ECONOMIC ANALYSIS OF STRATEGIES FOR CERVICAL CANCER PREVENTION AND CONTROL IN INDONESIA

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ECONOMIC ANALYSIS OF STRATEGIES FOR CERVICAL CANCER PREVENTION AND CONTROL IN INDONESIA

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ABSTRACT

Evidence-based decision-making of healthcare interventions emerges from economic analysis. This study aimed to determine the cost effectiveness of strategies for cervical cancer prevention and control in Indonesia.

An existing computer-based Markov model of the natural history of cervical cancer disease which was first developed for Thailand setting was adopted to simulate an age-stratified cohort of women in Indonesia. Seventeen strategies such as single or combination strategies of human papillomavirus (HPV) vaccination for adolescent girls at age 12 years old; screening with visual acetic acid (VIA) for women aged 30 – 45 years old; and screening with Pap smear for women aged 30 – 65 years old were analyzed and compared with existing strategy of treatment for cervical cancer or “do nothing” strategy. The strategies varied in combinations of intervention and interval for screenings. A base case of 20% screening coverage rate and 80% vaccination coverage rate was assumed. The scenarios of 50% and 80% screening coverage were also assigned. The study also analyzed the assumption of providing 2 and 3 vaccine doses.

All screening strategies had incremental cost effectiveness ratios (ICERs) less than per capita GDP of Indonesia in 2013 (IDR 35 million or USD 3,475). The most cost effective strategy with the lowest ICER was screening with VIA every 5 years, where the incremental cost effectiveness ratios (ICERs) were IDR -204,000 (USD -19.77) per quality adjusted life year (QALY), a cost saving strategy in a societal perspective; and IDR 634,000 (USD 61.45) per QALY, in a health system’s perspective. All strategies involving vaccination had ICERs between 1 – 3 times GDP. The ICER for providing HPV vaccination as single intervention revealed from this study were IDR 77.6 million (USD 7,522) per QALY and IDR 46.3 million (USD 4,490) per QALY for 3 and 2 doses assumptions, respectively, in a societal perspective. Meanwhile, in a health system’s perspective, ICER for vaccinations were IDR 77.8 million (USD 7,541) per QALY and IDR 48.4 million (USD 4,689) per QALY for 3 and 2 vaccine dose strategies, respectively.

Based on economic evidence, the results of the study support a continuation of the pilot program of VIA in Indonesia with economic evidence. Moreover, scaling up the screening program for the whole country, making the program equitable for every woman, is strongly recommended.

KEY WORDS: ECONOMIC ANALYSIS / MARKOV MODEL / CERVICAL CANCER / SCREENING / PAPILLOMAVIRUS VACCINES / INDONESIA

234 pages

CONTENTS

CONTENTS (cont.)

CONTENTS (cont.)

CONTENTS (cont.)

LIST OF TABLES

LIST OF TABLES (cont.)

LIST OF TABLES (cont.)

LIST OF FIGURES

LIST OF FIGURES (cont.)

LIST OF FIGURES (cont.)

LIST OF ABBREVIATIONS

AAT	Acetic acid test
AOGIN	Asia Oceania Research Organisation in Genital Infections and Neoplasia
ASR	Age-Standardized incidence Ratio
ASCUS	Atypical squamous cells of undertermined significance
ASEAN	Association of Southeast Asian Countries Nation
BIA	Budget impact analysis
BCR	Benefit to cost ratio
CBA	Cost benefit analysis
CBR	Cost to benefit ratio
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CrI	Credibility interval
CIS	Carcinoma in situ
CIN	Cervical intraepithelial neoplasia
CKC	Cold knife cone
CMA	Cost minimization analysis
CO_2	Carbon dioxide
COI	Cost of illness
C4P	Cervical Cancer Prevention and Control Costing
CUA	Cost utility analysis
DALY	Disability adjusted life year
DAM	Decision analytic modelling
DES	Discrete event simulation
DNA	Deoxyribonucleic acid
DRG	Diagnosis related group
DVI	Direct visual inspection
EPI	Expanded Programme on Immunization

LIST OF ABBREVIATIONS (cont.)

EQ-5D	EuroQol-5 dimensions
EVPI	Expected value of perfect information
FIG	Fully immunized girl
FIGO	The International Federation of Gynecology and Obstetrics
GDP	Gross domestic product
GNI	Gross national income
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRQOL	Health related quality of life
HSIL	High grade of squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICC	Invasive cervical cancer
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost utility ratio
INA-CBG	Indonesia-case base groups
INA-DRG	Indonesia-diagnose related groups
LBC	Liquid-based cytology
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low grade of squamous intraepithelial lesion
LY	Life Year
MCMC	Markov chain monte carlo
MOH	Ministry of Health
MOHA	Ministry of Home Affair
MOE	Ministry of Education
N_2O	Nitrous oxide
NPV	Negative predictive value
NPV	Net present value
NSB	National Statistical Bureau
Pap smear	Papanicolaou smear
PPV	Positive predictive value

LIST OF ABBREVIATIONS (cont.)

PSA	Probabilistic sensitivity analysis
PVLE	Present value of loss earning
QALY	Quality Adjusted Life Year
RCT	Randomized control trial
SE	Standard error of mean
STM	State transition model
SVA	Single visit approach
TBS	The Bethesda system
UK	United Kingdom
US	United State
USD	United State dollar
VAS	Visual analogue scale
VBA	Visual Basic Application
VIA	Visual Inspection with Acetic acid
VIAM	Visual Inspection with Acetic acid with low-level magnification
VILI	Visual inspection using Iodine solution
WHO	The World Health Organization
WTP	Willingness to pay
YLL	Years of life lost
c1_ini	Cost of treatment; stage I-initial
c2_ini	Cost of treatment; stage II-initial
c3_ini	Cost of treatment; stage III-initial
c4_ini	Cost of treatment; stage IV-initial
cColdknife	Cost of treatment by cold knife conization
cCryo	Cost of cryosurgery
cFU	Cost of follow up
cLEEP	Cost of treatment by Loop electrosurgical excision procedure
cPap	Cost of Pap smear
cPapConf	Cost of confirmation test of Pap smear
cSimhys	Cost of simple hysterectomy
cStaging	Cost of cervical cancer staging

LIST OF ABBREVIATIONS (cont.)

cVac	Cost of 3-doses Human papillomavirus vaccine
cVIA	Cost of VIA
False +ve	False positive
False -ve	False negative
p1_Dying	Probability of dying from invasive cervical cancer stage I
p2_Dying	Probability of dying from invasive cervical cancer stage II
p3_Dying	Probability of dying from invasive cervical cancer stage III
p4_Dying	Probability of dying from invasive cervical cancer stage IV
PapSe	Sensitivity of Pap smear on detection of pre-invasive cancer
PapSe_1	Sensitivity of Pap smear on detection of invasive cancer stage I
PapSp	Specificity of Pap smear on detection of pre-invasive cancer
pCIN1 to CIN23	Age-specific progression rate; CIN-1 => CIN-2 or CIN-3
pCIN1 to HPV,Healthy	Age-specific regression rate; CIN-1 => HPV infection or Healthy
pCIN23 to CIN1,Healthy	Regression rate from CIN-2/3 to CIN-1 or Healthy
pCIN23 to InvC	Progression rate; CIN-2/3 => invasive cancer
pCompCryo	Probability of having complication from cryosurgery
pDying	Age-specific probability of dying from general causes
pHPVtoCIN1	Progression rate; HPV infection => CIN-1
pHPVtoHealthy	Age-specific probability of regression; HPV infection => Healthy
pItoII	Progression rate; stage I => stage II
pIItoIII	Progression rate; stage II => stage III
pIIItoIV	Progression rate; stage III => stage IV
pIncHPV	Age-specific incidence of HPV infection
prCIN1 to Healthy	Proportion of CIN-1 reverting to Healthy
prCIN23 to Healthy	Proportion of CIN-2/3 reverting to Healthy
prSym1	Proportion of stage I having symptoms
prSym2	Proportion of stage II having symptoms
prSym3	Proportion of stage III having symptoms
prSym4	Proportion of stage IV having symptoms
RRVac	Relative risk of HPV vaccine
TpCIN1	All possible transition of “CIN-1” state

LIST OF ABBREVIATIONS (cont.)

TpCIN23	All possible transition of “CIN-2/3” state
TpHealthy	All possible transition of “Healthy” state
TpHPV infection	All possible transition of “HPV infection” state
TpStageI	All possible transition of invasive cervical cancer “Stage I”
TpStageII	All possible transition of invasive cervical cancer “Stage II”
TpStageIII	All possible transition of invasive cervical cancer “Stage III”
TpStageIV	All possible transition of invasive cervical cancer “Stage IV”
True +ve	True positive
True -ve	True negative
VIASe	Sensitivity of VIA on detection of pre-invasive cancer
VIASe_1	Sensitivity of VIA on detection of invasive cancer stage I
VIASp	Specificity of VIA on detection of pre-invasive cancer

CHAPTER I
INTRODUCTION

1.1 Background and Rationale

The global burden of cervical cancer is high including morbidity, mortality, and economic burden. Cervical cancer is the fourth most prevalent cancer in the world. In South-East Asian region, it is the second most prevalent cancer after breast cancer (1,2). The annual number of cases is 493,243 and approximately 275,000 women die every year from cervical cancer, as reported in 2007 (3), while in 2012 the annual new cases and death are 528,000 and 266,000, respectively (2). Cervical cancer cause 2.7 million years of life lost (YLL) in the year of 2000. The number of case is predicted to rise 430,000 per year by 2030. The economic burden of HPV-related disease is USD 3.4 billion per year in US (4). Of the total estimated HPV-attributable cancer, 94% affect women and 80% are in developing countries (5,6). Almost 99% of cervical cancer cases are caused by human papillomavirus (HPV). It is a DNA virus that infects epithelial (skin or mucosal) cells. There is known about 100 HPV genotypes and 15 of which are high risk types (7). About 70% of invasive cervical cancers in the world are attributed to HPVs 16 or 18, while 30% of the cases are caused by the other HPV genotypes (3).

Currently, there are two general strategies to prevent and control cervical cancer disease which are HPV vaccination and screenings. The screenings include cytology screening or Papanicolaou (Pap) test, screening tests based on visual examination of the uterine cervix (visual inspection with acetic acid or VIA), and HPV testing systems which able to detect the presence of viral markers (HPV-DNA in exfoliated cervical cells). The objective for cervical screening is to prevent invasive cervical cancer by detecting and treating women with high-grade cervical intraepithelial neoplasia (CIN 2 and 3 lesions). Within the last 3 decades, cytological screening has been available and established as an efficient strategy in many developed countries. The VIA screening is an adoption method from the cytology-

based screening programs to be implemented in developing countries. The HPV test system, the newest method, has the highest accuracy among all screening tools. However, this method is only affordable in middle and high income country due to the need of some levels of sophisticated technology. The goal of HPV vaccination is to reduce the incidence of anogenital cancer, which vaccination can achieve by inducing immunity against the high risk genotypes of HPV, thereby preventing persistent infection with these HPV types. Currently, there are two types of HPV vaccines available in the market, which are bivalent vaccine and quadrivalent vaccine. Bivalent vaccine able to protect against the two HPV types (HPV-16 and HPV-18) that cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers, while quadrivalent vaccine also able to protect against the two HPV types (HPV-6 and HPV-11) that cause 90% of genital warts (8-10).

Indonesia is one of developing countries whose population is at risk for cervical cancer about 79.14 million (female population aged ≥ 15 years old) in 2010. In Indonesia, cervical cancer is the second most frequent cancer in women of reproductive age 15-44 years old and the third most frequent in all age. The annual number of cases is 13,762 and each year 7,493 women die from cervical cancer; the age-standardized incidence rate (ASR) of cervical cancer in Indonesia is 12.7 per 100,000 women and year, as was reported in 2010(11). The number of cases and deaths from cervical cancer increase over the time. The crude incidence rate and crude mortality rate reported in 2012 are 17.0 per 100,000 and 7.7, respectively. (2). About 81.0% of invasive cervical cancers in Indonesia are attributed to HPVs 16 or 18. Risk factors of HPV infection and cervical cancer cases in Indonesia are young age at first intercourse, multiple sexual partners and high parity (12-14).

The facts that cervical cancer causes serious health problems including high morbidity, mortality, and economic burden in Indonesia need such strategies for cervical cancer prevention and control to be implemented. Currently, there is no strategy for cervical cancer prevention and control yet as routine organized-program in national level; the VIA pilot program has been started since 2007 in several provinces. Given the limited sources of budget to provide the health care services to all population, the government needs to set the priority of strategies to be implemented. WHO recommends a country to conduct economic evaluation before implementing

such strategies for cervical cancer prevention and control. Economic evaluation is a tool to help priority setting. It compares the consequences of interventions such screening and vaccination program with the costs and guides policy makers wishing to maximize the benefits produced by the scarce resources available to them (15). Many studies on economic evaluation related to HPV vaccination and screening for cervical cancer had been conducted in many countries (16-18). Most of the studies reported that HPV vaccination in female is cost-effective compare to screening strategy. Even though there are many results of economic evaluation provided from other studies, it is necessary to conduct the study in Indonesia setting to get more appropriate results based on Indonesia country-specific setting. Moreover, it can be useful as an additional knowledge in the field of economic evaluation in Indonesia and introduce the results of economic evaluation as one of considerations in health-policy decision-making.

1.2 Objectives

General objective

To conduct the economic analysis of strategies for cervical cancer prevention and control in Indonesia setting by providing a semi model-based economic evaluation.

Specific objective

1. To measure health and economic burden of cervical cancer disease in Indonesia.
2. To develop the economic evaluation models of strategies for cervical cancer prevention and control in Indonesia
3. To explore the most cost-effective strategy

1.3 Expected outcomes and benefits

The results of the study are expected to be an input for the government of Indonesia to formulate the decision making in cervical cancer prevention and control. Moreover this study efforts the development of economic evaluation study in

Indonesia and supports the introduction of economic evidence in healthcare-policy decision-making in Indonesia.

CHAPTER II
LITERATURE REVIEW

This chapter summarizes review of literature related to the topic of study and consists of part as follows:

1. Cervical cancer disease
    a. Epidemiology
        i. Global situation of cervical cancer epidemiology
        ii. Epidemiology of cervical cancer in Indonesia
    b. Etiology
        i. Global etiology of cervical cancer
        ii. Etiology of cervical cancer in Indonesia
    c. Natural history of cervical cancer
    d. Management of cervical cancer-related diseases
2. Health policy on cervical cancer prevention and control
    a. Effectiveness of strategies for cervical cancer prevention and control
    b. Guidelines for implementation of strategies for cervical cancer prevention and control
    c. Current strategies for cervical cancer prevention and control in Indonesia
3. Economic evaluation
    a. Methods of economic evaluation
    b. Decision modeling for economic evaluation
    c. Economic evaluation of cervical cancer prevention and control

2.1 Cervical cancer disease

2.1.1 Epidemiology

Global situation of cervical cancer epidemiology

Cervical cancer is one of diseases that causes serious health problems including high morbidity, mortality, and economic burden worldwide. Cervical cancer becomes the top leading cause of female cancer deaths in the world. From the data reported by the World Health Organization, the age standardized incidence rate (ASR) is 16 per 100,000 women, the annual newly diagnosed cases accounts for 493,243, and there are about 1.4 million prevalent cases and approximately 275,000 women die every year from cervical cancer in the year 2002 (3,5). According to the update data reported by GLOBOCAN in 2008, cervical cancer becomes the third most common cancer in women, and the seventh of overall, with an estimated 529,000 new cases (6). Based on more recent report by GLOBOCAN, the annual new cases and deaths of cervical cancer in 2012 are 528,000 and 266,000, respectively (2). The economic burden of the health care associated with cervical cancer and other human papillomavirus infections is high as it is second only to human immunodeficiency virus among sexually transmitted diseases. A review study mentioned that the annual direct costs associated with cervical cancer in the United States of America adjusted in the fiscal year of 2004 range from $US300-400 million and in contrast, the annual direct medical costs associated with cervical precancerous lesions range from $US700 million-$US2.3 billion (19). Other review study reported that the annual health care costs of human papillomavirus-related conditions in the US range from $2.25-4.6 billion (2005 US dollars). The diseases also impact to the health-related quality of life including areas of emotional, social, and sexual functioning (20).

Unfortunately, the global burden of cervical cancer mostly occurs in developing-countries whose low- and medium-resources. More than 80% of the cases worldwide occur in high risk regions including sub-Saharan Africa, South and Southeast Asia, and South and Central America (5). Among all the mortalities caused by cervical cancer, 88% of which occur in these regions which the highest number belongs to Asia region (6).

Epidemiology of cervical cancer in Indonesia

As in any other developing countries, cervical cancer in Indonesia remains a major health problem. The number of cases in term of incidence and mortality is statistically stabile and relatively tends to increase over the time. Epidemiological data related to cervical cancer in Indonesia has been reported, referring from hospital-based and population-based data.

Pathology-based data from hospital in 1988-1991 reported that cervix cancer is the most frequent and primary cancer with the rate range between 18.41-19.18% by year among the top 10 most frequent cancers in Indonesia, as well as the most frequent and primary cancer with the rate range between 28.66-29.63% by year among the top 10 most frequent cancer in female in Indonesia. These trends are similar by geographic distribution in different main island region in the country (21). Pathology-based data from top national referral hospital in 2002 revealed that cervical cancer is the most frequent cancer among females with the number of cases is 2,532 and followed by ovarian cancer and uterine cancer. The peak age of cervical cancer patients is 45-54 years. Data from various academic hospitals in 2007 showed that cervical cancer is the most common malignancy. The distribution of cervical cancer in each stage is 14.1%, 35.5%, 44.7%, 5.7%, respectively, in stage I, II, III, IV (12).

A population-based study conducted in three regions, Jakarta, Bali and Tasikmalaya, between October 2004 and February 2006 involving a total of 2,686 women aged 12-70 years gave result that the overall HPV prevalence is 11.4% (intermediate), age-standardized to the world standard population 11.6%. The overall age-specific prevalence in Indonesia is high in all ages (≥ 9.8%) and ranges from 9.8 to 13.3% in three regions (14). Data from the population-based cancer registry in Jakarta province showed the leading cancers among females in 2005-2007 to be breast cancer and cervical cancer, with the incidence rates are 18.6 per 100,000 and 9.25 per 100,000, respectively. Based on Basic Health Research 2007, cancer is the 7th cause of deaths (5.7% of all mortality). National prevalence of cancer is 4.3 per 1000 population (22).

Recently report from WHO in 2010 (11), provides key information on cervical cancer in Indonesia and its related issues. Indonesia is one of developing countries whose population at risk for cervical cancer about 79.14 million (female

population aged ≥ 15 years old). In Indonesia, cervical cancer is the second most frequent cancer in women of reproductive age 15-44 years and the third most frequent in all ages. The annual number of cases is 13,762 and each year 7,493 women die from cervical cancer. The number of case and death from cervical cancer are increasing over the time. The age-standardized incidence rate (ASR) of cervical cancer in Indonesia is 12.7 per 100,000 women and year. It is in the middle rank among Southeast Asian countries (6.8 to 27.4 per 100,000 women and year) and less than the world's ASR (16 per 100,000 women and year), but the number of cases is quite high due to the high number of population. Meanwhile, the recently report of cervical cancer epidemiology in Indonesia stated that its crude incidence and crude mortality rate were 17.0 and 7.7 per 100,000 population (2).

Among ASEAN country members, cervical cancer is the second most diagnosed cancer and the third leading cause of cancer deaths in females, accounting for 11% of the total new cancer cases and 9% of the total cancer deaths among female in 2008. The total burden of cancer in Indonesia is 1,841 DALYs lost per 100,000 in which cervical cancer is accounted for about 6.25% of the total cancer burden. The burden of cervical cancer in Indonesia among other ASEAN countries is in the middle rank after the highest number in Cambodia, followed by Myanmar, Laos, and Thailand (23).

2.1.2 Etiology

Global etiology of cervical cancer

Cervical cancer has been confirmed biologically and epidemiologically as the human cancer that is entirely attributable to infection (24-26). It is persistent infection with oncogenic human papillomavirus (HPV) that causally been associated with cervical cancer (27). Others than cervical cancer, there are some clinical sequelaes of HPV infections. The attributable to oncogenic HPV for some clinical sequelaes of HPV infections are as follows: cervical cancers (100%); anogenital cancers including anal (90%), vulvar (40%), vaginal (40%), and penile (40%); oropharyngeal cancers (12%), anogenital warts/candyloma (90%); and reccurent respiratory papillomatosis (28-31).

There are approximately 100 types of HPV have been identified (25,27,28). More than 40 types of HPV types are genital mucosal types (25,30,32)that regularly or sporadically infect the mucosal epithelial surfaces (33). Within these groups there are the “high-risk” types and the “low-risk” types (24,32,33) which are grouped by the level of oncogenicity (34). The high-risk group consists about 15 types including HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and type 82 (7). This group is known to be oncogenic (30,33), causing cervical precancerous lesions including low-grade and high-grade cervical cell abnormalities (in other term cervical intraepithelial neoplasia III/CIN III) that are precursors to cervical and anogenital cancers (28,30). While the low-risk group of HPV types includes HPV 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, and CP6108 (33,34). Other experts also classify HPV type 26, 53, and 66 as probable high-risk types (7). These groups can cause low-grade cervical cells changes and genital warts (28). Genital warts rarely progress to cancer, however they are considerable cause of morbidity and significantly contribute to health care cost in many countries (24).

Among the high-risk types, the most frequent oncogenic HPV types are HPV type 16, 18, 45, 31, 33, 52, 58 and type 35 (32). Although the HPV type-distribution in women with cervical cancer might be different by geographical areas, HPV 16 and 18 dominate the oncogenic HPVs in the genital tract (33) as it accounts for nearly 80% of all cervical cancer cases (24,30,33,35). Most studies and reviews mentioned that HPV 16 is associated with about 50-60% of the cervical cancers and HPV 18 with about 10-20% (5,27,35,36). HPV 6 and 11 cause more than 90% of genital warts (33,35) and responsible for some 10% of low grade cervical lesions (35). The knowledge of HPV type-distribution has advantage in developing the vaccines to prevent this viral-caused disease.

Despite of HPV as a necessary cause of cervical cancer, there is also the role of cofactors that would influence HPV acquisition, its persistence and the development and progression from cervical HPV infection to cancer. The cofactors could be defined as environmental cofactors, host cofactors, and viral cofactors. The environmental factors include long-term use of oral contraceptives or other hormonal influences, high parity, tobacco smoking, co-infection with HIV which are as

established cofactors; co-infection with other sexually-transmitted disease such as *Chlamydia trachomatis* and herpes simplex virus type-2, immunosuppression, and inappropriate nutrition or diet which are as other probable cofactors. Host cofactors include genetic and immunological host factors such as immune response, genetic susceptibility, and genetic variations of- and polymorphisms in human leukocyte antigen and other genes. Viral factors or genetics include HPV type variant such as genotype and molecular variants, viral load and viral integration to the genome of the host cell. Host factors and viral factors are likely to be important but have not been clearly identified (25,26,31,32).

Other important issue in HPV infection is that basically it is a sexually transmitted disease. Cervical cancer as genital HPV infection has the risk factors which are clearly related with the individual's sex behavior. The risk increases with the early age at the start of the first sexual relationships, high number of sexual partners throughout life, and sexual contacts with high risk individuals. Therefore male circumcision and the use of condom are factors that can reduce the transmission of cervical cancer although without totally preventing (28,31).

Etiology of cervical cancer in Indonesia

A hospital-based study to assess the HPV type distribution was conducted in Indonesia in the period October 2001 to March 2002 to detect HPV DNA in 96% of the cervical cancer specimens. There are 12 different HPV DNA types. The three most common types are 16 (44%), 18 (39%), and 52 (14%). In 14% of the specimens, multiple HPV types are present (37). An update population-based study was conducted from October 2004 to February 2006. The most prevalent types found are HPV 52, HPV 16, HPV 18, and HPV 39, respectively, 23.2, 18.0, 16.1, and 11.8% of the high-risk HPV types. In 20.7% infections, multiple types are involved. Remarkably, in Indonesia HPV 16 and HPV 18 are equally common in the general population, as they are in cervical cancer. HPV 52 is the most prevalent type in the general population (14). Other review study mentioned the five most prevalent HPV types in women with cervical cancer in Indonesia are HPV-18(43%), HPV-16 (38%), HPV-52 (9.1%), HPV-45 (7.4%) and HPV-82 (2.1%). The five most prevalent HPV types in women with normal cytology are HPV-51 (4.5%), HPV-16, HPV-18 and HPV-56 (2.0%), and HPV 52 (1.0%) (13).

HPV type distribution in Southeast Asia countries is similar to that of worldwide (13). HPV-16 and 18 are the two most common HPV types in Southeast Asia; although HPV-18 alone is relatively more frequent compared to the type distribution estimates in the rest of the world. This is noteworthy for Indonesia where HPV-18 is the leading HPV type in cervical cancer (12,13,37).

Based on current WHO estimation, the prevalence of HPV in the general population (among women with normal cytology) is 31%, prevalence of HPV type 16 and 18 among women with normal cytology is 4.0% and among women with cervical cancer is 80.1% (11).

Similar to other countries, factors that increase the risk of cervical cancer in Indonesia include young age at first intercourse, multiple sexual partner and high parity (12-14). Other risk factors identified are age over 50 years, lower education and unemployment (12,34).

2.1.3 Natural history of cervical cancer disease

The natural history of cervical cancer involves the changing of the cervical tissue from a normal state to varying states of cellular abnormalities that ultimately lead to cervical cancer (34). The process starts firstly from the HPV infection transmitted. Transmission modes proposed, but unproven, include vertical transmission during birth, genital skin to skin contact, and sexual abuse in children (38). The acquisition of HPV infection occurs soon after the onset of sexual activity (28), therefore the probability of HPV transmission increases after the initiation of sexual activity (39).

The natural history of HPV infection and cervical cancer is presented in Figure 2.1. The peak prevalence of transient infections with carcinogenetic types of HPV occurs among women during their teens and 20s, after the initiation of sexual activity (39). The prevalence of high-risk HPV types peaks at 30-50% for young women in age 20s and 30s. The prevalence declines to 15% for women 26-30 years of age, to 10% for women 31-35 and to an underlying population prevalence of 5-15% during the fourth, fifth, and sixth decades of life (35). Most HPV infections are transient and asymptomatic, in general cause no clinical problems. About 70% of new HPV infections clear within 1 year, 90% clear within 2 years (28). However, persistent

infection with oncogenic types of HPV can progress to precancerous lesions and to cancer (28,30). The progression from HPV infection to HPV persistence to the development of high-grade pre-cancer lesion and ultimately invasive cervical cancer appears to take a quite long time, on average, up to about 15 years (30).

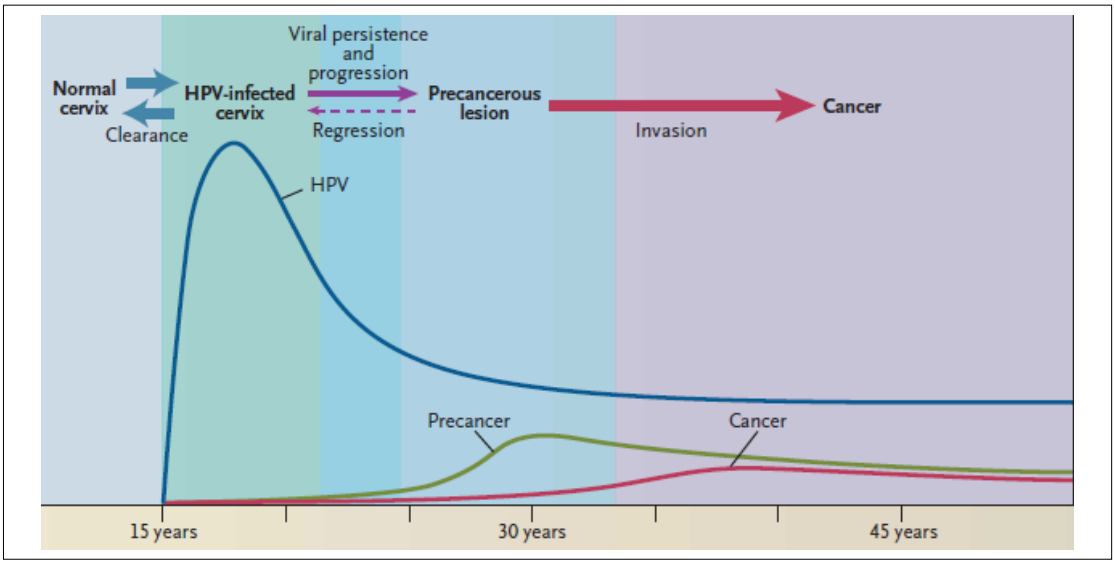


Figure 2.1 Natural history of HPV infection and cervical cancer (Source: (39)).

Natural history of pre-cancer

There are several morphological classifications to classify the cervical pre-cancer lesions, including the dysplasia carcinoma in situ (CIS) classification, the CIN (cervical intraepithelial neoplasia) classification, and the Bethesda System (TBS). These systems are developed based on cytology and histology as are reflected in Table 2.1 These classifications are recommended by WHO to be used for reporting (40).

Women with persistent oncogenic HPV infections have the greatest risk of developing cervical pre-cancer and cancer. Result from a population-based study showed that women with type-specific persistence for more than 2 years were 800 times more likely to develop to a high-grade cervical lesion (30). Not all persistent infectious progress to high-grade cervical lesion. Precursor lesions of the cervix persist longer and progress more quickly in women with oncogenic HPV infections than in women with non-oncogenic infections or without HPV (34). The half-life of infections by HPV has been estimated at 8-10 months for the high risk types and of approximately half that for low risk types (31). Sixty percent or more of cases of mild

dysplasia resolve spontaneously and only about 10% progress to moderate or severe dysplasia within 2–4 years; in some cases, moderate or severe dysplasia may occur without an earlier detectable mild dysplasia stage (40).

Table 2.1 Different terminologies used for cytological and histological reporting of cervical pre-cancer (Source: (40))

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
Pap	**Bethesda system**	**CIN**	**WHO descriptive classifications**
Class I	Normal	Normal	Normal
Class II	ASC-US /ASC-H	Atypia	Atypia
Class III	LSIL	CIN 1 including flat condyloma	Koilocytosis
Class III	HSIL	CIN 2	Moderate dysplasia
Class III	HSIL	CIN 3	Severe dysplasia
Class IV	HSIL	CIN 3	Carcinoma in situ
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion;HSIL: high-grade squamous intraepithelial lesion; ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells: cannot exclude a high-grade squamous epithelial lesion

Natural history of invasive cervical cancer

Invasive cervical cancer is defined by the invasion of abnormal cells into the thick fibrous connective tissue underlying the basement membrane. Less than 50% of cases of severe dysplasia progress to invasive carcinoma, with much lower rates seen in younger women (40). Time for progression from high grade lesion (CIN 2/3) to invasive cervical cancer has been described to take from 5 to 20 years. In screened populations, cervical cancer has been reported, before 20 years of age, gradually increasing to a plateau level by the early 30s that does not decrease in the later years. In unscreened populations, the incidence of cervical cancer continues to increase as a woman ages (38).

The most common symptoms of cervical cancer are post-coital bleeding, vaginal discharge or intermittent spotting. These symptoms should lead physician to perform a gynecological inspection, cervical cytology, Pap smears and/or cervical biopsies to result an accurate diagnosis. Cervical cancer is clinically staged. Clinical

stage is the most relevant prognostic factor in cervical cancer and the standard of care is still based on it (41). Cervical cancer staging from Federation International Gynaecology and Obstetrics (FIGO) classification as is presented in Table 2.2 is the most widely used classification. It is clinically assessed and based on tumor size, vaginal and/or parametrial involvement, and bladder/rectum tumoral extension (42).

