surgery

Item pricing

Unit prices are reported in the value of 2013 international dollars, using purchasing power parity (PPP). According to WHO, a PPP exchange rate is the number of units of a country currency required to buy the same amounts of goods and services in the domestic market as what can be bought with one U.S. dollar in the United States. International dollars are, therefore, a hypothetical currency allowing comparisons and integration of costs between countries (29). Unit prices are reported as 2013 international dollars, using the PPP exchange rate (1 International dollar I$ = 2,694.27 kips) (29).

Price per service was calculated by multiplying the cost per unit and the amount of units per service. Unit prices were as often as possible based on data coming from Lao PDR. A Lao hospital unit price list is available. Its numbers have been estimated through a costing survey performed at the departments of gyneco-obstretics of two reference hospitals in the Capital of Vientiane: Mahosot and Setthathirath hospitals in 2013-2014 (personal communication with a head of department of health insurance, Ministry of health, Lao PDR). The survey applied a step down allocation method to estimate the average cost per visit and per hospitalization. Capital costs were not considered due to the difficulty to make an estimation of their real value. Unit prices for missing items were essentially retrieved from the literature. The realism of the valuing procedure was validated by the Lao experts' committee.

The price of administration and labor cost in the screening facility are 14.48 I$ and 3.39 I$, respectively (Table 6). We used for the cost of the LEEP the average cost of one-day hospitalization in a gyneco-obstetric ward. The cost of a simple hysterectomy was considered to be the same as the average cost of a surgical operation. The complication of cryotherapy, LEEP and hysterectomy are rare. For that reason, they were not considered (Table 8).

The cost of invasive cervical cancer treatment was retrieved from a study done in 72-GAVI eligible countries (30). It includes the costs of treatment for localized, regional and distant cervical cancers (Table 8).

Vaccination cost

The cost of delivering HPV vaccines consisted of the price of the vaccine and the programmatic cost of vaccination delivery. The programmatic cost of 3-dose HPV vaccine per girl was retrieved from a pilot project on HPV vaccination in 5th grade girls in Vientiane capital in 2014. The programmatic cost included micro-planning, training, social mobilization, procurement, logistics, service delivery, supervision and waste management. The vaccine cost per dose was based on the purchasing cost from the Global Alliance for Vaccines and Immunization (GAVI) (4.5 US dollars per dose) (31) (Table 4).

1.8 Simulation analyses

The simulation process deterministically ran over a 100 years span to capture the short and long term benefits of vaccination. For each option, the output consisted of the cumulative number of cervical cancers per 1 000 women, the DALYs per 1 000 women and the cost of screening and treatment per 1 000 women. DALYs were calculated based on the WHO table without age weighting. The disability weight for cancer treatment was retrieved from the current literature (32). For each strategy, a C/E ratio was calculated using the reduction number of cervical cancer and DALY averted as denominators. In case of a non-dominant situation, strong or extended dominance, the incremental cost/effective ratio was calculated, expressing the incremental cost per unit of health benefit gained compared to the alternative intervention, which is generally the next option characterized by a higher cost and a higher effectiveness. Two types of dominance can be defined: the strong dominant type in which an option is more effective and less costly than its alternative, and the extended dominant type, also known as weak dominant, where strategies with a higher incremental cost-effectiveness ratio (ICER) are ruled out (33).

All costs and DALYs were discounted at a rate of 3% in base case simulations to convert future costs and life expectancies and duration of disability to their present value (1). However, other discount rates of 0% to 5% for DALYs and 6% for costs were also explored.

The results were interpreted taking into account the recommendations of the UN Commission on Macroeconomics and Health which proposes classifying cost-effectiveness studies into three categories: 1) highly cost-effective (ICER< Lao GDP per capita; 2) cost-effective (ICER between 1-3 times the GDP per capita); and 3) not cost-effective (ICER > 3 times the GDP per capita) (34). The GDP per capita in Lao PDR in 2013 was about 4,822 international dollars using the PPP exchange rate (35).

1.9 Sensitivity analyses

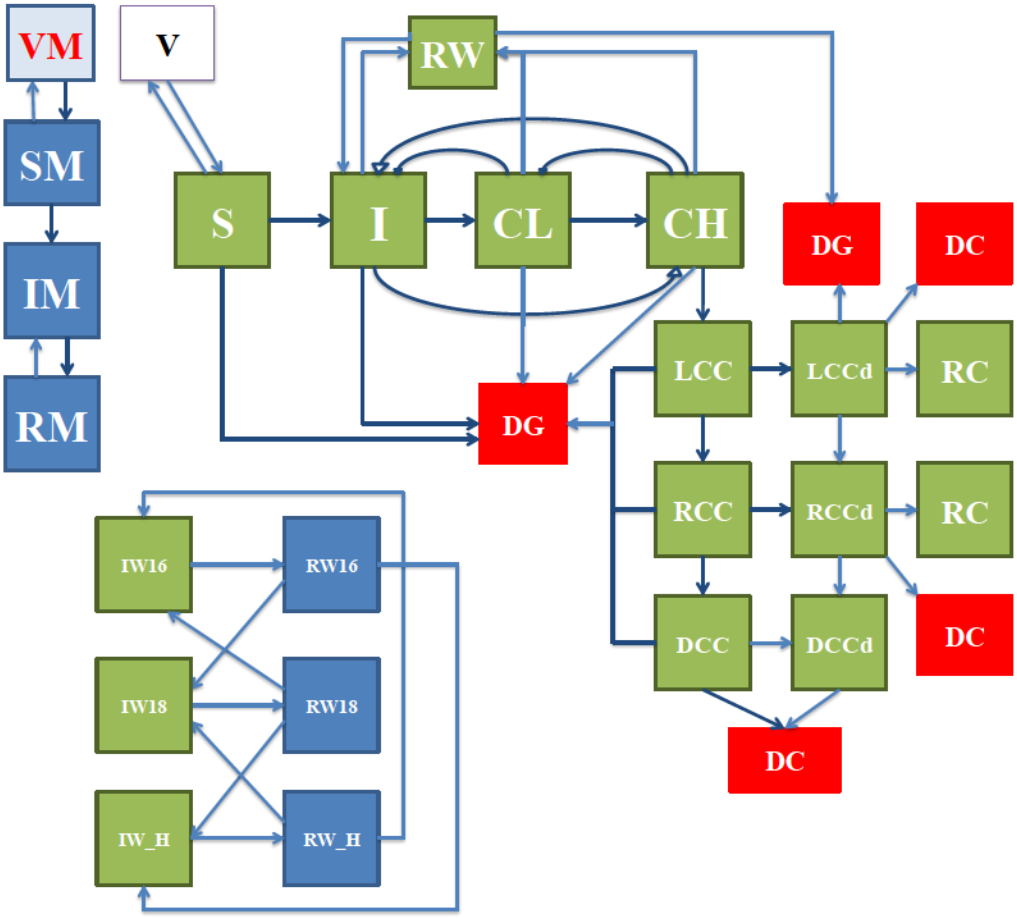
One-way sensitivity analyses were conducted on parameters using their lower and upper bound values retrieved from the literature to identify the parameters that might significantly influence the incremental cost-effectiveness ratio per DALY averted. One-way sensitivity analyses were performed by varying the values of the incidence of cervical cancer, vaccination coverage, vaccine efficacy, duration of vaccine protection, duration of natural immunity, cost of vaccine per dose, cost of cancer treatment, and discount rate.

Other sensitivity analyses were conducted to explore various factors, as the initial age of vaccination in girls (11, 12 and 13 years old), the effect of cervical cancers due to non-HPV types 16/18, the effect of 10 consecutive cohorts vaccination only, a time horizon of 30 and 50 years, and a program consisting in vaccinating boys only.

1.10 Model Validation process

The model was able to reproduce the 2014 Vientiane Capital expected values regarding demographic data, both for the female and the male populations. However the number of individuals was high for 10 to 25 year old individuals compared to expected values, while it was low for 25-35 year old individuals. The model reproduced results that were consistent with the incidence of cervical cancer and its mortality due to any high-risk HPV type according to the estimates of Globocan 2012 (figure 2). The proportion of cervical cancers related to HPV type 16 and 18 was about 75%. The calibrated infection rate was not different to that reported in the literature.

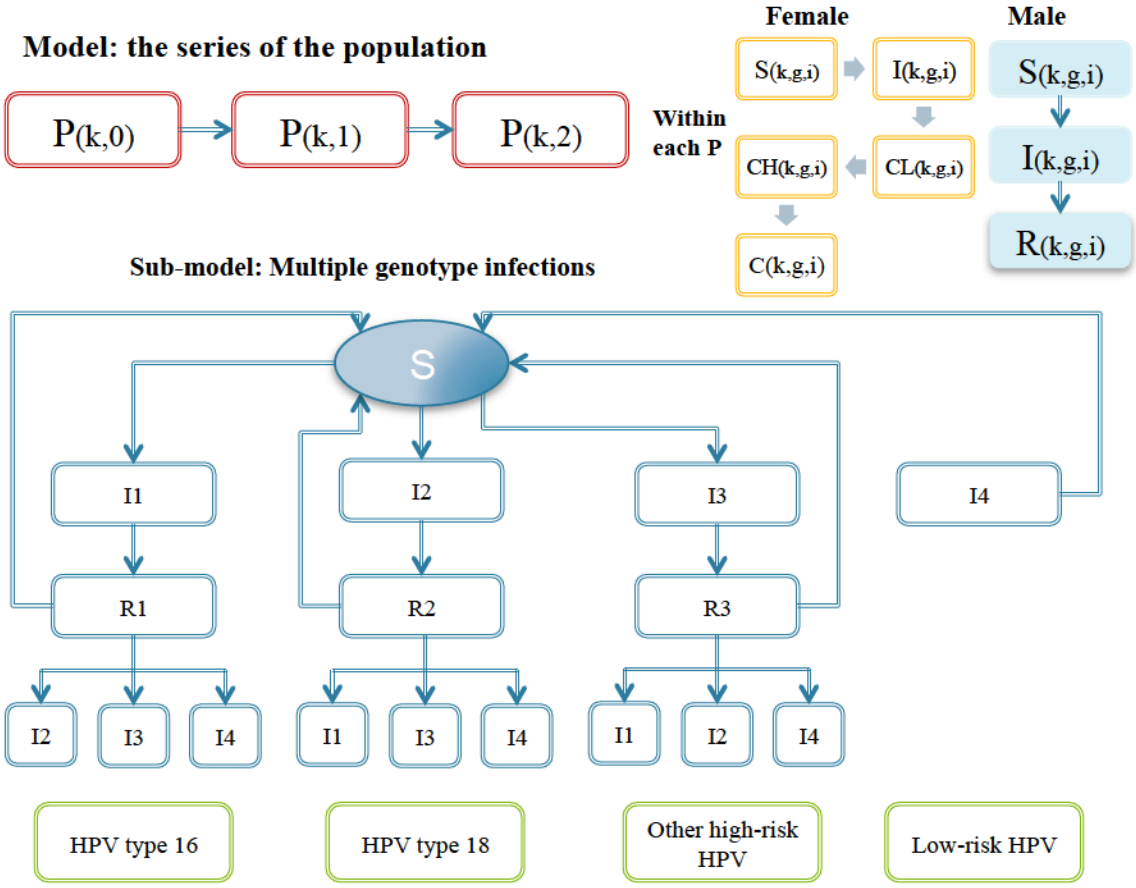
Figure 1: Model structure for natural history of Human Papillomavirus infection and cervical cancer



Overview of the ordinary differential equations

State transition equations

Female model (1)



$$S'_{k,0} = \mu P + \epsilon S_{(k-1),0} + \epsilon S_{(k-1),0} + \omega_k RW_{k,g,0} - [\lambda_{k,g} + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]S_{k,0}$$

$S'_{k,1} = \epsilon S_{(k-1),1} + [(\nu_k + \rho_k)\tau_k]S_{k,0} + \omega_k RW_{k,g,1} - (\lambda_{k,g} + \varphi + \theta_k + \epsilon)S_{k,1}$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$$S'_{k,2} = \epsilon S_{(k-1),1} + \varphi S_{k,g,1} + \omega_k RW_{k,g,2} - (\lambda_{k,g} + \theta_k + \epsilon)SV_{k,2}$$

$$I'_{k,g,0} = \epsilon I_{(k-1),g,0} + \lambda_{k,g}[S_{k,0} + (1 - x_g)RW_{k,g,0}] + \alpha_{k,g} CL_{k,g,0} + \psi_{k,g} CH_{k,g,0} - [\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + (\nu_k + \rho_k)\tau_k + \theta_k + \epsilon]I_{k,g,0}$$

$$I'_{k,g,1} = \epsilon I_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]I_{k,g,0} + \lambda_{k,g}[S_{k,1} + (1 - x_g)RW_{k,g,1}] + \alpha_{k,g} CL_{k,g,1} + \psi_{k,g} CH_{k,g,1} - (\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + \varphi + \theta_k + \epsilon)I_{k,g,1}$$

$$I'_{k,g,2} = \epsilon I_{(k-1),g,2} + \varphi I_{k,g,1} + \lambda_{k,g}[S_{k,2} + (1 - x_g)RW_{k,g,2}] + \alpha_{k,g} CL_{k,g,2} + \psi_{k,g} CH_{k,g,2} - (\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + \theta_k + \epsilon)I_{k,g,2}$$

$$CL'_{k,g,0} = \epsilon CL_{(k-1),g,0} + \eta_{k,g} I_{k,g,0} + \varpi_{k,g} CH_{k,g,0} + (1 - \hat{e}_k)TCL_{k,g,0} - [\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + (\nu_k + \rho_k)\tau_k + æ_k + \theta_k + \epsilon]CL_{k,g,0}$$

$$CL'_{k,g,1} = \epsilon CL_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]CL_{k,g,0} + \eta_{k,g}I_{k,g,1} + \varpi_{k,g}CH_{k,g,1} + (1 - \hat{e}_k)TCL_{k,g,1} - (\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + æ_k + \varphi + \theta_k + \epsilon)CL_{k,g,1}$$

$$CL'_{k,g,2} = \epsilon CL_{(k-1),g,2} + \varphi CL_{k,g,1} + \eta_{k,g}I_{k,g,2} + \varpi_{k,g}CH_{k,g,2} + (1 - \hat{e}_k)TCL_{k,g,2} - (\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + æ_k + \theta_k + \epsilon)CL_{k,g,2}$$

$$CH'_{k,g,0} = \epsilon CH_{(k-1),g,0} + \partial_{k,g}I_{k,g,0} + \pi_{k,g}CL_{k,g,0} + (1 - \varepsilon_k)TCH_{k,g,0} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + (\nu_k + \rho_k)\tau_k + \phi_k + \theta_k + \epsilon)CH_{k,g,0}$$

$$CH'_{k,g,1} = \epsilon CH_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]CH_{k,g,0} + \partial_{k,g}I_{k,g,i} + \pi_{k,g}CL_{k,g,i} + (1 - \varepsilon_k)TCH_{k,g,i} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + \phi_k + \varphi + \theta_k + \epsilon)CH_{k,g,i}$$

$$CH'_{k,g,2} = \epsilon CH_{(k-1),g,2} + \varphi CH_{k,g,1} + \partial_{k,g}I_{k,g,2} + 2 + (1 - \varepsilon_k)TCH_{k,g,2} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + \phi_k + \theta_k + \epsilon)CH_{k,g,2}$$

$$RW'_{k,g,0} = \epsilon RW_{(k-1),g,0} + \gamma_{k,g}I_{k,g,i} + \delta_{k,g}CL_{k,g,i} + \beta_{k,g}CH_{k,g,i} + \varepsilon_k TCH_{k,g,i} + \hat{e}_k TCL_{k,g,0} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]RW_{k,g,0}$$

$$RW'_{k,g,1} = \epsilon RW_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]RW_{k,g,0} + \gamma_{k,g}I_{k,g,1} + \delta_{k,g}CL_{k,g,1} + \beta_{k,g}CH_{k,g,1} + \varepsilon_k TCH_{k,g,1} + \hat{e}_k TCL_{k,g,1} - (1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \varphi + \epsilon]RW_{k,g,1}$$

$$RW'_{k,g,2} = \epsilon RW_{(k-1),g,2} + \varphi RW_{k,g,1} + \gamma_{k,g}I_{k,g,2} + \delta_{k,g}CL_{k,g,2} + \beta_{k,g}CH_{k,g,2} + \varepsilon_k TCH_{k,g,2} + \hat{e}_k TCL_{k,g,2} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \epsilon]RW_{k,g,2}$$

$$\nu_k = \frac{\epsilon C_k}{1 - C_k}$$

$$\rho_k = \frac{\epsilon COV_k}{1 - COV_k}$$

Invasive cervical cancer model (2)

$$LCC'_{k,g} = \mathcal{F}_{k,g}CH_{k,g} - \big((\mathfrak{D} + \phi_k)\mathcal{g} + h + \theta_k + \epsilon\big)LCC_{k,g}$$

$$RCC'_k = hLCC_k - \big((\mathbb{Q} + \phi_k)\Omega + \mathcal{H} + \theta_k + \epsilon\big)RCC_k$$

$$DCC'_k = \mathcal{H}RCC_k - \big((\mathcal{L} + \phi_k)\mathcal{A} + \lambda_k + \theta_k + \epsilon\big)DCC_k$$

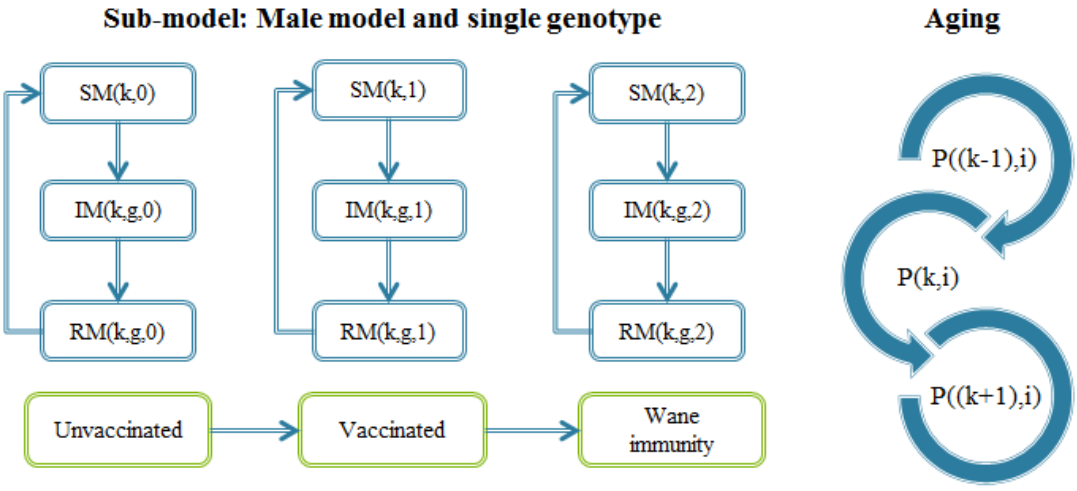
$$LCCd'_{k,g} = (\psi + \phi_k)\mathcal{g}LCC_{k,g} - (h + m_k + \theta_k + \epsilon)LCCd_{k,g}$$

$$RCCd'_k = (\mathbb{Q} + \phi_k)\Omega RCC_k + (1 - \mathcal{r}_k)hLCCd_k - (\mathcal{H} + \mathcal{n}_k + \theta_k + \epsilon)RCCd_k$$

$$DCCd'_k = (\mathcal{L} + \phi_k)\mathcal{A}DCC_k + (1 - \mathfrak{y}_k)\mathcal{H}RCCd_k - (\exists_k + \theta_k + \epsilon)DCCd_k$$

$$RC'_k = \mathcal{r}_k hLCCd_k + \mathfrak{y}_k \mathcal{H}RCCd_k - (\theta_k + \epsilon)RC_k$$

Male model (3)



$$SM'_{k,0} = \mu\sigma P + \epsilon SM_{(k-1),0} + \omega_k RM_{k,g,0} - [\lambda_{k,g} + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]SM_{k,0}$$

$$SM'_{k,1} = \epsilon SM_{(k-1),1} + [(\nu_k + \rho_k)\tau_k]SM_{k,0} + \omega_k RM_{k,g,1} - (\lambda_{k,g} + \theta_k + \varphi + \epsilon)SM_{k,1}$$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$$SM'_{k,2} = \epsilon SM_{(k-1),2} + \varphi SM_{k,1} + \omega_k RM_{k,g,2} - (\lambda_{k,g} + \theta_k + \epsilon)SM_{k,2}$$

$$IM'_{k,g,0} = \epsilon RM_{(k-1),g,0} + \lambda_{k,g}[SM_{k,0} + (1 - x_g)RM_{k,g,0}] - [\gamma_{k,g} + (\nu_k + \rho_k)\tau_k + \theta_k + \epsilon]IM_{k,g,0}$$

$$IM'_{k,g,1} = \epsilon RM_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]IM_{k,g,0} + \lambda_{k,g}[SM_{k,1} + (1 - x_g)RM_{k,g,1}] - [\gamma_{k,g} + \varphi + \theta_k + \epsilon]IM_{k,g,1}$$

$$IM'_{k,g,2} = \epsilon RM_{(k-1),g,2} + \varphi IM_{k,g,1} + \lambda_{k,g}[SM_{k,2} + (1 - x_g)RM_{k,g,2}] - [\gamma_{k,g} - (\gamma_{k,g} + \theta_k + \epsilon)]IM_{k,g,2}$$

$$RM'_{k,g,0} = \epsilon RM_{(k-1),g,0} + \gamma_{k,g} IM_{k,g,0} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]RM_{k,g,0}$$

$RM'_{k,g,1} = \epsilon RM_{(k-1),g,1} + \gamma_{k,g} IM_{k,g,1} + [(\nu_k + \rho_k)\tau_k] RM_{k,0} - ((1 - x_g)\lambda_{k,g} + \omega_k + \varphi + \theta_k + \epsilon) RM_{k,g,1}$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$RM'_{k,g,2} = \epsilon RM_{(k-1),g,2} + \varphi RM_{k,g,1} + \gamma_{k,g} IM_{k,g,2} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \epsilon] RM_{k,g,2}$

Precancerous lesions treatment model (4)

$TCL'_{k,g,0} = \epsilon TCL_{(k-1),g,0} + æ_k CL_{k,g,i} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + (\nu_k + \rho_k)\tau_k + \epsilon] TCL_{k,g,0}$

$TCL'_{k,g,1} = \epsilon TCL_{(k-1),g,1} + æ_k CL_{k,g,i} + [(\nu_k + \rho_k)\tau_k] TCL_{k,g,0} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \varphi + \epsilon] TCL_{k,g,1}$

$TCL'_{k,g,2} = \epsilon TCL_{(k-1),g,2} + \varphi TCL_{k,g,1} + æ_k CL_{k,g,i} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \epsilon] TCL_{k,g,2}$