Table 2.2 Carcinoma of the cervix of uteri-Staging (Source: (43))

FIGO Stages	Description
0	Carcinoma in situ (preinvasive carcinoma)
I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
IA	Invasive carcinoma diagnosed only by microscopy; all macroscopically visible lesions, even with superficial invasion, are stage IB
IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
IB	Clinically visible confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4 cm in greater dimension
II	Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina
IIA	Without parametrial invasion
IIB	With parametrial invasion
III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney
IIIA	Tumor involves lower third of vagina no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
IVB	Distant metastasis

If cervical cancer left untreated, it progresses in a predictable manner and will almost always lead to death (40). Mortality rates are substantially lower than the incidence; the ratio of mortality to incidence worldwide is 55%. Survival rates vary between region with quite good prognosis in low risk region (US and European countries) (44). Even among developing countries, a large variation in survival from cervical cancer is observed due to the variation in clinical stages of presentation and to the level of development of cancer related health services in the different countries (5). Five year survival rates for black patients in Uganda, Zimbabwe, and the Gambia are lower than 25%, while they are in the range of 30-50% in Cuba, India, Philippines; 50-60% in Costa Rica, Thailand, Turkey and in Mainland China; and more than 65% in Hongkong, Singapore and South Korea, similar to those in US and Europe (5). Five

years survival rate of stage I, II, III, IV cervical cancer in Indonesia are 50%, 40%, 20%, and 0%, respectively (12). Recent study reveals five years survival rates of cervical cancer in Indonesia are 73%, 52%, 36%, and 0% for stage I, II, III, and IV, respectively (45).

2.1.4 Management of cervical cancer-related diseases

The goal of cervical cancer-related management is to decrease the incidence and mortality of cervical cancer cases as well as improving patient's quality of life. Management of cervical cancer-related diseases could be defined as HPV vaccination, screening for cervical cancer, and treatment for precursor lesions and invasive cervical cancer.

HPV vaccination

The establishment of persistent HPV infection as a necessary causal of cervical cancer provides enormous potential for cancer prevention (5,27,35). Two public goals of an HPV vaccine are to reduce the incidence of cervical cancer and its precursor lesions as well as to reduce the incidence of other HPV-associated cancers and the benign conditions caused by HPV (30).

The clearly identification of HPV 16 and 18 to dominate the HPV-type distribution among women with cervical cancer (more than 80%); with low grade cervical lesions (LSIL) (25%) and with high grade lesions (HSIL) (50% to 60%) (35) as well as HPV 6 and 11 be responsible for 10% low grade cervical lesions and about 90% of the genital warts lead the development of vaccines containing those HPV types to prevent the oncogenic HPV infections and cervical cancers caused by those HPV types. At present, there are two vaccines, Gardasil® (46)and Cervarix® (47), purposed to prevent some oncogenic HPV infections. Details of the characteristics of those vaccines are presented in Table 2.3.

Table 2.3 Human papillomavirus vaccines (Sources: (30,33,46,47))

Characteristic	Gardasil®	Cervarix®
Year of US-FDA approval	2006	2009
Vaccine valency	Quadrivalent	Bivalent
L1 VLP antigens	HPV 6, 11, 16, 18	HPV 16, 18
Expression system	Yeast (S. cerevisidae)	Baculovirus
Adjuvant	ASO4	Aluminium
Volume and route	0.5 ml IM	0.5 ml IM
Schedule	0, 2, 6 months	0, 1, 6 months
Age recommended for vaccination	Female age 9-26 years	Female age 9-25 years
Protection	Cervical, vulvar, vaginal and anal cancer and their precursors caused by HPV 16 and 18; Genital warts caused by HPV 6 and 11	Cervical cancer and its precursor caused by HPV 16 and 18

According to some studies, the HPV vaccines have efficacy more than 90% to give protection against persistent infections caused by HPV type included in the vaccines. The vaccines also perform good safety with only minor side effects (27,28,33). It should be noted that the vaccines only give protection against specific HPV types that can cause cervical cancer (HPV 16 and 18). Therefore, they only can reduce the cervical cancer cases about 70-80%. Cross-protection data from current vaccines are limited. There is evidence from such studies that HPV 16/18 vaccines give cross-protection against persistent infection with non-vaccine oncogenic HPV types (HPV 31, 45), although the data are not statistically significant (30,33). Furthermore, these vaccines are prophylactic not therapeutic, they are unlikely to be effective as a treatment of women currently positive for a persistent HPV infection of the same type (35).

Screening for cervical cancer

Screening for cervical cancer is a public health intervention used on a population at risk, or target population. Screening is not undertaken to diagnose a disease, but to identify individuals with a high probability of having or of developing a cervical cancer disease (32,40). The objective for cervical screening is to prevent

invasive cervical cancer by detecting and treating women with high-grade cervical intraepithelial neoplasia (CIN 2 and 3 lesions). The relatively slow process of progression from HPV infection to pre-cancer lesions and to invasive cervical cancer allows the screening and early treatment programs to intervene this process (30). The effectiveness of screening is evaluated by the extent of reduction in cervical cancer incidence and mortality following screening. Cervical screening test such as cytology, visual and HPV tests are capable to identify women having pre-cancer lesions as well as early, preclinical invasive cancer (5).

- Cytology screening

The goal of cervical cytological screening programs is the detection of cervical cancer and precursor lesions. There are known two methods in cytology-based screening, namely conventional (Pap smear) and liquid-based cytology (LBC). In the Pap smear test, a sample of cells is taken from the transformation zone of the cervix using an extended-tip wooden spatula or brush; using a cotton swab is no longer recommended. The entire transformation zone should be sampled since this is where almost all high-grade lesions develop. The sample is then smeared onto a glass slide and immediately fixed with a solution to preserve the cells. The slide is sent to a cytology laboratory where it is stained and examined using a microscope to determine whether the cells are normal and to classify them appropriately (40). In the LBC technique, the cell sample is transferred to a liquid preservative solution, and the glass slide is prepared in the laboratory. The cell suspension remaining after preparation of the smear can be used for additional testing procedures. Quality control procedures are required for evaluation of the performance of the cytopathology laboratory as well as the performance of the health workers responsible for taking the samples (32).

Despite the success of widespread screening that resulted dramatic decreases in both the incidence of and mortality from cervical cancer in developed countries whose organized screening program, cytology screening with Pap test has limitations which the reported sensitivity and specificity of cytological screening vary widely due to a number of factors including small lesion size, inadequate sampling, and obscuring blood and debris which limit sensitivity (30). LBC was developed to improve the performance of Pap test (32) and was introduced in 1990s (40). However,

this technique is more expensive than conventional cytology and laboratory staff needed to be specially trained (40).

- Visual screening

This method is based on the fact that most precancerous and early cancerous lesions are visible to the naked eye after application of dilute acetic acid or Lugol's iodine solution (5). There are three techniques of visual screening including visual inspection with acetic acid (VIA), VIA with low-level magnification (VIAM) and visual inspection using Lugol's iodine solution (VILI) (32,40).

VIA, also known as direct visual inspection (DVI), as the acetic acid test (AAT), or cervicoscopy, is the most widely evaluated visual screening test (5). This technique involves naked-eye inspection of the cervix under bright light conditions at least 1 min after the application of 3-5% diluted acetic acid. The test can be carried out by nurses or midwives. It is a simple, inexpensive test, does not require a laboratory infrastructure. VIAM is VIA using a hand-held device to inspect the cervix. There is no evidence that this procedure improves the performance of the naked-eye visualization test. VILI stains glycogen stored in cervical epithelial cells. The yellow-colored changes associated with a positive VILI test result are recognized more easily by health workers than the acetowhite changes associated with VIA (32,40). The sensitivity data of VIA is similar to those for cervical cytology, while the specificity data is closer to those for HPV testing. The sensitivity data for VILI indicate that VILI is more sensitive test than VIA (32).

Visual screening has the advantages of relatively simple procedures, short-time, less costly than other approaches, providing result available immediately, allowing to provide a single visit approach for screening and treating. The disadvantages of this methods are the low positive predictive value of the test resulting in excessive diagnosis and treatment and unnecessary anxiety, the technique cannot be relied on in postmenopausal women due to the transformation zone of this women is often inside the cervical canal, no permanent record for being reviewed later (40).

- HPV testing

Given that invasive cervical cancer and its precursor lesions are associated with HPV infections of oncogenic types has led the development of using HPV testing as a primary screening tool for cervical neoplasia (5,30,32). HPV testing allows the

detection and subsequent eradication of pre-invasive cervical dysplasia (30); this method is based on the detection of high-risk HPV DNA in vaginal or cervical smears (40). Several techniques of HPV testing include hybrid capture as the most technique used, polymerase chain reaction (PCR) and enzyme immunoassay also been tested (30,32). In this method, sample of cells is collected from the cervix or vagina using a swab or small brush and then placed in a small container with a preservative solution. The specimen can be collected by a health care provider or by the woman herself, inserting a swab deep into the vagina. The specimens are then transported to the laboratory to be processed. HPV DNA-based test currently require sophisticated and expensive laboratory equipment (40).

A positive characteristic of HPV DNA-based is its higher sensitivity compared with cytology, but its specificity is lower than that of cytology in detecting high-grade lesions (5,30,32). If be applied in young women, this method could result the larger false-positive tests due to the high prevalence of HPV in young women (30,32), resulting in much unnecessary anxiety and other morbidities, as well as an increase in the cost of screening (32). Therefore, HPV DNA-based testing is only recommended to be used for screening tool in women over 30 years of age (30,32,40). Furthermore, this method should be used mainly in combination with other screening test to improve the sensitivity of the screening (40) and to allow extended screening intervals (30).

Treatment of cervical cancer-related diseases

- Management of positive screening test

Screening test could detect the women with cervical cytological abnormalities. The results of screening test lead the women requiring additional follow-up or evaluation to determine which women with cytological abnormalities are at risk for significant cervical disease (48). Based on the standard procedure, ideally the positive screening test should be followed by diagnosis procedures with colposcopy and biopsy. In particular, women with low-grade lesion or those with undetermined cytological diagnoses should have repeat cytology test, and only those with persistently positive results should undergo colposcopy (32).

Colposcopy is the examination of the lower genital tract and cervix using magnification from a colposcope with a good light source. The squamocolumnar

junction and transformation zone should be identified; this determines whether the examination is satisfactory or not. Acetic acid is then used to assess the size, shape, margin, and location of any neoplastic lesion. Finally, the findings then can be described based according to the nomenclature guidelines and to follow the further procedures (49). If any lesion is seen from colposcopy, biopsy should be completed. Biopsy is the removal of small areas of the cervix for histopathological diagnosis (40). Colposcopy may detect almost all cases of high-grade CIN (50), allowing early treatment of cervical cancer precursor. Unfortunately there are barriers of the establishment of colposcopy and biopsy services including the need of sophisticated and expensive instrument, the requirement of specialized training and exercise to maintain proficiency and the need of biopsy samples to be transported to a histopathology service which may be difficult in low-resource settings (40). If pre-cancer is diagnosed, it should be treated with cryotherapy, cervical conization including LEEP or cold knife conization (40,43).

Cryotherapy eliminates precancerous areas on the cervix by freezing them. It involves applying a highly cooled metal disc (cryoprobe) to the cervix, and freezing its surface using carbon dioxide (CO_2) or nitrous oxide (N_2O) gas. The procedure takes a relatively short time about 15 minutes and can be performed on an outpatient services (40). The equipment is simple, inexpensive, and requires few consumable supplies and no electricity (32). However, this procedure cannot be applied in larger lesions such as lesion extending into the endocervical canal (32,40).

Cervical cone techniques currently used include cold knife cone (CKC), loop electrosurgical excision procedures (LEEP and LLETZ), and laser conization. All three techniques are effective and safe in the treatment of CIN and studies have found no difference in the sample adequacy between the techniques (43).

Loop electrosurgical excision procedure (LEEP), also called large loop excision of the transformation zone (LLETZ), is the removal of abnormal areas from the cervix using a thin heated wire. It requires an electrosurgical unit that produces a constant low voltage and transmits it to a wire loop device, which is used to remove the abnormal tissue. LEEP aims to remove both the lesion and the entire transformation zone. LEEP serves double purposes; to treats the lesion and to

produces a specimen for pathological examination. The successful of LEEP in eradicating precancer is more than 90% of all cases (40).

Cold knife conization is the removal of a cone-shaped area from the cervix, including portions of the outer (ectocervix) and inner cervix (endocervix). It is a rather extensive operation, involving removal of a large area of the cervix with a scalpel, and is usually done under general or regional (spinal or epidural) anaesthesia. Cold knife conization should be reserved for cases that cannot be resolved with cryotherapy or LEEP excision. The procedures require providers with surgical skills, in an equipped surgical facility (40).

- Management of invasive cervical cancer

The best strategy for cervical cancer control is primary prevention, screening, and treatment of pre-invasive disease. Of necessity, cervical cancer treatment requires focused expertise and availability of operating theatres, chemotherapy, and radiotherapy, all of which carry high price tags (43). Treatment modalities for invasive cervical cancer are surgery or radiotherapy as primary therapy, or occasionally a combination of both. Chemotherapy is not used for primary therapy, but may be given concurrently with radiotherapy (40).

According to FIGO guidelines, the management of invasive cervical cancer is based on staging in to which the women have their conditions belong. The staging is based on clinical evaluation from several clinical examinations (51). Table 2.4 presents the management of invasive cervical cancer based on the clinical staging (43).

Table 2.4 FIGO guidelines for invasive cervical cancer management (Source: (43))

Stages	Standard treatment	Special consideration
IA1	Simple hysterectomy	Conservative – cone with clear margin
IA2	Simple or radical hysterectomy and bilateral pelvic lymphadenectomy depending on local or regional guidelines	Conservative – large cone or trachelectomy and bilateral pelvic Lymphadenectomy depending on local or regional guidelines
IB1	Radical hysterectomy and bilateral pelvic lymphadenectomy or radiotherapy	Conservative for small lesion - trachelectomy and bilateral pelvic lymphadenectomy
IB2	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy +/- adjuvant radiotherapy or chemoradiation	Neoadjuvant chemotherapy then surgery in selected patients
IIA 1 or 2	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy in selected patients +/- adjuvant radiotherapy or chemoradiation	Neoadjuvant chemotherapy then surgery in selected patients
IIB	Chemoradiation or radical hysterectomy and bilateral pelvic lymphadenectomy in selected patients +/-	Neoadjuvant chemotherapy then surgery in selected patients
IIIA or IIIB	Chemoradiation or radiotherapy	
IVA	Chemoradiation or radiotherapy	Pelvic exenteration
IVB	Palliative radiotherapy or Chemotherapy	End of life care especially adequate pain control and use of morphine

Surgery: Surgery aims to remove the primary tumor, with all its extensions, in a single operation. The operation undertaken will depend on the clinical stage of the tumor and the findings of the surgeon when the operation is in progress. The surgical procedures including some procedures as follows:

- Trachelectomy

Trachelectomy is the removal of the cervix. Radical trachelectomy includes removal of the parametria and upper vagina in addition to the cervix.

- Simple hysterectomy

Simple hysterectomy is the surgical removal of the entire uterus, including the cervix, either through an incision in the lower abdomen, or through the vagina. Simple hysterectomy can be performed in a regional or central hospital, by a general or gynaecological surgeon specialized in the treatment of cervical cancer.

- Radical hysterectomy

Radical hysterectomy is the surgical removal of the uterus, cervix, and surrounding tissues (parametria), including 2 cm of the upper vagina. This procedure

allows for the better cure rate. Radical hysterectomy is usually performed in a central hospital by a gynecological surgeon specialized in the treatment of cervical cancer.

- Bilateral pelvic lymphadenectomy or nodal dissection

This operation involves the removal of the three groups of lymph nodes in the pelvis, which often involved in invasive cervical cancer.

The main surgical procedures are radical hysterectomy and pelvic lymphadenectomy, although simple hysterectomy and trachelectomy are indicated in specific cases. Trachelectomy is offered to women with micro invasive cancer, who wish to have children in the future. A simple hysterectomy could treat patients in stage IA2 instead of radical hysterectomy that more preferred (40).

Radiotherapy: Radiotherapy plays a central role in the treatment of most invasive cervical cancers. It has mainly uses in cases with bulkier tumors; with extensive involvement of the lymph nodes seen on laparotomy (without hysterectomy); of patients who are unable to tolerate general anaesthesia. In addition to its curative role, radiation can also alleviate symptoms, especially bone pain and vaginal bleeding (40).

Types of radiotherapy including procedures as follows (40):

- Teletherapy

Teletherapy is also called external beam radiation therapy (EBRT). In this procedure, the source of radiation is distant from the patient.

- Brachytherapy

In brachytherapy, the radiation source is in close contact with the tumour. The radiation sources are placed inside an applicator in the uterus and vaginal vault (intracavitary brachytherapy).

- Teletherapy

Teletherapy is indicated when the entire area affected by the cancer cannot be removed by simple or radical hysterectomy. Brachytherapy is usually used in addition to teletherapy. Radiotherapy is conducted by a radiation oncologist and a radiotherapy technician with standard radiotherapy training.

Chemotherapy: Chemotherapy is not a primary mode of treatment for cervical cancer, but it may be used concurrently with surgery or radiation to treat

bulky tumours. Cisplatin is the most commonly used drug and is included in WHO's Model List of Essential Medicines (40).

2.2 Health Policy on Cervical Cancer Prevention and Control

2.2.1 Effectiveness of strategies for cervical cancer prevention and control

Cervical cancer prevention and control is now a possible effort that can be truth, with the introduction of prophylactic vaccines against the oncogenic HPV 16 and HPV 18 and with respect to the successful of screening as secondary prevention that already greatly reduced the burden of cervical cancer within a couple of decades. Despite the promising available strategies for prevention and control of cervical cancer, there are barriers to countries for implementing such programs, namely political barriers associated with political will issues, community and individual barriers including cultural norms, technical, and organizational barriers, and economic barriers, as well as structural barriers related to health systems; these barriers lead to inequities in cervical cancer disease burden (52-54). Cervical cancer prevention and control should be made accessible to all women in need.

In general, the strategies for prevention and control of cervical cancer include the modalities of primary prevention strategies (vaccination program), secondary prevention strategies (screening), and tertiary prevention strategies (treatment with standard-of-care).

2.2.2 Guidelines for implementation of strategies for cervical cancer prevention and control

WHO synthesized recommendations for comprehensive cervical cancer control including strategy involving health education as an integral part for comprehensive cervical cancer control and screening strategy (40). The screening strategies are as follows:

- Cytology based screenings

Cytology based screening is recommended for large-scale cervical cancer screening programs, if sufficient resources exist; age of screening starts at 25 years old

and ends at 65 years old, which for new programs should start at age 30 years old, for the existing programs should not less than 25 years old, and for once time screening in lifetime should at age between 35 and 45 years; the interval of screening is 3 years for the target population 25-49 years old and five years for the target population over 50 years old.

- Visual screening methods

Visual screening methods are recommended for used only in pilot projects and other closely monitored settings; and not for used in postmenopausal women.

- HPV DNA tests for primary screening methods

HPV DNA tests are recommended for used only in pilot projects and other closely monitored settings; can be used in conjunction with cytology or other screening tests, where sufficient resources exist; and should not begin before 30 years old of age.

Towards the HPV vaccination programs, WHO recommends that routine HPV vaccination of 9- to 13-year-old girls should be included in the national immunization programs of countries where: the prevention of cervical cancer disease is a public health priority; the introduction is programmatically feasible and economically sustainable; and the cost-effectiveness aspects have been duly considered (55). Therefore, a country should conduct economic analysis before introducing vaccination program to be included in national immunization program (56). In addition, WHO also recommends that such programs should be part of organized programs that include education about risk behaviors of HPV infection and information on the continued value of screening programs for cervical cancer (55).

More recently, Asia Oceania Research Organisation in Genital Infections and Neoplasia (AOGIN) proposed guidelines for low resource settings on strategies for cervical cancer prevention and control as follows (52):

- Primary prevention

HPV vaccination to teenagers before sexual exposure should be implemented at large, in accordance with the WHO recommendation. To be implemented as an effective public health tool, vaccine programs need appropriate delivery systems to achieve high coverage (57). The strategy of delivering HPV vaccines to school girls aged 11-13 years has shown good coverage rate. Combining

HPV vaccination with delivery of other health interventions or education to adolescent girl, may increase the cost-benefit of such programs (54).

- Secondary prevention

The choice of the screening should be based on local data of sensitivity and specificity of each method, as they can vary depending on the prevalence of HPV in population. The simplest method is VIA/VILI or, in the future, HPV detection using a low-cost test. It is desirable to use an adjunct method to confirm screening results using cytology, colposcopy, or cervicography and biopsy, before referring women to treatment, although "screen and treat" should be considered. Screening should start at age 30 or 35 years, depends on local data on HPV prevalence and incidence of cervical neoplasia; and should be offered to all women at least once in their lifetime, but preferably every 5 years, if using VIA, or every 10 years if using HPV testing.

Country specific decisions regarding the best strategy for cervical cancer prevention and control, including vaccination program and screening, require assessment of multiple factors such as epidemiologic data related to the disease burden, economic factor that needs cost-effectiveness information, affordability of government and community, social and cultural acceptability, and feasibility of such programs, as well as political factors. Models of disease prevention are useful guides to help in the evidence-based decision-making process. The decision analytic approach using computer-based modeling methods enables linkage of the knowledge gained from empirical studies to real-world situations. The application of this method to policy choice implies that resources should be used as efficiently as possible to maximize the health benefits to the population (57,58).

2.2.3 Current strategies for cervical cancer prevention and control in Indonesia

Currently, Indonesia have not implemented routine national program on cervical cancer prevention and control. It has started the national pilot program for screening with VIA in 2007 and has been continued and improved in several provinces. An evaluation study conducted in one province in Indonesia from 2007-2010, See and Treat model incorporating the VIA cervical cancer screening, found the

VIA test-positive rate was 4.21% (970/22,989) (59). This result indicates the need of continuing such program as the routine organized national program.

The services for cervical cancer screening and HPV vaccination have been provided by public and private sectors, for instance, VIA screenings are provided from the most basic level of health care in primary/community health care; while Pap smear screenings could be obtained in health facilities from district hospital as well as certain primary health care with complete facilities and health professionals; lastly the private sectors also provide for services including various methods of screening and HPV vaccination with relatively higher costs of services. Unfortunately, the health care system of Indonesia does not cover the costs of any routine strategies for cervical cancer prevention and control including such HPV vaccination and screening for cervical cancer. Given this situation of health care system, the target population of HPV infection and cervical cancer risk should pay out-of-pocket for getting such routine services. Therefore, those strategies are only received as a voluntary service by a few of target population. To achieve the goal for reduction the incidence and mortality of cervical cancer, the strategies for cervical cancer prevention and control should be implemented nationally, particularly for this kind of infectious disease.

Implementation of such national organized-programs for cervical cancer prevention and control particularly in limited-resources setting such as Indonesia needs to consider several aspects, including economic aspect. Hence, economic analysis is important in this circumstance.

2.3 Economic evaluation

2.3.1 Methods of economic evaluation

The basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered. Most economic evaluations have the similarity in identification of various types of costs and their subsequent measurement in monetary unit. However, they have differences in the nature of the consequences stemming from the alternatives being examined (60). Based on the differences of the consequences or so called outcomes, there are several techniques/methods used to conduct economic evaluation, including cost minimization

analysis (CMA), cost effectiveness analysis (CEA), cost benefit analysis (CBA), and cost utility analysis. In a circumstance where there is no measurement of consequence and solely cost measurement, then it uses cost analysis or cost of illness methods (60-62). Recently, a budget impact analysis (BIA) method was introduced to complete the result of CEA (63).

Cost minimization analysis (CMA)

In CMA, only the costs of the interventions under evaluation are measured; since this method assume that the health benefits/outcomes of the interventions are broadly identical/equivalent and therefore need to not be considered separately (61,62). CMA is not a unique study design that can be determined in advance because of the uncertainty around the estimates of costs and effects (60).

Cost effectiveness analysis (CEA)

CEA compares therapies whose outcomes can be measured in the same natural units (e.g. years of life saved, cases of diseases averted). It does not allow comparisons to be made between two totally different areas of interventions with different outcomes (62). CEA is the most commonly applied form of economic analysis in the health literature; it is being used in situations where a decision maker, operating with a given budget, is considering a limited range of options within a given field (60).

Cost utility analysis (CUA)

CUA is similar to cost effectiveness, however the outcome of interest is measured in a unit of utility (e.g. disability-adjusted life-years (DALYs) averted or quality-adjusted life-years (QALYs)) (62). CUA is more useful to decision-makers with abroad mandate than is CEA because of its broad applicability (60).

The basic steps to conduct CEA or CUA are as follows (61):

- Defining the problem: This step includes identifying the point of view or perspective from which the analysis is to be conducted, stating the problem that needs to be solved, and selecting the objectives for comparing the effectiveness of alternative interventions.
- Identifying the alternative interventions: This step identifies all relevant alternative interventions that can be described using decision trees or treatment models.

- Describing production relationships between inputs and outcomes; This step provides the technical framework for the quantitative assessment and comparison of net costs with net effectiveness. The methods for characterizing production relationships involve development of a model that specifies how inputs are combined and how much output will be produced by a given grouping of inputs.
- Estimating costs of interventions: This step includes identify, measure and value costs.
- Estimating outcomes of interventions: This step estimates the relevant outcomes resulted from intervention.
- Interpretation and presentation of results: This step brings together the result of costs and outcomes assessment, in the form ratio, to provide an overall indication of cost-effectiveness in a way that will inform decision-making.
- Sensitivity analysis: This step is required to test the sensitivity of the results changes due to the uncertainty of many estimates used.

Cost benefit analysis (CBA)

In CBA, the benefit is measured as the associated economic benefit of an intervention, and hence both costs and benefits are expressed in money. CBA allows comparisons between different areas (62). CBA is a basic tool that can be used to improve the decision making process in the allocation of funds to healthcare programs (61).

Steps in conducting CBA are as follows (61):

- Identifying the interventions to be evaluated
- Assessing the resources consumed, or costs of providing each intervention.
- Assessing the benefit of interventions
- Sum the value of all costs and benefits of each intervention
- Computing the net benefit or cost-to-benefit ratio of the interventions

Cost of illness (COI) and Cost Analysis

Cost-of-illness was the first economic evaluation technique used in the health field. The principal aim is to measure the economic burden of illness to society. However, its usefulness as a decision making tool has been questioned (64). Despite its lack in decision making tool, COI studies have several advantages that might be

considered. These advantages can be said as follows: they can provide information to support the political process as well as the management functions at different levels of the healthcare organizations; they can describe the relative burden of different disease and so be useful in helping to establish health services priorities; they are valuable in establishing the baseline state from which a proper economic evaluation study can begin (62,64). Whilst COI measures economic burden of disease, another term, cost analysis has the narrower scope that it is defined as costs of healthcare programs or treatments; however, it is a central feature of all economic evaluations (60).

Budget impact analysis (BIA)

The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource constraints. It can be used for budget planning, forecasting and for computing the impact of health technology changes on premiums in health insurance schemes. BIA is a complementary to CEA, whereas CEA evaluates the costs and outcomes of alternative technologies over a specified time horizon to estimate their economic efficiency, BIA addresses the financial stream of consequences related to the uptake and diffusion of technologies to assess their affordability (63). In practice, budget impact analysis (BIA) is used as a tool to predict and understand the potential financial impact of introducing a new pharmaceutical into a drug reimbursement system that has finite financial resources. In vaccination program, BIA estimates the financial impact on annual health care use and costs for the first, second, and subsequent years following the introduction of the vaccine (65).

Principle in conducting BIA (63):

- Defining the perspective
- Describing the intervention and choice of comparator
- Defining the time frame
- Defining the target population
- Assessing the direct cost of intervention
- Describing the budget impact model
- Conducting sensitivity analysis

Health administrators, when choosing the economic evaluation methods to be conducted to help the policy maker deciding which interventions should be

implemented from the consideration of economic-evidence, should consider many aspects such as what is the objective of economic evaluation they want to conduct, what kind of health interventions being considered, what are the results of economic evaluation being an interest of policy maker.

2.3.2 Decision modeling for health economic evaluation

Economic evaluation can be conducted using patient-level data, means the collections of data alongside randomized controlled trial. This study usually is conducted by pharmaceuticals companies as part of a trial that has been designed primarily for clinical purposes to get product licensing. This approach has advantage of having patient-specific data on both costs and outcomes that potentially attractive for analysis and internal validity. However, this approach also deals with many limitations (60,62,66).

Other than including economic data collected alongside randomized trials; there also likely to include clinical, cost, and health-related quality of life data from other types of study such as cohort studies and surveys. Decision analytic models provide a means of bringing this evidence together (60).

Decision analysis is as a systematic approach for decision making under uncertainty. A decision analytic model, in the context of economic evaluation, uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. Based on the inputs into the model, the likelihood of each consequence is expressed in terms of probabilities, and each consequence has a cost and an outcome. It is thus possible to calculate the expected cost and expected outcome of each option under evaluation. For a given option, the expected cost (outcome) is the sum of the costs (outcomes) of each consequence weighted by the probability of that consequence (67).

Based on that definition of decision analytic model, a model used in economic evaluation should contains key elements including probabilities, which is taken as a number indicating whether an event will or will not take place in the future; and expected values, consists of expected costs and expected outcomes, which are the cost or outcome of the intervention weighted by the probability of a patient following each pathway with that intervention (60,67).

The development of a decision analytic model for economic evaluation involves stages as follows:

- Determination of the decision problem: It could be done by identifying the question to be addressed in the economic evaluation (67). The objective of the project usually fall in one of several following categories: to guide clinical practice, inform a funding decision or reimbursement rate for a new intervention, optimize use of scarce resources, and guide public health practice (68).
- Defining the boundaries of model: Based on such consideration such as what possible consequences of the intervention under evaluation will be included in the model, which should be consistent with stated perspective; and the availability of data and the complexity of modeling task (60,67,69).
- Structuring the decision model: It should be structured to accommodate how the input parameters in the model to be related, the inputs and outputs are relevant with the decision-making perspective, in accordance with characteristic of intervention and good evidence about the natural history or characteristics of the disease (60,67,70).

There are several model structures are often used in economic evaluation as follows:

- Decision tree

Decision tree structure is one type of cohort models. A cohort model refers to decision models focusing on the average patient experience. The two most common cohort models used in decision analysis and predominating the economic evaluation literature review are the decision tree and Markov model (60,67). A decision tree is the simplest form and most common structure of decision models in economic evaluation. It may appropriate for decision problems with special characteristics (e.g. very short time horizon) (69). It represents individual's possible prognoses, following some sorts of intervention, by a series of pathways (60). The features of decision tree consist of a square decision node, a circular chance node, pathways, and probabilities (67).

- Markov model

Another type of cohort models is the Markov model. Markov model is also known as state-transitional model; it is applied when the conceptualization involves representing the disease or treatment process as a series of health states since it may be

simple to develop, debug, communicate, analyze, and readily accommodate the evaluation of parameter uncertainty (69). State-transition model (STM) can be used to compare various types of interventions, including primary prevention strategies (vaccination), screening strategies, diagnostic strategies, and treatment (71).

- Micro-simulation model

This model sometimes is also termed patient-level simulation model or individual sampling model or individual-based transition-model or first-order Monte Carlo (67,69,71). This model is an alternative, instead of Markov model, when the number of states grows too large, that cannot be accommodated in Markov model (69). The different of individual-level STM and cohort STM is that cohort models are analyzed as cohorts progressing through the states simultaneously, while individual-level STM keeps track of each individual's history (71).

- Dynamic transmission model

This model is applied when the disease or treatment process includes interaction between individuals (69). Dynamic model is often employed in economic evaluation of infectious diseases, since this model is capable of reproducing the direct and indirect effects that may arise from a communicable disease control program such as herd immunity effects (72). The static models, such as cohort models, do not take into account the indirect effects.

- Discrete event simulation (DES)

DES provides a flexible framework that can be used to model a wide variety of health care problems; since its ability to represent complex behavior within, and interactions between individuals, populations, and their environments (73). DES should also be used when the problem under the study involves constrained or limited resources (69).

Several issues should be noticed when employing model as a method and economic evaluation study, such as the following issues:

- Identifying and synthesizing evidence

These processes involve some activities to provide input parameters for the model from the evidence-based information (67).

- Dealing with uncertainty and heterogeneity (variability)

Uncertainty and heterogeneity exist in all economic evaluations. Uncertainty refers to situations where a model input is not known precisely; heterogeneity is concerned with situations where input parameters might vary systematically between recipients or locations. Uncertainty should be dealt with performing sensitivity analysis; while heterogeneity should be dealt with providing results presentation separately for each relevant subgroup of recipient (60,67).

- Assessing the value of additional research

The value of decision model is to bring available evidence within an appropriate model structure as an input into decision problems. The decision model; then will provide an estimate of expected costs and effects for each intervention being evaluated, based on currently available data, from which the preferred option can be identified accordingly. Nevertheless, the various forms of uncertainty of parameter uncertainty and structural uncertainty generate a distribution around overall expected costs and effects; resulting what is termed decision uncertainty, that is the probability that a given decision about a preferred intervention is the correct one. To accommodate this issue, such method as probabilistic sensitivity analysis could be conducted to perform the result termed cost-effectiveness acceptability curve (CEAC). Other method was also developed to interpret the expected costs of uncertainty as the expected value of perfect information (EVPI), that is, the monetary value associated with eliminating the possibility of making an incorrect decision. Both CEAC and EVPI provide value of additional research that can eliminate the wrong decision of the problems (60,67,74).

2.3.3 Economic evaluation of cervical cancer prevention and control

Economic evaluation studies of strategies for cervical cancer prevention and control

There are many studies on economic evaluation of cervical cancer-related already conducted in many settings all over the world and published elsewhere. Some of the studies are reviewed as follows:

- Economic evaluation of HPV vaccination

Goldie et al (75) conducted economic evaluation study of HPV 16 and 18 vaccination in 72 GAVI-eligible countries, including Indonesia. This study employed

a micro-simulation model to synthesize model input data and assumption adapted from other setting and estimate averted cases of cervical cancer, cancer deaths, life-expectancy gains, disability-adjusted life years (DALYs) averted and incremental cost-effectiveness ratios per DALY averted for vaccination under different cost, coverage and vaccine efficacy assumptions. This study also used ICER per DALY under the CUA evaluation to present the cost-effectiveness of HPV vaccination program using a per capita GDP threshold. Finally, this study suggested that by providing high coverage of vaccination and lowering vaccine costs, HPV 16,18 vaccination could be very cost-effective even in the poorest countries and provide comparable value for resources to other new vaccines such as rotavirus.

Marra et al (16) conducted systematic review on effectiveness and cost effectiveness of HPV vaccination from the articles published from 1996-2008. This study reviewed 21 articles that employed 22 models to assess the effectiveness and cost-effectiveness of HPV vaccination. Of those models, 10 were Markov models, 1 was hybrid and 11 were dynamic models. Dynamic models were used in articles which relatively published later. This review concluded that HPV vaccines will have substantial impact on the epidemiology of this disease, for instance reduce the incidence and mortality. All models in the study reviewed also showed that HPV vaccine in females is cost-effective, presented by the ICER per QALY and in general, the dynamic models that taken into account the herd immunity showed lower cost-effectiveness ratio than the Markov models.

Seto et al (17) conducted systematic review on cost effectiveness of HPV vaccines from the literature published from 1950 to 2010. Twenty nine studies were reviewed after excluding 13 articles that already reviewed by Marra et al (16). This review provided information about economic evaluation methods used, model approached as well as the results of economic evidence. Most studies employed static model particularly Markov models for conducting cost effectiveness analysis and cost utility analysis, instead of dynamic and hybrid models. Most studies were conducted in the setting of US and European countries, while some of them also are conducted in Asian countries; however none of this study was conducted in Indonesia. Cost-effectiveness of those studies was evaluated under the CEA (ICER per life years) and CUA (ICER per QALY) methods. Given the different model structure and input

parameters assumption as well as different economic evaluation methods, the consistent results, that routine vaccination of females is cost effective when compared to screening alone or treatment only, were occurred.

- Economic evaluation of screening for cervical cancer

Goldie et al (76) conducted cost effectiveness of cervical cancer screening in five developing countries including India, Kenya, Peru, South Africa, and Thailand. A computer based model of natural history of cervical cancer was employed in the study to assess cost effectiveness of varieties cervical cancer screening strategies including VIA, Pap smear, and HPV screening. The most cost effective strategies, presented in cost per year of life saved, were those that required the fewest visits, resulting in improved follow-up testing and treatment. Finally, the study suggested that cervical cancer screening strategies with VIA or HPV DNA test in one or two clinical visits are cost-effective alternatives to three visit of Pap smear in resource-poor settings.

Siebert et al (71) developed a Markov model for the natural history of cervical cancer and cervical cancer screening in German health care context. The model reflected the existing German practice standards toward cervical cancer that focus on screening using Pap smear intervention. The model was used to predict lifetime cervical cancer risk as well as lifetime cervical cancer mortality. The study suggested that annual Pap smear screening could prevent 98.7% of diagnosed cancer cases and 99.6% of deaths due to cervical cancer. The model resulted from the study provides a tool for evaluating the long-term effectiveness of different cervical cancer screening tests and strategies.

Recently, Voko et al (77) conducted cost effectiveness of cervical cancer screening in Hungary. They developed Markov model to assess cost effectiveness of the existing screening program which is screening test that combines cytology and colposcopy in gynecological outpatient services and of a planned new screening program (Pap smear only which is taken locally by public health nurses), both were compared with no screening. The study concluded that providing services closer to the population (the new proposed screening program) is a rational economic option for the reform of the Hungarian cervical cancer screening program.

Model in economic evaluation of interventions related to cervical cancer

Almost all of economic evaluation of intervention related to cervical cancer employed modeling to assess the cost effectiveness of such programs. Due to the absence of data on the long-term effectiveness of such programs for cervical cancer prevention and control, models have been developed to be employed in economic evaluation of those strategies (78,79). Most of those models reported in literature are cohort, dynamic, and hybrid models. Among them, Markov models are the dominant one (16,17,78).

The application of Markov models in the health care decision making follows the process including developing the adequate of model structure to reflect the natural history of the disease, providing relevant evidence of the model and input parameters, conducting evaluation with appropriate economic evaluation methods for comparing the interventions, enabling numerous uncertainty and variability analysis, and providing information for future re-evaluate research (80).

Markov model involves components such as Markov states, transitional probabilities, and weighted costs and outcomes (81). In cervical cancer disease, the health states are derived from the natural history of cervical cancer disease. The previous developed models involve the healthy condition, infection with HPV, numerous pre-cancer stages of cervical cancer, as well as numerous stages of invasive cervical cancer disease as the Markov states. Those model structures varied in the number of health states described and the detail of possible movement from one state to other state, usually including regression, progression, and recurrent process (16,17). Ideally, transitional probabilities were derived from observational studies in accordance with specific setting (82), however the availability of this data is very difficult to be obtained, therefore the following studies usually referred to the former studies in other settings. Costs and outcomes in most studies are usually parts that are estimated based on the specific data where the study setting conducted.

Guidelines for conducting economic evaluation of strategies for cervical cancer prevention and control

Inspired by the recommendation of WHO that the cost effectiveness of introducing HPV vaccination is considered before such strategy is implemented and the lack of the technical capacity of developing countries to perform and interpret results of economic appraisal of vaccines, Jit et al (56) conducted study to provide

information about the feasibility of using such models in a developing country setting. Results of this study indicated the usefulness of considering results from several models and sets of modeling assumptions in decision making.

Jit et al (83) also reported the consensus of an expert group convened by WHO, prioritizing key issues to be addressed when considering economic analysis to support HPV vaccination introduction in low- and middle- income countries, particularly. This report recommends that analyst informing policy decision should address the questions as follows: Is an economic analysis needed?; Should analysis address costs, epidemiological outcomes, or both?; If costs are considered, what sort of analysis is needed?; If outcomes are considered, what sort of model should be used?; How complex should the analysis be?; How should uncertainty be captured?; How should model results be communicated?

In conclusion, the analyst should select the appropriate analysis to ensure that all the important features of the decision problem are correctly represented, without the complexity of the analyses that unnecessary.

CHAPTER III
METHODOLOGY

This chapter includes parts as follows:

1. Study design
    a. Scope of study
    b. Decision analytical model
    c. Perspective of study
    d. Comparators.
2. Markov model
    a. Model structure
    b. Cervical cancer disease model assumption
    c. Intervention effects on cervical cancer disease model
    d. Model determination and evidence synthesizing
    e. Model calibration and validation
3. Budget impact model
4. Model Input
    a. Health state transitional probabilities
    b. Program effectiveness
    c. Costs parameter
    d. Utility data
5. Model output
6. Analysis and presentation
    a. Cost effectiveness ratio
    b. Sensitivity analysis

3.1 Study design

Scope of study

The goal of the study was economic evidence as an input to the decision maker regarding strategies for cervical cancer prevention and control in Indonesia. For this purpose, specific study design which was economic evaluation study was conducted.

This study applied decision-analytical models, particularly semi-modelling using primary and secondary data to conduct several techniques of economic evaluation of such strategies for cervical cancer prevention and control in Indonesia.

The economic evaluation techniques used in the study were as follows:

a. Cost utility analysis (CUA)

In this study, CUA was used to assess the cost-effectiveness comparing cost and quality adjusted life years (QALYs) gained resulted from the interventions for cervical cancer prevention and control.

b. Cost effectiveness analysis (CEA)

In this study, CEA was used to assess the cost-effectiveness comparing costs and outcomes of life years saved (LYs) resulted from the interventions for cervical cancer prevention and control.

c. Cost benefit analysis (CBA)

In this study, CBA was used to assess the net present value (NPV) and benefit-to-cost ratio (BCR)/cost-to-benefit ratio (CBR) of the interventions for cervical cancer prevention and control.

d. Budget impact analysis (BIA)

In this study, BIA was used to assess the projected budget for program implementation of such interventions for cervical cancer prevention and control in Indonesia.

Decision-analytical model

For CEA and CUA, Markov model with individual simulation was employed as a tool to produce the output values including life time costs, life years saved, and QALYs gained resulted from the interventions. These output values were used to estimate the cost-effectiveness under the scope of CEA and CUA study techniques. For CBA, Markov model with both individual simulation and hypothetical

cohort simulation were employed to calculate the costs and benefits of the interventions. Finally for BIA, Markov model was used to explore the life time budget impact for different interventions. An additional budget impact model was applied to estimate the budget impact for such interventions in short term duration. Duration of time horizon for Markov model was set as life time-time horizon, while for BIA-short duration model was set as 5 year-time horizon.

Time horizon

Duration of time horizon for Markov model was set as life time-time horizon, while for BIA-short duration model was set as 5 year-time horizon. All costs were presented in Indonesia Rupiah (IDR) for year 2013 value. Adjustments of costs from previous years were made using consumer price index (CPI) for all resources. Conversions from IDR to USD and vice versa were made using exchange rate of 2013 at IDR 10,318 per 1 USD.

Perspective of study

For CUA, CEA, and CBA, the study was held in the perspective of health system and societal as the scope of costs estimation. Meanwhile for BIA, the study was health in the perspective of healthcare provider.

Comparators

Several strategies for cervical cancer prevention and control in accordance with the establish guidelines that applicable for Indonesia setting were evaluated, including the strategies as follows:

a. HPV vaccination
b. Screening with Pap smear
c. Screening with VIA
d. Mixed strategies

Mixed strategies were combining strategy of HPV vaccination, screening with Pap smear and VIA. The mixed strategies were as follows:

- Strategy of screening with VIA and followed by sequential Pap smear
- Strategy of HPV vaccination and followed by screening with VIA
- Strategy of HPV vaccination and followed by screening with Pap smear
- Strategy of HPV vaccination and followed by screening with VIA and sequential Pap smear

In this study, the reference was current treatment strategy (no intervention). The strategies were also varied with 3 different scenarios based on screening coverage and 2 different assumptions of vaccine doses per fully immunized girls, as follows:

a. Scenario I: screening coverage of 20% for both VIA and Pap smear

The coverage of 20% was set based on the estimation of current implementation of VIA pilot program in selected region in Indonesia. This number is also the average coverage of screening for cervical cancer in developing countries.

b. Scenario II: screening coverage of 50% for both VIA and Pap smear

The coverage of 50% was the midpoint of possible coverage range and close to the average coverage of screening for cervical cancer in developed countries.

c. Scenario III: screening coverage of 80% for both VIA and Pap smear

The coverage of 80% was the best optimum estimation of screening coverage for cervical cancer in Indonesia.

d. Assumption of vaccine dose regimen

Two and three doses regimens per fully immunized girl were applied as recommended by WHO (84). A coverage rate of 80% for vaccination was used.

Overall, there were 18 strategies defined including the reference (do nothing) in each scenario of analysis, as described in Table 3.1. Parallel analysis was conducted for 3 different scenarios and 2 different vaccine doses assumptions.

Table 3.1 Strategies considered in model of cervical cancer prevention and control in Indonesia

Strategy	Description	Notation used in Tables and Figures
(1) No intervention	No preventive intervention, current strategy of treatment for invasive cervical cancer only	Do nothing
(2) Vaccine	Vaccination in girl at age 12 years	Vac 12Y LT
(3) Pap smear- triennially	Screening with Pap smear in woman between age 30-63 years with interval of 3 years	Pap q3Y (30-63)
(4) Pap smear–pent annually	Screening with Pap smear in woman between age 30-65 years with interval of 5 years	Pap q5Y (30-65)
(5) VIA-triennially	Screening with VIA in woman between age 30-45 years with interval of 3 years	VIA q3Y (30-45)
(6) VIA-pent annually	Screening with VIA in woman between age 30-45 years with interval of 5 years	VIA q5Y (30-45)
(7) Vaccine plus VIA-triennially	Vaccination in girl at age 12 years , followed by screening with VIA between age 30-45 years with interval of 3 years	Vac 12Y LT + VIA q3Y (30-45)
(8) Vaccine plus VIA- pent annually	Vaccination in girl at age 12 years , followed by screening with VIA between age 30-45 years with interval of 5 years	Vac 12Y LT + VIA q5Y (30-45)
(9) Vaccine plus Pap smear-triennially	Vaccination in girl at age 12 years , followed by screening with Pap smear between age 30-63 years with interval of 3 years	Vac 12Y LT + Pap q3Y (30-63)
(10) Vaccine plus Pap smear-pent annually	Vaccination in girl at age 12 years , followed by screening with Pap smear between age 30-65 years with interval of 5 years	Vac 12Y LT + Pap q5Y (30-65)
(11) VIA- triennially and Pap smear- triennially	Screening with VIA in woman between age 30-45 years with interval of 3 years and sequential Pap smear between age 48-63 years with interval of 3 years	VIA q3Y (30-45) + Pap q3Y (48-63)
(12) VIA- pent annually and Pap smear- pent annually	Screening with VIA in woman between age 30-45 years with interval of 5 years and sequential Pap smear between age 50-65 years with interval of 5 years	VIA q5Y (30-45) + Pap q5Y (50-65)
(13) VIA- pent annually and Pap smear-interval 3 years	Screening with VIA in woman between age 30-45 years with interval of 5 years and sequential with Pap smear between age 48-63 years with interval of 3 years	VIA q5Y (30-45) + Pap q3Y (48-63)
(14) VIA- triennially and Pap smear- pent annually	Screening with VIA in woman between age 30-45 years with interval of 3 years and sequential with Pap smear between age 50-65 years with interval of 5 years	VIA q3Y (30-45) + Pap q5Y (50-65)
(15) Vaccine plus VIA-triennially and Pap smear- triennially	Vaccination in girl at age 12 years, followed by screening with VIA in woman between age 30-45 years with interval of 3 years and sequential with Pap smear between age 48-63 years with interval of 3 years	Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)
(16) Vaccine plus VIA- pent annually and Pap smear-pent annually	Vaccination in girl at age 12 years, followed by screening with VIA in woman between age 30-45 years with interval of 5 years and sequential with Pap smear between age 50-65 years with interval of 3 years	Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)
(17) Vaccine plus VIA- pent annually and Pap smear-triennially	Vaccination in girl at age 12 years, followed by screening with VIA in woman between age 30-45 years with interval of 5 years and sequential with Pap smear between age 48-63 years with interval of 3 years	Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)
(18) Vaccine plus VIA-triennially and Pap smear- pent annually	Vaccination in girl at age 12 years, followed by screening with VIA in woman between age 30-45 years with interval of 3 years and sequential with Pap smear between age 50-65 years with interval of 5 years	Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)

3.2 Markov model

3.2.1 Model structure

A Markov model to simulate the decision analysis of strategies for cervical cancer prevention and control in Indonesia was constructed based on the natural history of cervical cancer disease (Figure 3.1). The model was an adaptation of prior published study (82) and had also been adapted by many studies. A computer-based Excel integrated with Visual Basic Application (VBA) was adopted from the previous developed model in Thailand and used to analyze the Markov model (85). The model had transitional probabilities in 1-year cycle between different health states describing the natural history of cervical cancer related disease. It was simulated for girl at age 12 years and followed until age 100 years.

Cervical cancer disease model assumption

The model consists of 10 different health states following the natural history of cervical cancer disease, as were seen in the square boxes; namely healthy state, HPV infection, pre-cancer stages including CIN-1 and CIN 2/3, and invasive cervical cancer consisting of invasive cervical cancer (ICC) stage I to IV; two states of death also are enabled, death due to the invasive cervical cancer and general causes. The arrows reflected the probable transition from one health state to other health states. Healthy women can have a chance to get the HPV infection; for those whose persistent infection can move to the further state which is pre-cancer or can undergo clearance and back to be healthy or stay with the infection. Inside the pre-cancer stage, the women can remain at the same state or move back to the previous states of infection and be healthy or move to further severity. Anyone who progresses to invasive cervical cancer state cannot move back to the previous states. Inside the invasive cervical state, the women can remain at the same stage of cancer or progress to the further severity state or can be death due to cancer; however they are impossible for moving back to the lower stage. All the women entering the model can also die from the general causes of death. All health states and possible transitions are shown in Table 3.2

The transitional probabilities represent the proportion of individual/women population movement in each cycle from one health state at time (t) to the next cycle

of health state (t+1). The transitional probabilities vary among all health states. Table 3.3 shows the transitional probabilities among all health states in the model.

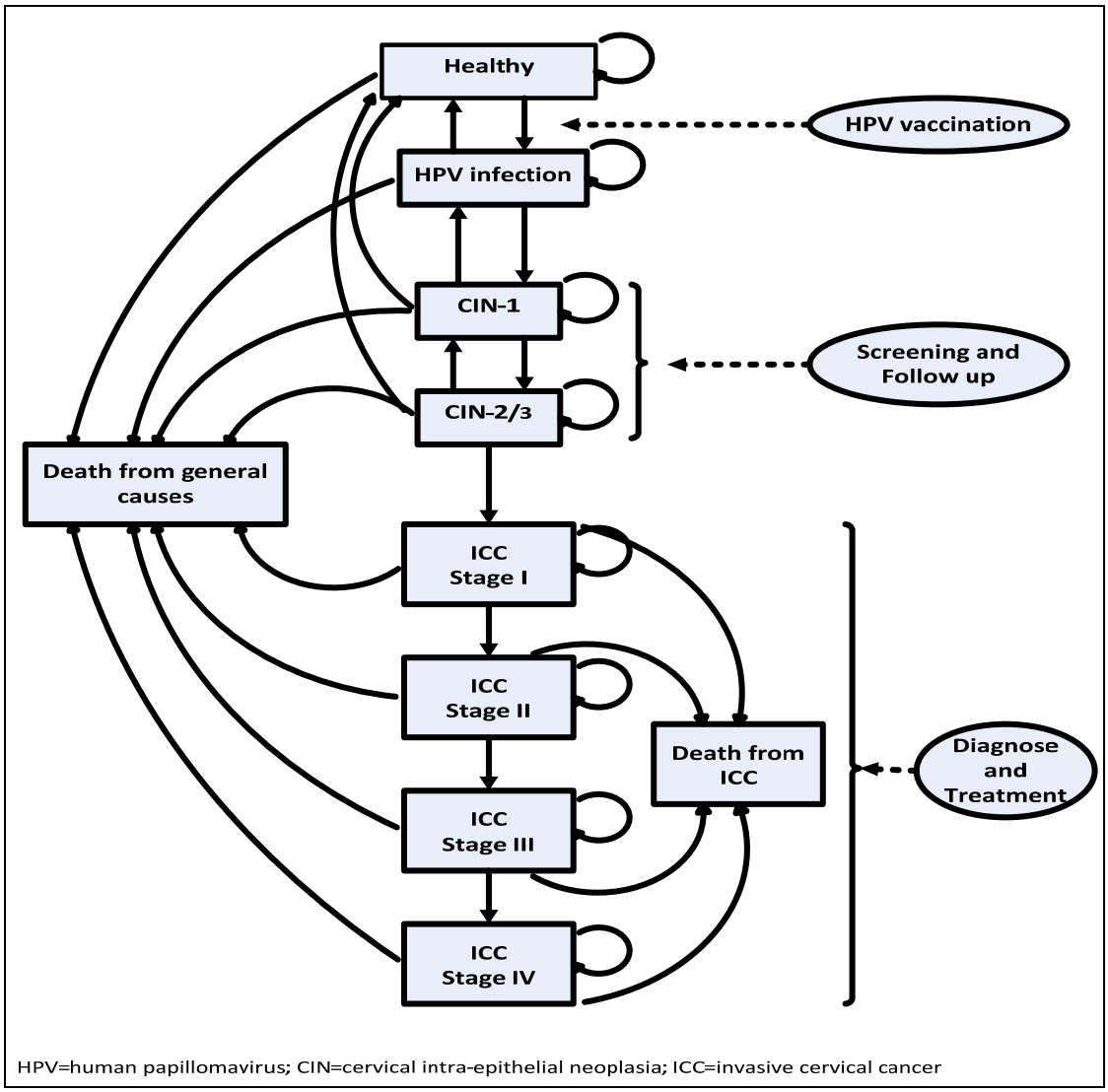


Figure 3.1 Model structure for the natural history and management of cervical cancer

Table 3.2 Health states and possible transitions among health states in Markov model of cervical cancer disease

Health state	Descriptions of health states	Possible transitions	
Healthy	Normal; absence of HPV infection and cervical cancer-related diseases	Preserve Progress Death	: Healthy : HPV infection : Death from general causes
HPV infection	Infected with human papillomavirus; no cytologic abnormality	Regress Preserve Progress Death	: Healthy : HPV infection : CIN-1 : Death from general causes
Pre-cancer states			
CIN-1	Cervical intra-epithelial neoplasia 1 (Low grade Squamous Intraepithelial Lesion)	Regress Preserve Progress Death	: Healthy HPV infection : CIN-1 : CIN 2/3 : Death from general causes
CIN-2/3	Cervical intra-epithelial neoplasia 2-3 (High grade Squamous Intraepithelial Lesion)	Regress Preserve Progress Death	: Healthy CIN-1 : CIN-2/3 : ICC Stage I : Death from general causes
Invasive cervical cancer states			
ICC Stage I	Invasive cervical cancer stage I	Preserve Progress Death	: ICC Stage I : ICC Stage II : Death from invasive cervical cancer Death from general causes
ICC Stage II	Invasive cervical cancer stage II	Preserve Progress Death	: ICC Stage II : ICC Stage III : Death from invasive cervical cancer Death from general causes
ICC Stage III	Invasive cervical cancer stage III	Preserve Progress Death	: ICC Stage III : ICC Stage IV : Death from invasive cervical cancer Death from general causes
ICC Stage IV	Invasive cervical cancer stage IV	Preserve Death	: ICC Stage IV : Death from invasive cervical cancer Death from general causes
Death states			
Death from ICC	Death caused by invasive cervical cancer-related diseases	Absorbing state	
Death from general causes	Death due to general causes	Absorbing state	

Table 3.3 Matrix of transitional probabilities of health states in cervical cancer disease model

Start of cycle	End of cycle					
Transition probabilities in healthy, HPV infection, and pre-cancer states						
	Healthy	**HPV infection**	**CIN-1**	**CIN-2/3**	**ICC-stage I**	**Death**
Healthy	1 – pHPV – pDying	pHPV	0	0	0	pDying
HPV infection	pHPVtoHealthy	1 – pHPVtoHealthy – pHPVtoCIN1 – pDying	pHPVtoCIN1	0	0	pDying
CIN-1	prCIN1toHealthy x pCIN1toHPVHealthy	(1 - prCIN1toHealthy) x pCIN1toHPVHealthy	1- pCIN1toHPVHealthy - pCIN1toCIN23 – pDying	pCIN1toCIN23	0	pDying
CIN-2/3	prCIN23toHealthy x pCIN23toCIN1Healthy	0	(1 - prCIN23toHealthy) x pCIN23toCIN1Healthy	1 - pCIN23toCIN1Healthy - pCIN23toICC1	pCIN23toICC1	pDying
Transition probabilities in invasive cervical cancer states						
	Stage I	**Stage II**	**Stage III**	**Stage IV**	**Death**	
Stage I	(1 – prSym1) x (1 - pICC1toICC2 - p1Dying – pDying)	(1 – prSym1) x pICC1toICC2	0	0	p1Dying + pDying	
I - initial	prSym1 x (1 - pICC1toICC2 - p1Dying – pDying)	0	0	0	p1Dying + pDying	
Stage II	0	(1 – prSym2) x (1 - pICC2toICC3 - p2Dying – pDying)	(1 – prSym2) x pICC2toICC3	0	p2Dying + pDying	
II - initial	0	prSym2 x (1 - pICC2toICC3 - p2Dying – pDying)	0	0	p2Dying + pDying	
Stage III	0	0	(1 – prSym3) x (1 – pICC3toICC4 – p3Dying – pDying)	(1 – prSym3) x pICC3toICC4	p3Dying + pDying	
III - initial	0	0	prSym3 x (1 – pICC3toICC4 – p3Dying – pDying)	0	p3Dying + pDying	
Stage IV	0	0	0	(1 - prSym4) x (1– p4Dying – pDying)	p4Dying + pDying	
IV - initial	0	0	0	prSym4 x (1– p4Dying – pDying)	p4Dying + pDying	

Abbreviations:

pHPV = transitional probability from healthy to HPV infection;
pHPVtoHealthy = transitional probability from HPV infection to healthy;
pHPVtoCIN1 = transitional probability from HPV infection to Cervical intra-epithelial neoplasia 1;
prCIN1toHealthy = proportion from Cervical intra-epithelial neoplasia 1 to healthy;
pCIN1toHPVHealthy = transitional probability from Cervical intra-epithelial neoplasia 1 to HPV and healthy;
pCIN1toCIN23 = transitional probability from Cervical intra-epithelial neoplasia 1 to Cervical intra-epithelial neoplasia 2/3;
prCIN23toHealthy = proportion from Cervical intra-epithelial neoplasia 2/3 to healthy;
pCIN23toCIN1Healthy = transitional probability from Cervical intra-epithelial neoplasia 2/3 to Cervical intra-epithelial neoplasia 1 and healthy;
pCIN23toICC1 = transitional probability from Cervical intra-epithelial neoplasia 2/3 to invasive cervical cancer stage I;
pICC1toICC2 = transitional probability from invasive cervical cancer stage I to invasive cervical cancer stage II;
prSym1 = probability of invasive cervical cancer stage I having symptom;
pICC2toICC3 = transitional probability from invasive cervical cancer stage II to invasive cervical cancer stage III;
prSym2 = probability of invasive cervical cancer stage II having symptom;
pICC3toICC4 = transitional probability from invasive cervical cancer stage III to invasive cervical cancer stage IV;
prSym3 = probability of invasive cervical cancer stage III having symptom;
prSym4 = probability of invasive cervical cancer stage IV having symptom;
pDying = probability of death from general causes;
p1Dying / p2Dying / p3Dying / p4Dying = probability of dying due to invasive cervical cancer stage I / II / III / IV.

Intervention effects on cervical cancer disease model

The intervention of such strategies for cervical cancer prevention and control to the cervical cancer disease model are reflected by the oval box, namely HPV vaccination, screening, and treatment strategy. Current strategy of diagnose and treatment will be used as the baseline. In this scenario, the women are assumed only receive the tertiary prevention with diagnose and followed by the standard treatment of invasive cervical cancer. For scenario with primary prevention, women will receive HPV vaccination at the targeted age. This vaccine will prevent infection of HPV thus reduce the probability of women being infected with HPV. For the scenario with screening strategies, the women will have screening in accordance with the suitable schedule based on age. The screening will detect if they have pre-cancer lesions or cancer then can be followed by early treatment to prevent the pre-cancer lesions progress to cancer or early stage of cancer move to more severe stages of invasive cervical cancer.

Subjects entering the model with various strategies and scenarios will pass the same pathways but with different probabilities influenced by the effect of interventions. Effects of interventions on the Markov model health states were assigned using decision tree models as provided in Appendix B. The decision tree models were also adopted from previous (85) study which developed based on guideline of standard management of cervical cancer related disease (40) as in Appendix A. The transitional probabilities of each strategy drive the value of model outputs including epidemiological, economic, and health outcomes output. Furthermore, the model outputs of each strategy could be analysed and compared to those of the baseline to identify the cost-effectiveness of such interventions of cervical cancer prevention and control.

3.2.2 Model determination and evidence synthesizing

In general, overall considered strategies for cervical cancer prevention and control in this model could be summarized into 4 groups: baseline / do nothing, vaccination, screening, and mixed/combining strategy. The determination of model assumption for each strategy could be described as follows:

a) Baseline (Do nothing)

Current strategy of diagnose and treatment was used as the baseline. Only women with cancerous lesions and having symptoms were referred to tertiary health centres and provided diagnose for staging based on FIGO staging system, followed by standard treatment of stage specific-invasive cervical cancer.

Input parameters in this model included transition probabilities between health states, the risk of infection by HPV high-risk group, utilities associated with disease states and costs (resource use) of standard treatment.

b) Vaccination strategy

For intervention with primary prevention, girls received HPV vaccination at the age of 12 years once at a life time. Coverage of 80% considering current coverage of EPI through school-based program in Indonesia was employed. The vaccine prevents infection of HPV thus reduces the probability of women being infected by HPV. This intervention affects the cervical cancer model output in term of reduction of HPV prevalence infection comparing to the baseline strategy and lead to the reduction of incidence and mortality of cervical cancer in the following years.

Since the vaccine was assumed to only provide protection from HPV type 16 and 18 infection, some immunized women still have a chance to get HPV infection from non-type HPV vaccine and surfer from cervical cancer disease. The women with related symptoms of invasive disease will be referred to tertiary health centers to perform diagnostic staging and stage specific-standard treatment.

Input parameters in this model included transition probabilities between health states, the risk of infection by HPV high-risk group driven by efficacy of vaccine, utilities associated with disease states and costs (resource use) of standard treatment, as well as cost for providing vaccination and efficacy of vaccine.