$TCH'_{k,g,0} = \epsilon TCH_{(k-1),g,0} + \phi_k CH_{k,g,0} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + (\nu_k + \rho_k)\tau_k + \epsilon] TCH_{k,g,0}$
$TCH'_{k,g,1} = \epsilon TCH_{(k-1),g,1} + \phi_k CH_{k,g,1} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \varphi + \epsilon] TCH_{k,g,1}$

$TCH'_{k,g,2} = \epsilon TCH_{(k-1),g,2} + \phi_k CH_{k,g,2} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \epsilon] TCH_{k,g,2}$

$\phi_k = \varsigma_k \varrho (1 - los\_final)$

Force of infection (5)

$$\lambda_{k,g} = A \sum_{k=1}^{N} Lamda_{k,g}$$

Where A is the adjustment of the total estimated force of infection, and N is the total number of age group and

$Lamda_{k,g} = \frac{\mathcal{T}_g M_k IM_{k,g}}{POPM_k}$ for female

$POPM_k = STT_k + IM_k + RM + VM_k$

And

$Lamda_{k,g} = \frac{\mathcal{T}_g M_k (IM_{k,g} + CL_{k,g} + CH_{k,g})}{POPF_k}$ for male

$POPF_k = S_k + I_k + CL + CH_k + RW + LCC_k + RCC_k + DCCd_k + LCCd_k + RCCd_k + DCCd_k$

Where M is the contact matrix

$M_k = \varsigma_1 MS_k + \frac{\varsigma_2 MS_k}{NG-1}$ where MS is new sexual partnership per month; ς_1 is the probability of having a sexual partner within the same age group; ς_2 is the probability of having a sexual partner within a different age group; and NG is the total number of age

Calibration: maximum likelihood estimation (6)

$LI_{k,g} = ICD_{k,g} \ln(IC) - IC$ where ICD is the observed incidence of invasive cervical cancer, and IC is expected incidence of invasive cervical cancer

Table 1: Abbreviation of the model structure variables

Variable	Meaning
$S_{k,..}$	Healthy women (age k, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$I_{k,g,..}$	Infection in females (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$RW_{k,g,..}$	Regression of infection or precancerous lesions (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$CL_{k,g,..}$	Low-grade Cervical Intraepithelial Neoplasia (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$CH_{k,g,..}$	High-grade Cervical Intraepithelial Neoplasia (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$LCC_{k,g}$	Undetected local cancer (age k, genotype g) at time t
RCC_k	Undetected regional cancer (age k) at time t
DCC_k	Undetected distant cancer (age k) at time t
$LCCd_{k,g}$	Detected local cancer (age k, genotype g) at time t
$RCCd_k$	Detected regional cancer (age k) at time t
$DCCd_k$	Detected distant cancer (age k) at time t
RC_k	Recovery from cancer treatment (age k) at time t
P	Total female population
$SM_{k,..}$	Healthy males (age k, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$IM_{k,g,..}$	Infection in males (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$RM_{k,g,..}$	Recovery with natural immunity in males (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$TCL_{k,g,..}$	Women with low-grade CIN receiving treatment (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$TCH_{k,g,..}$	Women with high-grade CIN receiving treatment (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$POPF_k$	Total female population (age k)
$POPM_k$	Total male population (age k)
IW16	HPV type 16 infected women
IW18	HPV type 18 infected women

IW_H	Other high-risk HPV infected women
RW16	Clearing up HPV type 16 infection with natural immunity against HPV type 16
RW18	Clearing up HPV type 18 infection with natural immunity against HPV type 18
RW_H	Clearing up other high-risk HPV infection with natural immunity against high-risk HPV
DG	Death due to other causes
DC	Death due to cervical cancer

Table 2: Abbreviation of model structure parameters

Parameters	Meaning
ϵ	Aging rate
μ	Birth rate
ω_k	Waning of HPV natural immunity (age k)
$\psi_{k,g}$	Waning of HPV vaccine-induced immunity (age k, genotype g)
$\gamma_{k,g}$	Regression rate from infection to healthy state (age k, genotype g)
$\delta_{k,g}$	Regression rate from low-grade CIN to healthy state (age k, genotype g)
$\alpha_{k,g}$	Regression rate from low-grade CIN to infection (age k, genotype g)
$\beta_{k,g}$	Regression rate from high-grade CIN to healthy state (age k, genotype g)
ε_k	Cure rate of high-grade Cervical Intraepithelial Neoplasia treatment (age k)
$\hat{e}_k$	Cure rate of low-grade Cervical Intraepithelial Neoplasia treatment (age k)
ν_k	Preadolescent vaccination coverage (age k)
$\lambda_{k,g}$	Infection rate (age k, genotype g)
θ_k	Death rate due to other causes in women (age k)
τ_k	Effectiveness of the vaccine (age k)
ρ_k	Vaccination coverage for catch-up component (age k)
$\eta_{k,g}$	Progression rate from infection to low-grade CIN (age k, genotype g)
$\partial_{k,g}$	Progression rate from infection to high-grade CIN (age k, genotype g)
x_g	Effectiveness of the natural immunity (age k)
$\pi_{k,g}$	Progression rate from low-grade CIN to high-grade CIN (age k, genotype g)
$\mathcal{F}_{k,g}$	Progression rate from high-grade CIN to invasive cervical cancer (age k, genotype g)
h	Progression rate from local cervical cancer to regional cervical cancer
$\mathcal{H}$	Progression rate from regional cervical cancer to distant cervical cancer
$\psi_{k,g}$	Regression rate from high-grade CIN to infection (age k, genotype g)
$\varpi_{k,g}$	Regression rate from high-grade CIN to low-grade CIN (age k, genotype g)
$\mathfrak{D}$	Symptomatic detection rate of local cervical cancer
$\mathbb{Q}$	Symptomatic detection rate of regional cervical cancer
$\mathcal{L}$	Symptomatic detection rate of distant cervical cancer
ϕ_k	Detection rate through screening for high-grade CIN (age k)
$æ_k$	Detection rate through screening for low-grade CIN (age k)
$\curlyvee_k$	Cure rate of local cervical cancer (age k)
$\mathfrak{y}_k$	Cure rate of regional cervical cancer (age k)

λ_k	Death rate due to distant cervical cancer in women who do not receive treatment (age k)
$\exists_k$	Death rate due to distant cervical cancer in women who receive treatment (age k)
m_k	Death rate due to local cervical cancer treatment (age k)
n_k	Death rate due to regional cervical cancer treatment (age k)
los_final	Proportion of loss to follow-up at three visits
C	Proportion of vaccinated preadolescent girls/boy vaccination
COV	Proportion of people given a catch-up component
ς_k	Screening coverage at age class k (age k)
ϱ	Sensitivity of screening test
g	Proportion of women with local cervical cancer who accept the treatment
Ω	Proportion of women with regional cervical cancer who accept the treatment
$\mathcal{A}$	Proportion of women with distant cervical cancer who accept the treatment
σ	Male to female population ratio
$\mathcal{T}_g$	Genotype-specific transmission probability

Table 3: Model parameters: force of infection

Age group	Male	Female	Adjusted ¶	Multiplier ‡	Source
Transmissibility per sexual partnership					Calibrated
HPP 16	0.355	0.355			
HPV 18	0.40	0.40			
Other-HR HPV	0.41	0.41			
Low-risk HPV	0.39	0.39			
Mean number of annual change of sexual partners among males and females					(36)
12-13	0.222	0.071	1	2.48-4.43	
14-15	0.673	0.283	1		
15-19	3.794	2.48	0.7		
20-24	5.802	2.442	0.7		
25-29	2.957	1.728	0.7		
30-34	2.113	0.971	0.7		
35-39	1.323	0.842	0.7		
40-44	1.323	0.842	1		
45-49	0.662	0.421	1		
50-54	0.662	0.421	2		
55-64	0.331	0.211	2		
65-74	0.166	0.106	3		
Sexual mixing matrix					(19)
Same age	0.6	0.6			
Different age	0.4	0.4			

¶ Adjusted values was applied to the force of infection model

‡ Multiplier values ranged according to related-scenarios of annual incidence rate of cervical cancer

Table 4: Summary of input parameters for the model

Parameters		Baseline values*	Source
Progression			
Healthy to infection † (-20 and +40%)	HPV-16	0.000175-0.003148 (0.0001426-0.00761)	Calibrated
	HPV-18	0.0004-0.000789 (0.000102-0.00168)	
	Other HR HPV	0.000206-0.004038 (0.0001703-0.00911)	
	LR HPV	0.000958-0.018412 (0.00069-0.0537)	
HPV DNA to CIN1‡	HR-16 HPV	0.005194-0.00901	(23)
	HR-18 HPV	0.002793-0.004845	
	HR-other HPV	0.007693-0.013345	

	LR-HPV	0.002397-0.001222
Proportion (%) of women who transition directly from HPV DNA to CIN2,3	HR-16 HPV	0.64
	HR-18 HPV	0.975
	HR-other HPV	0.966
	LR-HPV	0.98
CIN 1 to CIN 2,3 ‡	HR-16 HPV	0.00951-0.012363
	HR-18 HPV	0.0051-0.00663
	HR-other HPV	0.00747-0.009711
	LR-HPV	0.000149-0.000222
CIN 2,3 to local cancer	HR-16 HPV	0.000151-0.00906
	HR-18 HPV	0.000264-0.01584
	HR-other HPV	0.000199-0.01194
Local to regional invasive cancer		0.0200
Regional to distant invasive cancer		0.0250
Regression		
HPV DNA to Normal	HR-16 HPV	0.09089
	HR-18 HPV	0.09089
	HR-other HPV	0.09272
	LR-HPV	0.09699
CIN 1 to normal ‡‡	HR-16 HPV	0.03782
	HR-18 HPV	0.03782
	HR-other HPV	0.04575
	LR-HPV	0.01708
CIN 2,3 to Normal §§	HR-16 HPV	0.000798-0.000455
	HR-18 HPV	0.003556-0.011938
	HR-other HPV	0.002926-0.009823
	LR-HPV	0.001904-0.006392
	Other	
Immunity (%) (HR-HPV types only) ¶¶	HR-16 HPV	0.66
	HR-18 HPV	0.86
	HR-other HPV	0.59
Annual probability of symptom detection #	Local invasive cancer	0.33
	Regional invasive	0.60

	cancer		
	Distant cancer	0.9	
Proportion of cancer patient receiving the treatment	Local cancer	100%	Calibrated
	Regional cancer	87%	
	Distant cancer	78%	
Age-specific 5-year survival proportion after diagnosis and treatment (%) £	Local cancer	0.29-71%	Calibrated
	Regional cancer	0.24-78%	
Age-specific monthly probability of death	Complication of local cancer treatment	0.012-0.037	Calibrated
	Complication of regional cancer treatment	0.0098-0.028	
	Distant cancer (rate)	0.28-0.83	
Age-specific all cause death rates per person per year	Female	0,00106-0,4122	(37)
	Male	0.001-0.47	

* Baseline values are monthly age-specific probabilities, unless otherwise noted

† The transition from healthy state to infection is a force of infection derived from the number of sexual partner change, HPV type-specific transmissibility.

‡ HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; HR, high risk; LR, low risk

‡‡ 70% of women with CIN 1 regress to normal, 30% to HPV.

§§ 70% of women with CIN2,3 regress to normal, 15% to HPV, 15% to CIN 1.

¶¶ Immunity represents the degree to protection each woman faces against future type-specific infection after infection after first infection and clearance. The immunity was assumed to be lifelong.

The annual probability of symptom detection corresponds to 15% for local cancer and 85% for advanced cancer

£ Age-specific survival proportion was calibrate, based on a mortality rate estimated by Globocan (3).

Table 5: vaccination, screening, compliance and costing parameters

Items		**Value**	**Source** #
Vaccination coverage		70% (30-80%)	Assumption
Vaccine efficacy against HPV type 16 and 18 infection		100% (30-100%)	(38)
Wane of vaccine or natural immunity		Lifelong (10years to lifelong)	Assumption
Routine cervical cytology coverage		5.2% every 3 years	(3)
Cervical cytology	Sensitivity	59%	(26)
	Specificity	94%	
Colposcopy	Sensitivity	96%	(39)
	Specificity	48%	
True positive women received treatment†		55%	
Proportion of cure for LEEP	High-grade CIN	96.7%	(24)
Proportion of cure for simple hysterectomy (Any CIN)		99%	(40)
Lost to follow-up per visit		15%	Assumption
Cost of conventional cervical cytology‡§		48.27	Personal communication ¶

Cost of colposcopy‡		17.87	Personal communication ¶
Cost of biopsy‡§		45.69	
Cost of LEEP‡		120.40	Personal communication ¶
Cost of simple Hysterectomy ‡		1188.59	
Treatment cost of Local cancer ‡		745.57 (372.79-1491.15)	(30)
Treatment cost of regional cancer ‡		845.68 (422.85-1691.36)	(30)
Treatment cost of distant cancer ‡		845.68 (422.85-1691.36)	(30)
Cost of vaccination *		42.59	WHO (31)
Disability weight for diagnosis and primary therapy	Local cancer	0.2 (0.199-0.411)	(32)
	Regional cancer	0.411 (0·199-0.411)	
Disability weight for distant cancer		0.683 (0.356-0.683)	
Discount rate‡‡		3% (0-5%)	(1)

Note:

Databases of the department of health insurance, pathology center and department of national immunization program, Ministry of health, Lao PDR.

† A true positive result of cervical cytology was defined as a high-grade CIN, considering 15% loss to follow-up over the three expected visits (for screening, diagnostic test and treatment).

§ In the Vientiane Capital, four pathology technicians work together and can prepare a total of 50 smear slides for conventional cervical cytology per day. They can also prepare 10 histology slides per day. A pathologist needs 20 to 35 minutes for a cytology and histology examination.

‡ Cost is unit price per person, 2013 International dollars exchange using purchasing power parity (PPP) exchange rate (1 I$ = 2,694.27 kips) (29) and the price of cancer treatment was adjusted from 2005 to 2014 using consumer price index (77.33 in 2005 and 122.52 in 2014) (41)

* Vaccination costs include programmatic cost and vaccine cost, 29.09 and 13.5 international dollars per three doses, respectively. We communicate with WHO in Lao PDR to get the programmatic cost of vaccination. Vaccine cost varied from 13.5-300 international dollars per three doses

All costs varied +/- 75% in exception of cervical cancer treatment

¶ A head of department of health insurance, Ministry of health, Lao PDR was contacted for costing data

‡‡ Discount rate for cost is maximum of 6% and 5% for DALYs

Table 6: Calibration target

Calibration target		Source	Calibration target		Source
Female population¶		(41)	**Annual incidence rates of invasive cervical cancer per 100,000**		(3)
0- <5	44196		15-39	5.2	
5- <10	40488		40-44	26.9	
10 - <15	27947		45-49	33.3	
15 - < 20	31402		50-54	37.1	
20 - < 25	38205		55-59	36.9	
25 - < 30	48941		60-64	34.8	
30 - < 35	45627		65-69	33.7	
35 - < 40	32125		70-74	30.5	
40 - < 45	26762		>74	29	
45 - < 50	21895		**Annual mortality of invasive cervical cancer per 100,000**		
50 - < 55	17307		15-39	1.2	
55 - < 60	12766		40-44	9.6	
60 - < 65	8251		45-49	14.2	
65 - < 70	5,930		50-54	19.8	
70 - < 75	4152		55-59	23.9	
75+	6119		60-64	27.9	
Distribution of HPV types among women with cancer, Thai data		(21)	65-69	31.8	
			70-74	35.6	
			>74	39.4	
HPV1618	75.1				
Other-HR HPV‡	24.9				

¶ The proportion of male population to female population is 0.948
‡ HPV, human papillomavirus

Table 7: costing parameters for screening

Option	Items	Unit price (2013 I$)	Source
Conventional cervical cytology	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical staffs ¶	3.39	
	Cervical cytology laboratory equipment	11.20	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Laboratory staffs	3.54	
	Total	32.61	
Colposcopy	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical staff ¶	3.39	
	Total	17.87	

Note:
‡ Administration includes general and medical administration. General administration includes electricity, water and transportation supplies and other office martials and stuffs. Medical administration included training support and aids, and some medical equipment.
¶ Monthly salary also includes incentives, gasoline and overtime pay. Salary per hour = salary per day/8; Salary per day =(monthly salary x 12 months) / (52 weeks x 5 working days).

- Monthly average salary of gynecologist is 1303 dollars
- Monthly average salary of nurse is 736 dollars
- Monthly average salary of pathologist is 992 dollars
- Monthly average salary of pathology technician is 717 dollars

International dollars exchange using 2013 PPP exchange rate (1 I$ = 2,694.27 kips) (29)

Table 8: detail of laboratory cost

Item	Sub-item	Unit price (dollar)	Source
Conventional cervical cytology	Lab administration ‡	0.01	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Lab equipment #	11.20	
	Lab stuffs ¶	3.54	
	Total	14.75	
Histology	Lab administration ‡	14.48	
	Lab equipment *	15.47	
	Lab stuffs ¶	15.74	
	Total	45.69	

Note:
Consumable items included Brush, cover glass, Malinol, Gill hemato, OG-6, EA-50, mask, xytene, etanol, slide. LBC prep set, LBC liquid were added for Thin-Prep.
* Consumable items included Formaline, hematocyline , eosine, paraphine, casette, cyline, obsolute, acetone, malinone.
‡ Lab administration was retrieved from general administration allocated to laboratory in hospital per sample.
¶ This included both technical stuff and pathologist cost. Each cost is calculated by multiplying time spending to procedure with labor cost per hour.
International dollars exchange using 2013 PPP exchange rate (1 I$ = 2,694.27 kips) (29).

Table 9: Costing of precancerous treatment

Item	Sub-item	Unit price (dollar)	Source
LEEP	Administration ‡	27.66	Personal communication with a head of department of health insurance, Ministry of health, Lao PDR
	Drug and equipment cost *	57.05	
	Labor cost ‡‡	35.68	
	Total #	120.40	
Hysterectomy	Administration †	64.63	
	Drug and medical equipment cost †	204.23	
	Labor cost †	76.96	
	Subtotal	345.82	
	Hospitalization cost in 7 days §	842.78	
	Total #	1188.59	

Cancer treatment §§	Treatment cost of Local cancer	745.57 (372.79-1491.15)	(30)
	Treatment cost of regional cancer	845.68 (422.85-1691.36)	
	Treatment cost of distant cancer	845.68 (422.85-1691.36)	

Note:

‡ Administration included general and medical administration. General administration included electricity, water and transportation supplies and other office martials and stuffs. Medical administration included training support and aids, some medical equipment; inpatient for loop electrosurgical excision procedure (LEEP).

‡‡ Labor cost was calculated by multiplying the wage rate per hour by the time spent to provide treatment

* Drug and equipment cost consist of the average cost per patient of in and out clinics.

† Due to lack of data specific to obstetric surgery, administration, drug and medical equipment and labor cost of hysterectomy an average cost of a surgery case at the department of gyneco-obstetrics was used.

§ Hospitalization cost consists of the average cost of hospitalization per day at the department of gyneco-obstetric. We assumed that a patient was hospitalized for seven days

≠ Total cost did not include the cost of follow-up for precancerous lesion because, according to expert, patients are lost at follow-up.

§§ Cost is unit price per person, 2013 International dollars exchange using PPP exchange rate (1 I$ = 2,694.27 kips) (29) and the price of cancer treatment was adjusted from 2005 to 2014 using consumer price index (77.33 in 2005 and 122.52 in 2014) (41)

2. Result

Figure 2: model calibration to age-specific demographic distribution in female and male of Vientiane capital population

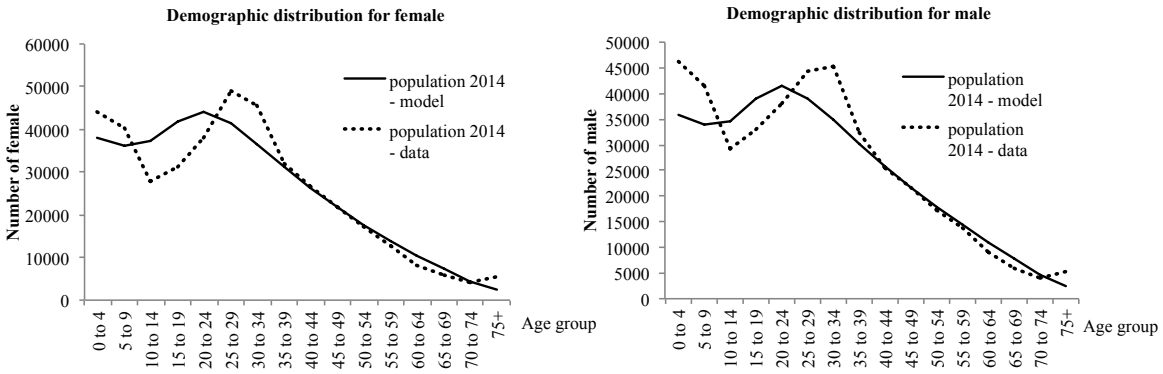


Figure 2: model calibration to age-specific demographic distribution in female and male of Vientiane capital population

Figure 3: Reduction of the infection rate for HPV type 16 over 100 years simulation

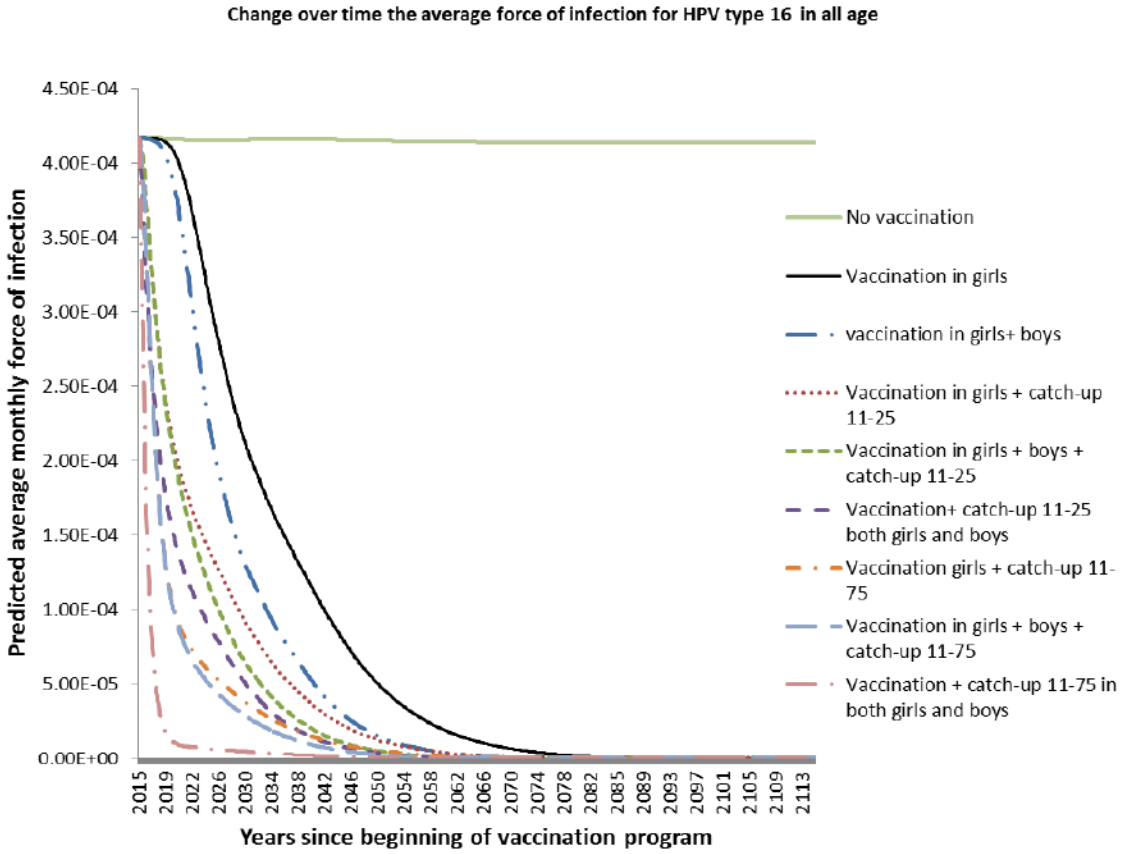


Figure 4: Reduction of the prevalence of HPV type 16 and 18 during 100 years simulation

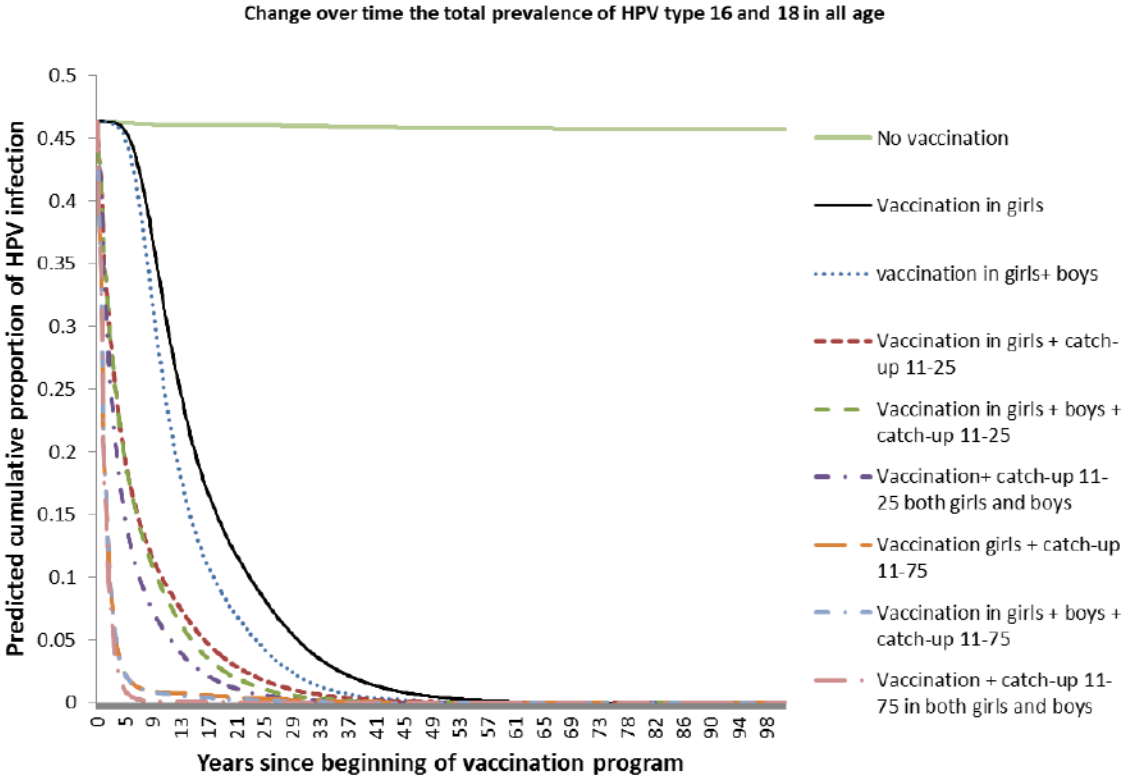


Table 10: the cost-effectiveness of HPV vaccination against cervical cancer due to all high-risk HPV

Number	Options	Total cost per 1000 women	Cancer due to other high-risk HPV per 1000 women	Cancer increase (%)	DALY averted per 1000 women	ICER (DALY)
1.	No vaccination with current screening	4716	1.36	Ref	Ref	-
2.	10 years old girls	21824	1.40	2.2	30.7	557
3.	10 years old girls+catch-up girls aged 11-25 years old	28033	1.39	2.2	34.7	1547
4.	10 years old girls+boys	38256	1.39	2.0	32.2	D
5.	10 years old girls+catch-up girls aged 11-75 years old	39285	1.39	2.0	36.7	5774
6.	10 years old girls+boys+catch-up girls aged 11-25 years old	44489	1.39	2.0	35.0	D
7.	10 years old girls+boys+catch-up girls and boys aged 11-25 years old	50436	1.39	1.9	35.5	D
8.	10 years old girls+boys+catch-up girls aged 11-75 years old	55746	1.39	1.9	36.7	D

9.	10 years old girls+boys+catch-up girls and boys aged 11-75 years old	72949	1.39	1.8	36.9	168320

Note: The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. The D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

Table 11: uni-variate sensitivity analyses of parameters influencing the incremental cost per DALY averted by vaccination strategies

Parameters			Baseline	Girl vaccination only	Girl + catch-up girls aged up to 25 years old	Girl and boy	Girl + catch-up girls aged up to 75 years old	Girl and boy + catch-up girls aged up to 25 years old	Girl and boy + catch-up girls and boys aged up to 25 years old	Girl and boy + catch-up girls aged up to 75 years old	Girl and boy + catch-up girls and boys aged up to 75 years old
10 consecutive cohorts vaccination		Total cost	4497	7676	10796	13810	16988	19951	25047	28236	45437
		DALY averted	Ref	18.4	25.6	32.1	33.6	34.4	36.0	36.4	36.9
		ICER	-	173	428	467	2112	3530	3359	7443	32586
Time horizon (years)	30	Total cost	6353	29627	46483	51684	68567	76576	76869	98960	145371
		DALY averted	Ref	2.5	6.9	3.6	7.2	7.7	10.7	10.7	10.9
		ICER	-	ED	ED	D	ED	ED	6608	ED	306225
	50	Total cost	6482	30695	42922	53778	65065	66048	71887	88200	122050
		DALY averted	Ref	11.5	18.4	13.7	22.0	18.8	19.3	22.1	22.3
		ICER	-	ED	1983	D	6043	D	D	ED	195543
Initial age (years)	11	Total cost	4497	21393	27237	37636	38489	43504	49100	54761	71612.9
		DALY averted	Ref	31.4	35.1	32.9	37.0	35.3	35.9	37.0	37.2
		ICER	-	537	1614	D	5791	D	D	ED	16935
	12	Total cost	4497	21197	26674	37263	37925	42762	48004	54020	70517
		DALY averted	Ref	31.8	35.0	33.2	37.0	35.3	35.8	37.0	37.2
		ICER	-	526	1682	D	5738	D	D	ED	16733
	13	Total cost	4497	21197	26297	37092	37546	42216	47099	53472	69611
		DALY	Ref	31.8	34.9	33.3	37.0	35.3	35.8	37.0	37.2

		averted									
		ICER	-	526	1616	D	5526	D	D	ED	16347
Vaccination coverage (%)	30	Total cost	4497	7470	8544	10440	10553	11540	12606	13563	16692
		DALY averted	Ref	25.8	30.4	29.7	33.4	32.4	33.7	34.5	35.8
		ICER	-	115	234	D	676	D	ED	ED	2558
	50	Total cost	4497	11683	14290	18699	19073	21334	23868	26125	33485
		DALY averted	Ref	29.5	33.8	31.7	36.1	34.5	35.3	36.3	36.9
		ICER	-	244	603	D	2086	D	D	ED	18015
	80	Total cost	4497	34017	44731	62210	64065	72946	83154	92285	121781
		DALY averted	Ref	31.6	35.4	32.9	37.2	35.5	36.0	37.2	37.3
		ICER	-	934	2848	D	10590	D	D	ED	577160
Vaccine cost per dose (I$)	30	Total cost	4497	52844	70372	98838	101940	116389	133044	147962	196064
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.3	35.9	37.0	37.2
		ICER	-	1555	4403	D	16384	D	D	D	520626
	50	Total cost	4497	77350	103756	146529	151258	172959	198012	220465	292802
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.3	35.9	37.0	37.2
		ICER	-	2343	6633	D	24654	D	D	D	782919
	100	Total cost	4497	138614	187215	265759	274553	314382	360431	401722	534647
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.3	35.9	37.0	37.2
		ICER	-	4312	12208	D	45329	D	D	D	1438653
Incidence of cervical cancer	- 20	Total cost	4429	21559	27777	37994	39036	44234	50182	55498	72700
		DALY averted	Ref	28.1	31.7	29.4	33.4	31.9	32.4	33.4	33.6
		ICER	-	609	1746	D	6612	D	D	D	206258

(%)	+40	Total cost	4745	21746	33943	38163	45172	50397	53363	61631	78839
		DALY averted	Ref	41.9	47.7	44.0	50.3	48.0	48.3	50.4	50.5
		ICER	-	406	2095	D	4306	D	D	D	180744
Duration of natural immunity (10 years)		Total cost	5011	21883	28016	38286	39214	44465	47426	55673	72886
		DALY averted	Ref	55.5	62.8	58.3	66.5	63.3	63.9	66.6	66.8
		ICER	-	304	835	D	3043	D	D	ED	99721
Duration of vaccine protection (10 years)		Total cost	4497	21695	27899	38089	39135	44319	50256	55570	72754
		DALY averted	Ref	22.8	28.3	28.6	32.0	32.1	33.3	34.5	35.6
		ICER	-	754	1131	ED	3037	ED	ED	6574	15622
Disability weight for local cancer treatment (0.411)		Total cost	4497	21599	27807	38030	39059	44263	50210	55520	72723
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.4	35.9	37.1	37.2
		ICER	-	549	1558	D	5835	D	D	ED	168320
30% efficacy		Total cost	4497	21643	27856	38061	39102	44300	50239	55557	72743
		DALY averted	Ref	28.3	32.8	31.0	35.3	33.8	34.8	35.7	36.5
		ICER	-	605	1393	D	4411	D	D	ED	28034
Cost of cancer treatment	Lower bound	Total cost	4218	21450	27699	37895	38979	44158	50112	55440	72645
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.3	35.9	37.0	37.2
		ICER	Ref	554	1570	D	5854	D	D	D	186215
	Upper bound	Total cost	5053	21898	28023	38302	39220	44474	50406	55681	72880
		DALY averted	Ref	31.1	35.1	32.6	37.0	35.3	35.9	37.0	37.2
		ICER	Ref	542	1538	D	5812	D	D	D	186183
Discount rate (%)	0	Total cost	2146	10134	16392	17744	24012	26982	27670	35291	52496
		DALY	Ref	25	28.2	26.2	28.4	28.7	29.8	29.9	30

	averted									
	ICER	-	319	1947	D	ED	ED	7141	ED	171545
5	Total cost	4497	21599	27807	38030	39059	44263	47230	55520	72723
	DALY averted	Ref	46.3	52.2	48.4	54.9	52.5	52.9	55.0	55.2
	ICER	-	369	1058	D	4097	D	D	ED	124047

Note:
The total cost and DALY averted are per 100 women.
ICER, the incremental cost of effectiveness ratio expressed as DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. The D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

Table 12: the cost-effectiveness of vaccination strategies for Vientiane province (smaller size of population)

Number	Options	Total cost per 1000 women	Cancer averted per 1000 women	Cancer averted per 1000 women	DALY averted per 1000 women	CER (cancer averted)	CER (DALY averted)	ICER (cancer averted)	ICER (DALY averted)
1.	No vaccination with current screening	2203	Ref	Ref	Ref	-	-	-	-
2.	10 years old girls	15403	1.7	86.8	19.3	9151	4257	7842	685
3.	10 years old girls+catch-up girls aged 11-25 years old	17848	1.8	92.4	20.7	9957	8104	22381	1727
4.	10 years old girls+boys	21436	1.8	95.0	21.3	11635	13398	71811	5957
5.	10 years old girls+catch-up girls aged 11-75 years old	28017	1.7	89.1	19.8	16218	9153	D	D
6.	10 years old girls+boys+catch-up girls aged 11-25 years old	30470	1.8	92.8	20.8	16928	14450	D	D
7.	10 years old girls+boys+catch-up girls and boys aged 11-25 years old	32811	1.8	93.5	21.0	18087	16938	D	D
8.	10 years old girls+boys+catch-up girls aged 11-75 years old	34060	1.8	95.1	21.3	18472	21566	D	D

9.	10 years old girls+boys+catch-up girls and boys aged 11-75 years old	40003	1.8	95.3	21.4	21650	26166	3495444	117542

Note: The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness. The D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

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Appendix 2: Methodology and additional findings for combined HPV vaccination screening model (Chapter 4)

Appendix 2: Methodology and additional findings for combined HPV vaccination screening model (Chapter 4)

1. Methodology

1.1 Simulation overview

Using a mathematical approach, a compartmental dynamic model of the natural history of HPV infection and cervical cancer was constructed and calibrated to reflect the Vientiane capital population in terms of age and sex distribution (1), as well as the age-specific incidence and mortality rates related to cervical cancer in 2014 (2). The model consisted of a dynamic cohort population categorized in one-year age groups. The model considered the occurrence of HPV infection and its progression to precancerous lesions and invasive cervical cancer (3), according to the probabilities of administrating a context-appropriate treatment for cervical precancerous and invasive cancers. Events defined in the model (such as Cervical Intraepithelial Neoplasia (CIN), cervical cancer, death) were probabilistically monthly imputed to the virtual population over the time course of the simulation. The parameters were retrieved from the literature.

The options included a girl vaccination program and the combination of screening strategies with/without the girl vaccination program. Screening techniques considered included VIA, rapid HPV DNA testing, combined VIA and conventional cytology testing and cytology-based screening. The virtual population was processed over a period of 100 years. This period of time was used to capture the long-term impact of HPV vaccination (4). Incremental cost/effectiveness ratios were computed on the simulation results. Sensitivity analyses were performed on a specific set of parameters expected to be the most influential on the outcomes (5).

1.2 Scenarios

The scenarios consisted of 1) a baseline (no vaccination), 2) a prevention programs consisting of a 10 years old girl HPV vaccination program and/or various pre-cancer screening options. Assumptions on screening strategies were based on feasibility considerations relevant to the Lao context. Currently, according to Lao experts, only cytology, visual inspection with acetic acid (VIA) and rapid HPV DNA testing are available in Vientiane Capital. The following prevention programs were therefore considered:

1. 10 years old girl vaccination
2. 10 years old girl vaccination and VIA screening
3. 10 years old girl vaccination and cytology screening

4. 10 years old girl vaccination and a combined testing of VIA and cytology screening
5. 10 years old girl vaccination and rapid HPV DNA testing
6. VIA screening alone
7. Cytology-based screening alone, either conventional and liquid-based cytology
8. Combination between VIA and cytology screening
9. Rapid HPV DNA testing

In each prevention scenario, screening programs with different initial ages of screening were considered, leading to the following categories of screening target populations:

a. 20-65 years old
b. 25-65 years old
c. 30-65 years old

Moreover, each screening option was evaluated according to the following time-frame, which refers to the current practice in Lao PDR, WHO recommendations and the current practice in some developed countries, respectively.

1) Yearly intervals
2) Three years intervals
3) Five years intervals.

Simulations were performed on various foreseeable combinations of screening options, taking into account the availability of treatments for precancerous lesions in the country (figure 2).

Table 1: Precancerous lesions screening options according to initiation age and frequency

Primary prevention	Secondary prevention (screening option)	Number of visits	Initiation age	Frequency
10 years old girl HPV vaccination	Visual Inspection with acetic acid (VIA)	1	20 years old 25years old 30 years old (VIA testing ends when women are 45 years old)	Yearly interval Three years interval Five years interval
	Cytology testing	3		
	Combination between VIA and Cytology testing	3		
	Rapid HPV DNA testing	2		

1.3 Model structure

Inspired by previous economic models of HPV vaccination (6-8), a dynamic transmission and compartment population-based model was created to reflect the expected effect of HPV vaccination programs, both in females and males. Susceptible girls and boys were considered to be at risk of being infected based on estimated infection rates between partners. For both males and females, the model considered if the HPV genotype was a 16, 18 or other high-risk types, or if it was of low-risk types.

The model considers that among infected women, some lesions regress thanks to a natural immunity against a specific HPV type, but these women remain susceptible to be infected with other HPV types. The infection might also persist and might then progress to Cervical Intraepithelial Neoplasia (low-grade CIN "CIN 1" or high-grade CIN "CIN 2/3", according to the Richard's modified classification) (9). A low-grade CIN might regress to either immunity state, or infection state (10-13) or progress to a high-grade CIN. In case of high-grade CIN, the lesion might regress to immunity state, infection state or low-grade CIN or might progress and become an invasive cervical cancer (local, regional and distant progression) (14, 15). Additionally, women may die of another cause than cervical cancer. Women diagnosed with precancerous lesions will be treated by either Loop Electrosurgical Excision procedure (LEEP) or hysterectomy except in case of VIA screening in which positive cases are treated by cryotherapy. Women with invasive cervical cancer might be symptomatically detected. Diagnosed invasive cervical cancer is treated accordingly, with a defined probability of recovery or treatment failure or death due to treatment complications (figure 1).
In males, the infection might persist or regress conferring them a natural immunity against a defined HPV genotype. The consequences of HPV infection in males, such as warts, were not included in the model because we were only interested in the impact of HPV vaccination on cervical cancer in women. Males could die from general causes (figure 1).

The model assumed that vaccinated people who entered into the vaccine protection compartment remained susceptible for HPV genotypes uncovered by the vaccine; consequently, they had a certain probability of being infected with HPV and getting an invasive cancer. Vaccinated people were susceptible to the 16/18 types HPV infection depending on assumptions done regarding the wane of vaccine immunity (figure 1).

Screening model, a high-grade CIN detected through a cytology-based and rapid HPV DNA testing, led to a treatment with LEEP or a hysterectomy, and to a stage-specific treatment for invasive cervical cancer. In case of VIA screening, a see-and-treat approach was considered, with true positives and false negatives high-grade CIN undergoing a treatment with cryotherapy. Treated cases regressed to healthy state with a specific-type natural immunity. Unscreened or undetected cases or treatment failures follow the natural history of HPV infection and cervical cancer (figure 2).

The model was validated by Lao experts in order to ensure that it realistically reflects the possibilities of routine screening and treating patients in the Vientiane capital context.

1.4 Parameters

The infection rate depended on the age-specific number of new sexual partners per month, the HPV genotype-specific transmissibility and the age-specific HPV prevalence in the opposite sex. To simplify the model, we considered all members of the population as heterosexuals. With each sexual partner, the HPV infection is probabilistically transmitted, depending on genotype-specific transmission probabilities and age-specific HPV prevalence in the opposite-sex population. A sexual relationship matrix group was constructed. The matrix consists of the monthly age-specific probability of having new sexual partners. Each age group has a probability of having a sexual intercourse with someone of the same or a different age group of 0.6 and 0.4 respectively, based on a previous national survey (16). The initial age of sexual intercourse is 15 years old or more in both girls and boys, according to the last survey performed in Vientiane capital city (17). Due to unknown parameters of the number of new sexual partners in Lao PDR, data from the UK (7) were used and calibrated to the age-specific incidence of cervical cancer in Lao PDR. The transmissibility of each HPV type was calibrated to take into account the proportion of genotype specific-HPV prevalence and the proportion of cervical cancers due to HPV type 16/18 (see table 3). The proportion of HPV types 16 and 18 among all-type HPV infections was, based on Thai data (18), assumed to be 45-50%. These infections may reasonably be assumed to be responsible for approximately 75% of the total incidence of invasive cervical cancer (19).

Monthly transition probabilities from one lesion state to another and regression rates were taken from Kim et al (20). For instance, the age-specific monthly probability that a HPV type 16 infection evolves to a low-grade CIN is 0.0047-0.0085, while the rate of transition from low to high-grade

CIN is 0.0001-0.0039. The annual rate of detecting an invasive cervical cancer through symptoms is 0.19, 0.6 and 0.9 for local, regional and distant cervical cancers, respectively (see table 4).
In the baseline option, the current conventional cervical cytology screening coverage was fixed at 5.2% every three years (2). The sensitivity and specificity of the cervical cytology and of colposcopy were retrieved from a systematic review and meta-analysis (21). A true positive result of cervical cytology was defined as a high-grade CIN. We assumed that 55% of them would receive the whole treatment regimen, considering 15% loss to follow-up over the three expected visits (for screening, diagnostic test and treatment). The proportion of treatment with LEEP or cryotherapy was based on experts' opinions. The rate of remission was retrieved from the literature (22, 23). The experts' panel consisted of two gynecologists with a practice focused on cervical cancer in Lao PDR, Dr. Phongsavan K. and Dr. Marsden E.D.

The proportion of women receiving cancer treatment among diagnosed patients and the stage-specific five-year survival rates due to cancer treatment complications were calibrated, based on the estimated mortality rates related to cervical cancer according to Globocan, 2012 (table 4) (2).
The sensitivity and specificity of the conventional cervical cytology to detect a high-grade CIN or worse were considered to be 59% (range: 29%-82%) and 94% (range: 88%-99%), respectively (21). Those for liquid-based cervical cytology were 88% (70-94%) and 88% (65-97), respectively (24). Those of VIA were 73.2% (range: 66.5–80%) and 86.7% (range: 82.9–90.4%), respectively (25). Those of the combined VIA and conventional cervical cytology testing were 87% (0.83-90%) and 79% (63-89%), respectively (26). Those of the Rapid HPV DNA testing were 81.5 % (range: 53.1%- 89.5%) and 91.6 % (range: 81.8%-97.4%), respectively (27). The model considers that colposcopy with direct biopsy is used to confirm a positive result from either a cervical cytology test or a rapid HPV DNA testing. The sensitivity and specificity of colposcopy were considered to be 96% (64 –99%) and 48% (30 –93%), respectively. Biopsy was assumed to have a sensitivity and a specificity of 100%. Treatment is provided in two cases: confirmed high-grade CINs and a positive result at the VIA screening test (table 6).