The use of 2 and 3 doses of HPV vaccine per fully immunized girl were assigned.

c) Screening strategy

For intervention with screening strategies, the women have screening in accordance with the suitable schedule based on target age. The screening detects the pre-cancer lesions or cancer then followed by early treatment to prevent pre-cancer lesions progress to cancer or early stage of cancer move to more severe stages of invasive cervical cancer.

Screening with VIA

The target age of screening with VIA is women at age 30-45 years. Women were assumed to receive VIA test in primary health centers. For screen-positive women who are suitable for cryotherapy, they will be treated at the time of screening. Those not suitable for cryotherapy, will be referred to secondary health centers for gold standard verification with colposcopy and biopsy tests. If pre-cancerous is diagnosed, they will be treated using LEEP, cold knife conization or simple hysterectomy, depends on lesion size and type. If cancerous is diagnosed, they will be referred to perform diagnostic staging and stage specific-standard treatment at tertiary health centers.

For women receiving VIA and reported as normal or negative for any lesions will undergo rescreening at period and interval as indicated in each specific strategy.

Input parameters in this model included transition probabilities between health states, the risk of infection by HPV high-risk group, utilities associated with disease states and costs (resource use) of standard treatment; as well as cost for providing screening and follow-up treatment for pre-cancer lesions, performance of VIA test in term of sensitivity and specificity as key parameter to determine the results of VIA test, proportion of women having positive test result to receive LEEP, cold knife conization or simple hysterectomy for pre-cancer treatment.

Screening with Pap smear

The target age of screening with Pap smear is women at age 30-65 years for screening with Pap smear alone or if given in sequential with VIA, Pap smear is given after target age of VIA. Women were assumed to receive Pap smears from at primary health centers. For those who were detected as having a high-grade squamous intraepithelial lesion (HSIL) or invasive cancer, they need to be confirmed and treated before progressing to more invasive lesions. The confirmations and treatment processes for pre-cancerous lesions (HSIL) are assumed to be available at secondary health centers. Similarly, the diagnostic staging and standard treatments for cancerous lesions are assumed to be available at tertiary health centers.

For women receiving a Pap smear and were defined as normal or negative for CIN or malignancy will undergo rescreening at period and interval as indicated in the specific strategy.

Women who are classified as CIN grade 1 (LSIL) will undergo a repeat smear in 1 year. Women who are classified as CIN grade 2 or grade 3 (HSIL) will be provided histopathological confirmation using colposcopy and biopsy, followed by standard treatment using loop electrosurgical excision procedure (LEEP), cold knife conization or simple hysterectomy, depends on lesion size and type, and repeat smear in 1 year. This study assumed that no women were lost due to follow up and treatment, and after standard treatment all women recovered to a healthy state within 1 year. Women who are classified with invasive cancer will be referred to tertiary health centers to perform cancer staging and standard treatment.

Input parameters in this model include transition probabilities between health states, the risk of infection by HPV high-risk group, utilities associated with disease states and costs (resource use) of standard treatment; as well as cost for providing screening and follow-up treatment for pre-cancer lesions, performance of Pap smear test in term of sensitivity and specificity as key parameter to determine the results of Pap smear test, proportion of women having positive test result to receive LEEP, cold knife conization or simple hysterectomy for pre-cancer treatment.

Model of screening with VIA and Pap smear alone were differentiated by the interval time of receiving test, which was 3 and 5 years. Program coverage of 20%, 50%, and 80% were assigned in all strategies of VIA and Pap smear screening.

d) Mixed strategy

Combining of screening

This model assumed the target age of VIA and Pap smear could not be overlapped in the same model, so the first screening method for women in this intervention is VIA at target age and followed by Pap smear as if after target age of VIA.

Similar to strategy of screening with VIA and Pap smear alone, in the combining of screening strategy, the effectiveness of both screening was incorporated into the same model as if its target age. All input parameter used in the VIA and Pap smear screening model were also used in this model. Models of mixed-screening

strategy were differed by the interval time of receiving test. Program coverage of 20%, 50%, and 80% were also assigned in all strategies of combining-VIA and Pap smear screening.

Combining vaccination and screening

In this model, girls received complete vaccination at age 12 years, followed by screening at target age of screening in accordance with the type of screening and strategy.

The effectiveness of both vaccination and screening was incorporated into the same model as if its target age. All input parameter used in the vaccination and screening model were also used in this model. Models of mixed-vaccination and screening strategy were differed by the interval time of receiving screening test. Screening coverage of 20%, 50%, and 80% as well as use of 2 and 3 HPV vaccine dose per fully immunized girl were also assigned in all mixed-strategies of vaccination and screening.

3.2.3 Model calibration and validation

Calibration is the process to derive the estimated value within model as the basis for its prediction. It involves the comparison of model outputs with empirical data and leads to the identification of model parameter values that achieve a good fit. Since the model in this study was based on natural history of cervical cancer disease, which is likely to change over time and might not the same across setting, thus calibration was needed.

In this study used, the model used the transitional probabilities of baseline mostly based on mathematical model for the natural history of cervical cancer related disease developed by Myers et al (82). Trial and error searching method was employed to compare the predicted output of epidemiological data resulted from model with the empirical data of calibration targets. The calibration targets included age specific of HPV infection prevalence, age specific of cervical cancer incidence, age specific of cervical cancer mortality, and stage specific of cervical cancer distribution. Empirical data of HPV infection prevalence was derived from previous study in Indonesia (14), cervical cancer incidence and mortality rate were derived from GLOBOCAN data 2012 (2), and lastly stage distribution data was obtained from hospital-based cancer

report in Indonesia provided by INASGO (86). The data of age-specific prevalence of HPV infection was obtained from population-based study in 3 regions of Indonesia involving 2,686 women. Though not represent the whole country of Indonesia, but the data was obtained from specific setting of Indonesia. The stage-specific of cancer distribution was calculated from 10,337 cervical cancer cases reported by 19 public hospitals in Indonesia.

For model validation, model outputs resulted from model with the calibrated-transitional probabilities were compared to the observed-empirical data of Indonesia. Goodness-of-fit of model with the empirical data was measured using visual and percentage deviation as qualitative and quantitative goodness-of-fit metrics, respectively. Percentage deviation of 10% was considered acceptable in this analysis, as was also applied in the previous study (87,88).

3.3 Budget impact model

The time horizons for budget impact analysis should relevant in accordance with the budgeting process and periods of the budget holder, which were usually short time periods of 1 to 5 years with the results presented for each budget period after the new intervention is covered. However, a long-term time horizons may be needed to illustrate the offsetting disease effects on budgets from the intervention that may occur in future year, such as in cervical cancer case. Therefore in this study, both long-term and short-term budget impact analyses were assigned (89). Lifetime-time horizon was applied to conduct long-term budget impact analysis; meanwhile a 5-year budget impact analysis was conducted to estimate the budget for implementing such strategies for cervical cancer prevention and control in Indonesia in short term-time horizon. For lifetime budget impact analysis, it employed the same Markov model as was used in cost effectiveness analysis. The interventions assigned were the best optimum strategies based on cost effectiveness analysis results.

For short-term budget impact analysis, the following strategies were assigned for 5-year time horizons:

– Vaccination at age 12 years, using the assumption of coverage rate 80% and assigning 2 and 3 doses of HPV vaccine per fully immunized girl.

– Screening with VIA for women at age 30-45 years with 5-year interval, using the assumption of coverage rate 20%, 50%, and 80%.

– Screening with Pap smear for women at age 30-65 years with 5-year interval, using the assumption of coverage rate 20%, 50%, and 80%.

The model construction for short-term budget impact analysis was illustrated in Figure 3.2.

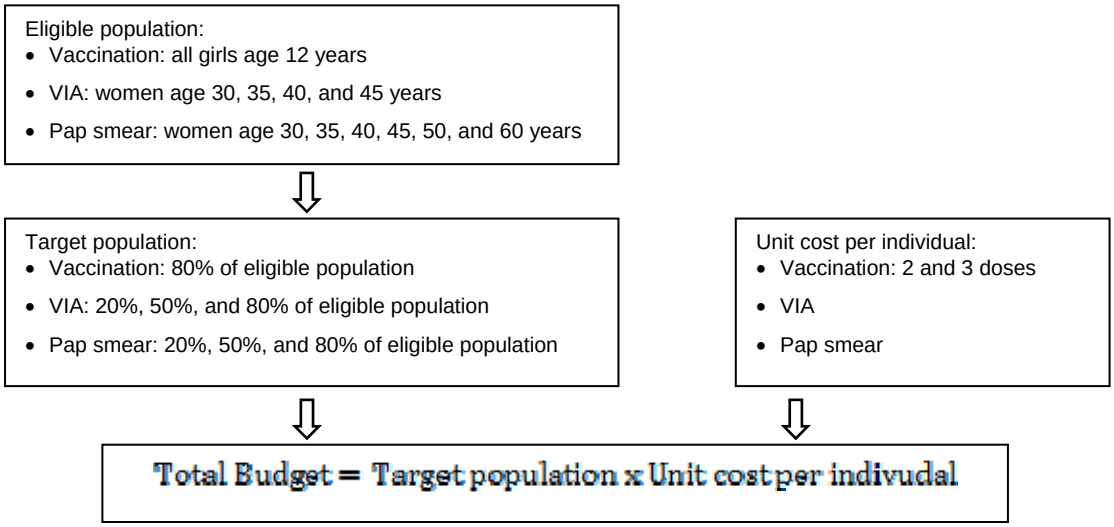


Figure 3.2 Model constructions for short-term budget impact analysis

The short-term budget impact analysis was projected for a cohort of age-targeted population in accordance to a certain strategy, starting in year 2015 to 2019. Unit cost of vaccination consisted of vaccine procurement cost and programmatic cost, which estimated using the WHO-C4P tool. Unit cost of screening of VIA and Pap smear included cost of screening service and cost of follow up and treatment for pre-cancer lesions. Unit costs of VIA and Pap smear was estimated using the decision tree analysis. Detail of costs valuations could be tracked in Appendix G.

3.4 Model input

This study used country-specific data of Indonesia for input parameters as much as possible, however if the input parameters could not be obtained from Indonesia setting, international data sources were adopted. Model parameters required in this study is summarized in Table 3.4.

Table 3.4 Parameters included in the model

Parameter	Type of data	Data sources / collection method
Transitional probabilities among health states	Secondary data	Literature review; calibration based on Indonesia empirical data
Program effectiveness:		
Efficacy of vaccination	Secondary data	Literature review; adoption
Accuracy of screening	Secondary data	Literature review; adoption
Coverage of vaccination and screening	Secondary data	Literature review; assumption
Costs:		
Cost of health care program		
Direct medical cost of vaccination / screening	Mixed-primary and secondary data	Literature review, MoH of Indonesia; calculated using WHO-C4P tool for vaccination / WHO-C4P tool for screening and treatment
Direct non-medical cost of vaccination / screening	Mixed-primary and secondary data	Literature review, Patients' interview; Cost of Illness study
Cost of illness		
Cost of pre-cancer treatment	Mixed-primary and secondary data	INA-DRG, Health insurance claims; re-calculation and extrapolation
Direct medical cost of invasive cervical cancer	Mixed-primary and secondary data	INA-DRG, Health insurance claims, literature review; calculation based on standard treatment guideline
Direct non-medical cost of invasive cervical cancer	Primary data	Patients' interview; Cost of illness study
Cost of morbidity	Primary data	Patients' interview; Cost of illness study
Cost of mortality	Secondary data	Literature review; calculation using PVLE method
Outcomes:		
Utility of pre-cancer patients	Secondary data	Literature review; assumption
Utility of invasive cervical cancer patients stage I-IV	Primary data	Patients' interview; estimation using EQ-5D preference based measure

3.4.1 Transitional probabilities

Transitional probabilities are the key parameter to synthesize evidence of expected output. In this study, transitional probabilities of baseline were mostly obtained from prior established study of mathematical model for natural history of cervical cancer related disease (82). Calibration was used to adjust transitional

probabilities values to result the fit predicted value with empirical data of Indonesia specific setting. Transitional probabilities values used in this model was based on calibration result.

3.4.2 Program effectiveness

The data related to vaccine and screening performance including vaccine efficacy, sensitivity, and specificity of screening are the important factor to predict the effectiveness of interventions. Program coverage is also another factor to lead the effectiveness of interventions. The data were obtained or assumed from literature review.

Effectiveness of HPV vaccine was estimated following previous study (90) and used the following equation:

$$eHPV = EfHPV \times pHPV$$

$$RRHPV = 1 - eHPV$$

Where:

eHPV = effectiveness of HPV vaccine to protect from all HPV infection

RRHPV = risk of infection by HPV

EfHPV = efficacy of HPV vaccine towards vaccine-HPV type (HPV 16 and 18)

pHPV = proportion of cervical cancer disease caused by HPV type 16 and 18

3.4.3 Costs parameters

Cost data consists of cost of healthcare program and cost of illness. Cost of program included cost of vaccination and cost of screening with VIA and Pap smear along with cost of pre-cancer treatment for the subjects who detected having pre-cancer lesions as results of screening. Cost of illness covered cost of treatment of invasive cervical cancer who diagnosed suffering from invasive cervical cancer. Each of these costs included cost categories such as direct medical cost, direct nonmedical cost, and indirect cost. Cost categories and cost components included in each analysis was varied based on the type of analysis (CEA/CUA/CBA/BIA) and perspectives of analysis (health system/societal) (91). Table 3.5 presents the cost categories along with components of each cost category and based on type of analysis or perspective

applied. In this study, all costs were presented in 2013 value using consumer index price for adjustment.

Table 3.5 Cost categories and cost components included in the model

Cost categories and components	Type of analysis and perspective							
	CUA		CEA		CBA		BIA	
	H	S	H	S	H	S	H	S
Cost of healthcare program:								
Cost of interventions (HPV vaccination/Screening with VIA/Screening with Pap smear)								
Direct medical cost of intervention								
Unit cost of each intervention	√	√	√	√	√	√	√	n/a
Direct non-medical cost of intervention								
Cost of transportation for receiving intervention	×	√	×	√	×	√	√	n/a
Cost of patient's time for receiving intervention	×	√	×	√	×	√	√	n/a
Cost of pre-cancer cancer treatment								
Direct medical cost of pre-cancer treatment								
Cost of colposcopy/biopsy service	√	√	√	√	√	√	√	n/a
Cost of cryotherapy service	√	√	√	√	√	√	√	n/a
Cost of LEEP service	√	√	√	√	√	√	√	n/a
Cost of cold-knife conization	√	√	√	√	√	√	√	n/a
Cost of follow-up after treatment	√	√	√	√	√	√	√	n/a
Direct non-medical cost of pre-cancer treatment								
Cost of transportation for receiving treatment	×	√	×	√	×	√	×	n/a
Cost of patient's time for receiving treatment	×	√	×	√	×	√	×	n/a
Cost of illness:								
Cost of invasive cervical cancer treatment								
Direct medical cost of ICC treatment								
Cost of clinical staging	√	√	√	√	√	√	×/√	n/a
Cost of surgery	√	√	√	√	√	√	×/√	n/a
Cost of radiotherapy	√	√	√	√	√	√	×/√	n/a
Cost of chemotherapy	√	√	√	√	√	√	×/√	n/a
Cost of follow-up treatment	√	√	√	√	√	√	×/√	n/a
Direct non-medical cost of ICC treatment								
Cost of patient's transportation	×	√	×	√	×	√	×	n/a
Cost of caregiver's transportation	×	√	×	√	×	√	×	n/a
Cost of patient's meal during treatment	×	√	×	√	×	√	×	n/a
Cost of caregiver's meal during patient's treatment	×	√	×	√	×	√	×	n/a
Cost of caregiver's time	×	√	×	√	×	√	×	n/a
Indirect cost								
Cost of morbidity	×	√	×	×	×	√	×	n/a
Cost of premature mortality	×	√	×	√	×	√	×	n/a

CUA= cost utility analysis; CEA=cost effectiveness analysis; CBA=cost benefit analysis; BIA=budget impact analysis; H=perspective of health system; S=perspective of societal; n/a=non-applicable; √=included; ×=not included.

Cost of healthcare program

Direct medical cost of vaccination and screening were calculated using the WHO-C4P (Cervical Cancer Prevention and Control Costing) tool. The C4P tool is a relatively new guideline in cervical cancer prevention and control costing developed by WHO in Excel-based format. It has been developed to give assistance in estimating the costs of cervical cancer interventions. Two modules of the generic tool were used, named HPV Vaccine Module and Cervical Cancer Screening and Treatment Module. The C4P tool addresses costing and planning issues; considering economic and financial perspective and providing input for Cost-Effectiveness and financial Analysis. The tool employs Excel-based model and consists of choice of inputs on strategies and assumptions, spreadsheets with data on population and infrastructure, and summary page on total costs (92).

The C4P tool for vaccination program guides the user to estimate the costs of activities that take place during introduction of HPV vaccination into national immunization program. These activities include the following: procurement of vaccines and injection supplies; micro-planning; training; social mobilization and information, education and communication (IEC); purchase of cold chain equipment; service delivery of vaccines to target population; monitoring and evaluation; supervision; and waste management (92). The C4P tool had been used for the first time in Tanzania to estimate the nationwide costing of HPV vaccination (93,94); the results were then used for study in other settings (95). The expected outputs from C4P tool calculation were financial and economic cost of HPV vaccination per dose administration and per fully immunized girl. The economic cost of HPV vaccination per dose was applied as input parameter in the Markov model as direct medical cost of vaccination.

Similarly, cost of screening was also estimated using the C4P tool for screening and treatment of cervical cancer. This tool incorporates calculation of programmatic cost of screening and service delivery of screening including follow-up treatment of screening result. Since costs of pre-cancer treatment were also incorporated in the Markov model, only programmatic cost and service delivery cost of VIA were taken from C4P output and included in the Markov model. This study assumed that VIA was provided at primary health center.

Unfortunately, the C4P does not provide calculation tool for screening with Pap smear. Hence, it was assumed that the programmatic cost of screening with Pap smear was the same with VIA while service delivery cost of Pap smear was taken from standards cost list of Indonesia-diagnose related group year 2008 (INA-DRG 2008) (96). Cost of Pap smear was calculated from INA-DRG by adjusting with CPI value from 2008 to 2013 (97) and proportion of hospital level utilization for cervical cancer treatment. It was assumed that screening with Pap smear was provided at primary health center (district hospital) and over.

Direct non-medical cost for intervention included transportation cost and patient's time cost for receiving intervention. Unit cost of transportation was obtained from primary data based on cost of illness conducted in this study, wage rate used to calculate patient's time cost was calculated from GNI per capita of Indonesia (97), and patient's time for receiving intervention was adopted from previous study by Goldie (76).

Cost of pre-cancer treatment

Cost of pre-cancer treatment depends on types of treatment which were loop electrosurgical excision procedure (LEEP), cold knife conization or simple hysterectomy. Unit cost of each type of pre-cancer treatment was obtained from INA-DRG by adjusted to 2013 value using CPI and considering proportion of hospital level utilization for cervical cancer treatment to represent national level cost. For calculating direct medical cost of pre-cancer treatment, it also considered the proportion of patients receiving the types of treatment.

Similar with intervention, direct non-medical cost of pre-cancer treatment also included transportation cost and patient's time cost for receiving treatment. The same method was also applied to estimate direct non-medical cost of pre-cancer treatment.

Cost of invasive cervical cancer treatment

Direct medical costs of invasive cervical cancer treatment were estimated based on standard treatment of cervical cancer. Stage specific of cervical cancer standard treatment developed by FIGO was adopted. The types of treatment included surgery, chemotherapy, radiotherapy, or combination among them. Unit cost of each treatment type was taken from standard cost list of INA-DRG 2008. The value was

adjusted to 2013 value using CPI and extrapolated to represent national level cost by considering the proportion of hospital level utilization for cervical cancer treatment. The proportion was estimated from the data of "Askes"-health insurance claims of cervical cancer admission in the hospital over all regions in Indonesia. The distribution of stage specific-invasive cervical cancer was estimated from data of hospital-based report that been published in the website of INASGO.

For direct non-medical and indirect costs, the data was directly collected from cervical cancer patients in Sardjito Hospital, Yogyakarta; employing cross-sectional approach and using the questionnaire developed by researchers. For this purpose, a number of patients to be respondents were calculated using the equation as follow (98):

$$n = \left(\frac{precision^2}{CV^2 \times Z^2_{1-\alpha/2}} + \frac{1}{N_0} \right)^{-1}$$

Where:

n = sample size

CV = coefficient of variance (ratio of mean and standard of deviation), obtained from the previous study

$Z_{1-\alpha/2}$= the abscissa of the normal curve that cuts off an area at the tails (1 – equals the desired confidence level); the value for Z is found in statistical tables, for the confidence level of 95%, Z value is 1.96

N_0 = total number of cases in prior year

Given the confidence level is 95%, level of precision is 10%, the estimated number of cases in prior year was 200, and coefficient of variance derived from the previous costing study (99) was 0.6; the value of sample size was equal to 82 samples. Finally, 87 convenience samples were recruited in this study.

Information received from patients' interview included cost of transportation and meal of patient and care giver for receiving treatment, patients' time spent for receiving treatment, caregivers' time spent for providing informal care during treatment and after discharge from hospital. Direct medical cost of treatment related to cervical cancer at health facilities before patient admitted to the hospital of study setting was also gathered.

Productivity cost of caregiver was estimated using human capital approach employing GNI per capita for the productivity value. For the morbidity cost, the same method was also used to estimate the productivity loss of patient for receiving treatment, and absent from work due to cervical cancer disease. Lastly, mortality cost was estimated as present value of loss earning (PVLE). Age specific of remaining life expectancy followed WHO-life table, productivity value used GNI per capita adjusted with GNI per capita growth and discount rate over the year. The PVLE was calculated using the following formulation (100):

$$PVLE\ (f) = \sum_{i=s}^{n} \frac{W}{(1+r)^{i-s}}$$

Where:

PVLE = Present value of loss earning

i = Age

s = Starting age

n = Life expectancy of age i

W = Annual wages

r = discount rate

3.4.1 Utility data

Utility is the result of health outcome measurement; this data was incorporated in the model to result output of QALY as the outcome in CUA. Recently, QALY is the gold standard of outcome used in economic evaluation.

In this study, utility of women in all health states except invasive cervical cancer and death was assumed as the perfect health status, which was 1. Death states had the worst health status, which was 0. Meanwhile, utility of cervical cancer patients were measured using preference-based measure instrument, which was EQ-5D-3L (101). The respondents were cervical cancer patient who received care at Dr. Sardjito hospital, a referral hospital, in Yogyakarta, Java Island, Indonesia in the period of June to December 2013.

The following equation was used to calculate the sample size (102):

$$n = \frac{Z^2_{1-\alpha/2}\,\sigma^2}{d^2}$$

Where:

n = sample size

$Z_{1-\alpha/2}$ = the abscissa of the normal curve that cuts off an area at the tails (1 – equals the desired confidence level); the value for Z is found in statistical tables, for the confidence level of 95%, Z value is 1.96

σ = standard of deviation

d = absolute precision or effect size

Using the above formula; if estimated of standard of deviation of utility derived from previous published article (103) is 0.2, the effect size for utility measured with EQ 5D from previous study (104) is 7%, the number of required sample for utility measurement is 32. Finally, convenience sample of 87 patients were interviewed to complete EQ-5D-3L questionnaire in Indonesian language.

The EQ-5D instrument consists of two parts: EQ-5D descriptive system and EQ-5D visual analog scale (EQ-5D VAS). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension of EQ-5D-3L, there are 3 possible response categories; no problem, moderate problem, and severe problem. The EQ-5D VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled as 'best imaginable health state' and 'worst imaginable health state'. The scale ranges from 0 for the worst health state to 100 for the best health state. The EQ-5D descriptive system provides EQ-5D health states recorded by an individual, while the EQ-5D VAS informed a quantitative measure of health outcome as judged by the individual respondents (patient-based measurement). Utility analysis requires a general population-based value set (as opposed to a patient-based set). Utility can be converted from EQ-5D health states using a country-specific scoring algorithm and value sets. In the absence of a country-specific value set, a value set from other settings can be applied.

At the moment, the EQ-5D-3L was available in Indonesian language version. However, the value set for Indonesian was not developed yet. Hence, value set from other country should be applied. It was unclear yet which of the foreign value

sets should be employed for Indonesia. Therefore, a specific analysis, namely agreement test was conducted to explore the most suitable value set to be adopted for Indonesia setting. Utility calculations using four different value sets of Malaysia (105), Singapore (106), Thailand (107), and UK (108) were compared to gain insight into their appropriateness to use in Indonesian population.

3.5 Model Output

For Markov model, the model was analyzed based on individual simulation of adolescent girl age 12 years and followed until age 100 years. After assigning intervention effect for each strategy, the model produced main output which was the proportion of cohort remaining in each health states for each of cycle in the model. The expected of model outputs were then summarized as follows:

a. Epidemiological output

Intervention impacts on epidemiology of cervical cancer were estimated in vital epidemiological parameters; incidence and mortality rate. Incidence and mortality rate of cervical cancer were calculated as crude incidence rate at population aged 0-74 years per 100,000 population. Incidence rate was summarized from the health state of initial-invasive cervical cancer from 4 stages, while mortality rate was summarized from the health state of cervical cancer related death from 4 stages. The incidence and mortality rate of each strategy was assigned.

b. Health-outcome output

The expected life years from every cycle-year were summarized as discounted expected life years applying the discount rate of 3% per annum using standard formula. QALYs were resulted from the model by incorporating utility of each health states with the discounted expected life years.

c. Economic output

The economic output consisted of life-time cost of program and life-time cost of illness. Life-time cost was derived from proportion of cohort remained in each health state and cycle multiplied by unit cost of accorded health states. The same as QALYs, lifetime cost was discounted using standard formula at the same rate of outcome.

3.6 Analysis and presentation

3.6.1 Cost effectiveness ratio

To summarize the result of economic evaluation, the life-time costs were summed up over the predicted outcome and compared with the baseline. For CUA and CEA, the cost effectiveness ratio was performed in terms of incremental cost effectiveness ratio (ICER). For CBA, the result was presented as net present value. The analysis used the following equation:

$$\text{ICER per LY gained} = \frac{[(CoIp + CoPp) - CoIc]}{(LYc - LYp)}$$

$$\text{ICER per QALY gained} = \frac{[(CoIp + CoPp) - CoIc]}{(QALYc - QALYp)}$$

$$NPV = (CoIc - CoIp) - CoPp$$

$$\text{Ratio benefit to cost} = \frac{(COIp - CPCp)}{CPCp}$$

$$\text{Ratio cost to benefit} = \frac{(COIp - CPCp)}{CPCp}$$

Where:

ICER per QALY gained = Incremental cost effectiveness ratio per quality adjusted life year gained

ICER per LY gained = Incremental cost effectiveness ratio per life year saved

NPV = Net present value

BCR = Benefit to Cost Ratio

CBR = Cost to Benefit Ratio

CoIp = Cost of illness under the intervention/healthcare program

CoIc = Cost of illness under the baseline

CoPp = Cost of the intervention

LYc = Life year gained under the baseline

LYp = Life year gained under the intervention/healthcare program

QALYc = Life year gained under the baseline

QALYp = Life year gained under the intervention/healthcare program

For CUA, besides summarizing the result of cost utility analysis as ICER per QALY, the incremental cost and incremental effect can be expressed

visually/graphically using the incremental cost effectiveness plane. The cost effectiveness plane is defined by a horizontal axis representing the incremental QALY and a vertical axis representing incremental cost. The horizontal axis divides the plane according to incremental cost (positive above and negative below) and the vertical axis divides the plane according to incremental effect (positive to the right and negative to the left). The four quadrants of a cost effectiveness plane is usually likened to the four points on a compass, which are NE/north-east, SE/south-east, SW/south-west, and NW/north-west. A strategy of health care intervention characterized by a certain cost and QALY was represented by a point on the cost effectiveness plane (109,110).

3.6.2 Sensitivity analysis

The impact of assumption or uncertain of each parameter on the overall results of economic evaluation study must be systematically evaluated through a process namely uncertainty or sensitivity analysis. In sensitivity analysis, model results are recalculated as important model parameters are varied across a plausible range of values (111). In this study, sensitivity analysis was conducted for the results of CUA. Four types of sensitivity analysis were used, as follows:

– Univariate or One-way sensitivity analysis

Univariate sensitivity analysis able to point out whether each parameter significantly influence overall results of economic evaluation. One-way sensitivity analysis presented the ranges of ICER changes from base case-ICER by varying some values of variables (input parameters) such as discounting rate, vaccine and screening coverage, vaccine and screening effectiveness, costs, and utility; using the minimum and maximum estimates. The ranges of parameter values for one-way sensitivities analysis were selected based on the difference approaches. Ranges of discount rate and program coverage were selected based on plausible range. Ranges of vaccine and screening effectiveness and utility were obtained from the 95% confidence interval reported in the study. Meanwhile, the ranges of cost parameters were set based on arbitrary value representing the worst and best case, which were 0.5 and 2 times of base case value. The results of one-way sensitivity analysis were presented as Tornado diagrams.

– Two-way sensitivity analysis

Two way sensitivity analysis assigned the influence of two different parameters on the overall model results simultaneously. The model applied data of screening performance from meta-analysis study conducted in other settings. The screening performance in Indonesia might differ from that of the study; hence two-way sensitivity analysis was conducted to explore the effect of different screening performance on ICER changing and in which thresholds of screening performance that the ICER changing is acceptable. In this analysis, sensitivity and specificity values were ranged from 0 to 1.

– Threshold analysis

Previous studies reported that interventions with vaccination were not cost-effective due to the high cost of vaccine. Therefore, threshold analysis was conducted to explore the effect of vaccine price changing on ICER and in which threshold of vaccine price that the intervention is acceptable. The wide range of vaccine prices were assigned to explore the break-even price of vaccine and ICER to be acceptable under the cost effectiveness threshold.

– Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to evaluate the uncertainty around ICER due to uncertain input parameters; the analysis was conducted simultaneously and randomly using Monte Carlo Simulation. Gamma distributions were assigned to all cost parameters, since they are restricted from 0 to positive infinity. Beta distributions were assigned to health states' transitional probabilities and programs accuracy estimates and coverages, since they are restricted from 0 to 1. By sampling from the input parameters' distribution, 10,000 estimates for the costs and effects of each strategy were generated. The results were presented as the cost effectiveness acceptability curve (CEAC) considering all possible input parameters in the model to illustrate the relationship between the value of ceiling ratio and the probability of favoring each intervention option.

In this study, CEAC was constructed using parametric approach which was net monetary benefit (NMB).

$$NMB = \lambda \times E - C$$

Where:

λ = cost effectiveness threshold; E = total effect (QALY); C = total cost

The probability was estimated as follow: in each of 10,000 iterations, the NMB was estimated; the option with the highest net benefit was then identified. The probability of being cost effective was then equivalent to the proportion of the 10,000 iterations for which each option had the highest net benefit. CEACs for multiple strategies assigned were estimated by plotting these proportions (y-axis) for different λ-values (x-axis) (112).

CHAPTER IV
RESULTS

This chapter is divided into parts as follows:

1. Model parameter values
    a. Transitional probabilities
    b. Program effectiveness
    c. Costs
    d. Utility
2. Model prediction and output
    a. Model prediction
    b. Epidemiological output
    c. Health outcomes output
    d. Economic output
3. Model analysis
    a. Incremental cost effectiveness ratio
    b. Net present value
    c. Incremental cost utility ratio
    d. Cost effectiveness plane and efficiency frontier
    e. Budget impact
4. Sensitivity analysis
    a. One-way sensitivity analysis of selected parameters
    b. Two-way sensitivity analysis of screening accuracy
    c. Threshold analysis of vaccine price
    d. Cost effectiveness acceptability curve

4.1 Model parameter values

4.1.1 Transitional probabilities

The calibration process is illustrated in Figure 4.1, while model validation of both deterministic and probabilistic is presented in Table 4.1. In addition, Table 4.2 shows the calibration results. Validation results showed that model output compared well with the empirical data as the percentage deviations between model predictions and empirical data were all acceptable (<10%).

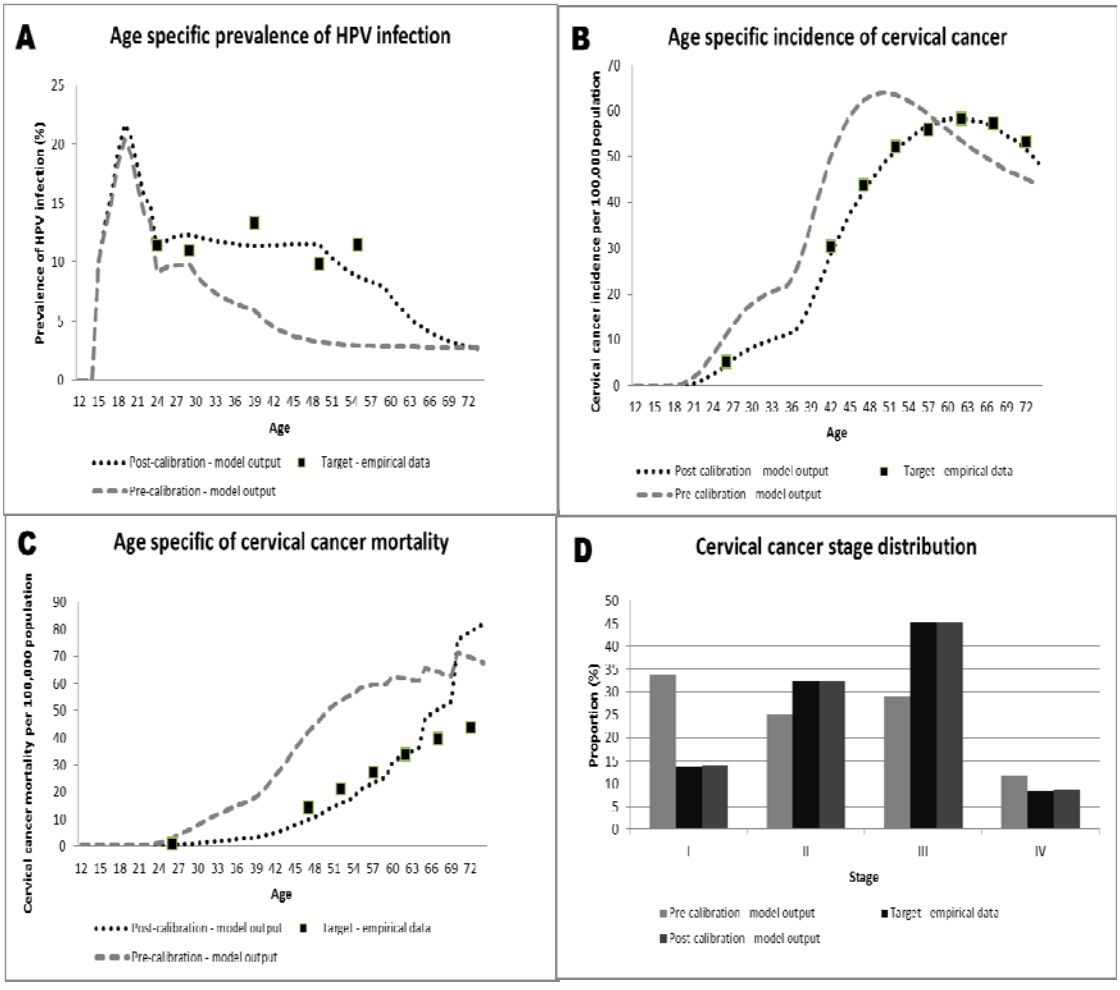


Figure 4.1 Comparison of predicted output and empirical data in the calibration process: (A) Age specific prevalence of HPV infection; (B) Age specific of cervical cancer incidence; (C) Age specific of cervical cancer mortality; (D) Stage specific of cervical cancer distribution

Table 4.1 Model validation with the empirical data of Indonesia setting

(A): Goodness of fit between empirical data and predicted-output of base case value

Target	Empirical data	Predicted-output of base case	Percentage of deviation
Prevalence of HPV infection at age 25-54 years (%)	11.41	11.50	0.79%
Cumulative incidence of cervical cancer at age 0-74 years (%)	1.89	1.87	0.87%
Crude incidence of cervical cancer at age 0-74 years (per 100,000 population)	16.34	16.34	0%
Crude mortality of cervical cancer at age 0-74 years (per 100,000 population)	6.85	6.86	0.11%
New cervical cancer cases at age 0-74 years (person)*	19,666	19,670	0.02%
Cervical cancer death at age 0-74 years (person)*	8,248	8,257	0.11%

*values were calculated based on Indonesian population in 2012; the same population used by GLOBOCAN for estimating cervical cancer incidence and mortality rate.

(B): Goodness of fit between empirical data and predicted-output of probabilistic value

Target	Empirical data	Predicted-output of probabilistic value**	95% CrI of predicted output from PSA**	Percentage of deviation
Prevalence of HPV infection at age 25-54 years (%)	11.41	11.48	7.42 – 16.26	0.59%
Cumulative incidence of cervical cancer at age 0-74 years (%)	1.89	1.85	0.91 – 3.26	1.68%
Crude incidence of cervical cancer at age 0-74 years (per 100,000 population)	16.34	16.09	7.71 – 28.60	1.51%
Crude mortality of cervical cancer at age 0-74 years (per 100,000 population)	6.85	6.66	3.08 – 12.07	0.11%
New cervical cancer cases at age 0-74 years (person)*	19,666	19,374	9,277 – 34,430	1.48%
Cervical cancer death at age 0-74 years (person)*	8,248	8,013	3,711 – 14,535	2.84%

*values were calculated based on Indonesian population in 2012; the same population used by GLOBOCAN for estimating cervical cancer incidence and mortality rate.
**values were based on results of probabilistic simulation of 25,000 iterations

Table 4.2 Transitional probabilities values resulted from calibration

Parameter	Original values*		Calibrated values	
	Base case	Range	Mean	Range
Prevalence of HPV infection; age 12[a]	0		0	-
Prevalence of CIN-1; age 12[a]	0		0	-
Age (years)-specific incidence of HPV infection				
12	0		0	-
13	0		0	-
14	0		0	-
15	0.100	0.5 – 2 x base case value	0.100	0.5 – 2 x base case value
16	0.100		0.100	
17	0.120		0.120	
18	0.150		0.150	
19	0.170		0.170	
20	0.150		0.150	
21	0.120		0.120	
22	0.100		0.100	
23	0.100		0.100	
24	0.050		0.058	
30	0.010		0.017	
40	0.005		0.018	
50	0.005		0.010	
60	0.005		0.003	
Progression rate; HPV infection to CIN-1	0.072	0.053 – 0.112	0.028	0.020 – 0.043
Progression rate (age); CIN-1 to CIN-2 or CIN-3				
12	0.017	0.017 – 0.058	0.017	0.017 – 0.058
35	0.069	0.058 – 0.109	0.069	0.058 – 0.109
Progression rate; CIN-2/3 to invasive cancer	0.050	0.035 – 0.067	0.050	0.035 – 0.067
Progression rate; stage I to stage II	0.438	N / A	0.438	0.219 – 0.875
Progression rate; stage II to stage III	0.536		0.536	0.268 – 1
Progression rate; stage III to stage IV	0.684		0.684	0.342 – 1
Age (year) specific probability of regression; HPV infection to Healthy				
12	0.552	0.457 – 0.785	0.552	0.457 – 0.785
25	0.370	0.329 – 0.457	0.370	0.329 – 0.457
30	0.103	0.068 – 0.138	0.103	0.068 – 0.138
Age (year) specific regression rate; CIN-1to HPV infection or Healthy				
12	0.161	0.142 – 0.235	0.161	0.142 – 0.235
35	0.082	0.058 – 0.142	0.082	0.058 – 0.142
Regression rate from CIN-2/3 to CIN-1/Healthy	0.069	0.058 – 0.109	0.069	0.058 – 0.109
Proportion of CIN-1 reverting to Healthy	0.900	0.500 – 1	0.900	0.500 – 1
Proportion of CIN-2/3 reverting to Healthy	0.500	0 – 0.500	0.500	0 – 0.500
Proportion of stage I having symptoms	0.150	N /A	0.062	0.031– 0.124
Proportion of stage II having symptoms	0.230		0.235	0.118 – 0.470
Proportion of stage III having symptoms	0.600		0.750	0.375 – 1
Proportion of stage IV having symptoms	0.900		0.825	0.413 – 1
Stage specific mortality[b]				
I	0.061	N/A	0.008	0.032 – 0.122
II	0.123		0.016	0.061– 0.245
III	0.185		0.024	0.092 – 0.370
IV	0.990		0.990	-
Age specific mortality[c]	N/I; see Appendix C			-

N/I = not identified; * = except if mentioned, the values were based on Myers(82); [a] = the values were based on Kulasingam(113); [b] = the values were based on Nuranna(45); [c] = the values were based on WHO-life table (114)

4.1.2 Program effectiveness parameter

Effectiveness of vaccination

HPV vaccination was assumed to be delivered through the school-based immunization program. The assumption of vaccination coverage in this study was based on consideration of vaccination coverage of current school-based NIP in Indonesia and school participation rate. The national average coverage rate of BIAS (school-based immunization program) in 2009 was 85% (115); while the national school participation rate for age of 12 years old was 98% (116). Hence, the HPV vaccination coverage in this model was assumed 80%.

Literature review of HPV vaccine efficacy was conducted to estimate the effectiveness of HPV vaccination. The efficacy of HPV vaccine towards infection of HPV type 16 and 18 had been summarized and published by previous meta-analysis studies (117-119). Rambout et al (117) summarized the relative risk of HPV vaccine towards HPV 16 and 18 infections within 12 months of observation was 0.26 (95% CI: [0.16, 0.41]). Lu et al (119) recapitulated the relative risks of HPV vaccine towards HPV 16, HPV 18, and cumulative of HPV 31, 33, 45, 52, 58 within 6 months of observation were 0.15 (95% CI: [0.1, 0.23]), 0.24 (95% CI: [0.14, 0.42]), and 0.77 (95% CI: [0.72, 0.83]), respectively. Most recent study by Delere et al (118)summarized the relative risks of HPV vaccine towards HPV 16 and 18 infections were 0.1 (95% CI: [0.05, 0.21]) and 0.05 (95% CI: [0.01, 0.16]) for duration of observation <5 years and >5 years, respectively. Regardless, this study assumed that the efficacy of vaccine towards infection of HPV 16 and 18 was 100%, as was applied in previous study (90). The effect of vaccine cross-protection towards other HPV genotypes was not taken into account. The proportion of cervical cancer disease caused by HPV 16 and 18 varied across countries (120). Based on meta-analysis estimation by that study, the proportion of cervical cancer caused by HPV type 16 and 18 for region including Indonesia was 68%. Hence, the vaccine effectiveness was assumed 68% and the risk of infection by HPV was assumed 32%. Values of 20% and 40% of HPV relative risk were assigned in sensitivity analysis.

Effectiveness of screening for cervical cancer

In this study, 20% screening coverage for both VIA and Pap smear was assumed in the base case. This coverage was based on coverage of VIA pilot program

implemented in several regions in Indonesia (121) which also was the average coverage rate of cervical cancer screening in developing countries (122). Another assumptions of screening coverage, 50% and 80%, were also assigned in the model. A 50% screening coverage rate was the closely average coverage rate of screening in developed countries (122), while 80% was the optimum screening coverage that might be achieved in Indonesia.

Literature review was conducted to reveal information regarding screening performance. The expected information was the screening performance with clear information of disease threshold definition and reference standard. Chen et al (123) conducted meta-analysis to assess the accuracy of 6 common cervical screening strategies including VIA and Pap smear from 22 cross-sectional studies. The study summarized that the combined estimates of sensitivity for visual inspection with acetic acid (VIA), magnified visual inspection with acetic acid (VIAM), VILI, Hybrid Capture 2 assay (HPV DNA test), conventional Papanicolaou smear, and LBC (cytology-based screening) were 77%, 64%, 91%, 74%, 59%, and 88%, respectively; while the combined values of specificity of these screening strategies were 87%, 86%, 85%, 92%, 94%, and 88%, respectively; the diagnostic odds ratio were 22.43, 10.30, 57.44, 33.26, 22.49, and 51.56, respectively. The study also explored that the accuracy of screening strategies were significantly different among studies conducted in different regions; suggesting that the estimation of accuracy of such screening strategies should consider the specific-setting data.

There are few limited studies regarding effectiveness of strategies for cervical cancer prevention and control conducted in Indonesia setting. A study conducted by Wiyono et al (124) and published in national journal, assessed the accuracy of screening strategies including VIA and Pap test. This study involved 120 subjects in Dr. Kariadi Hospital Indonesia, resulted the calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The sensitivity of Pap test was 55%, specificity 90%, PPV 84% and NPV 69% whether VIA had sensitivity 84%, specificity 89%, PPV 87% and NPV 86%. The study concluded that VIA has high sensitivity for early detection of cervical pre-cancer lesion and should be considered as cervical cancer screening method in developing countries. Rachmadi et al (125) reported the accuracy of cytomorphological analysis

of uterine cervical Pap smears in relation to HPV infection in Indonesian women. This study, involved 140 smears collected in three different areas in Indonesia, found the overall sensitivity of 42% and sensitivity of 90%. Finally, the study suggested Pap smear methods to be more important in developing countries compared to molecular HPV testing that still poses a major financial, logistic and expertise problems. Unfortunately, these studies were unclear regarding the disease threshold identified. Hence, these might not appropriate to be used in the economic evaluation study of cervical cancer screening.

This study then used the screening performance data from meta-analysis study conducted by Chen et al (123), in which sensitivity and specificity for visual inspection with acetic acid (VIA) were 77% (95% CI: [75%, 78%]) and 87% (95% CI: [86%, 87%]), respectively, whereas sensitivity and specificity for Pap smear were 59% (95% CI: [56%, 62%]) and 94% (95% CI: [93%, 94%]), respectively.

4.1.3 Costs parameter

Cost of program

- Direct medical cost of vaccination and screening

In this study, direct medical cost of HPV vaccination and screening included cost of providing service and programmatic cost. Direct medical cost of vaccination was obtained from output of C4P for vaccination. Direct medical costs of VIA and Pap smear were summarized from programmatic cost of C4P output and unit cost of screening service from INA-CBG tariff (126). Cost of HPV vaccination and screening was calculated using C4P tool by modeling approach employing the data of current NIP in Indonesia, pilot program of VIA, and assumptions. Input data for this model was obtained from primary data by interviewing staffs of Ministry of Health of Indonesia and secondary data from government published report and literature review. Cost of program was presented based on the activities on program as follows: micro planning, training, social mobilization and information-education-communication, and supervision-monitoring-evaluation. Additional activities for vaccination program were vaccine and injection supplies, service delivery, cold chain equipment, and other (e.g. waste management). Finally, costs of providing vaccination per dose and per fully

immunized girls were summarized. Similarly, cost of providing screening for cervical cancer was also calculated.

Among all costs of activity, vaccine procurement (including syringe and safety box) accounts for the largest of financial and economic costs. Excluding procurement, the largest share of costs goes towards service delivery, followed by supervision-monitoring-evaluation. The average costs per dose and per FIG were greatly higher if the vaccine costs were included. Without vaccine costs, the financial costs for providing vaccination were USD 1.26 and 3.99 per dose and per fully immunized girl, respectively. Whilst the economic costs for providing vaccinations were USD 2.16 and USD 6.83 per dose and per fully immunized girl, respectively. Including vaccine cost of base case assumption, the financial costs for providing vaccination were USD 49.48 and USD 157.04 per dose and per fully immunized girl, respectively. Whilst the economic costs for providing vaccinations were USD 50.58 and USD 159.88 per dose and per fully immunized girl, respectively. Similar with cost of vaccination, the largest share of costs of screening went towards service delivery, followed by supervision-monitoring-evaluation. Financial and economic costs of VIA per screened woman were USD 6.48 and USD 8.41, respectively. Without service delivery or programmatic cost only, the financial and economic costs for providing screening were USD 1.59 and USD 1.64, respectively.

WHO-C4P tool was applicable to estimate the costs of programs of cervical cancer prevention and control in Indonesia. The following outputs of the tool were used as input parameter in economic evaluation study of strategies for cervical cancer prevention and control in Indonesia: economic cost of HPV vaccination per dose (USD 50.58), and economic cost of programmatic cost of screening (USD 1.64). Converting the value to 2013 Indonesian currency, the direct medical cost for providing HPV vaccination was estimated as IDR 550,000 per dose. Whereas the programmatic cost of screening was IDR 17,000. Given the unit costs of VIA and Pap smear services from INA-CBG list of IDR 25,000 and IDR 125,000, the direct medical costs of VIA and Pap smear inputted in the model were estimated as IDR 40,000 and IDR 140,000, respectively. The detail valuation of cost of program could be tracked in Appendix D.

- Direct medical cost of pre-cancer treatment

Direct medical costs of pre-cancer treatment applied in the model were based on the follow up of screening test results which categorized as true positive, true negative, false positive, and false negative. The cost estimation was in respect to cost of each follow-up treatment type and probability of receiving treatment which was differed by the degree of pre-cancer lesions severity in which the valuation was guided by decision trees as were shown in Figure 3.3 and 3.4. Follow up and treatment for pre-cancer included cytology test, colposcopy-biopsy, cryotherapy, LEEP, cold knife conization, and simple hysterectomy. The unit costs of each treatment type were obtained from INA-DRG 2008 list (96) which adjusted by hospital type utilization and value conversion to 2013 using CPI. Meanwhile, the probabilities of receiving certain treatment were obtained from previous study (76). The valuations could be detected in Appendix E. The values of these costs are also presented in Table 4.12. Cost of follow up and treatment for VIA with positive result was about 10 times higher than that of negative result, while cost of follow up for Pap smear with positive result was about 5 times higher than that of negative result. Moreover, cost of pre-cancer for CIN-2/3 following VIA screening was slightly greater compared to that of Pap smear.

- Direct non-medical cost

Direct non-medical cost included travel cost and time cost of patient for seeking screening and follow-up treatment for detected pre-cancer. Estimation of the costs considered unit cost of transportation by health facility level, wage rates, and patients' time spent for seeking screening and follow up care. Unit costs of transportation by health facility level were obtained from primary data of cost of illness study conducted in this study, wage rates was calculated from GNI per capita of Indonesia in 2013, patients' time was adopted from previous study conducted in developing country (76). Detail of cost valuations were provided in Appendix E, while the summary of costs are also presented in Table 4.12. Direct non-medical cost of interventions and pre-cancer treatments were accounted for about 18% - 95% with the average of 44% as compared to direct medical cost.

Cost of illness

- Direct medical cost of invasive cervical cancer

Direct medical cost of invasive cervical cancer included in the model was divided into cost of initial treatment and cost of subsequent years. Cost of initial treatment was estimated per patient for the whole set of treatment, once in lifetime and given in the first year after diagnose. Cost of subsequent years after initial treatment was estimated per patient per year for remaining lifetime, consisting of recurrence and routine follow up treatment costs. Method for estimating the costs followed previous studies (90,127-129). The costs were estimated based on standard treatment of invasive cervical cancer following the guideline from FIGO (FIGO). The guideline provides the management of invasive cervical cancer with certain type of treatment for each cancer stage. The treatments for initial period include conization, simple and radical hysterectomy, radiotherapy, and chemotherapy; whilst the treatments for recurrence comprise of chemotherapy, radiotherapy, and pelvic exenteration; lastly the routine follow up for subsequent years involves pelvic examination and cytology test. In order to estimate these costs, the following data input was required: stage distribution of cervical cancer, probability of receiving certain treatment type in each stage, probability of recurrence in each stage, and unit cost of certain treatment types. Stage distribution of cervical cancer was estimated from hospital-based report from INASGO (ref), probability of patient receiving certain treatment type and having recurrence in each stage referred to previous study (128), lastly unit cost of certain treatment type applied INA-DRG list with adjustment by hospital utilization to get average national cost and using CPI to convert the values to 2013 values. Cost of initial treatment also included direct medical cost for seeking treatment related to cervical cancer in other health facilities out of tertiary hospital side such as primary, secondary health center, midwife and physician private clinics, and traditional healing. Stage specific initial and subsequent year's costs of invasive cervical cancer inputted in the model were presented in Table 4.3. Cost valuations could be revealed in Appendix G.

- Direct non-medical cost

Similar with direct medical cost, direct non-medical cost was also separated into cost of initial treatment and subsequent years treatment. Direct non-

medical costs consisted of meal and travel costs of patient and care giver during seeking treatment and care giver's time cost for providing informal care. Input data for estimating the costs included number of out-patient and in-patient visit per year for any treatment, patient time loss for seeking treatment, care giver time loss for providing informal care, unit cost of meal and transportation, and wage rates. All those data excluding wage rate was assumed based on primary data of patient's interview and estimated based on standard treatment of cervical cancer; while wage rates employed GNI per capita in 2013. Table 4.3 includes the values of these costs; while the valuation is provided in Appendix F.

- Indirect cost

Indirect cost was inputted in the model to assign CEA and CBA. Indirect cost of cervical cancer consisted of morbidity and mortality cost of patient. In which morbidity cost included productivity losses of patient for seeking treatment and absent from work due to the disease; while mortality cost was productivity losses due to premature mortality related to the disease. Input for these costs included time losses of patient for seeking treatment and absent from work due to the illness which were obtained from patients' interview, age-specific remaining life expectancy from life table, and wage rates which estimated from GNI per capita of Indonesia in 2013. The cost valuations are described in Appendix G, while the costs values are included in Table 4.3.

There were slightly differences of costs of invasive cervical cancer by cancer stage, which the highest cost was in stage I and the lowest cost was in stage IV. Costs of cervical cancer in subsequent years after initial treatment were about 18% of initial treatments' costs. Direct non-medical costs were about 55% of direct medical costs, whereas morbidity costs were comparable with direct medical costs.

4.1.4 Utility

Agreement test was conducted to gain insight of most suitable foreign value set to be employed for calculating utility from EQ-5D health state of Indonesian cervical cancer patients. Utilities were calculated based on the Malaysia (MY) (130), Singapore (SG) (106), Thailand (TH) (107), and UK value sets (108). The differences of the utility scores derived from the four value sets were determined using Friedman

test, followed by Wilcoxon signed rank test. The agreement among these utility and VAS scores was assessed by intra-class correlations coefficients (ICCs) and Bland-Altman plots. The validity of utility scores was examined using convergent and known-group validity tests. Convergent validity employing Spearman's rho correlation was conducted to assess the association between the utility and the patient's characteristics of age, marital status, education level, disease stage, and duration of illness. Known-group validity employing Kruskal-Wallis test was conducted to examine the ability of the four value sets to discriminate the cancer disease stage. Detail results of descriptive statistics of health-related quality of life of cervical cancer patients in Indonesia and agreement test are provided in Appendix H.

Although no substantial superior in term of psychometric properties was found, we suggested that the MY value set was more suitable to be employed compare to other value sets (SG, TH, and UK) due the following reasons. First, VAS scores of Indonesian sample had more agreement with the utility scores derived from Malaysia value set than with the utility scores derived from the other three value sets. Although VAS scores represent patient's own health state assessment in contrast with utility scores that represent health states of general population, the previous studies concluded that VAS scores were predictable from the EQ-5D health state classification, the same data used to obtain utility scores (131,132). Second, Malaysia seems to have a relatively different in socio-demographic variables compare to Thailand, Singapore, and UK, but is closer to Indonesia. HRQOL although not always, were often associated with the socio-demographics of particular country (133-136). Third, previous HRQOL studies in Childhood-acute lymphoblastic leukemia patients conducted in Indonesia, Malaysia, Singapore, and Thailand using the same instruments found that both Indonesian and Malaysian samples seemed to have the higher quality of life compared to Thai and Singaporean samples (137-139).

The mean (SD) utility scores used in the economic evaluation study were 0.85 (0.19), 0.76 (0.20), 0.71 (0.21), and 0.77 (0.13) for cervical cancer patients in stage I, II, III, and IV, respectively.

Table 4.3 presents the input parameter values used in the model along with the probabilistic type and values used for sensitivity analysis.

Table 4.3 Summary of parameter values used in the model

Parameters	Mean	SE	Distribution
Transitional probabilities			
Prevalence of HPV infection; age 12	0	-	Fixed
Prevalence of CIN-1; age 12	0	-	Fixed
Age (years)-specific incidence of HPV infection			
12	0	-	Fixed
13	0	-	Fixed
14	0	-	Fixed
15	0.100	0.038	Beta
16	0.100	0.038	Beta
17	0.120	0.046	Beta
18	0.150	0.057	Beta
19	0.170	0.065	Beta
20	0.150	0.057	Beta
21	0.120	0.046	Beta
22	0.100	0.038	Beta
23	0.100	0.038	Beta
24	0.058	0.022	Beta
30	0.017	0.006	Beta
40	0.018	0.007	Beta
50	0.010	0.004	Beta
60	0.003	0.001	Beta
Progression rate; HPV infection to CIN-1	0.028	0.006	Beta
Progression rate (age); CIN-1 to CIN-2 or CIN-3			
12	0.017	0.010	Beta
35	0.070	0.013	Beta
Progression rate; CIN-2/3 to invasive cancer	0.050	0.008	Beta
Progression rate; stage I to stage II	0.438	0.167	Beta
Progression rate; stage II to stage III	0.536	0.187	Beta
Progression rate; stage III to stage IV	0.684	0.168	Beta
Age (year) specific probability of regression; HPV infection to Healthy			
12	0.552	0.084	Beta
25	0.370	0.033	Beta
30	0.103	0.018	Beta
Age (year) specific regression rate; CIN-1to HPV infection or Healthy			
12	0.161	0.024	Beta
35	0.082	0.021	Beta
Regression rate from CIN-2/3 to CIN-1/Healthy	0.069	0.013	Beta
Proportion of CIN-1 reverting to Healthy	0.900	0.128	Beta
Proportion of CIN-2/3 reverting to Healthy	0.500	0.128	Beta
Proportion of stage I having symptoms	0.062	0.024	Beta
Proportion of stage II having symptoms	0.235	0.090	Beta
Proportion of stage III having symptoms	0.750	0.159	Beta
Proportion of stage IV having symptoms	0.825	0.150	Beta
Stage specific mortality			
I	0.008	0.023	Beta
II	0.016	0.047	Beta
III	0.024	0.071	Beta
IV	0.990	-	Fixed
Age specific mortality	See Appendix C		Fixed

Table 4.3 Summary of parameter values used in the model (Cont')

Parameters	Mean	SE	Distribution
Program effectiveness			
HPV Vaccine			
Relative risk of HPV infection	0.32	0.051	Beta
Pap smear			
Sensitivity of pre-invasive	0.59	0.015	Beta
Sensitivity of stage I	0.800		
Sensitivity of stage II, III, IV	1.000		
Specificity	0.940	0.003	Beta
VIA			
Sensitivity	0.77	0.008	Beta
Sensitivity of stage I	0.900		
Sensitivity of stage II, III, IV	1.000		
Specificity	0.870	0.003	Beta
Program acceptability			
Pap smear	0.200	A coverage of 50 and 80	
VIA	0.200	were also assessed	
HPV vaccine	0.800		
Cost of program			
Direct medical cost of screening and follow-up treatment(IDR)			
Direct medical costs of HPV vaccination			
3 doses per fully immunized girl	1,650,000	165,000	Gamma
2 doses per fully immunized girl	1,100,000	110,000	Gamma
Direct medical costs of screening with VIA			
VIA with negative result	40,000	40,000	Gamma
VIA with positive result	454,106	454,106	Gamma
Direct medical costs of screening with Pap smear			Gamma
Pap smear with negative result	140,000	140,000	Gamma
Pap smear with positive result	856,281	856,281	Gamma
Direct medical cost of pre-cancer treatment			Gamma
Treatment of CIN-2/3 (after VIA)	1,975,606	1,975,606	Gamma
Treatment of CIN-2/3 (after Pap smear)	1,561,501	1,561,501	Gamma
Direct non-medical cost of screening and follow-up treatment(IDR)			
Direct non-medical costs of HPV vaccination			Gamma
3 doses per fully immunized girl	104,382	104,382	Gamma
2 doses per fully immunized girl	69,588	69,588	Gamma
Direct non-medical costs of screening with VIA			Gamma
VIA with negative result	37,754	37,754	Gamma
VIA with positive result	81,427	81,427	Gamma
Direct non-medical costs of screening with Pap smear			
Pap smear with negative result	71,068	71,068	Gamma
Pap smear with positive result	223,935	223,935	Gamma
Direct non-medical cost of pre-cancer treatment			
Treatment of CIN-2/3 (after VIA)	386,260	386,260	Gamma
Treatment of CIN-2/3 (after Pap smear)	309,273	309,273	Gamma

Table 4.3 Summary of parameter values used in the model (Cont')

Parameters	Mean	SE	Distribution
Cost of illness			
Direct medical costs of invasive cervical cancer (IDR)			
Cost of staging	3,457,218	3,457,218	Gamma
Initial treatment of stage I	27,904,258	27,904,258	Gamma
Initial treatment of stage II	24,393,026	24,393,026	Gamma
Initial treatment of stage III	25,046,436	25,046,436	Gamma
Initial treatment of stage IV	22,513,108	22,513,108	Gamma
Follow-up treatment of stage I	3,081,644	3,081,644	Gamma
Follow-up treatment of stage II	4,634,955	4,634,955	Gamma
Follow-up treatment of stage III	6,188,266	6,188,266	Gamma
Follow-up treatment of stage IV	3,318,017	3,318,017	Gamma
Direct non-medical costs of invasive cervical cancer (IDR)			
Initial treatment of stage I	14,912,800	14,912,800	Gamma
Initial treatment of stage II	12,147,440	12,147,440	Gamma
Initial treatment of stage III	13,551,897	13,551,897	Gamma
Initial treatment of stage IV	13,667,266	13,667,266	Gamma
Follow-up treatment of stage I	1,876,529	1,876,529	Gamma
Follow-up treatment of stage II	2,613,843	2,613,843	Gamma
Follow-up treatment of stage III	3,763,953	3,763,953	Gamma
Follow-up treatment of stage IV	2,153,558	2,153,558	Gamma
Morbidity costs of invasive cervical cancer (IDR)			
Initial treatment of stage I	24,855,000	24,855,000	Gamma
Initial treatment of stage II	18,383,718	18,383,718	Gamma
Initial treatment of stage III	20,916,995	20,916,995	Gamma
Initial treatment of stage IV	21,582,237	21,582,237	Gamma
Follow-up treatment of stage I	2,841,566	2,841,566	Gamma
Follow-up treatment of stage II	3,662,899	3,662,899	Gamma
Follow-up treatment of stage III	5,959,055	5,959,055	Gamma
Follow-up treatment of stage IV	2,802,617	2,802,617	Gamma
Mortality costs of invasive cervical cancer			
Age-specific PVLE due to premature mortality	See Appendix F		
Utility parameters			
Healthy/HPV infection/pre-cancer CIN1-3 without complication	1.000	1.000	Beta
Cervical cancer stage I	0.847	0.06	Beta
Cervical cancer stage II	0.762	0.03	Beta
Cervical cancer stage III	0.709	0.04	Beta
Cervical cancer stage IV	0.766	0.07	Beta

4.2 Model prediction and output

4.2.1 Model prediction

Figures 4.2 to 4.5 show the predictions of strategies for cervical cancer prevention and control on epidemiological characteristics of cervical cancer disease visually. Figure 4.2 presents the effect of vaccination of girls at age 12 years old with coverage rate of 80% prevented the HPV infection and resulted in reduction of HPV infection prevalence about 37%. Figure 4.3 shows comparison of effects of vaccination and screening strategy given as a single strategy on cervical cancer incidence. Vaccination strategy seemed to result the greatest reduction of cervical cancer incidence, and followed by Pap smear strategy which provided longer period of screening compared to VIA strategy. In intervention with screening, the incidence was greatly higher in younger age of women which indicated the early detection of invasive cervical cancer but then in the elder age of women the incidence was lower as compared to do nothing (Figure 4.4). Combining strategies, shortening interval of screening, and increasing screening coverage rates seemed to expand the strategies effects on reduction of cervical cancer incidence (Figure 4.4 and 4.5).