Precancerous lesions and cancer stage treatment

The average rate of remission following cryotherapy was considered to be 94% (85-95%) and 86% (83-89%) for low and high-grade CINs, respectively. Success rates for LEEP and hysterectomy were supposed to be 96.7% (90-98%) and 99% (90-100%), respectively (23). The proportion of positive women treated with LEEP or hysterectomy depends on their age. For women aged 35 years or less, it was considered that 80% (50-100%) would be treated with LEEP and 20% (0-50%) with a hysterectomy. For those older than 35 year old, the numbers were reversed: 20% (0-50%) with

LEEP and 80% (50-100%) with hysterectomy. The remission rate of stage-specific invasive cervical cancer was calibrated, based on the estimate mortality related to cervical cancer in Lao PDR (2) (table 6).

Compliance

Patients' compliance was considered at two levels: consent to participate in a screening program and compliance with the health care provider's recommendations. In all options, base case analyses are performed with a screening coverage assumed to be 50% (range: 10%-80%). Loss to follow-up was assumed to be 15% per visit (range: 0%-50%). Based on a previous study on VIA see-and-treat approach conducted in Lao PDR (28), we assumed that all women with a positive screening result accepted to be treated, and that no women underwent a follow-up visit after a precancerous lesion treatment (table 7).

The coverage of HPV vaccination both in girls and boys was assumed to be about 70% (30-80%), with 100% (50-100%) effectiveness against HPV type 16 and 18 and a lifelong protection (10 years to lifelong).

1.5 Model calibration

The population was stratified by gender and age. The model is in the form of a realistic age structured (RAS) model. The equations were numerically solved in Berkeley Madonna version 8.3.18 (29). The model was calibrated using maximum likelihood for the age-specific distribution of the 2014-estimated incidence of cervical cancer and mortality related to cervical cancer data in Lao PDR. Thai data on the prevalence of HPV infection and the prevalence of low-grade and high-grade CIN were used to guide their age-specific distributions. The demographic distribution followed an exponential distribution using UN data to predict the changing birth and death rates over time for Lao PDR (30). To calibrate the age-specific incidence of cervical cancer, we assumed that only the infection rate was different from the Kim et al. model (20). We consequently calculated an infection rate multiplier to calibrate the incidence of cervical cancer according to the Globocan estimates and used under and over estimates in sensitivity analyses (table 5).

The calibration of parameters for the age and stage-specific mortality rates of cervical cancer was conducted by varying the proportion of women receiving treatment for local, regional and distant cancer, the monthly death rates due to treatment complications and the age and stage-specific remission rates. The true proportion of women receiving a treatment in Lao PDR is unknown; we therefore estimated its value according to the experts' opinion. The best guess of the proportion of

women receiving a treatment for a local, regional or distant cancer was 100%, 80% and 70%, respectively.

1.6 Costs

One should stress the fact that no economic evaluation of health interventions has ever been done in Lao PDR. This section refers therefore to a component that required some approximations, as the structure supporting the health care system has not been built to provide the required information for conducting economic evaluations. We recognized that this is a limit, but also considered that undertaking this component would open doors to the realization of further studies on the value of money spent in the Lao PDR health care sector.

The perspective considered was essentially the perspective of the public health care system. Only direct medical costs and the programmatic cost of vaccination implementation were considered.

Items

Items were related to the consumption of medical resources for the diagnosis and treatment of cervical cancer and HPV (screening facilities, laboratory, diagnostic tests, hospitalizations, and treatment), as well as the vaccination cost (programmatic cost). A preliminary list of items was built with the help of gynecologists and pathologists working in Lao PDR. These items consisted of:

1. Screening related items: include support items, medical administration, and labor costs. The ingredients of support items consisted of the cost of electricity, water and transportation supplies and other office materials and staffs. Medical administration included training support and medical equipment. Labor cost included the time spent by the gynecologist and the nurse for screening activities. The cytology alone or combined with VIA options requires three visits. The first visit is for screening, the second for receiving the result and making an appointment for positive case. The third is for a colposcopy with direct biopsy. Meanwhile, rapid HPV DNA testing requires two visits. The first is for primary screening, the second for a colposcopy with direct biopsy in case of a positive result. VIA requires only one "see-and-treat approach" visit.
2. Laboratory related items: items were listed according to a pathologist's advice. Cervical cytology and histology exams included administration, consumable and labor costs. Consumable items for cervical cytology included cover glass, malinol, Gill hemato, OG-6, EA-50, mask, xytene, etanol, and slide. For histology exams, the ingredients included formaline, hematocyline, eosine, paraphine, 167assette, cyline, obsolute, acetone and malinone. In the Vientiane Capital, four pathology technicians work together and can prepare a total of 50 smear

slides for conventional cervical cytology per day. They can also in total prepare 10 histology slides per day. A pathologist needs 20 to 35 minutes for a cytology and histology examination. Other materials used for a cytology examination could not be identified due to lack of information. Meanwhile, the laboratory cost of rapid HPV DNA testing included administration and material costs (table 9).

3. Medication and surgery: the items of precancerous lesions treatment included support activities, drugs, and equipment and labor costs. Cryotherapy is performed in outpatient clinics; LEEP requires one day of hospitalization and simple hysterectomy 7-days.
4. Vaccination included the vaccine cost and programmatic cost, which included micro-planning, training, social mobilization, procurement, logistics, service delivery, supervision and waste management.
5. Programmatic cost of screening included quality control, training, administration and recruitment costs.

Quantification

There are no national guidelines for cervical cancer control in Lao PDR. Quantities were therefore estimated based on experts' opinion.

1. Time spent for screening is supposed to be about 20 minutes for VIA and cervical cytology. Meanwhile, time spent for cervical cytology and histology interpretations is supposed to be about 20 and 35 minutes per case, respectively.
2. The number of visits considered is one for VIA screening and three for other screening strategies.
3. Only consumable items of cytology and histology laboratory were considered. In the Vientiane Capital, four pathology technicians work together and spent a day to prepare 50 to 80 smear lames for conventional and liquid-based cervical cytology, respectively. They also prepare in total 10 histology lames per day. A pathologist needs 20 to 35 minutes per cytology and histology case, respectively.
4. Other quantities were approximated, for instance: hospitalization, surgery

Item pricing

Unit prices are reported in the value of 2013 international dollars, using purchasing power parity (PPP). According to WHO, a purchasing power parity (PPP) exchange rate is the number of units of a country currency required to buy the same amounts of goods and services in the domestic market as what can be bought with one U.S. dollar in the United States. International dollars are, therefore, a hypothetical currency allowing comparisons and integration of costs between countries (31).

Price per service was calculated by multiplying the cost per unit and the amount of units per service. Unit prices were as often as possible based on data coming from Lao PDR. A Lao hospital unit price list is available. Its numbers have been estimated through a costing survey performed at the departments of gyneco-obstretics of two reference hospitals in the Capital of Vientiane: Mahosot and Setthathirath hospitals in 2013-2014 (personal communication with a head of department of health insurance, Ministry of health, Lao PDR). The survey applied a step down allocation method to estimate the average cost per visit and per hospitalization. Capital costs were not considered due to the difficulty to make an estimation of their real value. Unit prices for missing items were essentially retrieved from the literature. The realism of the valuing procedure was validated by the Lao experts' committee (table 8).

The price of administration and labor cost in the screening facility are 14.48 I$ and 3.39 I$, respectively. The price of rapid HPV DNA testing is 14.85 I$ per test, based on a previous study performed in rural China (32). We expected this cost to be quite similar to the cost in the Lao context based on assumptions made in the Chinese study for mass screening. We used for the cost of the LEEP the average cost of one-day hospitalization in a gyneco-obstetric ward. The cost of a simple hysterectomy was considered to be the same as the average cost of a surgical operation. The complication of cryotherapy, LEEP and hysterectomy are rare. For that reason, they were not considered (table 8).

The cost of invasive cervical cancer treatment was retrieved from a study done in 72-GAVI eligible countries (33). It includes the costs of treatment for localized, regional and distant cervical cancers (table 10).

Programmatic cost of screening

The programmatic costs were based on the literature. The cost of each item was estimated from a proportion of the direct medical cost of vaccination, as calculated in previous studies in developing countries (32, 34). Programmatic cost of VIA screening strategy was estimated at 48% of the total direct medical costs, 23% for quality control and training and 25% for administration and recruitment. The same method of calculation was attributed to a cervical cytology or a combined testing with a VIA program. Programmatic costs for HPV DNA testing was estimated at 35% of the total direct cost, 10% (32) and 25% for quality control and training and administration and recruitment, respectively.

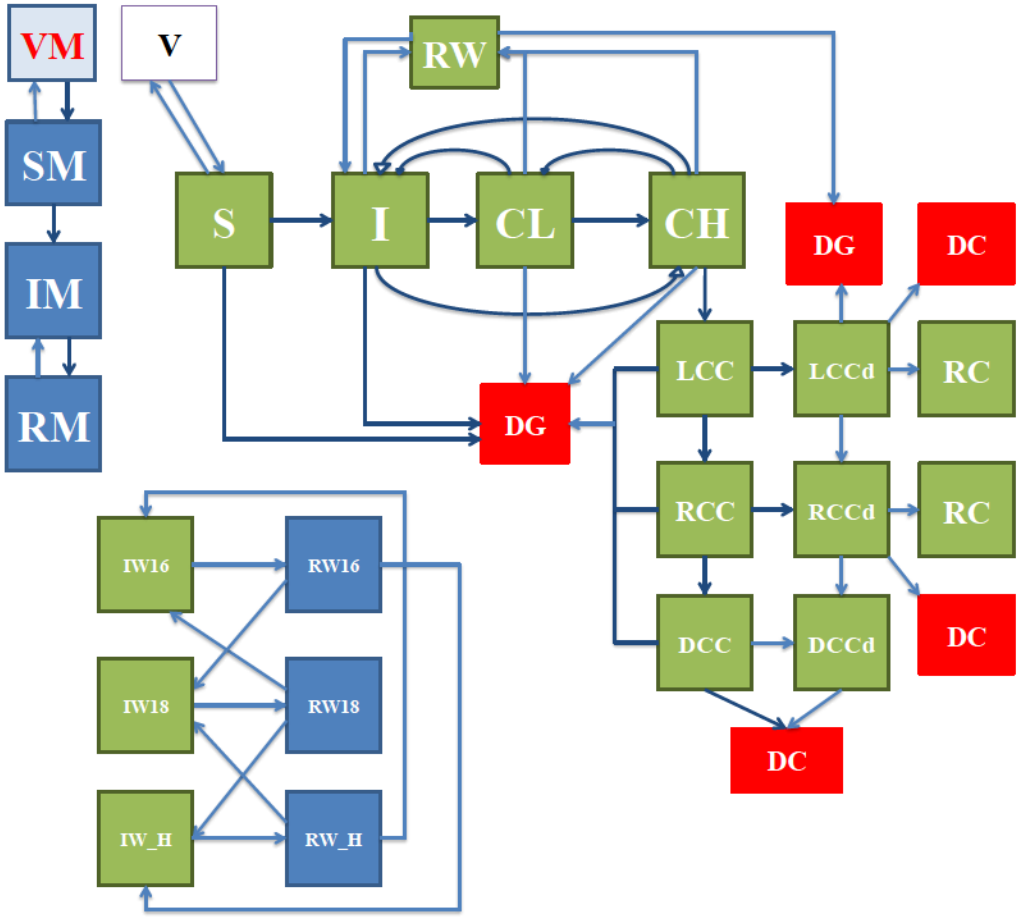
Vaccination cost

The cost of delivering HPV vaccines consisted of the price of the vaccine and the programmatic cost of vaccination delivery. The programmatic cost of 3-dose HPV vaccine per girl was retrieved from a pilot project on HPV vaccination in 5th grade girls in Vientiane capital in 2014. The vaccine cost per dose was based on the purchasing cost from the Global Alliance for Vaccines and Immunization (GAVI) (4.5 US dollars per dose) (35).

1.7 Model Validation process

The model was able to reproduce the 2014 Vientiane Capital expected values regarding demographic data, both for the female and the male populations. However the number of individuals was high for 10 to 25 year old individuals compared to expected values, while it was low for 25-35 year old individuals. The model reproduced results that were consistent with the incidence of cervical cancer and its mortality due to any high-risk HPV type according to the estimates of Globocan 2012. The proportion of cervical cancers related to HPV type 16 and 18 was about 75%. The calibrated infection rate was not different to that reported in the literature (figure 3).

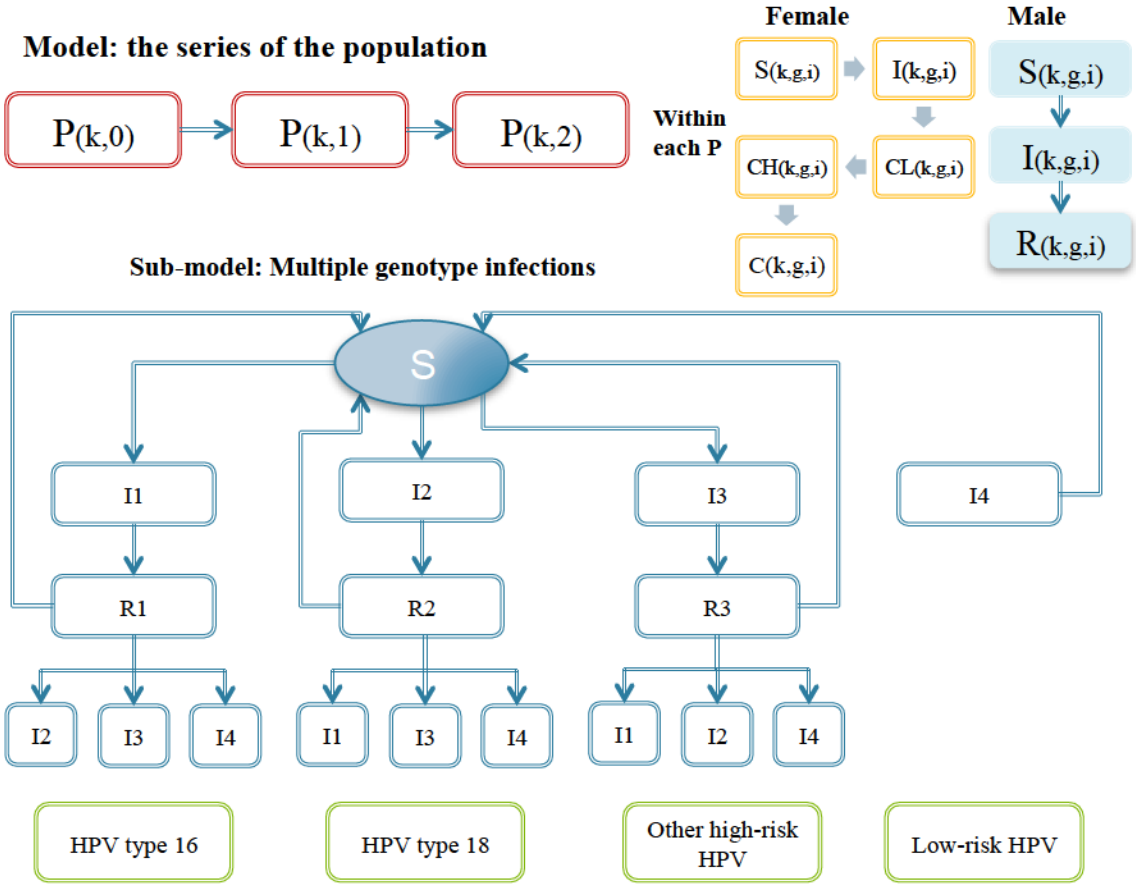
Figure 1 : Model structure for natural history of Human Papillomavirus infection and cervical cancer



Overview of the ordinary differential equations

State transition equations

Female model (1)



$$S'_{k,0} = \mu P + \epsilon S_{(k-1),0} + \epsilon S_{(k-1),0} + \omega_k RW_{k,g,0} - [\lambda_{k,g} + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]S_{k,0}$$

$S'_{k,1} = \epsilon S_{(k-1),1} + [(\nu_k + \rho_k)\tau_k]S_{k,0} + \omega_k RW_{k,g,1} - (\lambda_{k,g} + \varphi + \theta_k + \epsilon)S_{k,1}$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$$S'_{k,2} = \epsilon S_{(k-1),1} + \varphi S_{k,g,1} + \omega_k RW_{k,g,2} - (\lambda_{k,g} + \theta_k + \epsilon)SV_{k,2}$$

$$I'_{k,g,0} = \epsilon I_{(k-1),g,0} + \lambda_{k,g}[S_{k,0} + (1 - x_g)RW_{k,g,0}] + \alpha_{k,g} CL_{k,g,0} + \psi_{k,g} CH_{k,g,0} - [\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + (\nu_k + \rho_k)\tau_k + \theta_k + \epsilon]I_{k,g,0}$$

$$I'_{k,g,1} = \epsilon I_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]I_{k,g,0} + \lambda_{k,g}[S_{k,1} + (1 - x_g)RW_{k,g,1}] + \alpha_{k,g} CL_{k,g,1} + \psi_{k,g} CH_{k,g,1} - (\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + \varphi + \theta_k + \epsilon)I_{k,g,1}$$

$$I'_{k,g,2} = \epsilon I_{(k-1),g,2} + \varphi I_{k,g,1} + \lambda_{k,g}[S_{k,2} + (1 - x_g)RW_{k,g,2}] + \alpha_{k,g} CL_{k,g,2} + \psi_{k,g} CH_{k,g,2} - (\gamma_{k,g} + \eta_{k,g} + \partial_{k,g} + \theta_k + \epsilon)I_{k,g,2}$$

$$CL'_{k,g,0} = \epsilon CL_{(k-1),g,0} + \eta_{k,g} I_{k,g,0} + \varpi_{k,g} CH_{k,g,0} + (1 - \hat{e}_k)TCL_{k,g,0} - [\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + (\nu_k + \rho_k)\tau_k + æ_k + \theta_k + \epsilon]CL_{k,g,0}$$

$$CL'_{k,g,1} = \epsilon CL_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]CL_{k,g,0} + \eta_{k,g}I_{k,g,1} + \varpi_{k,g}CH_{k,g,1} + (1 - \hat{e}_k)TCL_{k,g,1} - (\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + æ_k + \varphi + \theta_k + \epsilon)CL_{k,g,1}$$

$$CL'_{k,g,2} = \epsilon CL_{(k-1),g,2} + \varphi CL_{k,g,1} + \eta_{k,g}I_{k,g,2} + \varpi_{k,g}CH_{k,g,2} + (1 - \hat{e}_k)TCL_{k,g,2} - (\pi_{k,g} + \alpha_{k,g} + \delta_{k,g} + æ_k + \theta_k + \epsilon)CL_{k,g,2}$$

$$CH'_{k,g,0} = \epsilon CH_{(k-1),g,0} + \partial_{k,g}I_{k,g,0} + \pi_{k,g}CL_{k,g,0} + (1 - \varepsilon_k)TCH_{k,g,0} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + (\nu_k + \rho_k)\tau_k + \phi_k + \theta_k + \epsilon)CH_{k,g,0}$$

$$CH'_{k,g,1} = \epsilon CH_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]CH_{k,g,0} + \partial_{k,g}I_{k,g,i} + \pi_{k,g}CL_{k,g,i} + (1 - \varepsilon_k)TCH_{k,g,i} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + \phi_k + \varphi + \theta_k + \epsilon)CH_{k,g,i}$$

$$CH'_{k,g,2} = \epsilon CH_{(k-1),g,2} + \varphi CH_{k,g,1} + \partial_{k,g}I_{k,g,2} + 2 + (1 - \varepsilon_k)TCH_{k,g,2} - (\mathcal{F}_{k,g} + \beta_{k,g} + \psi_{k,g} + \varpi_{k,g} + \phi_k + \theta_k + \epsilon)CH_{k,g,2}$$

$$RW'_{k,g,0} = \epsilon RW_{(k-1),g,0} + \gamma_{k,g}I_{k,g,i} + \delta_{k,g}CL_{k,g,i} + \beta_{k,g}CH_{k,g,i} + \varepsilon_k TCH_{k,g,i} + \hat{e}_k TCL_{k,g,0} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]RW_{k,g,0}$$

$$RW'_{k,g,1} = \epsilon RW_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]RW_{k,g,0} + \gamma_{k,g}I_{k,g,1} + \delta_{k,g}CL_{k,g,1} + \beta_{k,g}CH_{k,g,1} + \varepsilon_k TCH_{k,g,1} + \hat{e}_k TCL_{k,g,1} - (1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \varphi + \epsilon]RW_{k,g,1}$$

$$RW'_{k,g,2} = \epsilon RW_{(k-1),g,2} + \varphi RW_{k,g,1} + \gamma_{k,g}I_{k,g,2} + \delta_{k,g}CL_{k,g,2} + \beta_{k,g}CH_{k,g,2} + \varepsilon_k TCH_{k,g,2} + \hat{e}_k TCL_{k,g,2} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \epsilon]RW_{k,g,2}$$

$$\nu_k = \frac{\epsilon C_k}{1 - C_k}$$

$$\rho_k = \frac{\epsilon COV_k}{1 - COV_k}$$

Invasive cervical cancer model (2)

$$LCC'_{k,g} = \mathcal{F}_{k,g}CH_{k,g} - \big((\mathfrak{D} + \phi_k)\mathcal{g} + h + \theta_k + \epsilon\big)LCC_{k,g}$$

$$RCC'_k = hLCC_k - \big((\mathbb{Q} + \phi_k)\Omega + \mathcal{H} + \theta_k + \epsilon\big)RCC_k$$

$$DCC'_k = \mathcal{H}RCC_k - \big((\mathcal{L} + \phi_k)\mathcal{A} + \curlywedge_k + \theta_k + \epsilon\big)DCC_k$$