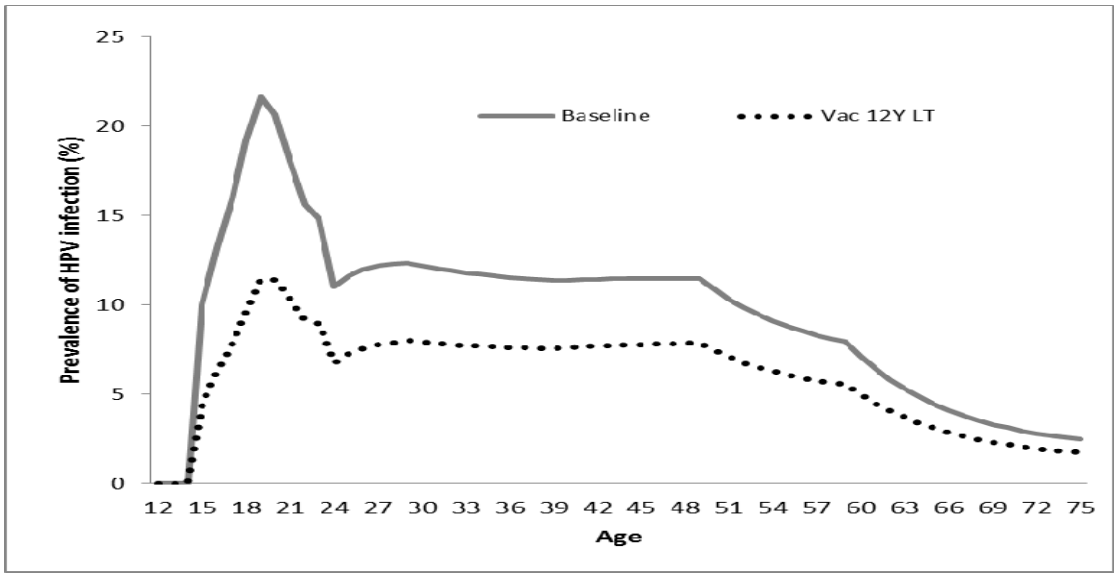


Figure 4.2 Model prediction on prevalence of HPV infection

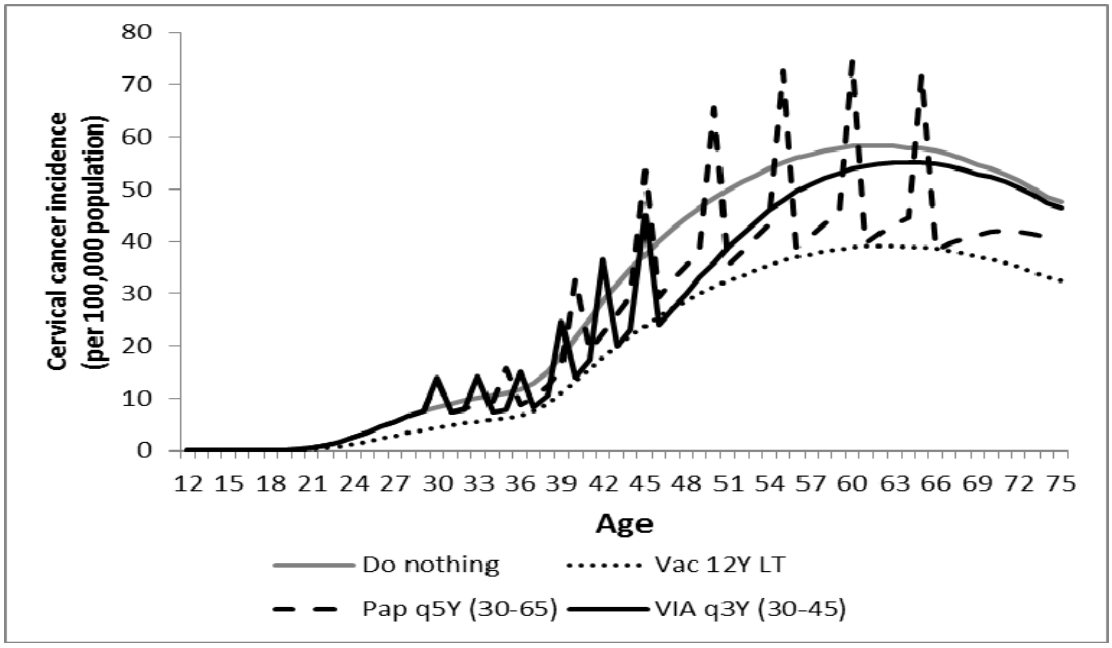


Figure 4.3 Model prediction on cervical cancer incidence resulted from different strategies of cervical cancer prevention and control

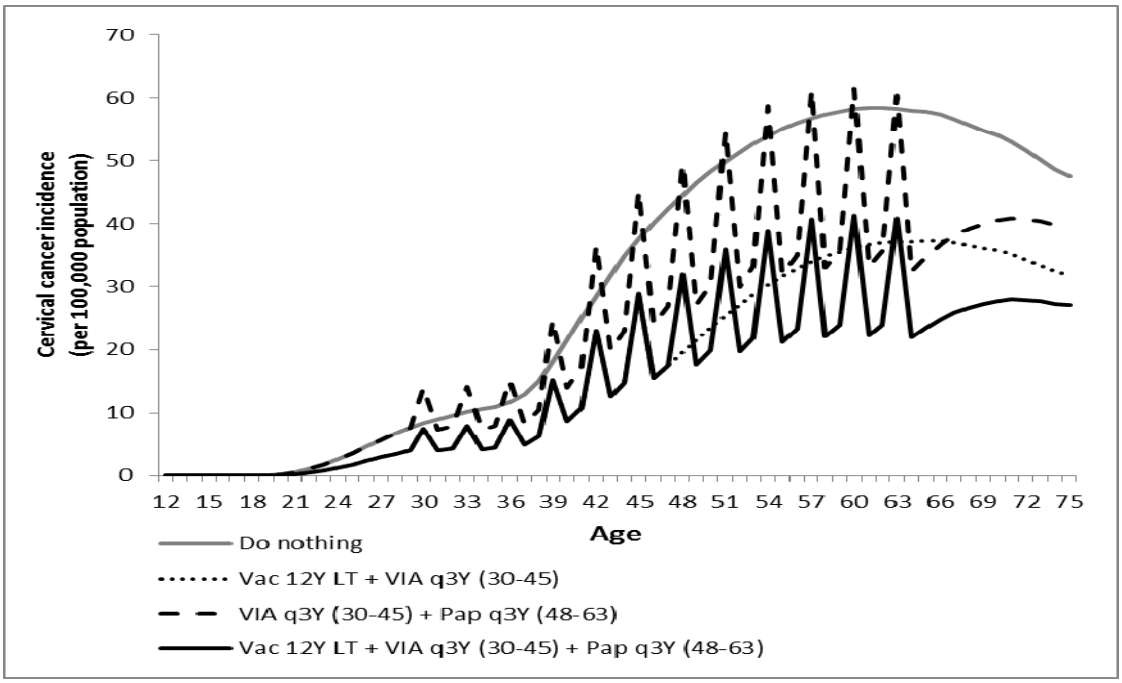


Figure 4.4 Model prediction on cervical cancer incidence resulted from different combination of strategies of cervical cancer prevention and control

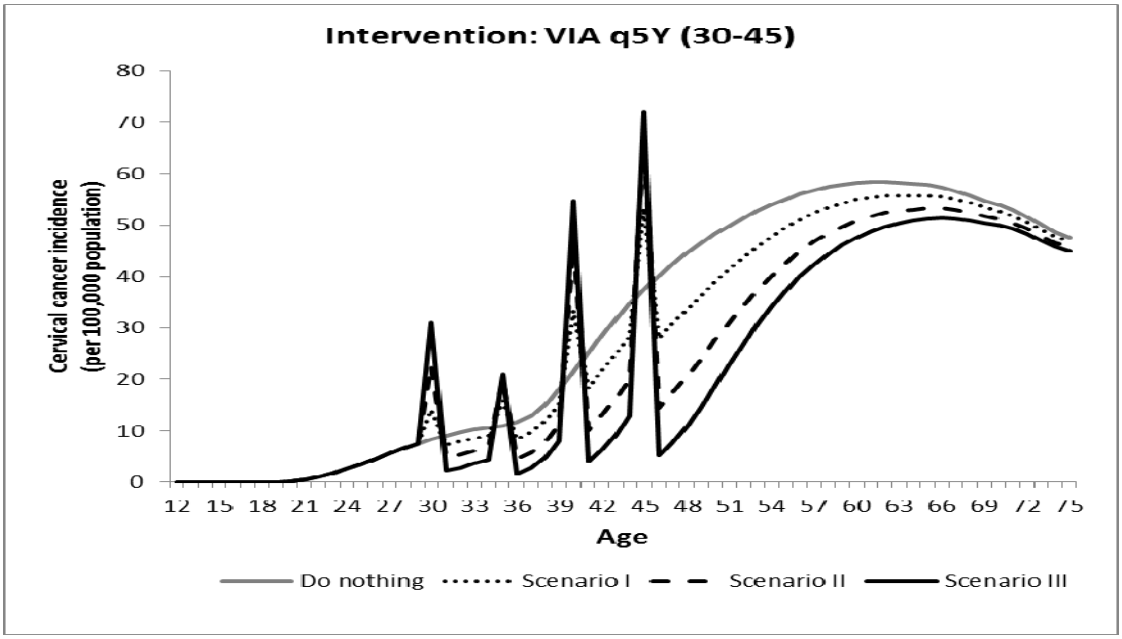


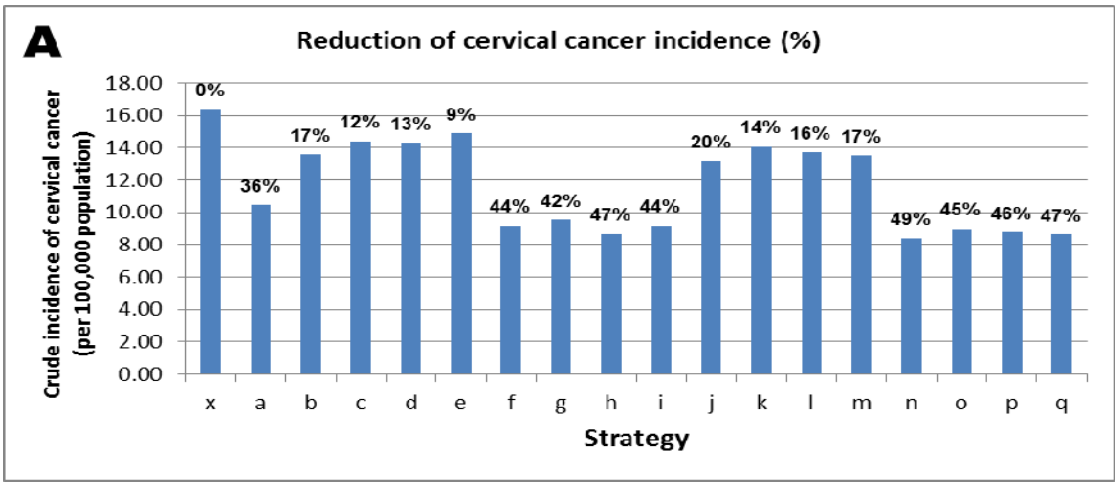
Figure 4.5 Model prediction on cervical cancer incidence resulted from different coverage of screening strategies of cervical cancer prevention and control

4.2.2 Epidemiological output

Figure 4.6 to 4.8 presents the impact of strategies for cervical cancer prevention and control on reduction of cervical cancer incidence in Indonesia, predicted by model. HPV vaccination to girls at age 12 years old at coverage rate of 80% reduced the lifetime of cervical cancer incidence by 36%. Compared to other strategies of screening with Pap smear or VIA alone at coverage rate of 20% (base case), vaccination gave the highest reduction of cervical cancer incidence. Screening with VIA alone resulted the lower reduction of cervical cancer incidence compared to screening with Pap smear alone, since the target age of VIA was shorter than Pap smear. Combination of VIA screening and sequential Pap smear increased the effect of disease reduction about 30% compared to each of strategy alone; while combination of vaccination and either VIA or Pap smear increased the effect of disease reduction about 20% compared to effect of vaccination alone and more than double compared to that of VIA or Pap smear alone. Combination of vaccination, followed by VIA and sequential Pap smear resulted the highest effect of disease reduction among all strategies, which was about half reduction of cervical cancer incidence compared to doing nothing.

Increasing the coverage rate of screening at 50% and 80% increased the effect of strategy on disease reductions by about double and triple, respectively compared to base case coverage rate. Screening with Pap smear alone at coverage rate of 50% and screening with VIA alone at coverage rate of 80% resulted the similar effect on reduction of cervical cancer incidence compared to HPV vaccination at coverage rate of 80%. Combination of the three strategies at the best coverage rate scenario (80%) reduced the cervical cancer incidence up to 72%.

Impacts of strategies for cervical cancer prevention and control on reduction of cervical cancer mortality in Indonesia predicted by the model were illustrated in Figure 4.9 to 4.11 Comparing those strategies gave the similar pattern of result in reduction of cervical cancer mortality as the reduction of cervical cancer incidence.



List of strategies

x = Do nothing	i = Vac 12Y LT + Pap q5Y (30-65)
a = Vac 12Y LT	j = VIA q3Y (30-45) + Pap q3Y (48-63)
b = Pap q3Y (30-63)	k = VIA q5Y (30-45) + Pap q5Y (50-65)
c = Pap q5Y (30-65)	l = VIA q5Y (30-45) + Pap q3Y (48-63)
d = VIA q3Y (30-45)	m = VIA q3Y (30-45) + Pap q5Y (50-65)
e = VIA q5Y (30-45)	n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)
f = Vac 12Y LT + VIA q3Y (30-45)	o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)
g = Vac 12Y LT + VIA q5Y (30-45)	p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)
h = Vac 12Y LT + Pap q3Y (30-63)	q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)

Figure 4.6 Crude incidence rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and reduction of cervical cancer incidence (%) in scenario I

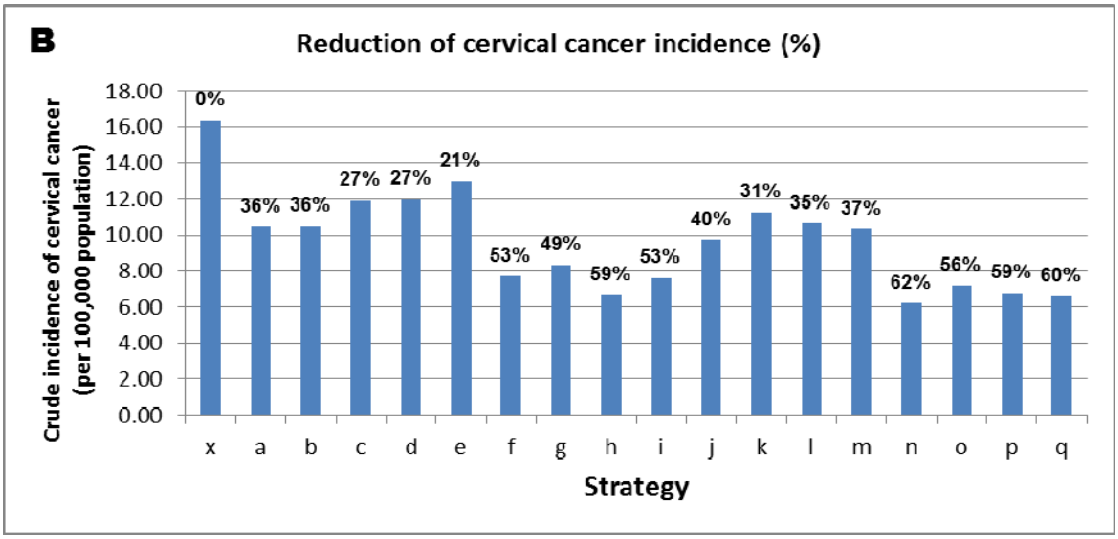


Figure 4.7 Crude incidence rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and reduction of cervical cancer incidence (%) in scenario II

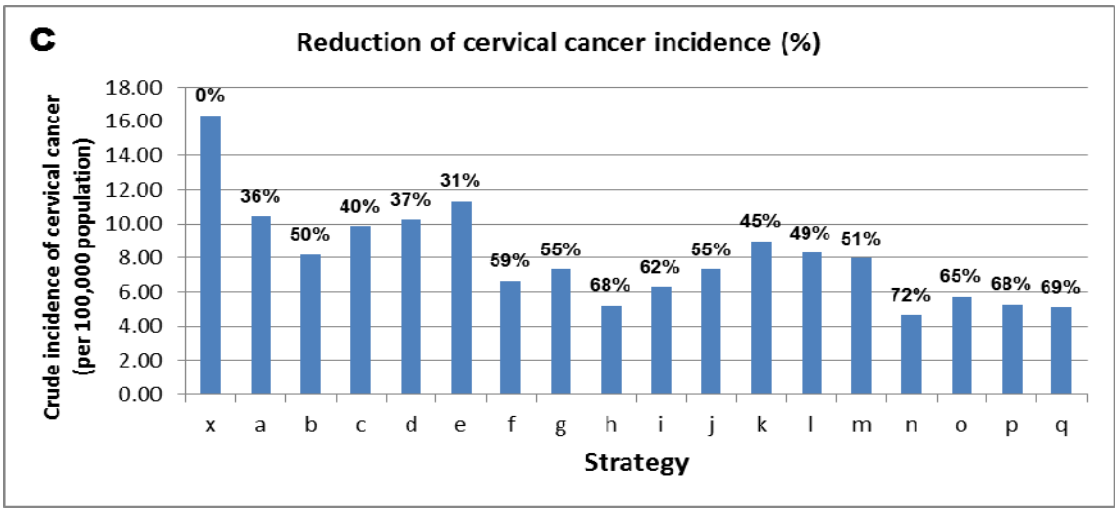
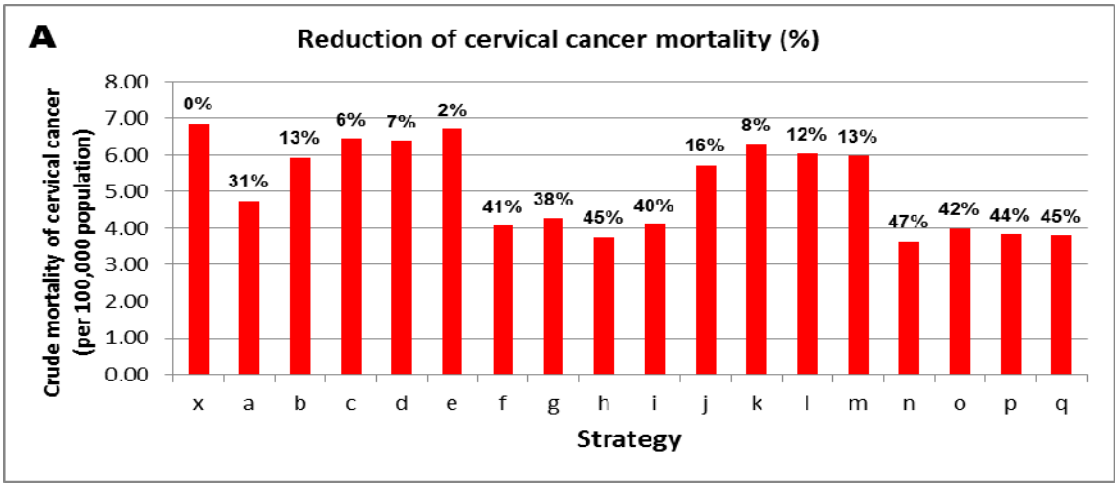


Figure 4.8 Crude incidence rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and reduction of cervical cancer incidence (%) in scenario III



List of strategies

x = Do nothing	i = Vac 12Y LT + Pap q5Y (30-65)
a = Vac 12Y LT	j = VIA q3Y (30-45) + Pap q3Y (48-63)
b = Pap q3Y (30-63)	k = VIA q5Y (30-45) + Pap q5Y (50-65)
c = Pap q5Y (30-65)	l = VIA q5Y (30-45) + Pap q3Y (48-63)
d = VIA q3Y (30-45)	m = VIA q3Y (30-45) + Pap q5Y (50-65)
e = VIA q5Y (30-45)	n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)
f = Vac 12Y LT + VIA q3Y (30-45)	o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)
g = Vac 12Y LT + VIA q5Y (30-45)	p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)
h = Vac 12Y LT + Pap q3Y (30-63)	q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)

Figure 4.9 Crude mortality rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and cervical cancer mortality reduction (%) in scenario I

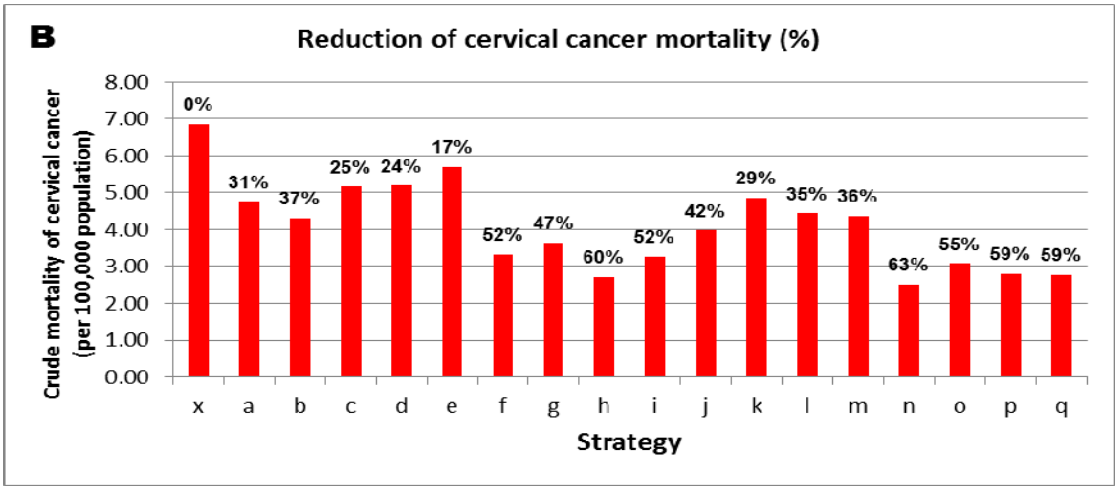


Figure 4.10 Crude mortality rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and cervical cancer mortality reduction (%) in scenario II

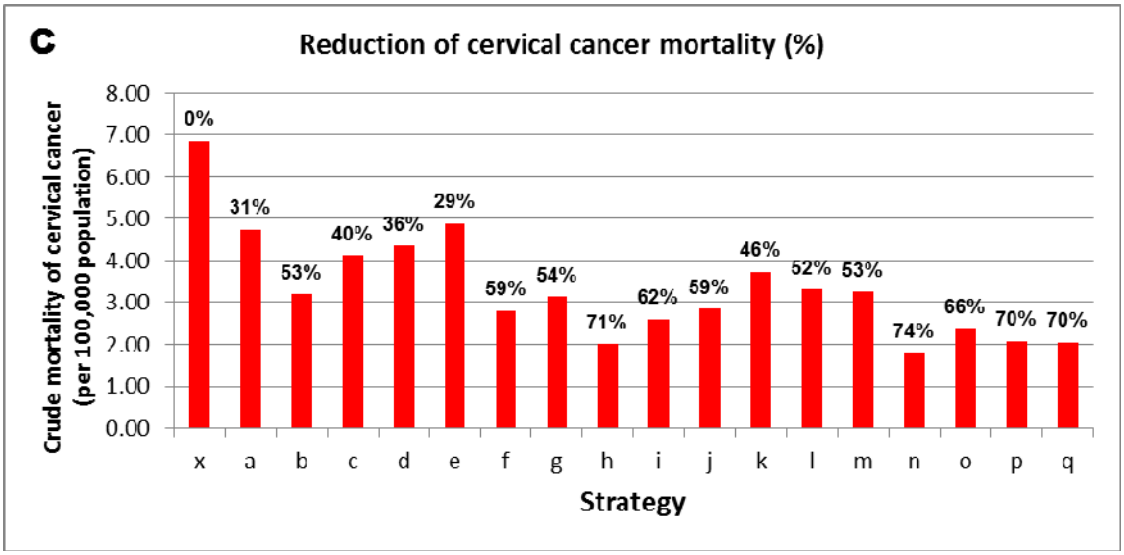


Figure 4.11 Crude mortality rate of cervical cancer disease among population at age 0-74 years old (per 100,000 population) and cervical cancer mortality reduction (%) in scenario III

4.2.3 Health outcomes output

The model produced health outcomes outputs in terms of undiscounted life expectancy, discounted life expectancy (life years gained/life years saved), and discounted quality adjusted life years (QALYs) gained. Table 4.4 and Table 4.5 presented discounted life years (LYs) gained and QALYs gained resulted from providing each strategy and scenario for cervical cancer prevention and control. Incremental LYs and incremental QALYs of each strategy, compared to do nothing as a reference, were used as denominator in calculating the ICER.

Table 4.4 Life years gained resulted from interventions for cervical cancer prevention and control

Intervention	LYs gained		
	Scenario I	**Scenario II**	**Scenario III**
Do nothing	28.2771	28.2771	28.2771
Vac 12Y LT	28.2864	28.2864	28.2864
Pap q3Y (30-63)	28.2829	28.2889	28.2926
Pap q5Y (30-65)	28.2811	28.2859	28.2897
VIA q3Y (30-45)	28.2814	28.2861	28.2891
VIA q5Y (30-45)	28.2802	28.2841	28.2873
Vac 12Y LT + VIA q3Y (30-45)	28.2891	28.2920	28.2939
Vac 12Y LT + VIA q5Y (30-45)	28.2883	28.2908	28.2927
Vac 12Y LT + Pap q3Y (30-63)	28.2901	28.2939	28.2963
Vac 12Y LT + Pap q5Y (30-65)	28.2889	28.2920	28.2945
VIA q3Y (30-45) + Pap q3Y (48-63)	28.2836	28.2899	28.2937
VIA q5Y (30-45) + Pap q5Y (50-65)	28.2816	28.2869	28.2910
VIA q5Y (30-45) + Pap q3Y (48-63)	28.2824	28.2882	28.2921
VIA q3Y (30-45) + Pap q5Y (50-65)	28.2828	28.2888	28.2927
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	28.2906	28.2946	28.2970
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	28.2893	28.2927	28.2952
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	28.2898	28.2935	28.2960
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	28.2900	28.2938	28.2963

The values of LYs were higher than QALYs values. QALYs were calculated from LYs and adjusted with utility, in which the utility value of healthy was 1 and decreased in invasive cervical cancer stages. Meanwhile, the incremental QALYs of each strategy were slightly greater than the incremental LYs. It reflected the impact of interventions on preventing the future incidence of cervical cancer, in which the disease worsen quality of health state.

When comparing the incremental LYs and incremental QALYs gained among different scenario, the values increased in approximately twice and three times in scenario II and III, respectively, compared to base case scenario.

Table 4.5 Quality of life adjusted years gained resulted from interventions for cervical cancer prevention and control

Intervention	QALYs gained		
	Scenario I	Scenario II	Scenario III
Do nothing	28.2619	28.2619	28.2619
Vac 12Y LT	28.2768	28.2768	28.2768
Pap q3Y (30-63)	28.2703	28.2790	28.2849
Pap q5Y (30-65)	28.2675	28.2745	28.2802
VIA q3Y (30-45)	28.2682	28.2750	28.2797
VIA q5Y (30-45)	28.2663	28.2721	28.2768
Vac 12Y LT + VIA q3Y (30-45)	28.2807	28.2850	28.2879
Vac 12Y LT + VIA q5Y (30-45)	28.2796	28.2831	28.2861
Vac 12Y LT + Pap q3Y (30-63)	28.2822	28.2878	28.2915
Vac 12Y LT + Pap q5Y (30-65)	28.2804	28.2849	28.2885
VIA q3Y (30-45) + Pap q3Y (48-63)	28.2714	28.2808	28.2868
VIA q5Y (30-45) + Pap q5Y (50-65)	28.2684	28.2762	28.2823
VIA q5Y (30-45) + Pap q3Y (48-63)	28.2696	28.2781	28.2842
VIA q3Y (30-45) + Pap q5Y (50-65)	28.2702	28.2790	28.2851
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	28.2828	28.2888	28.2927
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	28.2809	28.2859	28.2898
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	28.2818	28.2872	28.2910
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	28.2820	28.2877	28.2915

4.2.4 Economic output

Output of costs were break-downed into cost of program for providing intervention of vaccination and/or screening and cost of illness for treating invasive cervical cancer. Table 4.6 to 4.11 reveal the description of costs of each strategy from different scenario of screening coverage and vaccine doses. Costs were also categorized based on the health system and societal perspective. Moreover, costs of illness under societal perspective were separately presented for costs used in CUA and CEA/CBA due to different scope of costs included in the analysis. For CEA and CBA, cost of illness included direct medical cost for cervical cancer treatment, direct non-medical cost for meal and transportation of patient and care giver and care giver's time cost, and indirect cost of morbidity and mortality of patient. Whereas in CUA, cost of illness included direct medical cost and direct non-medical cost, while indirect cost was not included to avoid double counting as it was assumed had been covered in QALY estimation.

The base line or do nothing had no cost of program but it had the highest costs for invasive cervical cancer treatment. The costs of program were relatively low for strategies with VIA and/or Pap smears. However, the costs were significantly higher if the strategies involved HPV vaccination. In contrast, the treatment costs of invasive cervical cancer were lowest for strategies with HPV vaccination. In comparison to the health system's perspective, the societal perspective offered slightly higher costs of program but is about 25% greatly higher for the costs of cervical cancer treatment and reached more than 20 times when including cost of morbidity and mortality. This could reflect the fact that the household paid a substantial amount of money for patients with invasive cervical cancer, yet much economic burden when considering the productivity loss for seeking treatment, absent from work due to the illness, and premature mortality.

For the different coverage of screening (scenario II and III), costs of program gradually increased, in opposition cost of illness gradually decreased. As for strategies involving HPV vaccination, strategies with two doses of vaccine per fully immunized girl had costs of program lower about 30% compared to that of three doses; however, it did not affect the values of costs of illness.

Table 4.6 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario I, given 3 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	1,320	271	1,404	421	6,104
Pap q3Y (30-63)	172	358	244	555	7,686
Pap q5Y (30-65)	112	382	159	591	8,289
VIA q3Y (30-45)	59	375	84	582	8,293
VIA q5Y (30-45)	40	391	56	606	8,656
Vac 12Y LT + VIA q3Y (30-45)	1,376	238	1,485	370	5,330
Vac 12Y LT + VIA q5Y (30-45)	1,358	248	1,458	385	5,557
Vac 12Y LT + Pap q3Y (30-63)	1,487	227	1,642	351	4,914
Vac 12Y LT + Pap q5Y (30-65)	1,429	242	1,559	374	5,303
VIA q3Y (30-45) + Pap q3Y (48-63)	121	347	171	538	7,453
VIA q5Y (30-45) + Pap q5Y (50-65)	78	373	110	578	8,109
VIA q5Y (30-45) + Pap q3Y (48-63)	101	362	144	561	7,792
VIA q3Y (30-45) + Pap q5Y (50-65)	97	358	138	555	7,759
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	1,436	220	1,570	340	4,769
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	1,395	236	1,511	366	5,191
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	1,418	229	1,543	355	4,981
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	1,413	227	1,538	351	4,972

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

Table 4.7 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario II, given 3 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	1,320	271	1,404	421	6,104
Pap q3Y (30-63)	426	280	605	433	5,717
Pap q5Y (30-65)	279	322	395	499	6,730
VIA q3Y (30-45)	146	315	209	488	6,921
VIA q5Y (30-45)	98	343	140	531	7,521
Vac 12Y LT + VIA q3Y (30-45)	1,460	201	1,606	311	4,470
Vac 12Y LT + VIA q5Y (30-45)	1,414	218	1,540	338	4,847
Vac 12Y LT + Pap q3Y (30-63)	1,734	176	1,995	272	3,644
Vac 12Y LT + Pap q5Y (30-65)	1,591	203	1,790	315	4,300
VIA q3Y (30-45) + Pap q3Y (48-63)	298	260	424	402	5,333
VIA q5Y (30-45) + Pap q5Y (50-65)	193	304	274	471	6,371
VIA q5Y (30-45) + Pap q3Y (48-63)	250	285	356	441	5,863
VIA q3Y (30-45) + Pap q5Y (50-65)	240	278	342	431	5,812
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	1,608	164	1,816	253	3,404
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	1,506	192	1,670	298	4,075
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	1,562	179	1,750	278	3,737
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	1,552	176	1,736	272	3,724

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

Table 4.8 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario III, given 3 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	1,320	271	1,404	421	6,104
Pap q3Y (30-63)	677	222	963	343	4,360
Pap q5Y (30-65)	444	272	630	420	5,466
VIA q3Y (30-45)	232	271	332	420	5,958
VIA q5Y (30-45)	157	301	224	467	6,575
Vac 12Y LT + VIA q3Y (30-45)	1,543	173	1,726	268	3,862
Vac 12Y LT + VIA q5Y (30-45)	1,470	192	1,620	298	4,253
Vac 12Y LT + Pap q3Y (30-63)	1,980	139	2,347	215	2,767
Vac 12Y LT + Pap q5Y (30-65)	1,752	171	2,019	265	3,484
VIA q3Y (30-45) + Pap q3Y (48-63)	472	199	673	307	3,934
VIA q5Y (30-45) + Pap q5Y (50-65)	307	248	436	383	5,001
VIA q5Y (30-45) + Pap q3Y (48-63)	397	226	565	350	4,476
VIA q3Y (30-45) + Pap q5Y (50-65)	382	219	544	339	4,432
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	1,778	124	2,060	192	2,499
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	1,616	156	1,828	242	3,193
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	1,705	142	1,954	219	2,841
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	1,689	138	1,933	213	2,833

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

Table 4.9 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario I, given 2 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	880	271	936	421	6,104
Pap q3Y (30-63)	172	358	244	555	7,686
Pap q5Y (30-65)	112	382	159	591	8,289
VIA q3Y (30-45)	59	375	84	582	8,293
VIA q5Y (30-45)	40	391	56	606	8,656
Vac 12Y LT + VIA q3Y (30-45)	936	238	1,017	370	5,330
Vac 12Y LT + VIA q5Y (30-45)	918	248	990	385	5,557
Vac 12Y LT + Pap q3Y (30-63)	1,047	227	1,174	351	4,914
Vac 12Y LT + Pap q5Y (30-65)	989	242	1,091	374	5,303
VIA q3Y (30-45) + Pap q3Y (48-63)	121	347	171	538	7,453
VIA q5Y (30-45) + Pap q5Y (50-65)	78	373	110	578	8,109
VIA q5Y (30-45) + Pap q3Y (48-63)	101	362	144	561	7,792
VIA q3Y (30-45) + Pap q5Y (50-65)	97	358	138	555	7,759
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	996	220	1,102	340	4,769
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	955	236	1,043	366	5,191
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	978	229	1,075	355	4,981
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	973	227	1,070	351	4,972

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

Table 4.10 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario II, given 2 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	880	271	936	421	6,104
Pap q3Y (30-63)	426	280	605	433	5,717
Pap q5Y (30-65)	279	322	395	499	6,730
VIA q3Y (30-45)	146	315	209	488	6,921
VIA q5Y (30-45)	98	343	140	531	7,521
Vac 12Y LT + VIA q3Y (30-45)	1,020	201	1,138	311	4,470
Vac 12Y LT + VIA q5Y (30-45)	974	218	1,072	338	4,847
Vac 12Y LT + Pap q3Y (30-63)	1,294	176	1,527	272	3,644
Vac 12Y LT + Pap q5Y (30-65)	1,151	203	1,322	315	4,300
VIA q3Y (30-45) + Pap q3Y (48-63)	298	260	424	402	5,333
VIA q5Y (30-45) + Pap q5Y (50-65)	193	304	274	471	6,371
VIA q5Y (30-45) + Pap q3Y (48-63)	250	285	356	441	5,863
VIA q3Y (30-45) + Pap q5Y (50-65)	240	278	342	431	5,812
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	1,168	164	1,348	253	3,404
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	1,066	192	1,202	298	4,075
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	1,122	179	1,282	278	3,737
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	1,112	176	1,268	272	3,724

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

Table 4.11 Break down of life time cost for offering strategies for cervical cancer prevention and control in scenario III, given 2 doses of HPV vaccine per fully immunized girl*

Strategy	Health system's perspective		Societal perspective		
	CoP	CoI	CoP	CoI	
	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA/ CEA/ CBA	CUA	CEA/ CBA
Do nothing	0	428	0	664	9,536
Vac 12Y LT	880	271	936	421	6,104
Pap q3Y (30-63)	677	222	963	343	4,360
Pap q5Y (30-65)	444	272	630	420	5,466
VIA q3Y (30-45)	232	271	332	420	5,958
VIA q5Y (30-45)	157	301	224	467	6,575
Vac 12Y LT + VIA q3Y (30-45)	1,103	173	1,258	268	3,862
Vac 12Y LT + VIA q5Y (30-45)	1,030	192	1,152	298	4,253
Vac 12Y LT + Pap q3Y (30-63)	1,540	139	1,879	215	2,767
Vac 12Y LT + Pap q5Y (30-65)	1,312	171	1,551	265	3,484
VIA q3Y (30-45) + Pap q3Y (48-63)	472	199	673	307	3,934
VIA q5Y (30-45) + Pap q5Y (50-65)	307	248	436	383	5,001
VIA q5Y (30-45) + Pap q3Y (48-63)	397	226	565	350	4,476
VIA q3Y (30-45) + Pap q5Y (50-65)	382	219	544	339	4,432
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	1,338	124	1,592	192	2,499
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	1,176	156	1,360	242	3,193
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	1,265	142	1,486	219	2,841
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	1,249	138	1,465	213	2,833

*Numbers presented in this table were in thousands IDR

CoP = cost of healthcare program/intervention, CoI = cost of illness, CUA = cost utility analysis, CEA = cost effectiveness analysis, CBA = cost benefit analysis

4.3 Cost effectiveness ratio

4.3.1 Incremental cost effectiveness ratio

Cost effectiveness analysis focuses on the effectiveness measurement in natural unit. In this study, cost effectiveness analysis considered the effectiveness of health interventions in terms of discounted life-time life years gained, number of cervical cancer cases everted, and number of cervical cancer death averted. Incremental cost effectiveness ratios (ICERs) including ICER per LY gained, ICER per case averted, and ICER per death averted were performed to explore the most cost effective strategy.

In order to identify which strategy represented better value for money, the ICER per LY gained of the strategies should be considered in respect to the cost effectiveness threshold of specific setting. In the absence of national cost effectiveness threshold for Indonesia setting, a recommendation to adopt 1 and 3 times GDP per capita as cost effectiveness thresholds was employed. A strategy was considered "very cost effective" and "cost effective" if the ICER per LYs was below IDR 35,000,000; and between IDR 35,000,000 and IDR 105,000,000, respectively.

Table 4.12 to 4.14 present ICER per LYs of all strategies for cervical cancer prevention and control assigned in cost effectiveness analysis. Under the societal perspective, all strategies were cost saving; they gained more LYs saved but did not require additional resources for performing the heath care program, yet resulted lower resource for the disease burden as compared to the baseline of doing nothing. This saving mostly came from the lower productivity loss due to morbidity and mortality of cervical cancer. Under the health system's provider, the ICERs ranged from IDR 912,000 per LY to IDR 124,432,000 per LY for the base case scenario with 3 vaccine doses assumption. The lowest ICER belonged to strategy of VIA pent-annually alone, while the highest belonged to strategy of vaccination alone. When the screening coverage rate increased, the ICERs of strategies with screening gradually increased; although the health outcomes increased but the resources also increased to greater degree. For strategies involving vaccination, when using 2 doses instead of 3 doses of vaccine, the ICERs were about 30% lower. All strategies of screening either single or combination strategy were very cost effective in all

scenarios. Meanwhile, almost all strategies involving vaccination were cost effective in all scenarios. The exception was for strategy of vaccination alone with 3 doses which had ICER above 3 times GDP or not cost effective; however when the vaccine dose was reduced to be 2 doses, the ICER decreased to be IDR 77,374,000 per LY, so the strategy was cost effective.

The purpose of cost effectiveness analysis is to help the decision makers allocate healthcare resources efficiently. It can indicate which strategy among number of health care programs represents the best value for money. It can give an answer of how much health benefits obtained over amount of money. Instead of LY gained, the other health benefit such as number of cases and death averted are very common to be measured in cost effectiveness analysis to reflect the health benefit resulted from such strategy for health care intervention.

Table 4.12 ICER per life year gained of strategies for cervical cancer prevention and control in scenario I*

Strategies	ICER per LYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	-266,978	-216,943	77,374	124,432
Pap q3Y (30-63)	-274,433	-274,433	17,470	17,470
Pap q5Y (30-65)	-274,294	-274,294	16,594	16,594
VIA q3Y (30-45)	-266,106	-266,106	1,509	1,509
VIA q5Y (30-45)	-266,163	-266,163	912	912
Vac 12Y LT + VIA q3Y (30-45)	-265,008	-226,137	62,090	98,649
Vac 12Y LT + VIA q5Y (30-45)	-265,625	-224,056	65,612	104,708
Vac 12Y LT + Pap q3Y (30-63)	-263,998	-228,185	64,728	98,410
Vac 12Y LT + Pap q5Y (30-65)	-264,954	-225,514	67,652	104,746
VIA q3Y (30-45) + Pap q3Y (48-63)	-292,639	-292,639	6,102	6,102
VIA q5Y (30-45) + Pap q5Y (50-65)	-292,510	-292,510	5,158	5,158
VIA q5Y (30-45) + Pap q3Y (48-63)	-298,997	-298,997	6,627	6,627
VIA q3Y (30-45) + Pap q5Y (50-65)	-286,554	-286,554	4,774	4,774
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	-271,854	-237,156	58,440	91,073
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	-270,912	-232,538	62,621	98,713
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	-272,919	-236,234	61,061	95,564
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	-269,946	-233,808	59,673	93,661

*Numbers presented in this table were rounded off to the nearest thousand

ICER: Incremental cost effectiveness ratio; LY: Life years; IDR: Indonesian rupiah

Table 4.13 ICER per life year gained of strategies for cervical cancer prevention and control in scenario II*

Strategies	ICER per LYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	-266,978	-216,943	77,374	124,432
Pap q3Y (30-63)	-272,820	-272,820	23,598	23,598
Pap q5Y (30-65)	-272,938	-272,938	19,566	19,566
VIA q3Y (30-45)	-267,835	-267,835	3,742	3,742
VIA q5Y (30-45)	-267,044	-267,044	1,897	1,897
Vac 12Y LT + VIA q3Y (30-45)	-263,587	-232,200	53,238	82,757
Vac 12Y LT + VIA q5Y (30-45)	-264,454	-230,256	55,897	88,060
Vac 12Y LT + Pap q3Y (30-63)	-259,426	-231,623	61,979	88,128
Vac 12Y LT + Pap q5Y (30-65)	-262,013	-230,705	61,981	91,425
VIA q3Y (30-45) + Pap q3Y (48-63)	-294,798	-294,798	10,132	10,132
VIA q5Y (30-45) + Pap q5Y (50-65)	-293,208	-293,208	7,055	7,055
VIA q5Y (30-45) + Pap q3Y (48-63)	-299,212	-299,212	9,705	9,705
VIA q3Y (30-45) + Pap q5Y (50-65)	-289,249	-289,249	7,784	7,784
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	-273,867	-247,090	51,728	76,913
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	-273,405	-243,376	53,313	81,555
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	-275,607	-247,069	53,291	80,131
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	-271,798	-243,816	51,448	77,766

*Numbers presented in this table were rounded off to the nearest thousand

ICER: Incremental cost effectiveness ratio; LY: Life years; IDR: Indonesian rupiah

Table 4.14 ICER per life year gained of strategies for cervical cancer prevention and control in scenario III*

Strategies	ICER per LYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	-266,978	-216,943	77,374	124,432
Pap q3Y (30-63)	-270,916	-270,916	30,332	30,332
Pap q5Y (30-65)	-271,762	-271,762	22,734	22,734
VIA q3Y (30-45)	-269,488	-269,488	6,246	6,246
VIA q5Y (30-45)	-268,046	-268,046	2,964	2,964
Vac 12Y LT + VIA q3Y (30-45)	-262,680	-234,855	50,479	76,648
Vac 12Y LT + VIA q5Y (30-45)	-263,790	-233,916	50,754	78,850
Vac 12Y LT + Pap q3Y (30-63)	-254,500	-230,158	65,122	88,016
Vac 12Y LT + Pap q5Y (30-65)	-259,148	-232,210	60,743	86,078
VIA q3Y (30-45) + Pap q3Y (48-63)	-296,830	-296,830	14,623	14,623
VIA q5Y (30-45) + Pap q5Y (50-65)	-294,220	-294,220	9,100	9,100
VIA q5Y (30-45) + Pap q3Y (48-63)	-299,439	-299,439	13,025	13,025
VIA q3Y (30-45) + Pap q5Y (50-65)	-292,069	-292,069	11,090	11,090
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	-273,987	-250,450	52,024	74,161
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	-274,472	-248,706	49,819	74,053
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	-275,913	-251,132	51,839	75,146
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	-272,659	-248,306	49,940	72,844

*Numbers presented in this table were in thousands IDR

ICER: Incremental cost effectiveness ratio; LY: Life years; IDR: Indonesian rupiah

4.3.2 Net benefit and ratio of benefit-cost

Cost-benefit analysis (CBA) offers a method of economic evaluation that values all benefits against all costs. The resulting cost-benefit ratio gives an indication of whether or not the benefits outweigh the costs of an intervention. The monetization of outcomes in CBA enables inter sectors comparisons, for instance it can help the decision makers to address the distribution of budget between different ministries.

In this study, results of analysis using CBA technique were presented as net benefit in term of net present value (NPV) and ratio of benefit-to-cost/cost-to-benefit. A positive NPV means that benefits outweighs costs and the strategy should be considered. A negative NPV means that the costs outweigh the benefits. An NPV of 0 means the benefits are equal to the costs. A benefit to cost ratio (BCR) greater than 1 means the benefits outweigh the costs and the investment should be considered. If the ratio is less than 1, the costs outweigh the benefits. If the BCR is equal to 1, the benefits equal the costs. A cost to benefit ratio (CBR) has the opposite meanings.

Table 4.15 to 4.20 describe the NPV per capita, NPV for a size of 2013 cohort of girls aged 12 years old, and BCR/CBR of each strategy for cervical cancer prevention and control in Indonesia resulted from CBA in this study. Under the health system's perspective, all strategies had negative NPV and BCR less than 1. This indicated that considering only saving of treatment cost as a benefit in the health intervention, the strategies for cervical cancer prevention and control would not cost-benefit since the costs of program outweighed the benefits of treatment costs saving. In the table, results of analysis under the health system's perspective were presented as cost to benefit ratio (CBR) to show the excess of costs over the benefits. The strategy of VIA pent-annually alone had the lowest CBRs in all scenarios which were nearly 1, indicating lowest excess costs over the benefits as compared to other strategies.

Under the societal perspective, all strategies had BCR greater than 1 and positive NPV. This indicated that considering the morbidity and mortality costs as benefits, providing strategies for cervical cancer prevention and control could gain benefits greater than costs of program. The strategy of VIA pent-annually had the greatest BCRs in all scenarios; however, the NPVs were lower as compared to other strategies. The greater NPVs were resulted by combining strategies of screening with

VIA and Pap smear as well as combining strategies of vaccination and both screenings.

Table 4.15 Net benefit of strategies for cervical cancer prevention and control in scenario I, given 3 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,028	4,458	2	-1,163	-2,557	8
Pap q3Y (30-63)	1,607	3,532	8	-102	-225	2
Pap q5Y (30-65)	1,089	2,393	8	-66	-145	2
VIA q3Y (30-45)	1,159	2,548	15	-7	-14	1
VIA q5Y (30-45)	824	1,811	16	-3	-6	1
Vac 12Y LT + VIA q3Y (30-45)	2,722	5,982	3	-1,187	-2,609	7
Vac 12Y LT + VIA q5Y (30-45)	2,522	5,542	3	-1,178	-2,590	8
Vac 12Y LT + Pap q3Y (30-63)	2,981	6,551	3	-1,286	-2,825	7
Vac 12Y LT + Pap q5Y (30-65)	2,675	5,879	3	-1,242	-2,731	8
VIA q3Y (30-45) + Pap q3Y (48-63)	1,912	4,203	12	-40	-88	1
VIA q5Y (30-45) + Pap q5Y (50-65)	1,317	2,894	13	-23	-51	1
VIA q5Y (30-45) + Pap q3Y (48-63)	1,600	3,517	12	-35	-78	2
VIA q3Y (30-45) + Pap q5Y (50-65)	1,640	3,603	13	-27	-60	1
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	3,198	7,028	3	-1,228	-2,699	7
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	2,835	6,231	3	-1,203	-2,645	7
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	3,013	6,621	3	-1,219	-2,678	7
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	3,027	6,652	3	-1,213	-2,665	7

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

Table 4.16 Net benefit of strategies for cervical cancer prevention and control in scenario II, given 3 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,028	4,458	2	-1,163	-2,557	8
Pap q3Y (30-63)	3,215	7,065	6	-278	-611	3
Pap q5Y (30-65)	2,411	5,299	7	-173	-380	3
VIA q3Y (30-45)	2,407	5,290	13	-34	-74	1
VIA q5Y (30-45)	1,875	4,121	14	-13	-29	1
Vac 12Y LT + VIA q3Y (30-45)	3,461	7,607	3	-1,234	-2,711	6
Vac 12Y LT + VIA q5Y (30-45)	3,150	6,923	3	-1,205	-2,648	7
Vac 12Y LT + Pap q3Y (30-63)	3,897	8,566	3	-1,483	-3,259	7
Vac 12Y LT + Pap q5Y (30-65)	3,448	7,577	3	-1,366	-3,003	7
VIA q3Y (30-45) + Pap q3Y (48-63)	3,780	8,308	10	-130	-286	2
VIA q5Y (30-45) + Pap q5Y (50-65)	2,891	6,355	12	-70	-153	2
VIA q5Y (30-45) + Pap q3Y (48-63)	3,318	7,292	10	-108	-237	2
VIA q3Y (30-45) + Pap q5Y (50-65)	3,382	7,433	11	-91	-200	2
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	4,317	9,488	3	-1,344	-2,953	6
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	3,792	8,333	3	-1,271	-2,793	6
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	4,050	8,902	3	-1,314	-2,887	6
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	4,076	8,959	3	-1,300	-2,858	6

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

Table 4.17 Net benefit of strategies for cervical cancer prevention and control in scenario III, given 3 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,028	4,458	2	-1,163	-2,557	8
Pap q3Y (30-63)	4,213	9,260	5	-472	-1,037	3
Pap q5Y (30-65)	3,440	7,560	6	-288	-632	3
VIA q3Y (30-45)	3,247	7,136	11	-75	-165	1
VIA q5Y (30-45)	2,738	6,017	13	-30	-67	1
Vac 12Y LT + VIA q3Y (30-45)	3,949	8,679	3	-1,289	-2,832	6
Vac 12Y LT + VIA q5Y (30-45)	3,663	8,051	3	-1,235	-2,714	6
Vac 12Y LT + Pap q3Y (30-63)	4,423	9,722	3	-1,692	-3,718	7
Vac 12Y LT + Pap q5Y (30-65)	4,033	8,864	3	-1,495	-3,286	7
VIA q3Y (30-45) + Pap q3Y (48-63)	4,930	10,835	8	-243	-534	2
VIA q5Y (30-45) + Pap q5Y (50-65)	4,099	9,009	10	-127	-279	2
VIA q5Y (30-45) + Pap q3Y (48-63)	4,496	9,881	9	-196	-430	2
VIA q3Y (30-45) + Pap q5Y (50-65)	4,560	10,022	9	-173	-381	2
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	4,978	10,941	3	-1,474	-3,240	6
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	4,516	9,925	3	-1,345	-2,955	6
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	4,741	10,420	3	-1,419	-3,118	6
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	4,770	10,484	3	-1,399	-3,076	6

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

Table 4.18 Net benefit of strategies for cervical cancer prevention and control in scenario I, given 2 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,496	5,486	4	-723	-1,590	6
Pap q3Y (30-63)	1,607	3,532	8	-102	-225	2
Pap q5Y (30-65)	1,089	2,393	8	-66	-145	2
VIA q3Y (30-45)	1,159	2,548	15	-7	-14	1
VIA q5Y (30-45)	824	1,811	16	-3	-6	1
Vac 12Y LT + VIA q3Y (30-45)	3,189	7,010	4	-747	-1,642	5
Vac 12Y LT + VIA q5Y (30-45)	2,989	6,570	4	-738	-1,623	5
Vac 12Y LT + Pap q3Y (30-63)	3,449	7,580	4	-846	-1,858	5
Vac 12Y LT + Pap q5Y (30-65)	3,143	6,907	4	-802	-1,764	5
VIA q3Y (30-45) + Pap q3Y (48-63)	1,912	4,203	12	-40	-88	1
VIA q5Y (30-45) + Pap q5Y (50-65)	1,317	2,894	13	-23	-51	1
VIA q5Y (30-45) + Pap q3Y (48-63)	1,600	3,517	12	-35	-78	2
VIA q3Y (30-45) + Pap q5Y (50-65)	1,640	3,603	13	-27	-60	1
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	3,665	8,056	4	-788	-1,732	5
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	3,303	7,259	4	-763	-1,678	5
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	3,480	7,649	4	-779	-1,711	5
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	3,495	7,681	4	-773	-1,698	5

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

Table 4.19 Net benefit and benefit to cost ratio of strategies for cervical cancer prevention and control in scenario II, given 2 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,496	5,486	4	-723	-1,590	6
Pap q3Y (30-63)	3,215	7,065	6	-278	-611	3
Pap q5Y (30-65)	2,411	5,299	7	-173	-380	3
VIA q3Y (30-45)	2,407	5,290	13	-34	-74	1
VIA q5Y (30-45)	1,875	4,121	14	-13	-29	1
Vac 12Y LT + VIA q3Y (30-45)	3,929	8,635	4	-794	-1,744	4
Vac 12Y LT + VIA q5Y (30-45)	3,618	7,951	4	-765	-1,681	5
Vac 12Y LT + Pap q3Y (30-63)	4,365	9,594	4	-1,043	-2,292	5
Vac 12Y LT + Pap q5Y (30-65)	3,915	8,605	4	-926	-2,036	5
VIA q3Y (30-45) + Pap q3Y (48-63)	3,780	8,308	10	-130	-286	2
VIA q5Y (30-45) + Pap q5Y (50-65)	2,891	6,355	12	-70	-153	2
VIA q5Y (30-45) + Pap q3Y (48-63)	3,318	7,292	10	-108	-237	2
VIA q3Y (30-45) + Pap q5Y (50-65)	3,382	7,433	11	-91	-200	2
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	4,785	10,516	5	-904	-1,986	4
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	4,259	9,362	5	-831	-1,825	5
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	4,518	9,930	5	-874	-1,920	5
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	4,544	9,987	5	-860	-1,891	4

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

Table 4.20 Net benefit of strategies for cervical cancer prevention and control in scenario III, given 2 doses of HPV vaccine per fully immunized girl

Strategies	Societal perspective			Health system's perspective		
	NPV[a]	NPV[b]	BCR	NPV[a]	NPV[b]	CBR
Do nothing	Ref	Ref	Ref	Ref	Ref	Ref
Vac 12Y LT	2,496	5,486	4	-723	-1,590	6
Pap q3Y (30-63)	4,213	9,260	5	-472	-1,037	3
Pap q5Y (30-65)	3,440	7,560	6	-288	-632	3
VIA q3Y (30-45)	3,247	7,136	11	-75	-165	1
VIA q5Y (30-45)	2,738	6,017	13	-30	-67	1
Vac 12Y LT + VIA q3Y (30-45)	4,417	9,707	5	-849	-1,865	4
Vac 12Y LT + VIA q5Y (30-45)	4,131	9,079	5	-795	-1,747	4
Vac 12Y LT + Pap q3Y (30-63)	4,891	10,750	4	-1,252	-2,751	5
Vac 12Y LT + Pap q5Y (30-65)	4,501	9,892	4	-1,055	-2,319	5
VIA q3Y (30-45) + Pap q3Y (48-63)	4,930	10,835	8	-243	-534	2
VIA q5Y (30-45) + Pap q5Y (50-65)	4,099	9,009	10	-127	-279	2
VIA q5Y (30-45) + Pap q3Y (48-63)	4,496	9,881	9	-196	-430	2
VIA q3Y (30-45) + Pap q5Y (50-65)	4,560	10,022	9	-173	-381	2
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	5,446	11,969	4	-1,034	-2,273	4
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	4,984	10,953	5	-905	-1,988	4
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	5,209	11,448	5	-979	-2,151	4
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	5,238	11,512	5	-959	-2,109	4

NPVa = net present value per capita; values were presented in thousands IDR; NPVb = net present value for a 2013 cohort of girls age 12 years (2,197,835 girls), values were presented in billions IDR;

BCR = benefit to cost ratio, the numbers presented were rounded to zero decimal;

CBR = cost to benefit ratio, the numbers presented were rounded to zero decimal.

4.3.3 Incremental cost utility ratio (ICUR)

The different in techniques of economic analysis is the benefit measures. In cost utility analysis, the benefits are expressed as QALYs. The cost effectiveness ratio to compare benefits over costs in CUA is called incremental cost utility ratio (ICUR). However, the term of ICER per QALY is mostly used instead of ICUR.

Table 4.21 to 4.23 present the values of ICER per QALY of each strategy. In this study, 1 and 3 times Indonesia GDP per capita (IDR 35,000,000 and IDR 105,000,000) were used as cost effectiveness thresholds in the analysis. All strategies had the ICER per QALY values below the value of 3 times Indonesia GDP per capita. Strategies with screening had the ICER per QALY values greatly lower compared to strategies involving vaccination. Strategy of VIA pent annually had the lowest ICER per QALY in all scenarios. At the base case scenario, the strategy of VIA pent annually under the societal perspective even had negative ICER per QALY, indicated that the strategy was cost-saving and gained more benefit compared to do nothing. All screening strategies, whether VIA or Pap smear alone and combination of VIA with sequential Pap smear, had the ICER per QALY below 1 times GDP, the range was between IDR (-204,000) – 16,140,000 per QALY at the base case scenario and IDR (-204,000) – 27,935,000 per QALY in all scenarios. Following the recommendation of WHO to use GDP per capita as a threshold for cost-effectiveness ratio, all strategies with screening were considered “very cost effective”. When the strategy involved vaccination, the value of ICER per QALY significantly increased.

Strategies with vaccination alone either using 2 or 3 doses had the ICER per QALY at the range between IDR 46,324,000 – 77,808,000 per QALY, categorized between 1 – 3 times of GDP per capita. Hence, the strategies with vaccination alone were considered “cost effective”. At the base case scenario, all strategies of vaccination followed by screening were also cost effective. If the coverage rate of screening was increased, in scenario II and III, some strategies involving combination vaccination and screening were very cost effective, particularly strategies of vaccination and VIA screening as well as combination of vaccination and screening with VIA and Pap smear at the lower number of vaccine doses. All strategies involving vaccination at 3 doses had the ICER per QALY between 1 – 3 times of GDP per capita, indicated a cost effective strategy. Comparing the values of ICER per

QALY between 2 and 3 doses of vaccine used, a strategy with 2 vaccine doses had ICER per QALY about 30% lower than that of 3 vaccine doses, which is in line with the different of cost of program needed to implement the strategy.

Table 4.21 ICER per QALY gained of strategies for cervical cancer prevention and control in scenario I*

Strategies	ICER per QALYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	46,324	77,611	48,382	77,808
Pap q3Y (30-63)	16,140	16,140	12,217	12,217
Pap q5Y (30-65)	15,387	15,387	11,687	11,687
VIA q3Y (30-45)	384	384	1,044	1,044
VIA q5Y (30-45)	-204	-204	634	634
Vac 12Y LT + VIA q3Y (30-45)	38,364	63,186	39,649	62,995
Vac 12Y LT + VIA q5Y (30-45)	40,189	66,617	41,713	66,568
Vac 12Y LT + Pap q3Y (30-63)	42,441	65,513	41,699	63,397
Vac 12Y LT + Pap q5Y (30-65)	43,240	68,488	43,308	67,054
VIA q3Y (30-45) + Pap q3Y (48-63)	4,796	4,796	4,214	4,214
VIA q5Y (30-45) + Pap q5Y (50-65)	3,901	3,901	3,585	3,585
VIA q5Y (30-45) + Pap q3Y (48-63)	5,306	5,306	4,592	4,592
VIA q3Y (30-45) + Pap q5Y (50-65)	3,527	3,527	3,305	3,305
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	37,144	59,473	37,608	58,608
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	39,121	63,679	40,074	63,170
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	38,541	62,080	39,180	61,319
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	37,562	60,768	38,318	60,144

*Numbers presented in this table were rounded off to the nearest thousand.