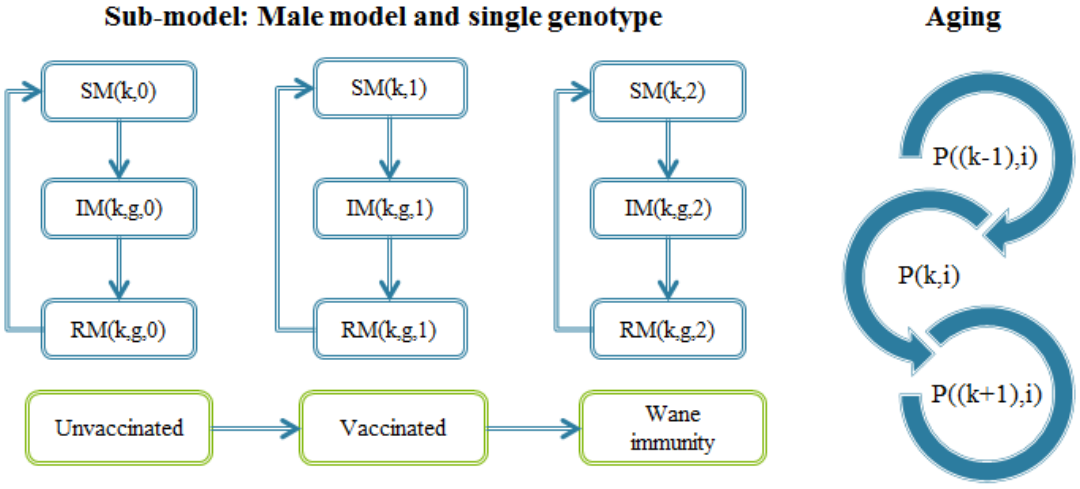
$$LCCd'_{k,g} = (\psi + \phi_k)\mathcal{g}LCC_{k,g} - (h + m_k + \theta_k + \epsilon)LCCd_{k,g}$$

$$RCCd'_k = (\mathbb{Q} + \phi_k)\Omega RCC_k + (1 - \curlyvee_k)hLCCd_k - (\mathcal{H} + \curlywedge_k + \theta_k + \epsilon)RCCd_k$$

$$DCCd'_k = (\mathcal{L} + \phi_k)\mathcal{A}DCC_k + (1 - \mathfrak{y}_k)\mathcal{H}RCCd_k - (\exists_k + \theta_k + \epsilon)DCCd_k$$

$$RC'_k = \curlyvee_k hLCCd_k + \mathfrak{y}_k \mathcal{H}RCCd_k - (\theta_k + \epsilon)RC_k$$

Male model (3)



$$SM'_{k,0} = \mu\sigma P + \epsilon SM_{(k-1),0} + \omega_k RM_{k,g,0} - [\lambda_{k,g} + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]SM_{k,0}$$

$$SM'_{k,1} = \epsilon SM_{(k-1),1} + [(\nu_k + \rho_k)\tau_k]SM_{k,0} + \omega_k RM_{k,g,1} - (\lambda_{k,g} + \theta_k + \varphi + \epsilon)SM_{k,1}$$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$$SM'_{k,2} = \epsilon SM_{(k-1),2} + \varphi SM_{k,1} + \omega_k RM_{k,g,2} - (\lambda_{k,g} + \theta_k + \epsilon)SM_{k,2}$$

$$IM'_{k,g,0} = \epsilon RM_{(k-1),g,0} + \lambda_{k,g}[SM_{k,0} + (1 - x_g)RM_{k,g,0}] - [\gamma_{k,g} + (\nu_k + \rho_k)\tau_k + \theta_k + \epsilon]IM_{k,g,0}$$

$$IM'_{k,g,1} = \epsilon RM_{(k-1),g,1} + [(\nu_k + \rho_k)\tau_k]IM_{k,g,0} + \lambda_{k,g}[SM_{k,1} + (1 - x_g)RM_{k,g,1}] - [\gamma_{k,g} + \varphi + \theta_k + \epsilon]IM_{k,g,1}$$

$$IM'_{k,g,2} = \epsilon RM_{(k-1),g,2} + \varphi IM_{k,g,1} + \lambda_{k,g}[SM_{k,2} + (1 - x_g)RM_{k,g,2}] - [\gamma_{k,g} - (\gamma_{k,g} + \theta_k + \epsilon)]IM_{k,g,2}$$

$$RM'_{k,g,0} = \epsilon RM_{(k-1),g,0} + \gamma_{k,g} IM_{k,g,0} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + (\nu_k + \rho_k)\tau_k + \epsilon]RM_{k,g,0}$$

$RM'_{k,g,1} = \epsilon RM_{(k-1),g,1} + \gamma_{k,g} IM_{k,g,1} + [(\nu_k + \rho_k)\tau_k]RM_{k,0} - ((1 - x_g)\lambda_{k,g} + \omega_k + \varphi + \theta_k + \epsilon)RM_{k,g,1}$ where vaccinated people remains susceptible for other HPV types rather than type 16/18

$RM'_{k,g,2} = \epsilon RM_{(k-1),g,2} + \varphi RM_{k,g,1} + \gamma_{k,g} IM_{k,g,2} - [(1 - x_g)\lambda_{k,g} + \omega_k + \theta_k + \epsilon]RM_{k,g,2}$

Precancerous lesions treatment model (4)

$TCL'_{k,g,0} = \epsilon TCL_{(k-1),g,0} + æ_k CL_{k,g,i} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + (\nu_k + \rho_k)\tau_k + \epsilon]TCL_{k,g,0}$

$TCL'_{k,g,1} = \epsilon TCL_{(k-1),g,1} + æ_k CL_{k,g,i} + [(\nu_k + \rho_k)\tau_k]TCL_{k,g,0} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \varphi + \epsilon]TCL_{k,g,1}$

$TCL'_{k,g,2} = \epsilon TCL_{(k-1),g,2} + \varphi TCL_{k,g,1} + æ_k CL_{k,g,i} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \epsilon]TCL_{k,g,2}$

$TCH'_{k,g,0} = \epsilon TCH_{(k-1),g,0} + \phi_k CH_{k,g,0} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + (\nu_k + \rho_k)\tau_k + \epsilon]TCH_{k,g,0}$
$TCH'_{k,g,1} = \epsilon TCH_{(k-1),g,1} + \phi_k CH_{k,g,1} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \varphi + \epsilon]TCH_{k,g,1}$

$TCH'_{k,g,2} = \epsilon TCH_{(k-1),g,2} + \phi_k CH_{k,g,2} - [(\theta_k + (1 - \varepsilon_k) + \varepsilon_k + \epsilon]TCH_{k,g,2}$

$\phi_k = \varsigma_k \varrho(1 - los\_final)$

Force of infection (5)

$$\lambda_{k,g} = A \sum_{k=1}^{N} Lamda_{k,g}$$

Where A is the adjustment of the total estimated force of infection, and N is the total number of age group and

$Lamda_{k,g} = \frac{\mathcal{T}_g M_k IM_{k,g}}{POPM_k}$ for female

$POPM_k = STT_k + IM_k + RM + VM_k$

And

$Lamda_{k,g} = \frac{\mathcal{T}_g M_k (IM_{k,g} + CL_{k,g} + CH_{k,g})}{POPF_k}$ for male

$POPF_k = S_k + I_k + CL + CH_k + RW + LCC_k + RCC_k + DCCd_k + LCCd_k + RCCd_k + DCCd_k$

Where M is the contact matrix

$M_k = \mathfrak{s}_1 MS_k + \frac{\mathfrak{s}_2 MS_k}{NG-1}$ where MS is new sexual partnership per month; $\mathfrak{s}_1$ is the probability of having a sexual partner within the same age group; $\mathfrak{s}_2$ is the probability of having a sexual partner within a different age group; and NG is the total number of age

Calibration: maximum likelihood estimation (6)

$LI_{k,g} = ICD_{k,g} \ln(IC) - IC$ where ICD is the observed incidence of invasive cervical cancer, and IC is expected incidence of invasive cervical cancer

Table 1: Abbreviation of the model structure variables

Variable	Meaning
$S_{k,..}$	Healthy women (age k, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$I_{k,g,..}$	Infection in females (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$RW_{k,g,..}$	Regression of infection or precancerous lesions (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$CL_{k,g,..}$	Low-grade Cervical Intraepithelial Neoplasia (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$CH_{k,g,..}$	High-grade Cervical Intraepithelial Neoplasia (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$LCC_{k,g}$	Undetected local cancer (age k, genotype g) at time t
RCC_k	Undetected regional cancer (age k) at time t
DCC_k	Undetected distant cancer (age k) at time t
$LCCd_{k,g}$	Detected local cancer (age k, genotype g) at time t
$RCCd_k$	Detected regional cancer (age k) at time t
$DCCd_k$	Detected distant cancer (age k) at time t
RC_k	Recovery from cancer treatment (age k) at time t
P	Total female population
$SM_{k,..}$	Healthy males (age k, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$IM_{k,g,..}$	Infection in males (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$RM_{k,g,..}$	Recovery with natural immunity in males (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$TCL_{k,g,..}$	Women with low-grade CIN receiving treatment (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$TCH_{k,g,..}$	Women with high-grade CIN receiving treatment (age k, genotype g, 0 is unvaccinated, 1 is vaccinated and 2 is waned status) at time t
$POPF_k$	Total female population (age k)
$POPM_k$	Total male population (age k)
IW16	HPV type 16 infected women
IW18	HPV type 18 infected women

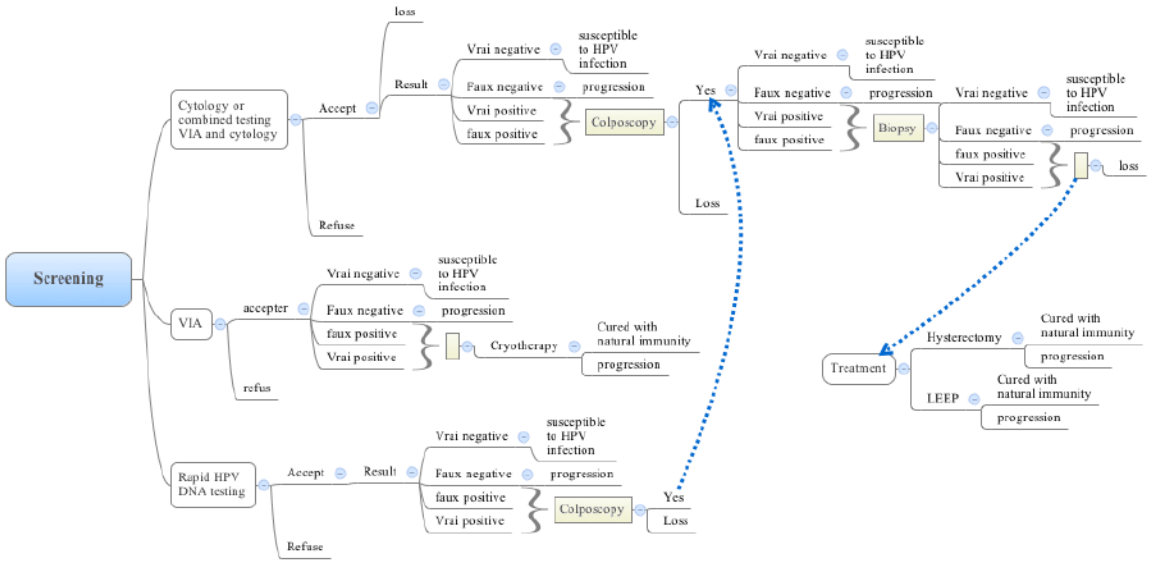
IW_H	Other high-risk HPV infected women
RW16	Clearing up HPV type 16 infection with natural immunity against HPV type 16
RW18	Clearing up HPV type 18 infection with natural immunity against HPV type 18
RW_H	Clearing up other high-risk HPV infection with natural immunity against high-risk HPV
DG	Death due to other causes
DC	Death due to cervical cancer

Table 2: Abbreviation of model structure parameters

Parameters	Meaning
ϵ	Aging rate
μ	Birth rate
ω_k	Waning of HPV natural immunity (age k)
$\psi_{k,g}$	Waning of HPV vaccine-induced immunity (age k, genotype g)
$\gamma_{k,g}$	Regression rate from infection to healthy state (age k, genotype g)
$\delta_{k,g}$	Regression rate from low-grade CIN to healthy state (age k, genotype g)
$\alpha_{k,g}$	Regression rate from low-grade CIN to infection (age k, genotype g)
$\beta_{k,g}$	Regression rate from high-grade CIN to healthy state (age k, genotype g)
ε_k	Cure rate of high-grade Cervical Intraepithelial Neoplasia treatment (age k)
$\hat{e}_k$	Cure rate of low-grade Cervical Intraepithelial Neoplasia treatment (age k)
ν_k	Preadolescent vaccination coverage (age k)
$\lambda_{k,g}$	Infection rate (age k, genotype g)
θ_k	Death rate due to other causes in women (age k)
τ_k	Effectiveness of the vaccine (age k)
ρ_k	Vaccination coverage for catch-up component (age k)
$\eta_{k,g}$	Progression rate from infection to low-grade CIN (age k, genotype g)
$\partial_{k,g}$	Progression rate from infection to high-grade CIN (age k, genotype g)
x_g	Effectiveness of the natural immunity (age k)
$\pi_{k,g}$	Progression rate from low-grade CIN to high-grade CIN (age k, genotype g)
$\mathcal{F}_{k,g}$	Progression rate from high-grade CIN to invasive cervical cancer (age k, genotype g)
h	Progression rate from local cervical cancer to regional cervical cancer
$\mathcal{H}$	Progression rate from regional cervical cancer to distant cervical cancer
$\psi_{k,g}$	Regression rate from high-grade CIN to infection (age k, genotype g)
$\varpi_{k,g}$	Regression rate from high-grade CIN to low-grade CIN (age k, genotype g)
$\mathfrak{D}$	Symptomatic detection rate of local cervical cancer
$\mathbb{Q}$	Symptomatic detection rate of regional cervical cancer
$\mathcal{L}$	Symptomatic detection rate of distant cervical cancer
ϕ_k	Detection rate through screening for high-grade CIN (age k)
$æ_k$	Detection rate through screening for low-grade CIN (age k)
$\mathcal{r}_k$	Cure rate of local cervical cancer (age k)
$\mathfrak{y}_k$	Cure rate of regional cervical cancer (age k)

λ_k	Death rate due to distant cervical cancer in women who do not receive treatment (age k)
$\exists_k$	Death rate due to distant cervical cancer in women who receive treatment (age k)
m_k	Death rate due to local cervical cancer treatment (age k)
n_k	Death rate due to regional cervical cancer treatment (age k)
los_final	Proportion of loss to follow-up at three visits
C	Proportion of vaccinated preadolescent girls/boy vaccination
COV	Proportion of people given a catch-up component
ς_k	Screening coverage at age class k (age k)
ϱ	Sensitivity of screening test
$\mathcal{g}$	Proportion of women with local cervical cancer who accept the treatment
Ω	Proportion of women with regional cervical cancer who accept the treatment
$\mathcal{A}$	Proportion of women with distant cervical cancer who accept the treatment
σ	Male to female population ratio
$\mathcal{T}_g$	Genotype-specific transmission probability

Figure 2: The screening model for cytology, VIA, rapid HPV DNA testing and combined testing VIA and cytology



Note: The cytology alone option or combined with VIA is a three-visit approach. The first visit refers to a primary screening; second refers to receiving the result and making an appointment for positive case. Third refers to colposcopy with direct biopsy. Meanwhile, rapid HPV DNA testing is a two-visit approach. The first visit refers to primary screening. Second refers to colposcopy with direct biopsy in positive case. VIA is considered as single-visit approach "see-and-treat approach"

Figure 3: Model calibration to age-specific incidence and mortality of cervical cancer

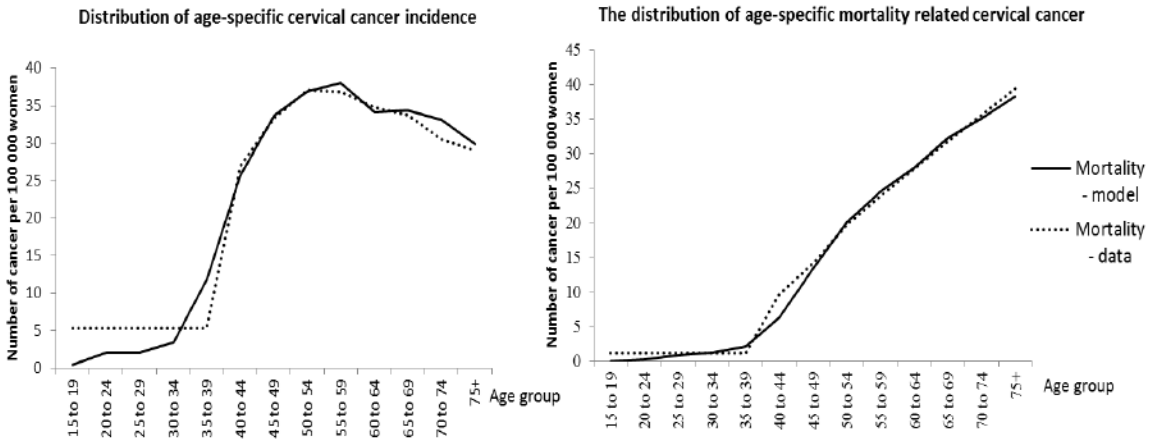


Table 4: Model parameters: force of infection

Age group	Male	Female	Adjusted ¶	Multiplier ‡	Source
Transmissibility per sexual partnership					Calibrated
HPP 16	0.355	0.355			
HPV 18	0.40	0.40			
Other-HR HPV	0.41	0.41			
Low-risk HPV	0.39	0.39			
Mean number of annual change of sexual partners among males and females					(36)
12-13	0.222	0.071	1	2.48-4.43	
14-15	0.673	0.283	1		
15-19	3.794	2.48	0.7		
20-24	5.802	2.442	0.7		
25-29	2.957	1.728	0.7		
30-34	2.113	0.971	0.7		
35-39	1.323	0.842	0.7		
40-44	1.323	0.842	1		
45-49	0.662	0.421	1		
50-54	0.662	0.421	2		
55-64	0.331	0.211	2		
65-74	0.166	0.106	3		
Sexual mixing matrix					(16)
Same age	0.6	0.6			
Different age	0.4	0.4			

¶ Adjusted values was applied to the force of infection model
‡ Multiplier values ranged according to related-scenarios of annual incidence rate of cervical cancer

Table 5: Summary of input parameters for the model

Parameters		Baseline values*	Source
Progression			
Healthy to infection † (-20 and +40%)	HPV-16	0.000175-0.003148 (0.0001426-0.00761)	Calibrated
	HPV-18	0.0004-0.000789 (0.000102-0.00168)	
	Other HR HPV	0.000206-0.004038 (0.0001703-0.00911)	
	LR HPV	0.000958-0.018412 (0.00069-0.0537)	
HPV DNA to CIN1‡	HR-16 HPV	0.005194-0.00901	(20)
	HR-18 HPV	0.002793-0.004845	
	HR-other HPV	0.007693-0.013345	

	LR-HPV	0.002397-0.001222
Proportion (%) of women who transition directly from HPV DNA to CIN2,3	HR-16 HPV	0.64
	HR-18 HPV	0.975
	HR-other HPV	0.966
	LR-HPV	0.98
CIN 1 to CIN 2,3 ‡	HR-16 HPV	0.00951-0.012363
	HR-18 HPV	0.0051-0.00663
	HR-other HPV	0.00747-0.009711
	LR-HPV	0.000149-0.000222
CIN 2,3 to local cancer	HR-16 HPV	0.000151-0.00906
	HR-18 HPV	0.000264-0.01584
	HR-other HPV	0.000199-0.01194
Local to regional invasive cancer		0.0200
Regional to distant invasive cancer		0.0250
Regression		
HPV DNA to Normal	HR-16 HPV	0.09089
	HR-18 HPV	0.09089
	HR-other HPV	0.09272
	LR-HPV	0.09699
CIN 1 to normal ‡‡	HR-16 HPV	0.03782
	HR-18 HPV	0.03782
	HR-other HPV	0.04575
	LR-HPV	0.01708
CIN 2,3 to Normal §§	HR-16 HPV	0.000798-0.000455
	HR-18 HPV	0.003556-0.011938
	HR-other HPV	0.002926-0.009823
	LR-HPV	0.001904-0.006392
	Other	
Immunity (%) (HR-HPV	HR-16 HPV	0.66

types only) ¶¶	HR-18 HPV	0.86	
	HR-other HPV	0.59	
Annual probability of symptom detection #	Local invasive cancer	0.33	
	Regional invasive cancer	0.60	
	Distant cancer	0.9	
Proportion of cancer patient receiving the treatment	Local cancer	100%	Assumption
	Regional cancer	87%	
	Distant cancer	78%	
Age-specific 5-year survival proportion after diagnosis and treatment (%) £	Local cancer	0.29-71%	Calibrated
	Regional cancer	0.24-78%	
Age-specific monthly probability of death	Complication of local cancer treatment	0.012-0.037	Calibrated
	Complication of regional cancer treatment	0.0098-0.028	
	Distant cancer (rate)	0.28-0.83	
Age-specific all cause death rates per person per year	Female	0,00106-0,4122	(37)
	Male	0.001-0.47	

* Baseline values are monthly age-specific probabilities, unless otherwise noted

† The transition from healthy state to infection is a force of infection derived from the number of sexual partner change, HPV type-specific transmissibility.

‡ HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; HR, high risk; LR, low risk

‡‡ 70% of women with CIN 1 regress to normal, 30% to HPV.

§§ 70% of women with CIN2,3 regress to normal, 15% to HPV, 15% to CIN 1.

¶¶ Immunity represents the degree to protection each woman faces against future type-specific infection after infection after first infection and clearance. The immunity was assumed to be lifelong.

The annual probability of symptom detection corresponds to 15% for local cancer and 85% for advanced cancer

£ Age-specific survival proportion was calibrate, based on a mortality rate estimated by Globocan (2).

Table 6: Calibration target

Calibration target		**Source**	**Calibration target**		**Source**
Female population¶		(38)	**Annual incidence rates of invasive cervical cancer per 100,000**		(2)
0- <5	44196		15-39	5.2	
5- <10	40488		40-44	26.9	
10 - <15	27947		45-49	33.3	
15 - < 20	31402		50-54	37.1	
20 - < 25	38205		55-59	36.9	
25 - < 30	48941		60-64	34.8	
30 - < 35	45627		65-69	33.7	
35 - < 40	32125		70-74	30.5	
40 - < 45	26762		>74	29	
45 - < 50	21895		**Annual mortality of**		

			invasive cervical cancer per 100,000	
50 - < 55	17307		15-39	1.2
55 - < 60	12766		40-44	9.6
60 - < 65	8251		45-49	14.2
65 - < 70	5,930		50-54	19.8
70 - < 75	4152		55-59	23.9
75+	6119		60-64	27.9
Distribution of HPV types among women with cancer, Thai data		(18)	65-69	31.8
			70-74	35.6
			>74	39.4
HPV1618	75.1			
Other-HR HPV‡	24.9			

¶ The proportion of male population to female population is 0.948
‡ HPV, human papillomavirus

Table 7: Summary of input other parameters for the model

Parameters	Value (range)	Distribution	Source
VIA			
Sensitivity (95% Confidence interval)	73.2% (66.5–80.0%)	Beta	(25)
Specificity (95% CI)	86.7% (82.9–90.4%)	Beta	
Conventional cervical cytology			
Sensitivity for CIN23	59% (29-82%)	Beta	(21)
Specificity	94% (88-99%)	Beta	
ThinPrep Cervical cytology			
Sensitivity for CIN23	88% (70-94%)	Beta	(21, 39)
Specificity	88% (65-97%)	Beta	(24)
Combined testing VIA and conventional cytology			
Sensitivity to detect high-grade CIN	87% (83-90%)	Beta	(26)
Specificity	79% (63-89%)	Beta	
Rapid HPV DNA testing			
Sensitivity to detect high-grade CIN	81.5 % (53.1- 89.5%)	Beta	(27)
Specificity	91.6 % (81.8%-97.4%)	Beta	
Colposcopy			(40)
Sensitivity for high-grade CIN	96% (64 –99%)	Beta	
Sensitivity	48% (30 –93%)	Beta	
Probability of treatment for High grade CIN in Cervical cytology			
≤ 35 years	LEEP: 80% (50-80%) Hysterectomy: 20% (20-50%)	Beta	Assumption #
> 35 years	Hysterectomy: 80% (50-80%) LEEP: 20% (20-50%)	Beta	

Proportion of recovery			
Cryotherapy			
Low-grade CIN	94% (85-95)	Beta	(41)
High-grade CIN	86% (83-89)	Beta	
LEEP: High-grade CIN	96.7% (90-98 %)	Beta	(22)
Hysterectomy: Any CIN	99% (90-100%)	Beta	(42)
Local cervical cancer		Beta	Calibrated
Regional cervical cancer		Beta	Calibrated
Mortality related to invasive cancer treatment		Beta	Calibrated
Local cervical cancer		Beta	Calibrated
Regional cervical cancer			Calibrated
Age-specific mortality of all-cause mortality			
Vaccine efficacy against HPV type 16 and 18 infection	100%		(43)

Note:

Assumption was based on experts' opinion

Women with local cervical cancer are treated by hysterectomy

Women with regional cervical cancer are treated by chemoradiation

Women with distant cancer are given palliative care

Table 8: compliance

Item		Percentage (%)	Distribution
Screening coverage (assumptions according to experts)	No screening program (VIA and cervical cytology)	5% (0-20%)	Beta
	Screening program (Cervical cytology or VIA or Rapid HPV DNA testing)	First time: 70% (30-70%)	Beta
		Following time: 10% (0-50)	Beta
Loss of follow-up of at screening visit, according to statistics at the pathology center	Per visit	15% (0-50)	Beta
Among women with suspicion of invasive cervical cancer, percentage undergoing a full diagnosis procedure		60% (40-100)	Beta
Percentage of women with local cervical cancer undergoing treatment	Surgery	80% (50-100)	Beta
	Other (palliative or nor care)	20% (0-50)	Beta
	Loss to follow-up	10% (0-50)	Beta
Percentage of women with regional cervical cancer undergoing a treatment in Thailand/Vietnam/China	Chemoradiation	80% (0-50)	Beta
	Loss to follow-up	20% (0-50)	Beta
Percentage of women with distant cervical cancer receiving palliative care	No care	100%	Beta

Table 9: Costing parameters

Option	Items	Unit price (2013 I$)	Source
VIA	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical staff ¶	3.39	
	Subtotal	17.87	
	Programmatic cost §	8.58	(32, 34)
	Total	26.45	
Conventional cervical cytology	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical staffs ¶	3.39	
	Cervical cytology laboratory equipment	11.20	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Laboratory staffs	3.54	
	Subtotal	32.61	
	Programmatic cost §	15.65	(32, 34)
	Total	48.27	
Liquid-based (Thin-Prep) cervical cytology	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical stuff ¶	3.39	
	Cervical cytology laboratory equipment	20.96	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Laboratory staffs	4.55	
	Subtotal	43.39	
	Programmatic cost §	20.83	(32, 34)
	Total	64.21	
VIA+ Conventional cervical cytology	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical stuff ¶	6.78	
	Cervical cytology laboratory equipment	11.20	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Laboratory staffs	3.56	
	Subtotal	36.03	
	Programmatic cost §	14.89	(32, 34)
	Total	50.91	
Rapid test of HPV DNA testing	Administration ‡	14.48	Personal communication with a head of department of health insurance. Ministry of health, Lao PDR
	Medical stuff ¶	3.39	
	Cervical cytology laboratory equipment	14.85	Personal communication with a head of department of Pathology center, University of Health Science, Ministry of Health, Lao PDR
	Laboratory staffs	2.23	
	Subtotal	34.94	

	Programmatic cost §	12.23	(32, 34)
	Total	47.18	
Colposcopy	Administration ‡	14.48	Personal communication with a head of
	Medical staff ¶	3.39	department of health insurance. Ministry
	Total	17.87	of health, Lao PDR

‡ Administration includes general and medical administration. General administration includes electricity, water and transportation supplies and other office martials and stuffs. Medical administration included training support and aids, and some medical equipment.

¶ Monthly salary also includes incentives, gasoline and overtime pay. Salary per hour = salary per day/8; Salary per day =(monthly salary x 12 months) / (52 weeks x 5 working days).

- Monthly average salary of gynecologist is 1303 dollars
- Monthly average salary of nurse is 736 dollars
- Monthly average salary of pathologist is 992 dollars
- Monthly average salary of pathology technician is 717 dollars

§ Programmatic cost was 48% of direct medical cost. 23% for quality control and training and 25% for administration and recruitment

International dollars exchange using 2013 purchasing power parity (PPP) exchange rate (1 I$ = 2,694.27 kips) (31)

Table 10: Detail of laboratory cost

Item	Sub-item	Unit price (dollar)	Source
Conventional	Lab administration ‡	0.01	Personal communication
cervical cytology	Lab equipment #	11.20	with a head of department of
	Lab stuffs ¶	3.54	Pathology center, University
	Total	14.75	of Health Science, Ministry
Liquid-based	Lab administration ‡	0.01	of Health, Lao PDR
cervical cytology	Lab equipment #	20.96	
	Lab stuffs ¶	4.55	
	Total	25.52	
Histology	Lab administration ‡	14.48	
	Lab equipment *	15.47	
	Lab stuffs ¶	15.74	
	Total	45.69	

Note:

Consumable items included Brush, cover glass, Malinol, Gill hemato, OG-6, EA-50, mask, xytene, etanol, slide. LBC prep set, LBC liquid were added for Thin-Prep.

* Consumable items included Formaline, hematocyline , eosine, paraphine, casette, cyline, obs olute, acetone, malinone

‡ Lab administration was retrieved from general administration allocated to laboratory in hospital per sample.

¶ This included both technical stuff and pathologist cost. Each cost is calculated by multiplying time spending to procedure with labor cost per hour

International dollars exchange using purchasing power parity (PPP) exchange rate (1 I$ = 2,694.27 kips) (31)

Table 11: Costing of precancerous treatment

Item	Sub-item	Unit price (dollar)	Source
Cryotherapy	Administration ‡	10.66	Personal communication with a head of department of health insurance, Ministry of health, Lao PDR
	Drug and equipment cost *	5.41	
	Labor cost ‡‡	7.52	
	Total #	23.59	
LEEP	Administration ‡	27.66	
	Drug and equipment cost *	57.05	
	Labor cost ‡‡	35.68	
	Total #	120.40	
Hysterectomy	Administration †	64.63	
	Drug and medical equipment cost †	204.23	
	Labor cost †	76.96	
	Subtotal	345.82	
	Hospitalisation cost in 7 days §	842.78	
	Total #	1188.59	
Cancer treatment §§	Treatment cost of Local cancer	745.57 (372.79-1491.15)	(33)
	Treatment cost of regional cancer	845.68 (422.85-1691.36)	
	Treatment cost of distant cancer	845.68 (422.85-1691.36)	

Note:

‡ Administration included general and medical administration. General administration included electricity, water and transportation supplies and other office martials and stuffs. Medical administration included training support and aids, some medical equipment; outpatient administration for cryotherapy and inpatient for loop electrosurgical excision procedure (LEEP).

‡‡ Labor cost was calculated by multiplying the wage rate per hour by the time spent to provide treatment

* Drug and equipment cost consist of the average cost per patient of in and out clinics.

† Due to lack of data specific to obstetric surgery, administration, drug and medical equipment and labor cost of hysterectomy an average cost of a surgery case at the department of gyneco-obstetrics in Mahosot and Setthathirath hospitals was used.

§ Hospitalization cost consists of the average cost of hospitalization per day at the department of gyneco-obstetric in Mahosot and Setthathirath hospitals. We assumed that a patient was hospitalized for seven days

≠ Total cost did not include the cost of follow-up for precancerous lesion because, according to expert, patients are lost at follow-up.

§§ Cost is unit price per person, 2013 International dollars exchange using purchasing power parity (PPP) exchange rate (1 I$ = 2,694.27 kips) (31) and the price of cancer treatment was adjusted from 2005 to 2014 using consumer price index (77.33 in 2005 and 122.52 in 2014) (38)

2. Result

Table 12.1: Base case analyses of cost-effectiveness of prevention strategies against cervical cancer in women in Lao PDR

Option	Cancer per 1000 women	Cancer reduction per 1000 women (N)	Cancer reduction (%)	DALY averted per 1000 women	DALY averted per 1000 women	Cost of screening and treatment per 1000 women	Cost of cancer treatment per 1000 women	Cost of vaccination per 1000 women	Total cost per 1000 women	CER (cancer)	CER (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
Baseline	4.8	Ref	Ref	57.9	Ref	3940	776	0	4716	-	-	-	-
vaccine	2.1	2.6	54.9	27.2	30.7	3901	524	17399	21824	8362	710	D	D
Yearly VIA alone_20-65	0.8	4.0	84.0	9.7	48.2	87213	204	0	87417	21885	1813	D	D
Three-yearly VIA alone_20-65	1.7	3.1	65.2	20.7	37.2	29102	362	0	29464	9500	791	ED	ED
Five-yearly VIA alone_20-65	2.3	2.4	51.2	28.8	29.1	17470	461	0	17932	7370	616	ED	ED
Yearly VIA alone_25-65	0.8	3.9	82.3	10.7	47.2	75484	216	0	75700	19343	1603	ED	ED
Three-yearly VIA alone_25-65	1.8	2.9	62.0	22.6	35.3	25186	380	0	25566	8672	723	ED	ED
Five-yearly VIA alone_25-65	2.5	2.3	47.7	30.9	27.0	15119	479	0	15598	6878	577	11302	895
Yearly VIA alone_30-65	1.0	3.8	79.9	12.2	45.7	64028	234	0	64261	16929	1405	ED	ED
Three-yearly VIA alone_30-65	2.0	2.8	57.9	25.1	32.8	21362	404	0	21766	7913	663	12771	1064
VIA alone_30-65	2.7	2.1	43.5	33.4	24.5	12823	502	0	13325	6448	544	4166	351
Yearly conventional cytology_20-65	1.3	3.5	73.0	15.0	42.9	148114	338	0	148452	42787	3457	D	D
Three-yearly conventional cytology_20-65	2.6	2.1	44.3	31.7	26.2	49717	536	0	50253	23888	1916	D	D
Five-yearly conventional cytology_20-65	3.3	1.4	29.5	40.4	17.6	29922	621	0	30542	21748	1739	D	D
Yearly conventional cytology_25-65	1.4	3.3	70.2	16.5	41.4	128256	356	0	128612	38529	3105	D	D
Three-yearly conventional cytology_25-65	2.8	1.9	40.8	33.7	24.2	43082	554	0	43636	22517	1801	D	D
Five-yearly conventional cytology_25-65	3.5	1.3	26.6	42.1	15.8	25933	636	0	26568	21037	1678	D	D
Yearly conventional cytology_30-65	1.6	3.2	66.5	18.6	39.3	108931	381	0	109312	34604	2782	D	D

Table 12.2: Base case analyses of cost-effectiveness of prevention strategies against cervical cancer in women in Lao PDR (continued)

Option	Cancer per 1 000 women	Cancer reduction per 1000 women (N)	Cancer reduction (%)	DALY averted per 1 000 women	DALY averted per 1 000 women	Cost of screening and treatment per 1 000 women	Cost of cancer treatment per 1 000 women	Cost of vaccination per 1 000 women	Total cost per 1 000 women	CER (cancer)	CER (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
Baseline	4.8	Ref	Ref	57.9	Ref	3940	776	0	4716	-	-	-	-
Vaccine	2.1	2.6	54.9	27.2	30.7	3901	524	17399	21824	8362	710	D	D
Yearly VIA alone_20-65	0.8	4.0	84.0	9.7	48.2	87213	204	0	87417	21885	1813	D	D
Three-yearly VIA alone_20-65	1.7	3.1	65.2	20.7	37.2	29102	362	0	29464	9500	791	ED	ED
Five-yearly VIA alone_20-65	2.3	2.4	51.2	28.8	29.1	17470	461	0	17932	7370	616	ED	ED
Yearly VIA alone_25-65	0.8	3.9	82.3	10.7	47.2	75484	216	0	75700	19343	1603	ED	ED
Three-yearly VIA alone_25-65	1.8	2.9	62.0	22.6	35.3	25186	380	0	25566	8672	723	ED	ED
Five-yearly VIA alone_25-65	2.5	2.3	47.7	30.9	27.0	15119	479	0	15598	6878	577	11302	895
Yearly VIA alone_30-65	1.0	3.8	79.9	12.2	45.7	64028	234	0	64261	16929	1405	ED	ED
Three-yearly VIA alone_30-65	2.0	2.8	57.9	25.1	32.8	21362	404	0	21766	7913	663	12771	1064
VIA alone_30-65	2.7	2.1	43.5	33.4	24.5	12823	502	0	13325	6448	544	4166	351
Yearly conventional cytology_20-65	1.3	3.5	73.0	15.0	42.9	148114	338	0	148452	42787	3457	D	D
Three-yearly conventional cytology_20-65	2.6	2.1	44.3	31.7	26.2	49717	536	0	50253	23888	1916	D	D
Five-yearly conventional cytology_20-65	3.3	1.4	29.5	40.4	17.6	29922	621	0	30542	21748	1739	D	D
Yearly conventional cytology_25-65	1.4	3.3	70.2	16.5	41.4	128256	356	0	128612	38529	3105	D	D
Three-yearly conventional cytology_25-65	2.8	1.9	40.8	33.7	24.2	43082	554	0	43636	22517	1801	D	D
Five-yearly conventional cytology_25-65	3.5	1.3	26.6	42.1	15.8	25933	636	0	26568	21037	1678	D	D
Yearly conventional cytology_30-65	1.6	3.2	66.5	18.6	39.3	108931	381	0	109312	34604	2782	D	D
Three-yearly conventional cytology_30-65	3.0	1.7	36.6	36.2	21.8	36622	577	0	37199	21390	1709	D	D
Five-yearly conventional cytology_30-65	3.7	1.1	23.1	44.1	13.8	22048	654	0	22701	20659	1647	D	D
Yearly liquid-based cytology_20-65	1.0	3.8	79.8	11.0	46.9	199751	272	0	200023	52697	4263	D	D

Table 12.3: Base case analyses of cost-effectiveness of prevention strategies against cervical cancer in women in Lao PDR (continued)

Option	Cancer per 1 000 women	Cancer reduction per 1 000 women (N)	Cancer reduction (%)	DALY averted per 1 000 women	DALY averted per 1 000 women	Cost of screening and treatment per 1 000 women	Cost of cancer treatment per 1 000 women	Cost of vaccination per 1 000 women	Total cost per 1 000 women	CER (cancer)	CER (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
Three-yearly liquid-based cytology_20-65	2.1	2.7	56.5	24.5	33.5	67039	450	0	67488	25147	2018	D	D
Five-yearly liquid-based cytology_20-65	2.8	2.0	41.6	33.2	24.7	40368	542	0	40910	20697	1653	D	D
Yearly liquid-based cytology_25-65	1.1	3.7	77.7	12.2	45.8	172928	288	0	173216	46882	3784	D	D
Three-yearly liquid-based cytology_25-65	2.2	2.5	53.0	26.5	31.5	58086	470	0	58556	23263	1861	D	D
Five-yearly liquid-based cytology_25-65	2.9	1.8	38.2	35.1	22.8	34987	559	0	35546	19578	1559	D	D
Yearly liquid-based cytology_30-65	1.2	3.6	74.7	13.8	44.1	146828	309	0	147137	41439	3338	D	D
Three-yearly liquid-based cytology_30-65	2.4	2.3	48.6	29.0	28.9	49374	495	0	49868	21588	1723	D	D
Five-yearly liquid-based cytology_30-65	3.1	1.6	34.2	37.5	20.4	29748	581	0	30329	18669	1485	D	D
Yearly combined VIA and cytology testing_20-65	1.0	3.8	79.7	11.1	46.8	167016	274	0	167290	44165	3572	D	D
Three-yearly combined VIA and cytology testing_20-65	2.1	2.7	56.1	24.7	33.3	56119	452	0	56571	21205	1701	D	D
Five-yearly combined VIA and cytology testing_20-65	2.8	2.0	41.2	33.4	24.5	33813	544	0	34357	17532	1400	D	D
Yearly combined VIA and cytology testing_25-65	1.1	3.7	77.5	12.3	45.7	144608	290	0	144898	39310	3173	D	D
Three-yearly combined VIA and cytology testing_25-65	2.3	2.5	52.6	26.7	31.3	48639	472	0	49111	19637	1571	D	D
Five-yearly combined VIA and cytology testing_25-65	3.0	1.8	37.8	35.3	22.6	29315	562	0	29877	16607	1323	D	D
Yearly combined VIA and cytology testing_30-65	1.2	3.5	74.5	14.0	44.0	122813	311	0	123124	34771	2801	D	D
Three-yearly combined VIA	2.5	2.3	48.3	29.2	28.7	41361	497	0	41858	18249	1457	D	D

and cytology testing_30-65													
Five-yearly combined VIA and cytology testing_30-65	3.1	1.6	33.8	37.7	20.2	24938	583	0	25521	15865	1262	D	D

Table 12.2: Base case analyses of cost-effectiveness of prevention strategies against cervical cancer in women in Lao PDR (continued)

Option	Cancer per 1 000 women	Cancer reduction per 1 000 women (N)	Cancer reduction (%)	DALY averted per 1 000 women	DALY averted per 1 000 women	Cost of screening and treatment per 1 000 women	Cost of cancer treatment per 1 000 women	Cost of vaccination per 1 000 women	Total cost per 1 000 women	CER (cancer)	CER (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
Yearly rapid HPV DNA testing_20-65	0.9	3.9	82.1	9.7	48.2	148098	248	0	148346	38024	3077	D	D
Three-yearly rapid HPV DNA testing_20-65	1.8	2.9	61.2	21.7	36.2	49856	414	0	50270	17291	1388	D	D
Five-yearly rapid HPV DNA testing_20-65	2.5	2.2	46.7	30.1	27.8	30081	506	0	30587	13770	1100	D	D
Yearly rapid HPV DNA testing_25-65	0.9	3.8	80.2	10.7	47.2	128229	263	0	128492	33711	2723	D	D
Three-yearly rapid HPV DNA testing_25-65	2.0	2.7	57.8	23.6	34.3	43225	434	0	43659	15900	1272	D	D
Five-yearly rapid HPV DNA testing_25-65	2.7	2.1	43.3	32.1	25.8	26093	524	0	26618	12946	1031	D	D
Yearly rapid HPV DNA testing_30-65	1.1	3.7	77.5	12.3	45.7	108925	283	0	109208	29660	2391	D	D
Three-yearly rapid HPV DNA testing_30-65	2.2	2.5	53.5	26.1	31.8	36783	459	0	37242	14654	1170	D	D
Five-yearly rapid HPV DNA testing_30-65	2.9	1.9	39.1	34.6	23.4	22217	547	0	22764	12254	974	D	D
Yearly VIA alone_20-65 + vaccination	0.6	4.1	87.0	8.1	49.8	87151	181	17350	104683	25303	2101	422480	30462
Three-yearly VIA alone_20-65 + vaccination	1.1	3.6	76.7	14.3	43.6	29090	293	17380	46763	12825	1072	D	ED
Five-yearly VIA alone_20-65 + vaccination	1.4	3.4	71.0	17.7	40.2	17461	354	17387	35202	10424	875	ED	ED
Yearly VIA alone_25-65 + vaccination	0.6	4.1	86.5	8.5	49.4	75450	187	17365	93002	22631	1881	D	24136

Three-yearly VIA alone_25-65 + vaccination	1.1	3.6	76.1	14.7	43.2	25176	300	17386	42862	11852	992	D	ED
Five-yearly VIA alone_25-65 + vaccination	1.4	3.3	70.5	18.1	39.8	15112	360	17391	32862	9813	825	D	ED
Yearly VIA alone_30-65 + vaccination	0.7	4.1	85.7	9.0	49.0	64008	195	17372	81575	20013	1666	85116	6733
Three-yearly VIA alone_30-65 + vaccination	1.2	3.6	75.2	15.3	42.6	21354	309	17388	39051	10919	916	4468	2544
VIA alone_30-65 + vaccination	1.4	3.3	69.7	18.6	39.3	12817	368	17392	30577	9234	778	15718	1362
Yearly conventional cytology_20-65 + vaccination	0.9	3.8	80.3	11.3	46.7	147959	285	17395	165638	43392	3548	D	D
Three-yearly conventional cytology_20-65 + vaccination	1.5	3.3	68.4	18.6	39.3	49550	402	17397	67348	20711	1713	D	D
Five-yearly conventional cytology_20-65 + vaccination	1.7	3.0	63.6	21.7	36.3	29783	447	17398	47628	15760	1313	D	D
Yearly conventional cytology_25-65 + vaccination	1.0	3.8	79.7	11.6	46.3	128080	292	17395	145767	38487	3149	D	D
Three-yearly conventional cytology_25-65 + vaccination	1.5	3.2	67.8	19.0	39.0	42914	408	17397	60718	18828	1558	D	D
Five-yearly conventional cytology_25-65 + vaccination	1.8	3.0	63.1	22.0	36.0	25798	451	17398	43647	14548	1213	D	D
Yearly conventional cytology_30-65 + vaccination	1.0	3.7	78.8	12.2	45.8	108727	302	17395	126424	33731	2763	D	D
Three-yearly conventional cytology_30-65 + vaccination	1.6	3.2	67.1	19.5	38.5	36451	416	17397	54264	17020	1411	D	D
Five-yearly conventional cytology_30-65 + vaccination	1.8	3.0	62.5	22.4	35.6	21917	458	17398	39772	13387	1118	D	D
Yearly liquid-based cytology_20-65 + vaccination	0.7	4.0	84.3	8.8	49.1	199620	237	17394	217251	54242	4425	D	D
Three-yearly liquid-based cytology_20-65 + vaccination	1.3	3.5	73.0	15.6	42.3	66866	351	17396	84613	24372	2001	D	D
Five-yearly liquid-based cytology_20-65 + vaccination	1.5	3.2	67.7	19.0	39.0	40208	401	17397	58007	18024	1489	D	D
Yearly liquid-based cytology_25-65 + vaccination	0.8	4.0	83.7	9.2	48.7	172773	244	17395	190411	47881	3907	D	D
Three-yearly liquid-based cytology_25-65 + vaccination	1.3	3.4	72.4	16.0	41.9	57905	357	17397	75658	21976	1806	D	D

Five-yearly liquid-based cytology_25-65 + vaccination	1.6	3.2	67.2	19.3	38.6	34827	406	17398	52631	16484	1363	D	D
Yearly liquid-based cytology_30-65 + vaccination	0.8	3.9	82.9	9.7	48.2	146639	253	17395	164287	41686	3405	D	D
Three-yearly liquid-based cytology_30-65 + vaccination	1.3	3.4	71.6	16.6	41.4	49181	366	17397	66944	19668	1619	D	D
Five-yearly liquid-based cytology_30-65 + vaccination	1.6	3.2	66.4	19.8	38.1	29587	414	17398	47399	15007	1243	D	D
Yearly combined VIA and cytology testing_20-65 + vaccination	0.8	4.0	84.2	8.9	49.0	166884	238	17394	184517	46126	3763	D	D
Three-yearly combined VIA and cytology testing_20-65 + vaccination	1.3	3.5	72.9	15.7	42.2	55947	352	17396	73696	21266	1746	D	D
Five-yearly combined VIA and cytology testing_20-65 + vaccination	1.5	3.2	67.6	19.1	38.9	33655	402	17397	51455	16018	1324	D	D
Yearly combined VIA and cytology testing_25-65 + vaccination	0.8	4.0	83.6	9.3	48.7	144453	245	17395	162093	40811	3331	D	D
Three-yearly combined VIA and cytology testing_25-65 + vaccination	1.3	3.4	72.3	16.1	41.8	48459	358	17397	66214	19268	1584	D	D
Five-yearly combined VIA and cytology testing_25-65	1.6	3.2	67.0	19.4	38.5	29158	407	17398	46963	14736	1219	D	D
Yearly combined VIA and cytology testing_30-65 + vaccination	0.8	3.9	82.8	9.7	48.2	122624	254	17395	140273	35639	2911	D	D
Three-yearly combined VIA and cytology testing_30-65 + vaccination	1.4	3.4	71.5	16.7	41.3	41170	368	17397	58935	17348	1428	D	D
Five-yearly combined VIA and cytology testing_30-65 + vaccination	1.6	3.2	66.3	19.9	38.0	24779	415	17398	42592	13509	1119	D	D
Yearly rapid HPV DNA testing_20-65 + vaccination	0.7	4.1	85.7	16.7	41.3	147975	219	17394	165588	40650	3314	D	D
Three-yearly rapid HPV DNA testing_20-65 + vaccination	1.2	3.6	75.0	14.4	43.5	49687	328	17396	67411	18914	1549	D	D

Five-yearly rapid HPV DNA testing_20-65 + vaccination	1.4	3.3	69.6	17.8	40.2	29918	379	17397	47694	14424	1188	D	D
Yearly rapid HPV DNA testing_25-65 + vaccination	0.7	4.0	85.1	8.3	49.6	128081	225	17395	145701	36014	2937	D	D
Three-yearly rapid HPV DNA testing_25-65 + vaccination	1.2	3.5	74.4	14.8	43.1	43044	334	17397	60775	17193	1409	D	D
Five-yearly rapid HPV DNA testing_25-65 + vaccination	1.5	3.3	69.0	18.1	39.8	25927	385	17398	43710	13326	1098	D	D
Yearly rapid HPV DNA testing_30-65 + vaccination	0.7	4.0	84.4	8.8	49.2	108742	234	17395	126370	31501	2571	D	D
Three-yearly rapid HPV DNA testing_30-65 + vaccination	1.3	3.5	73.5	15.3	42.6	36586	344	17397	54327	15542	1275	D	D
Five-yearly rapid HPV DNA testing_30-65 + vaccination	1.5	3.2	68.2	18.6	39.3	22047	393	17398	39837	12280	1014	D	D

Note:

Baseline refers to no vaccination with 5.2% cytology screening for women aged 18-68 years old.

Vaccination is for 10-years-old girls. Cytology refers to conventional cervical cytology; LBC refers to liquid-based cervical cytology; HPV testing refers to rapid HPV DNA testing; VIA+cytology refers to the combined testing VIA and cytology.

The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness.

D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

ED refers to extendedly dominance, which has higher ICER than the next ICER.

Table 12.2: Base case analyses of cost-effectiveness of prevention strategies against cervical cancer in women in Lao PDR (continued)

Option	Cancer per 1 000 women	Cancer reduction per 1 000 women (N)	Cancer reduction (%)	DALY averted per 1 000 women	DALY averted per 1 000 women	Cost of screening and treatment per 1 000 women	Cost of cancer treatment per 1 000 women	Cost of vaccination per 1 000 women	Total cost per 1 000 women	CER (cancer)	CER (DALY averted)	ICER (cancer reduction)	ICER (DALY averted)
Baseline	4.8	Ref	Ref	57.9	Ref	3940	776	0	4716	-	-	-	-
vaccine	2.1	2.6	54.9	27.2	30.7	3901	524	17399	21824	8362	710	D	D
Yearly VIA alone_20-65	0.8	4.0	84.0	9.7	48.2	87213	204	0	87417	21885	1813	D	D
Three-yearly VIA alone_20-65	1.7	3.1	65.2	20.7	37.2	29102	362	0	29464	9500	791	ED	ED
Five-yearly VIA alone_20-65	2.3	2.4	51.2	28.8	29.1	17470	461	0	17932	7370	616	ED	ED
Yearly VIA alone_25-65	0.8	3.9	82.3	10.7	47.2	75484	216	0	75700	19343	1603	ED	ED

Three-yearly VIA alone_25-65	1.8	2.9	62.0	22.6	35.3	25186	380	0	25566	8672	723	ED	ED
Five-yearly VIA alone_25-65	2.5	2.3	47.7	30.9	27.0	15119	479	0	15598	6878	577	11302	895
Yearly VIA alone_30-65	1.0	3.8	79.9	12.2	45.7	64028	234	0	64261	16929	1405	ED	ED
Three-yearly VIA alone_30-65	2.0	2.8	57.9	25.1	32.8	21362	404	0	21766	7913	663	12771	1064
VIA alone_30-65	2.7	2.1	43.5	33.4	24.5	12823	502	0	13325	6448	544	4166	351
Yearly conventional cytology_20-65	1.3	3.5	73.0	15.0	42.9	148114	338	0	148452	42787	3457	D	D
Three-yearly conventional cytology_20-65	2.6	2.1	44.3	31.7	26.2	49717	536	0	50253	23888	1916	D	D
Five-yearly conventional cytology_20-65	3.3	1.4	29.5	40.4	17.6	29922	621	0	30542	21748	1739	D	D
Yearly conventional cytology_25-65	1.4	3.3	70.2	16.5	41.4	128256	356	0	128612	38529	3105	D	D
Three-yearly conventional cytology_25-65	2.8	1.9	40.8	33.7	24.2	43082	554	0	43636	22517	1801	D	D
Five-yearly conventional cytology_25-65	3.5	1.3	26.6	42.1	15.8	25933	636	0	26568	21037	1678	D	D
Yearly conventional cytology_30-65	1.6	3.2	66.5	18.6	39.3	108931	381	0	109312	34604	2782	D	D
Three-yearly conventional cytology_30-65	3.0	1.7	36.6	36.2	21.8	36622	577	0	37199	21390	1709	D	D
Five-yearly conventional cytology_30-65	3.7	1.1	23.1	44.1	13.8	22048	654	0	22701	20659	1647	D	D
Yearly liquid-based cytology_20-65	1.0	3.8	79.8	11.0	46.9	199751	272	0	200023	52697	4263	D	D
Three-yearly liquid-based cytology_20-65	2.1	2.7	56.5	24.5	33.5	67039	450	0	67488	25147	2018	D	D
Five-yearly liquid-based cytology_20-65	2.8	2.0	41.6	33.2	24.7	40368	542	0	40910	20697	1653	D	D
Yearly liquid-based cytology_25-65	1.1	3.7	77.7	12.2	45.8	172928	288	0	173216	46882	3784	D	D
Three-yearly liquid-based cytology_25-65	2.2	2.5	53.0	26.5	31.5	58086	470	0	58556	23263	1861	D	D
Five-yearly liquid-based cytology_25-65	2.9	1.8	38.2	35.1	22.8	34987	559	0	35546	19578	1559	D	D
Yearly liquid-based	1.2	3.6	74.7	13.8	44.1	146828	309	0	147137	41439	3338	D	D

cytology_30-65													
Three-yearly liquid-based cytology_30-65	2.4	2.3	48.6	29.0	28.9	49374	495	0	49868	21588	1723	D	D
Five-yearly liquid-based cytology_30-65	3.1	1.6	34.2	37.5	20.4	29748	581	0	30329	18669	1485	D	D
Yearly combined VIA and cytology testing_20-65	1.0	3.8	79.7	11.1	46.8	167016	274	0	167290	44165	3572	D	D
Three-yearly combined VIA and cytology testing_20-65	2.1	2.7	56.1	24.7	33.3	56119	452	0	56571	21205	1701	D	D
Five-yearly combined VIA and cytology testing_20-65	2.8	2.0	41.2	33.4	24.5	33813	544	0	34357	17532	1400	D	D
Yearly combined VIA and cytology testing_25-65	1.1	3.7	77.5	12.3	45.7	144608	290	0	144898	39310	3173	D	D
Three-yearly combined VIA and cytology testing_25-65	2.3	2.5	52.6	26.7	31.3	48639	472	0	49111	19637	1571	D	D
Five-yearly combined VIA and cytology testing_25-65	3.0	1.8	37.8	35.3	22.6	29315	562	0	29877	16607	1323	D	D
Yearly combined VIA and cytology testing_30-65	1.2	3.5	74.5	14.0	44.0	122813	311	0	123124	34771	2801	D	D
Three-yearly combined VIA and cytology testing_30-65	2.5	2.3	48.3	29.2	28.7	41361	497	0	41858	18249	1457	D	D
Five-yearly combined VIA and cytology testing_30-65	3.1	1.6	33.8	37.7	20.2	24938	583	0	25521	15865	1262	D	D
Yearly rapid HPV DNA testing_20-65	0.9	3.9	82.1	9.7	48.2	148098	248	0	148346	38024	3077	D	D
Three-yearly rapid HPV DNA testing_20-65	1.8	2.9	61.2	21.7	36.2	49856	414	0	50270	17291	1388	D	D
Five-yearly rapid HPV DNA testing_20-65	2.5	2.2	46.7	30.1	27.8	30081	506	0	30587	13770	1100	D	D
Yearly rapid HPV DNA testing_25-65	0.9	3.8	80.2	10.7	47.2	128229	263	0	128492	33711	2723	D	D
Three-yearly rapid HPV DNA testing_25-65	2.0	2.7	57.8	23.6	34.3	43225	434	0	43659	15900	1272	D	D
Five-yearly rapid HPV DNA testing_25-65	2.7	2.1	43.3	32.1	25.8	26093	524	0	26618	12946	1031	D	D
Yearly rapid HPV DNA testing_30-65	1.1	3.7	77.5	12.3	45.7	108925	283	0	109208	29660	2391	D	D

Three-yearly rapid HPV DNA testing_30-65	2.2	2.5	53.5	26.1	31.8	36783	459	0	37242	14654	1170	D	D
Five-yearly rapid HPV DNA testing_30-65	2.9	1.9	39.1	34.6	23.4	22217	547	0	22764	12254	974	D	D
Yearly VIA alone_20-65 + vaccination	0.6	4.1	87.0	8.1	49.8	87151	181	17350	104683	25303	2101	422480	30462
Three-yearly VIA alone_20-65 + vaccination	1.1	3.6	76.7	14.3	43.6	29090	293	17380	46763	12825	1072	D	ED
Five-yearly VIA alone_20-65 + vaccination	1.4	3.4	71.0	17.7	40.2	17461	354	17387	35202	10424	875	ED	ED
Yearly VIA alone_25-65 + vaccination	0.6	4.1	86.5	8.5	49.4	75450	187	17365	93002	22631	1881	D	24136
Three-yearly VIA alone_25-65 + vaccination	1.1	3.6	76.1	14.7	43.2	25176	300	17386	42862	11852	992	D	ED
Five-yearly VIA alone_25-65 + vaccination	1.4	3.3	70.5	18.1	39.8	15112	360	17391	32862	9813	825	D	ED
Yearly VIA alone_30-65 + vaccination	0.7	4.1	85.7	9.0	49.0	64008	195	17372	81575	20013	1666	85116	6733
Three-yearly VIA alone_30-65 + vaccination	1.2	3.6	75.2	15.3	42.6	21354	309	17388	39051	10919	916	4468	2544
VIA alone_30-65 + vaccination	1.4	3.3	69.7	18.6	39.3	12817	368	17392	30577	9234	778	15718	1362
Yearly conventional cytology_20-65 + vaccination	0.9	3.8	80.3	11.3	46.7	147959	285	17395	165638	43392	3548	D	D
Three-yearly conventional cytology_20-65 + vaccination	1.5	3.3	68.4	18.6	39.3	49550	402	17397	67348	20711	1713	D	D
Five-yearly conventional cytology_20-65 + vaccination	1.7	3.0	63.6	21.7	36.3	29783	447	17398	47628	15760	1313	D	D
Yearly conventional cytology_25-65 + vaccination	1.0	3.8	79.7	11.6	46.3	128080	292	17395	145767	38487	3149	D	D
Three-yearly conventional cytology_25-65 + vaccination	1.5	3.2	67.8	19.0	39.0	42914	408	17397	60718	18828	1558	D	D
Five-yearly conventional cytology_25-65 + vaccination	1.8	3.0	63.1	22.0	36.0	25798	451	17398	43647	14548	1213	D	D
Yearly conventional cytology_30-65 + vaccination	1.0	3.7	78.8	12.2	45.8	108727	302	17395	126424	33731	2763	D	D
Three-yearly conventional cytology_30-65 + vaccination	1.6	3.2	67.1	19.5	38.5	36451	416	17397	54264	17020	1411	D	D

Five-yearly conventional cytology_30-65 + vaccination	1.8	3.0	62.5	22.4	35.6	21917	458	17398	39772	13387	1118	D	D
Yearly liquid-based cytology_20-65 + vaccination	0.7	4.0	84.3	8.8	49.1	199620	237	17394	217251	54242	4425	D	D
Three-yearly liquid-based cytology_20-65 + vaccination	1.3	3.5	73.0	15.6	42.3	66866	351	17396	84613	24372	2001	D	D
Five-yearly liquid-based cytology_20-65 + vaccination	1.5	3.2	67.7	19.0	39.0	40208	401	17397	58007	18024	1489	D	D
Yearly liquid-based cytology_25-65 + vaccination	0.8	4.0	83.7	9.2	48.7	172773	244	17395	190411	47881	3907	D	D
Three-yearly liquid-based cytology_25-65 + vaccination	1.3	3.4	72.4	16.0	41.9	57905	357	17397	75658	21976	1806	D	D
Five-yearly liquid-based cytology_25-65 + vaccination	1.6	3.2	67.2	19.3	38.6	34827	406	17398	52631	16484	1363	D	D
Yearly liquid-based cytology_30-65 + vaccination	0.8	3.9	82.9	9.7	48.2	146639	253	17395	164287	41686	3405	D	D
Three-yearly liquid-based cytology_30-65 + vaccination	1.3	3.4	71.6	16.6	41.4	49181	366	17397	66944	19668	1619	D	D
Five-yearly liquid-based cytology_30-65 + vaccination	1.6	3.2	66.4	19.8	38.1	29587	414	17398	47399	15007	1243	D	D
Yearly combined VIA and cytology testing_20-65 + vaccination	0.8	4.0	84.2	8.9	49.0	166884	238	17394	184517	46126	3763	D	D
Three-yearly combined VIA and cytology testing_20-65 + vaccination	1.3	3.5	72.9	15.7	42.2	55947	352	17396	73696	21266	1746	D	D
Five-yearly combined VIA and cytology testing_20-65 + vaccination	1.5	3.2	67.6	19.1	38.9	33655	402	17397	51455	16018	1324	D	D
Yearly combined VIA and cytology testing_25-65 + vaccination	0.8	4.0	83.6	9.3	48.7	144453	245	17395	162093	40811	3331	D	D
Three-yearly combined VIA and cytology testing_25-65 + vaccination	1.3	3.4	72.3	16.1	41.8	48459	358	17397	66214	19268	1584	D	D
Five-yearly combined VIA and cytology testing_25-65	1.6	3.2	67.0	19.4	38.5	29158	407	17398	46963	14736	1219	D	D

Yearly combined VIA and cytology testing_30-65 + vaccination	0.8	3.9	82.8	9.7	48.2	122624	254	17395	140273	35639	2911	D	D
Three-yearly combined VIA and cytology testing_30-65 + vaccination	1.4	3.4	71.5	16.7	41.3	41170	368	17397	58935	17348	1428	D	D
Five-yearly combined VIA and cytology testing_30-65 + vaccination	1.6	3.2	66.3	19.9	38.0	24779	415	17398	42592	13509	1119	D	D
Yearly rapid HPV DNA testing_20-65 + vaccination	0.7	4.1	85.7	16.7	41.3	147975	219	17394	165588	40650	3314	D	D
Three-yearly rapid HPV DNA testing_20-65 + vaccination	1.2	3.6	75.0	14.4	43.5	49687	328	17396	67411	18914	1549	D	D
Five-yearly rapid HPV DNA testing_20-65 + vaccination	1.4	3.3	69.6	17.8	40.2	29918	379	17397	47694	14424	1188	D	D
Yearly rapid HPV DNA testing_25-65 + vaccination	0.7	4.0	85.1	8.3	49.6	128081	225	17395	145701	36014	2937	D	D
Three-yearly rapid HPV DNA testing_25-65 + vaccination	1.2	3.5	74.4	14.8	43.1	43044	334	17397	60775	17193	1409	D	D
Five-yearly rapid HPV DNA testing_25-65 + vaccination	1.5	3.3	69.0	18.1	39.8	25927	385	17398	43710	13326	1098	D	D
Yearly rapid HPV DNA testing_30-65 + vaccination	0.7	4.0	84.4	8.8	49.2	108742	234	17395	126370	31501	2571	D	D
Three-yearly rapid HPV DNA testing_30-65 + vaccination	1.3	3.5	73.5	15.3	42.6	36586	344	17397	54327	15542	1275	D	D
Five-yearly rapid HPV DNA testing_30-65 + vaccination	1.5	3.2	68.2	18.6	39.3	22047	393	17398	39837	12280	1014	D	D

Note:

Baseline refers to no vaccination with 5.2% cytology screening for women aged 18-68 years old.

Vaccination is for 10-years-old girls. Cytology refers to conventional cervical cytology; LBC refers to liquid-based cervical cytology; HPV testing refers to rapid HPV DNA testing; VIA+cytology refers to the combined testing VIA and cytology.

The incremental cost of effectiveness ratio expressed as cancer prevented or DALY averted is listed in order of increasing cost. In non-dominant strategy, the ICER was calculated by devising different cost to different effectiveness.

D refers to strong dominance, which is expressed as higher cost, but lower effectiveness than alternative options.

ED refers to extendedly dominance, which has higher ICER than the next ICER.

Sensitivity analysis

Table 13: Univariate sensitivity analyses of impact of cost of vaccine and screening coverage on ICER per DALY averted by screening strategies

Options	Vaccination coverage (%)†					Screening coverage (%)¶				
	10	30	50	70	80	10	30	50	70	80
Triennial VIA_30-65 + vaccination	146	365	784	1763	2987	108	1019	1445	1826	2011
Quinquennial VIA_30-65 + vaccination	101	440	534	778	1088	D	658	1019	1284	1406
Quinquennial conventional cytology_30-65 + vaccination	68	160	345	784	1333	D	3504	3709	3995	4147
Quinquennial liquid-based cytology_30-65 + vaccination	79	194	423	965	1642	1736	2930	3455	3932	4166
Quinquennial combined VIA and cytology_30-65 + vaccination	78	193	420	958	1631	943	2351	2836	3252	3452
Triennial rapid HPV DNA_30-65 + vaccination	119	315	695	1588	2704	1060	2102	2738	3334	3628
Quinquennial rapid HPV DNA_30-65 + vaccination	86	215	470	1072	1826	285	1624	2102	2493	2678

Note:
† For different vaccination coverage, the comparison is between combined screening with girl vaccination and screening alone
¶ For different screening coverage, the comparison is between combined screening with girl vaccination and girl vaccination alone
D refers domination

Table 14: Univariate sensitivity analyses of impact of cost of vaccine and screening coverage on ICER per DALY averted by screening strategies

Options	Cost of vaccine per dose (I$)†					
	4.5	10	30	50	70	100
Triennial VIA_30-65 + vaccination	1763	2451	3700	7447	9946	13694
Quinquennial VIA_30-65 + vaccination	1165	1620	2447	4929	6583	9065
Quinquennial conventional cytology_30-65 + vaccination	784	1093	1656	3343	4468	6156

Quinquennial liquid-based cytology_30-65 + vaccination	965	1345	2038	4114	5499	7576
Quinquennial combined VIA and cytology_30-65 + vaccination	958	1336	2024	4086	5461	7524
Triennial rapid HPV DNA_30-65 + vaccination	1588	2214	3352	6767	9044	12459
Quinquennial rapid HPV DNA_30-65 + vaccination	1072	1495	2265	4573	6112	8420

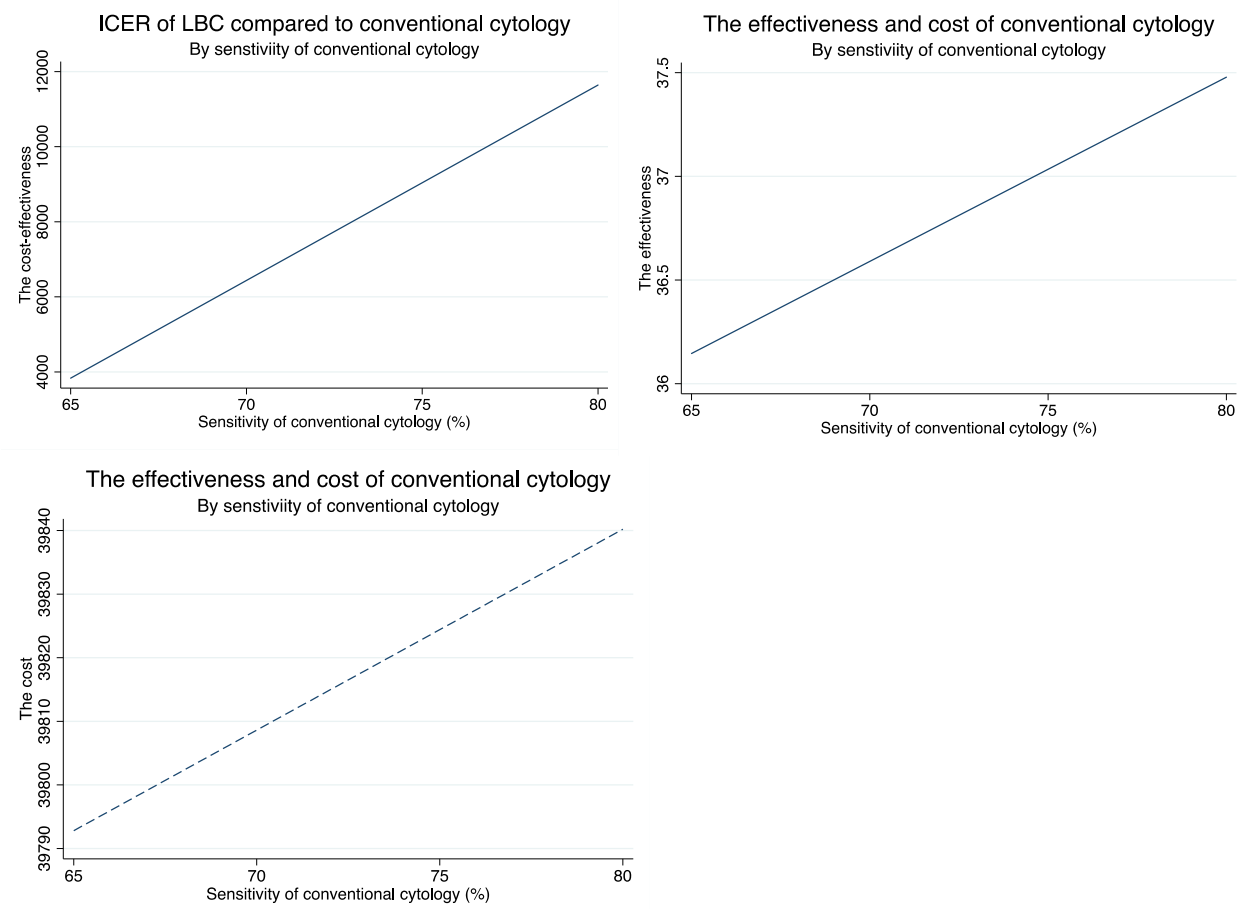
Note:
† For different cost of vaccine, the comparison is between combined screening with girl vaccination and screening alone
D refers domination

Table 15: Univariate sensitivity analyses of impact of number of loss to follow-up and sensitivity of VIA on ICER per DALY averted by screening strategies

Options	Loss to follow-up (%)			Sensitivity decrease (%)†			
	0	5	10	10	20	30	50
Quinquennial conventional cytology_30-65 + vaccination	41757	D	D	D	D	D	23156
Quinquennial liquid-based cytology_30-65 + vaccination	5281	8515	31226	D	76554	14449	4469
Quinquennial combined VIA and cytology_30-65 + vaccination	3959	6449	26601	D	87116	10378	2813
Triennial rapid HPV DNA_30-65 + vaccination	5904	8386	16085	21156	8565	4669	1768
Quinquennial rapid HPV DNA_30-65 + vaccination	3502	5016	9619	12997	5484	3069	1222
Triennial conventional cytology_30-65 + vaccination¶				1667	1935	2269	3323
Quinquennial conventional cytology_30-65 + vaccination¶				1217	1462	1779	2850

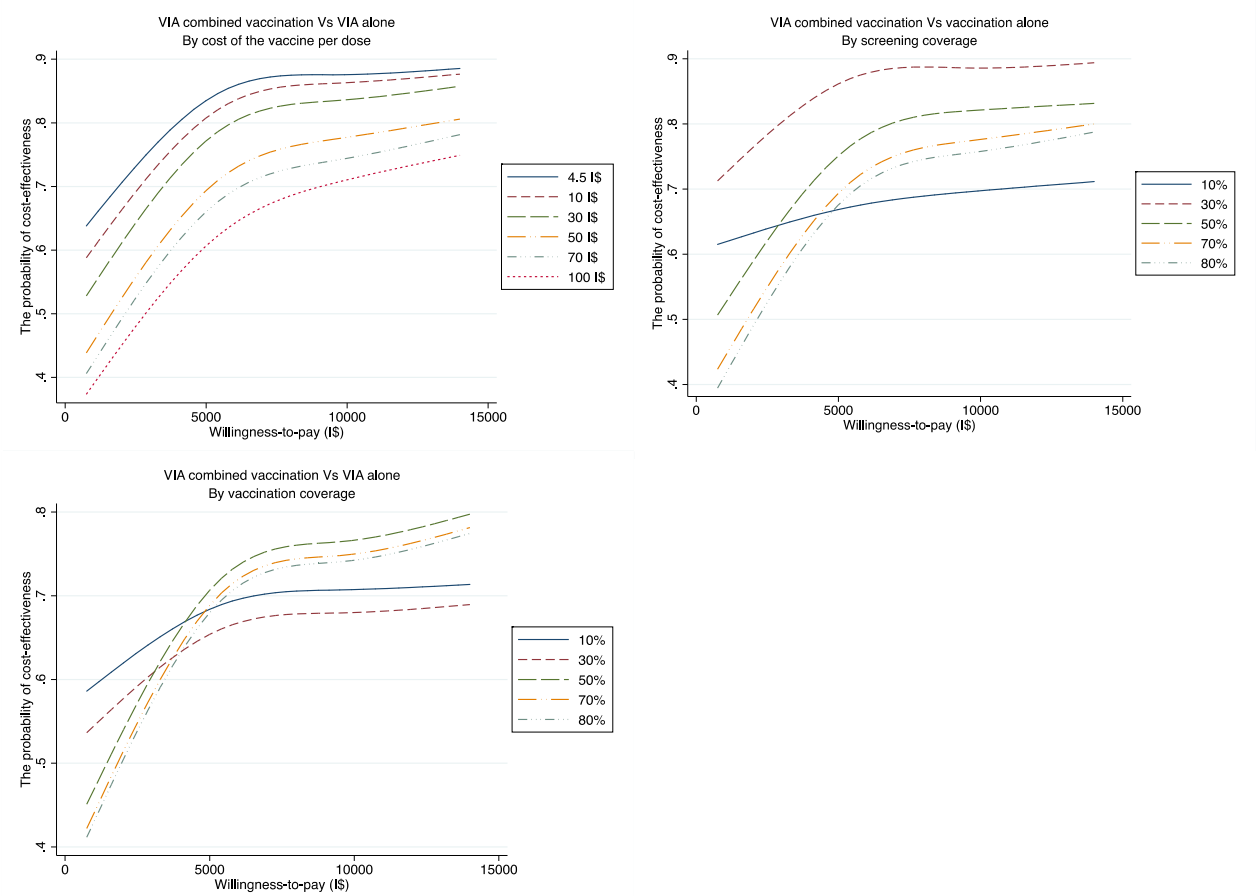
Note:
Except noted, all screening strategies are compared to VIA. Screening with 5-year interval is compared 5-year interval of VIA, and 3-year interval compared to 3-year interval of VIA.
All screening strategies are combined with girl vaccination, including VIA
† The sensitivity is assumed to be less than in base case in %.
¶ The strategy is compared to vaccination alone
D refers domination

Figure 4: The incremental cost-effectiveness of liquid-based cytology compared to conventional cytology by different sensitivity of conventional cytology



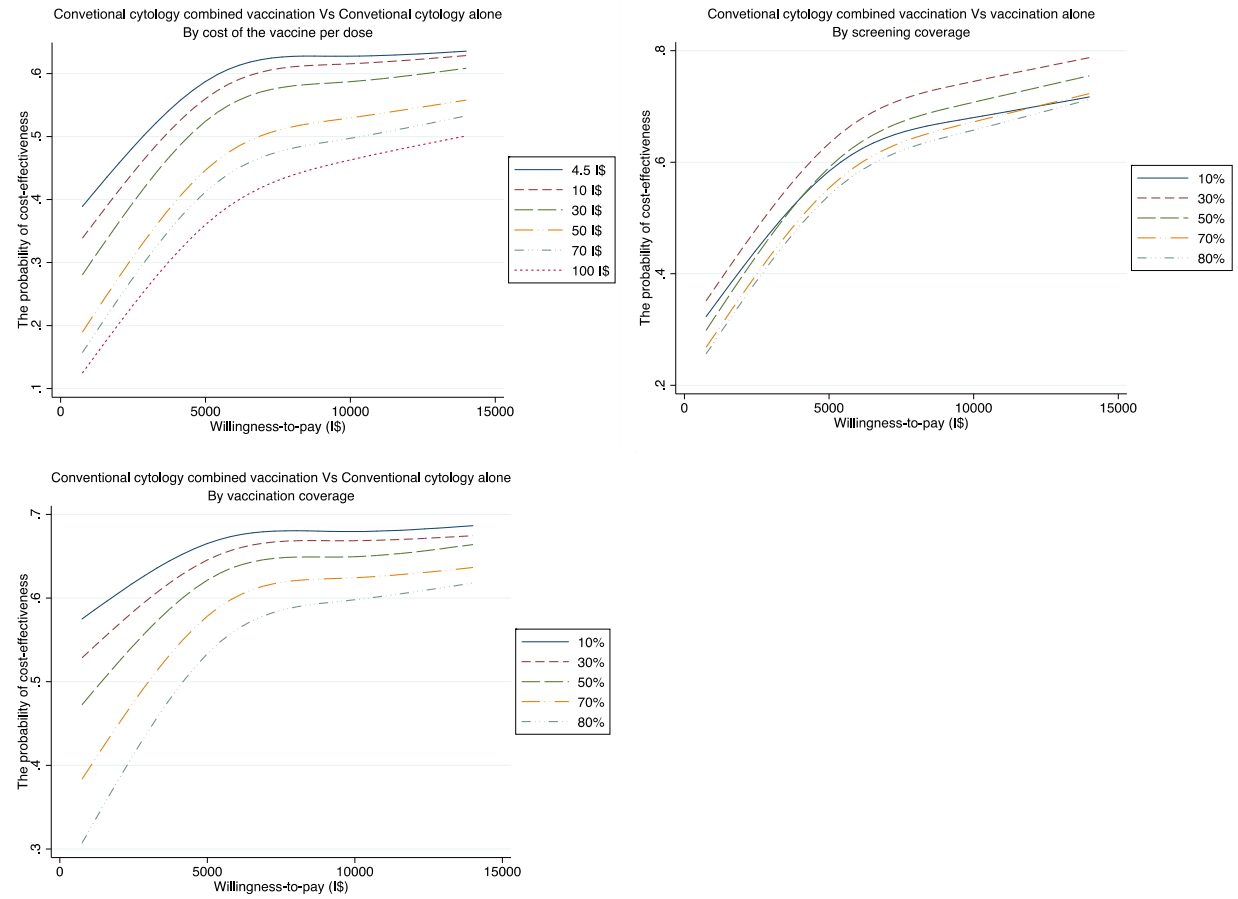
Note:
The screening is five-yearly
The strategies are combined with girl vaccination
The threshold of cost-effectiveness is 4822

Figure 5: The probability of cost-effectiveness of five-yearly VIA combined with vaccination by cost of vaccine, screening and vaccination coverage.



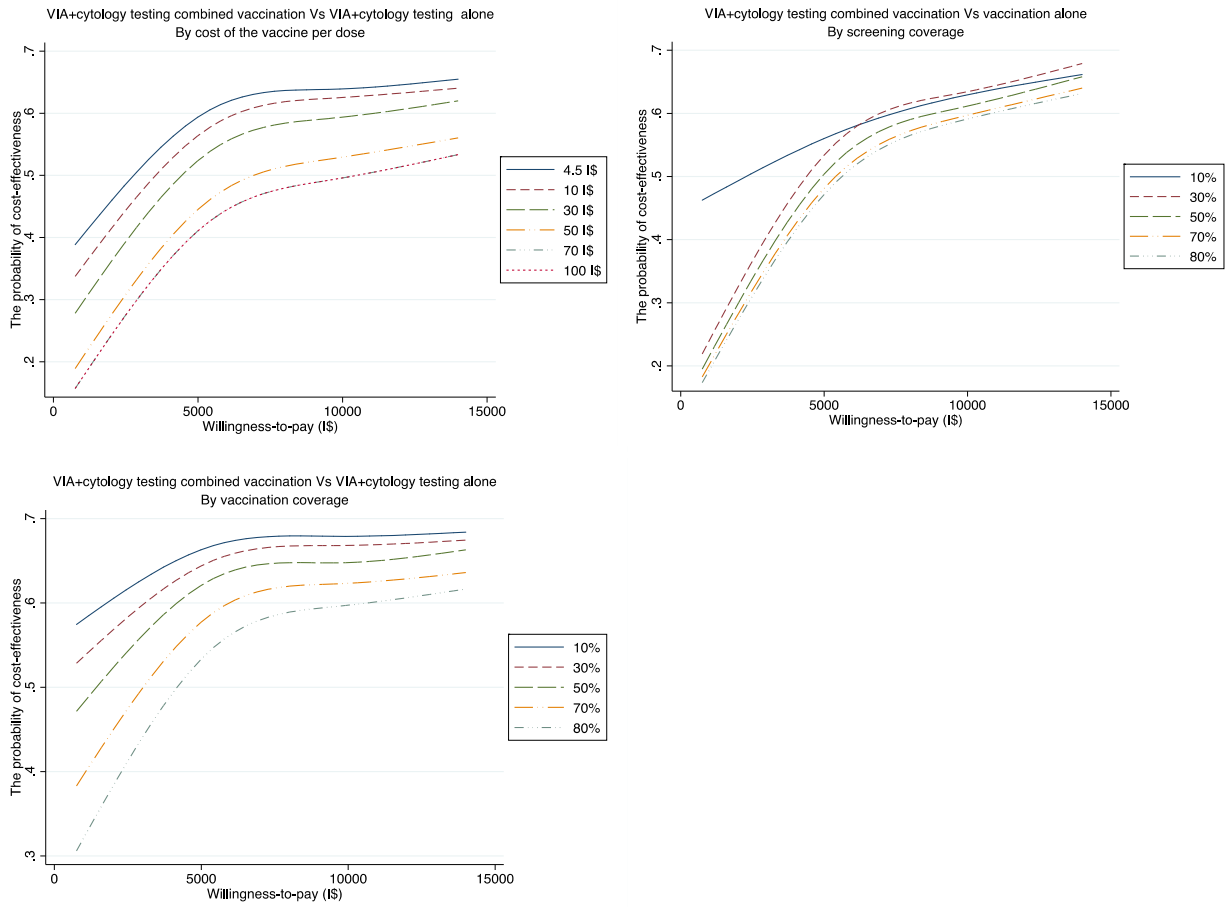
Note : By cost of vaccine and vaccination coverage, the combined strategy is compared to VIA alone. By screening coverage, the combined strategy is compared to vaccination alone.

Figure 6: The probability of cost-effectiveness of five-yearly conventional cytology combined with vaccination by cost of vaccine, screening and vaccination coverage.



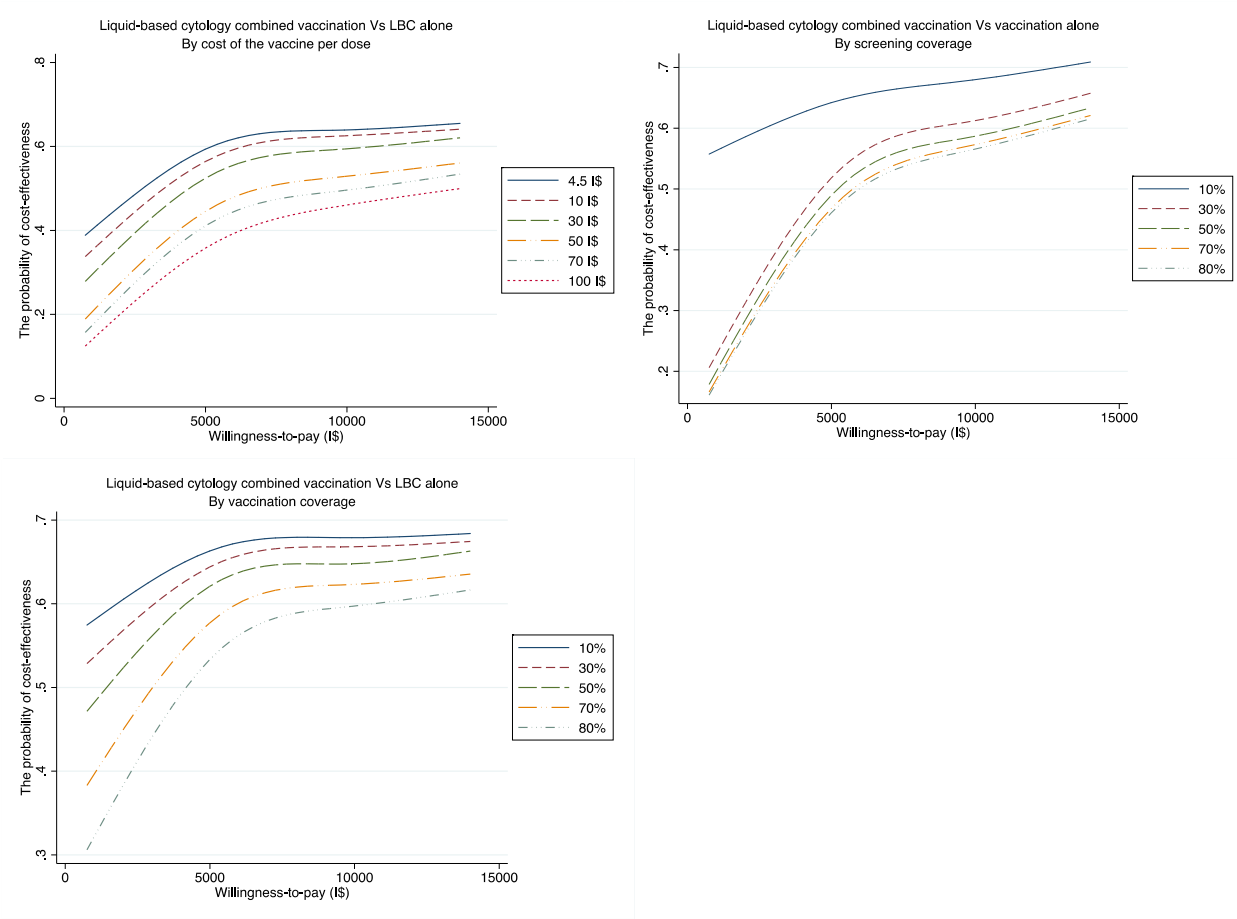
Note : By cost of vaccine and vaccination coverage, the combined strategy is compared to conventional cytology alone. By screening coverage, the combined strategy is compared to vaccination alone.

Figure 7: The probability of cost-effectiveness of five-yearly combined VIA and cytology testing in addition to vaccination by cost of vaccine, screening and vaccination coverage.



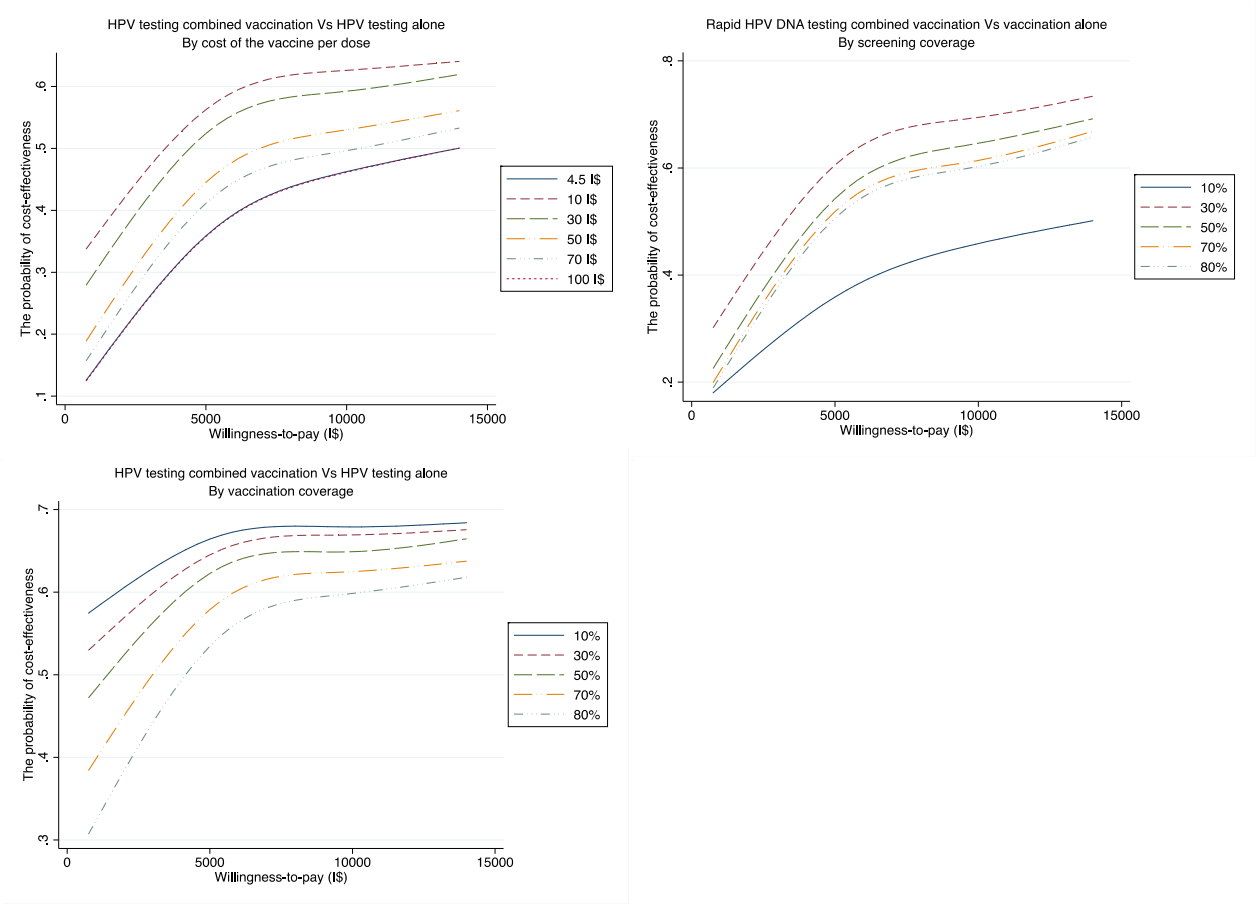
Note : By cost of vaccine and vaccination coverage, the combined strategy is compared to combined VIA and cytology testing alone. By screening coverage, the combined strategy is compared to vaccination alone.

Figure 8: The probability of cost-effectiveness of five-yearly liquid-based cytology combined with vaccination by cost of vaccine, screening and vaccination coverage.



Note : By cost of vaccine and vaccination coverage, the combined strategy is compared to liquid-based cytology alone. By screening coverage, the combined strategy is compared to vaccination alone.

Figure 9: The probability of cost-effectiveness of five-yearly rapid HPV DAN testing combined with vaccination by cost of vaccine, screening and vaccination coverage.



Note : By cost of vaccine and vaccination coverage, the combined strategy is compared to rapid HPV DNA testing alone. By screening coverage, the combined strategy is compared to vaccination alone.

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