ICER: Incremental cost effectiveness ratio; QALY: Quality adjusted life years; IDR: Indonesian rupiah

Table 4.22 ICER per QALY gained of strategies for cervical cancer prevention and control in scenario II*

Strategies	ICER per QALYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	46,324	77,611	48,382	77,808
Pap q3Y (30-63)	21,840	21,840	16,222	16,222
Pap q5Y (30-65)	18,194	18,194	13,657	13,657
VIA q3Y (30-45)	2,551	2,551	2,558	2,558
VIA q5Y (30-45)	764	764	1,310	1,310
Vac 12Y LT + VIA q3Y (30-45)	33,987	54,232	34,339	53,380
Vac 12Y LT + VIA q5Y (30-45)	35,099	57,121	35,995	56,706
Vac 12Y LT + Pap q3Y (30-63)	43,909	61,996	40,321	57,332
Vac 12Y LT + Pap q5Y (30-65)	42,300	62,649	40,285	59,423
VIA q3Y (30-45) + Pap q3Y (48-63)	8,591	8,591	6,873	6,873
VIA q5Y (30-45) + Pap q5Y (50-65)	5,716	5,716	4,855	4,855
VIA q5Y (30-45) + Pap q3Y (48-63)	8,215	8,215	6,629	6,629
VIA q3Y (30-45) + Pap q5Y (50-65)	6,393	6,393	5,313	5,313
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	34,772	52,125	33,522	49,843
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	34,789	54,259	34,567	52,879
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	35,408	53,903	34,537	51,932
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	34,014	52,163	33,368	50,437

*Numbers presented in this table were rounded off to the nearest thousand

ICER: Incremental cost effectiveness ratio; QALY: Quality adjusted life years; IDR: Indonesian rupiah

Table 4.23 ICER of strategies for cervical cancer prevention and control in scenario III*

Strategies	ICER per QALYs gained (in thousands IDR)			
	Societal perspective		Health system's perspective	
	2 doses of HPV vaccine	3 doses of HPV vaccine	2 doses of HPV vaccine	3 doses of HPV vaccine
Do nothing	Reference	Reference	Reference	Reference
Vac 12Y LT	46,324	77,611	48,382	77,808
Pap q3Y (30-63)	27,935	27,935	20,504	20,504
Pap q5Y (30-65)	21,134	21,134	15,723	15,723
VIA q3Y (30-45)	4,927	4,927	4,217	4,217
VIA q5Y (30-45)	1,798	1,798	2,033	2,033
Vac 12Y LT + VIA q3Y (30-45)	33,097	51,059	32,586	49,479
Vac 12Y LT + VIA q5Y (30-45)	32,508	51,853	32,867	51,062
Vac 12Y LT + Pap q3Y (30-63)	48,277	64,079	42,275	57,136
Vac 12Y LT + Pap q5Y (30-65)	43,337	60,935	39,683	56,234
VIA q3Y (30-45) + Pap q3Y (48-63)	12,697	12,697	9,749	9,749
VIA q5Y (30-45) + Pap q5Y (50-65)	7,636	7,636	6,200	6,200
VIA q5Y (30-45) + Pap q3Y (48-63)	11,280	11,280	8,775	8,775
VIA q3Y (30-45) + Pap q5Y (50-65)	9,466	9,466	7,465	7,465
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)	36,371	51,563	33,579	47,867
Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)	33,586	50,344	32,402	48,164
Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)	35,741	51,793	33,578	48,675
Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)	34,238	50,019	32,362	47,204

*Numbers presented in this table were rounded off to the nearest thousand

ICER: Incremental cost effectiveness ratio; QALY: Quality adjusted life years; IDR: Indonesian rupiah

4.3.4 Cost effectiveness plane and efficiency frontier

Besides summarizing the results of CUA as ICER per QALY, the results were also presented graphically using cost effectiveness plane. Figure 4.12 to 4.17 show the cost effectiveness plane of all strategies for cervical cancer prevention and control, categorized by the scenarios of vaccine coverage rates, perspective of study, and assumption of HPV vaccine used.

The cost effectiveness plane consisted of 4 quadrants, NE/north-east, SE/south-east, SW/south-west, and NW/north-west. Each point in the cost effectiveness plane represented each strategy that characterizing its incremental QALY and incremental cost compared to the baseline. The baseline of doing nothing was placed at the meeting point of horizontal and vertical axis at the 0 value of both incremental QALY and incremental cost. The thresholds for acceptability of cost effectiveness were also represented on the cost effectiveness plane by lines with slopes reflecting the amount of 1 and 3 times GDP per capita (IDR 35,000,000 and IDR 105,000,000) as the cost effectiveness thresholds in the analysis.

Most of strategies fell in quadrant NE, indicating that the new strategies proposed had greater QALY but also higher cost. Few strategies, which were strategy involving VIA pent annually alone fell in quadrant SE, indicating that the strategy was dominant over the baseline. No strategy was in quadrant SW and NW, indicating that none of strategy resulted the health outcome (QALY) worse than that of do nothing.

All points fell below the line of 3 GDP-threshold, indicating there was no strategy that not cost effective. The group of points with screening strategies fell below the line of 1 GDP-threshold, indicating that these strategies were very cost effective; while the points involving vaccination mostly fell between the lines of 1 and 3 GDP-thresholds. However the points of screening strategies were in the left side of that of vaccination strategies, reflecting that vaccination strategies gained more health outcomes compared to screening strategies. When the coverage rates of screening increased, as were shown in cost effectiveness plane of scenario II and III, the points of screening strategies shifted to the right side indicating the better health outcomes were resulted. At the screening coverage of 50%, some of screening strategies gained better health outcomes as compared to strategy of vaccination alone. Moreover, at screening coverage of 80%, the screening strategies gained the health outcomes which

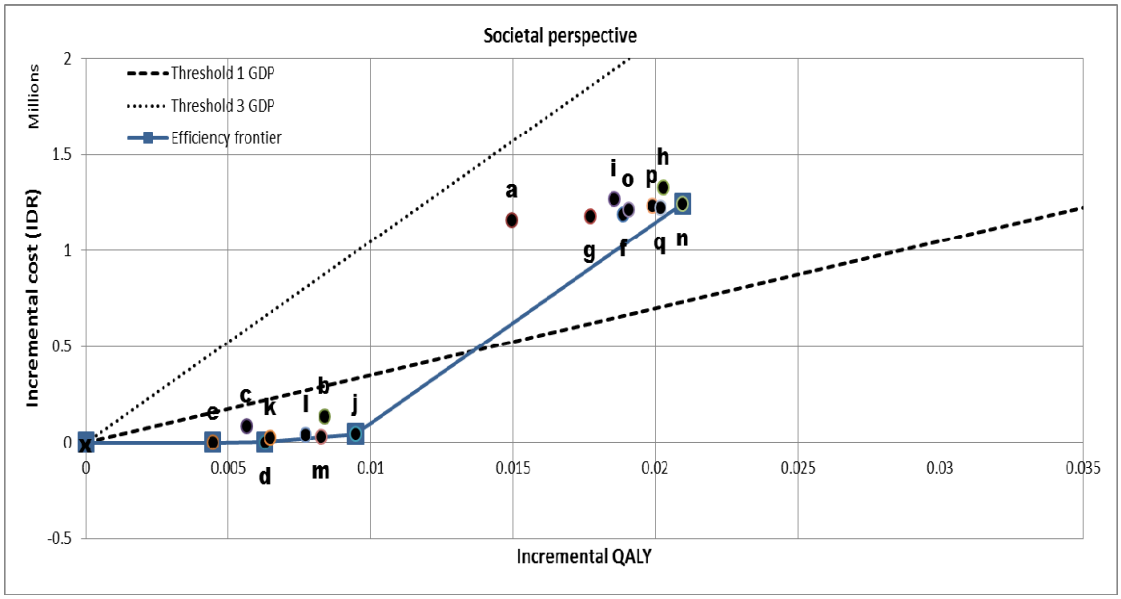
were comparable to vaccination alone (VIA pent annually), better than vaccination alone (VIA triennially, Pap smear triennially and pent-annually, and some strategies of combination of VIA and Pap smear), and even better than combination of vaccination and screening (VIA and Pap smear triennially). This result indicated that at the high coverage rate, screening strategy could replace vaccination for gaining greater health outcomes but with the lower cost.

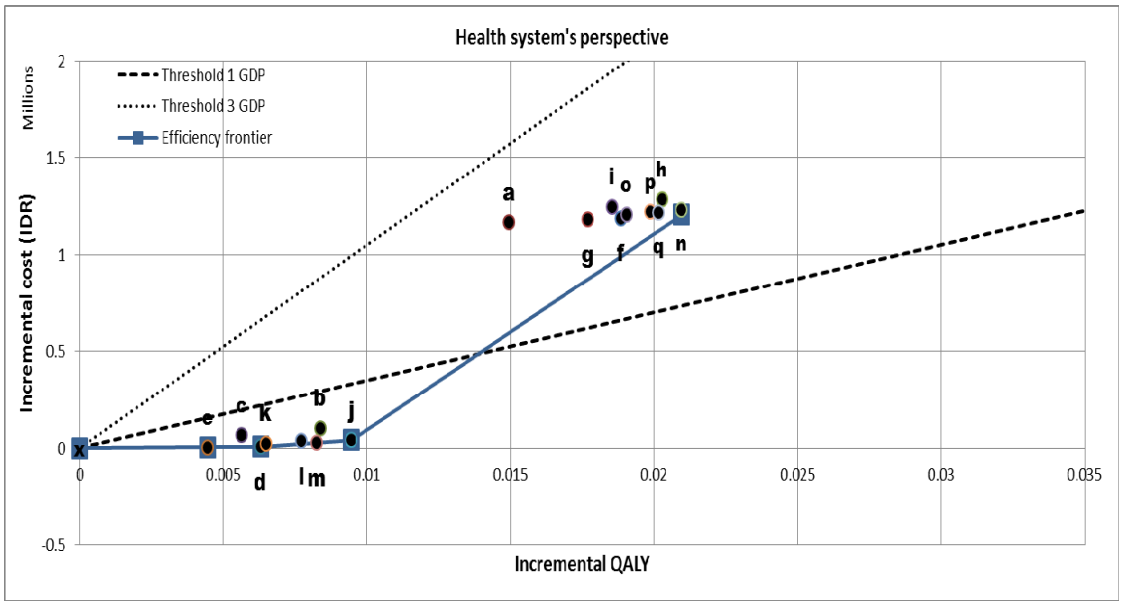
As for the different assumption of vaccine dose per fully immunized girl, the lower vaccine dose decreased the incremental cost without changing the health outcomes. Hence, the points of vaccination strategies of 2 vaccine doses on the cost effectiveness plane moved down and some strategies of combining vaccination and screening fell below the line of 1 GDP-threshold. This indicated if reducing vaccine dose from 3 to 2 doses would lead the cost effectiveness result from “cost effective” to be “very cost effective”. Nevertheless, the strategy of vaccination alone still stayed the same in between the lines of 1 and 3 GDP-threshold.

Lastly, for the comparison of cost effectiveness plane of strategies for cervical cancer prevention and control under the perspective of health system and societal, the results of both perspectives were nearly similar.

Since there were so many mutually exclusive strategies were assigned in the analysis and resulted non-dominated strategies, an efficiency frontier was conducted. Efficiency frontier involved the process to select the best optimum choices among non-dominated strategies. For this, the ICERs of strategies were calculated by comparing each strategy to the next more costly and more effective strategy. Finally, efficiency frontiers of increasingly more costly and more effective strategy were produced. The efficiency frontier was shown on every cost effectiveness plane. At the base case scenario, the best optimum choices for cervical cancer prevention and control based on efficiency frontier were VIA pent-annually, VIA triennially, combination of VIA and Pap smear triennially, and combination of vaccination followed by VIA triennially and Pap smear triennially, respectively. Meanwhile, the best optimum choices of strategies in scenario II and III were VIA pent-annually, VIA triennially, combination of VIA triennially and Pap smear triennially, combination of VIA triennially and Pap smear pent-annually and combination of vaccination followed by VIA and Pap smear triennially, respectively. The results of efficiency frontier of

strategies in different perspective of analysis and different assumption of vaccine dose were the same.

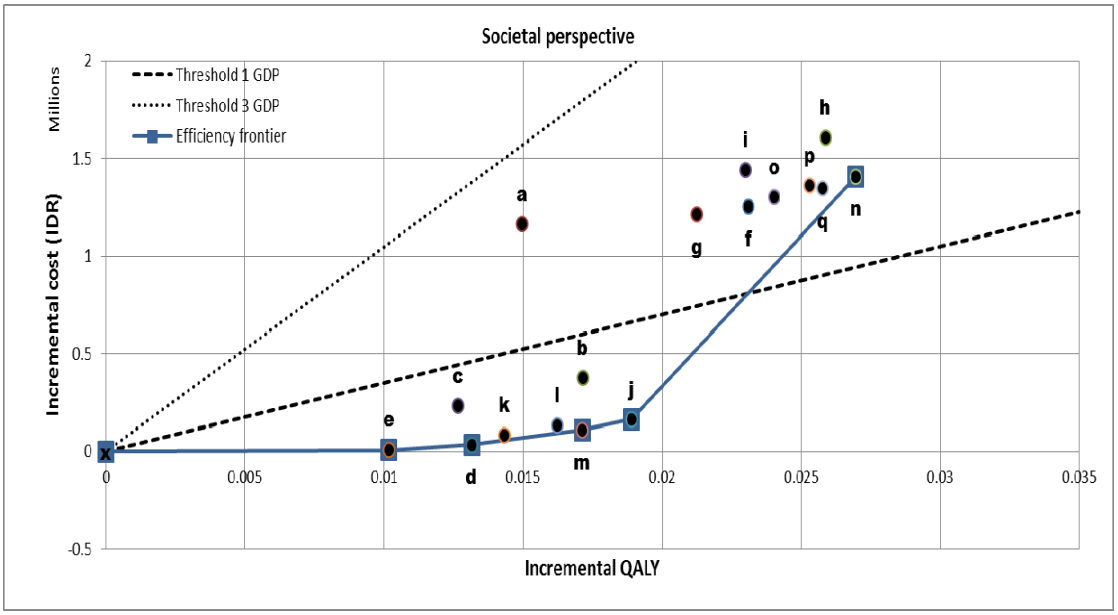


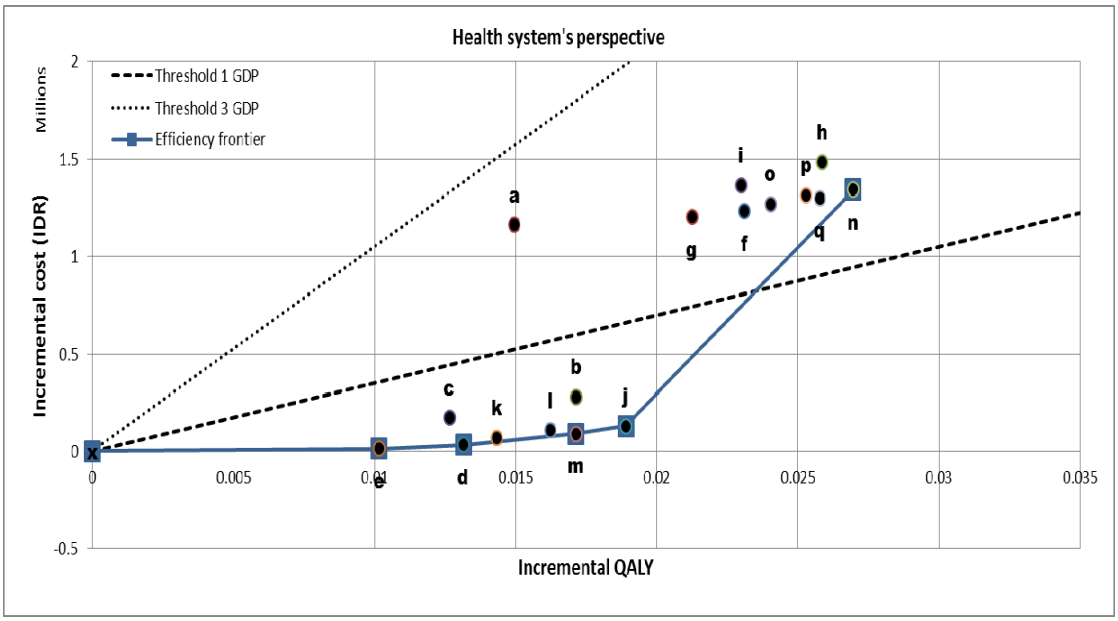


List of strategies

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.12 Cost effectiveness plane and efficient frontier of strategies for cervical cancer prevention and control using scenario I; given 3 doses of HPV vaccine per fully immunized girl

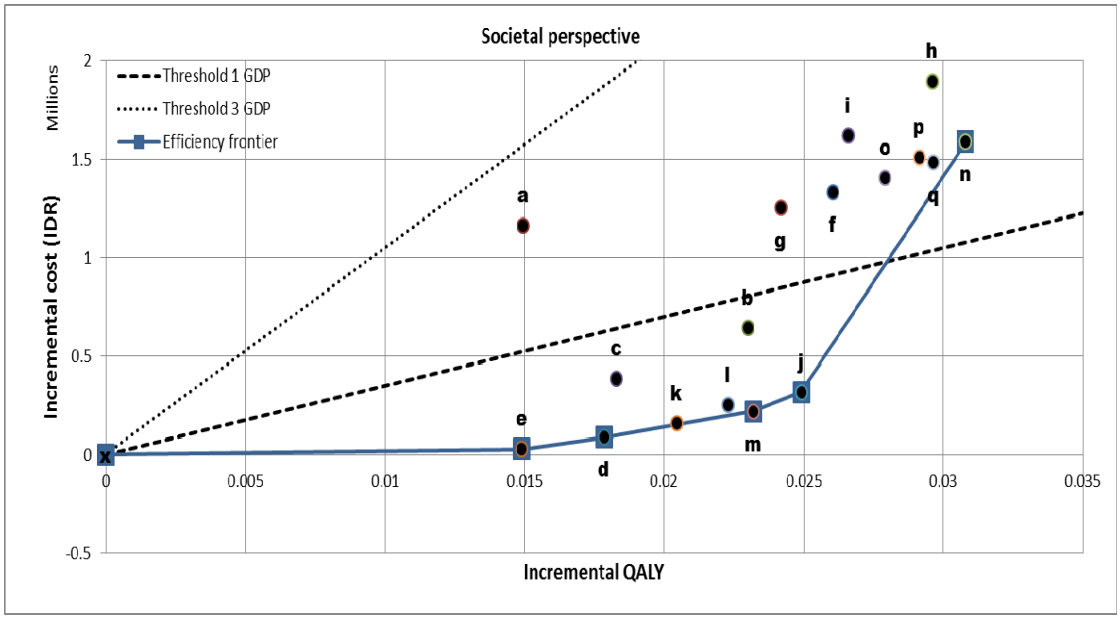


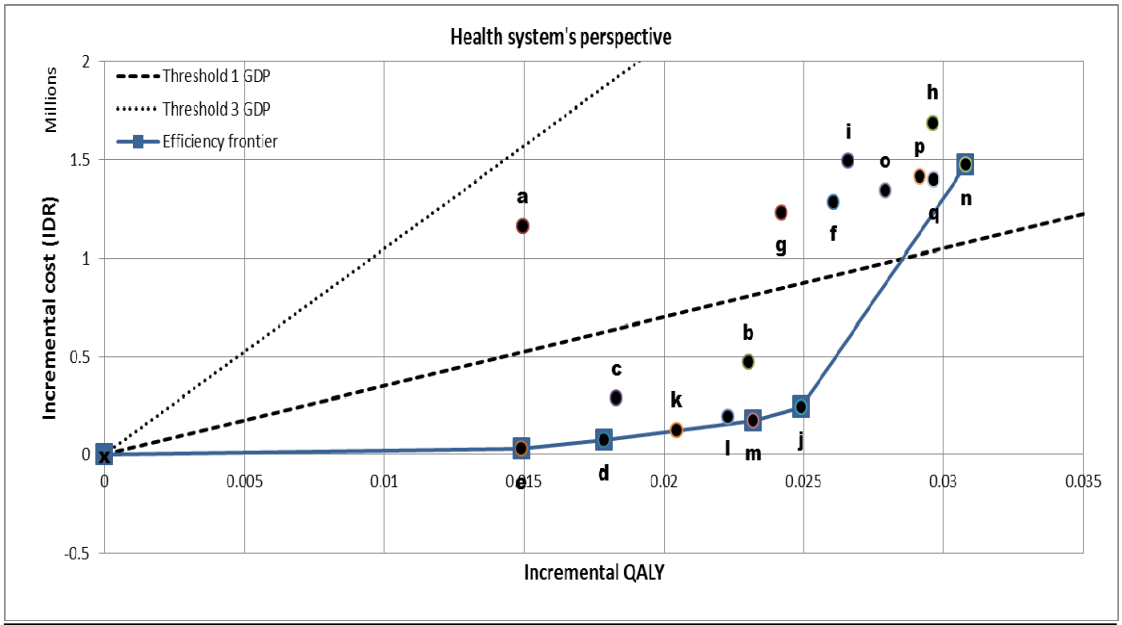


List of strategies

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.13 Cost effectiveness plane and efficiency frontier of strategies for cervical cancer prevention and control using scenario II; given 3 doses of HPV vaccine per fully immunized girl

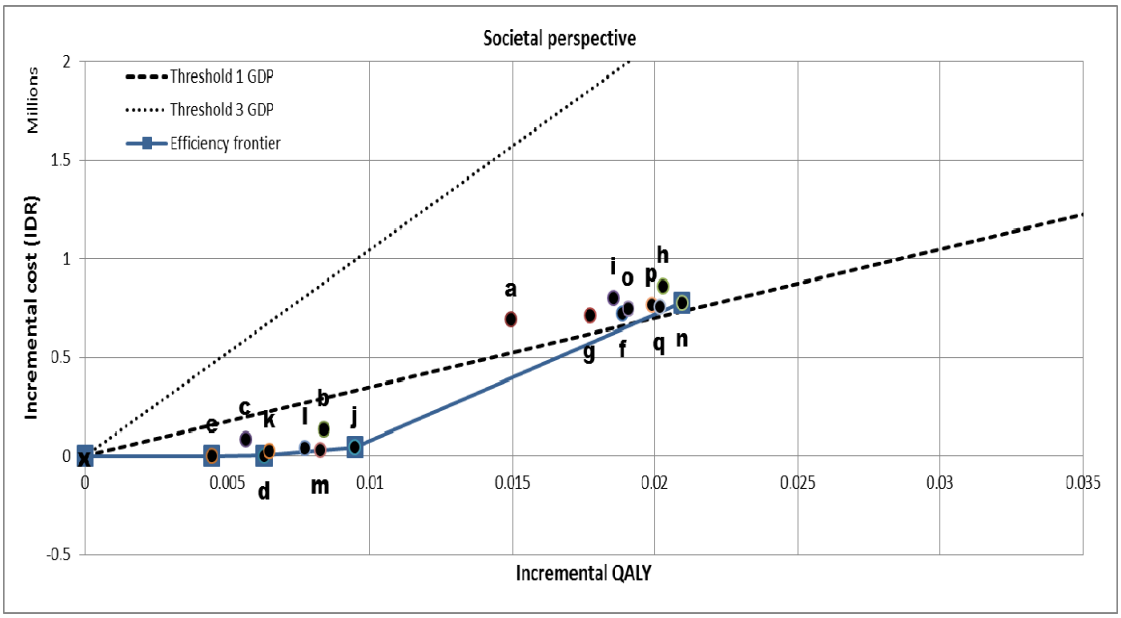


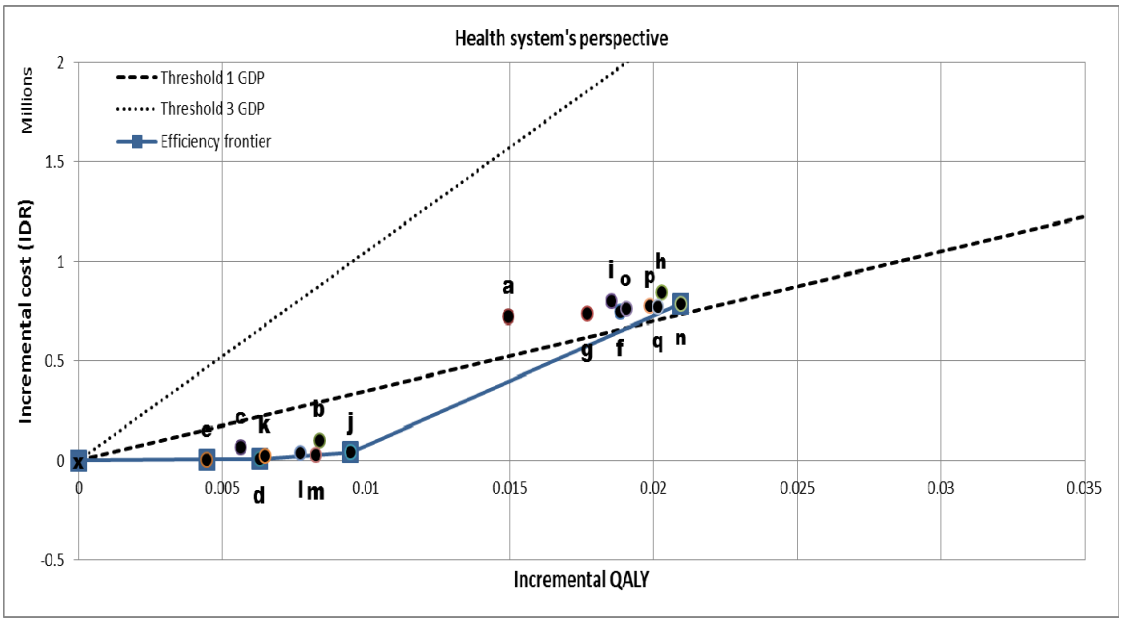


List of strategies

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.14 Cost effectiveness plane and efficiency frontier of strategies for cervical cancer prevention and control using scenario III; given 3 doses of HPV vaccine per fully immunized girl

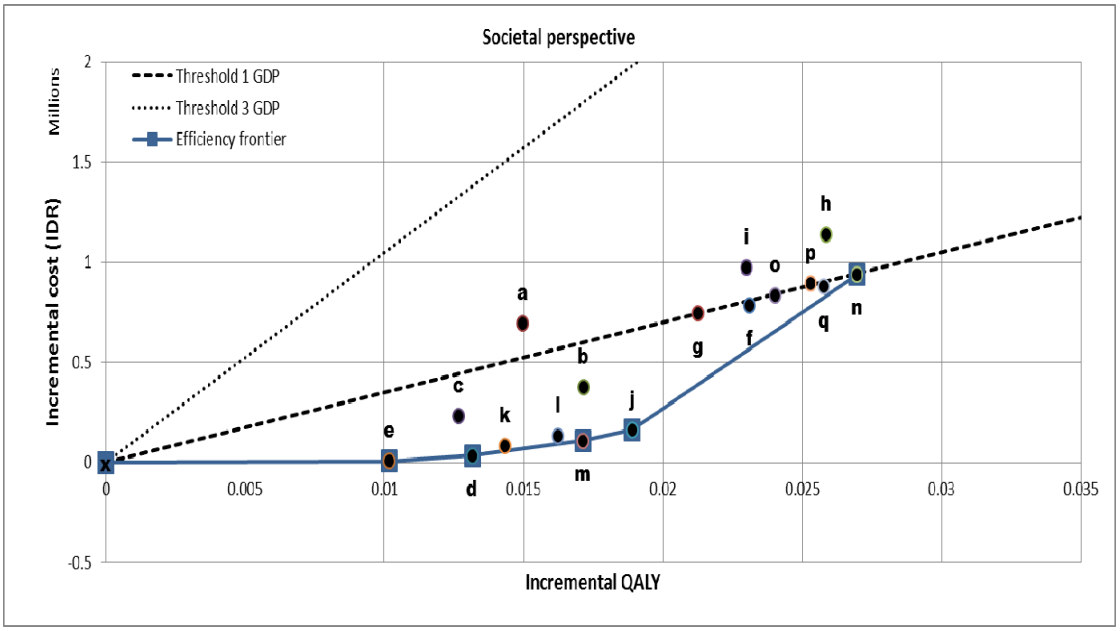


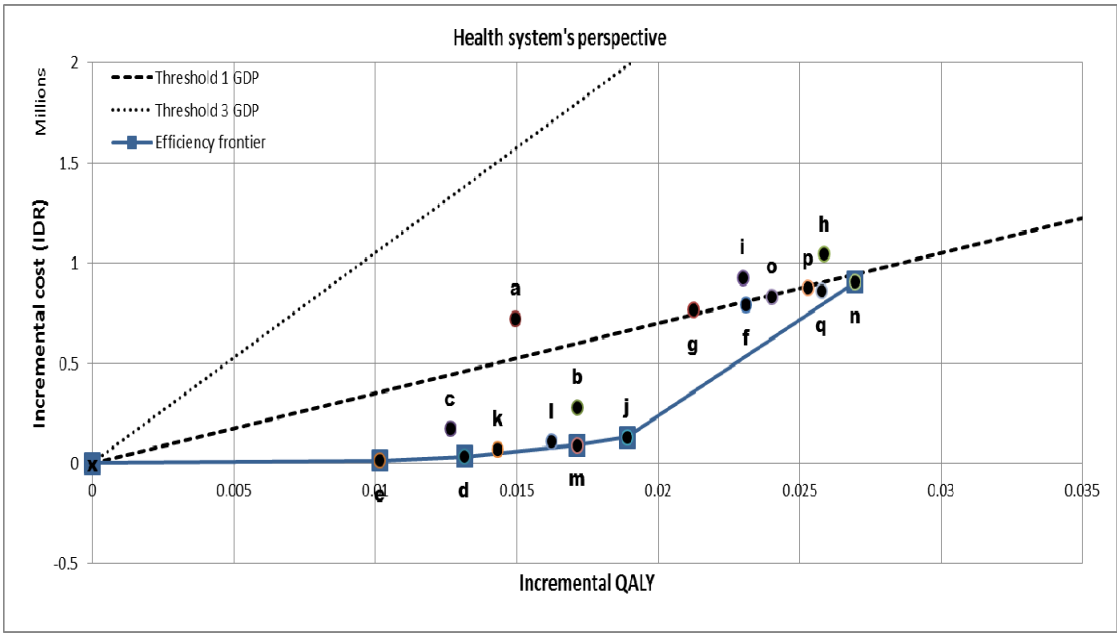


List of strategies

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.15 Cost effectiveness plane and efficiency frontier of strategies for cervical cancer prevention and control using scenario I; given 2 doses of HPV vaccine per fully immunized girl

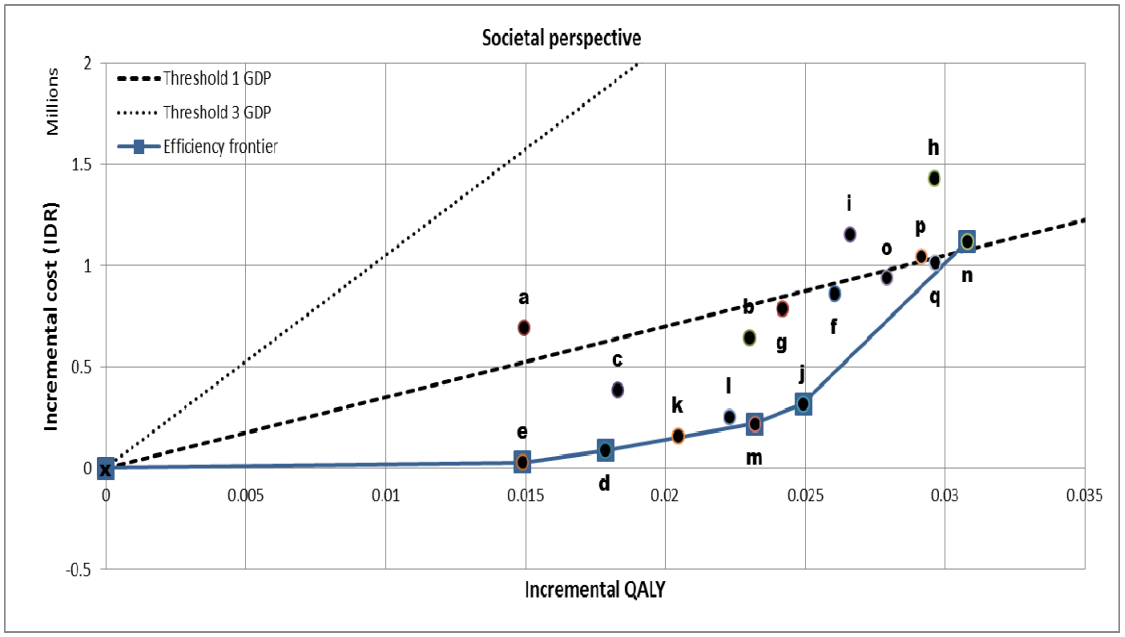


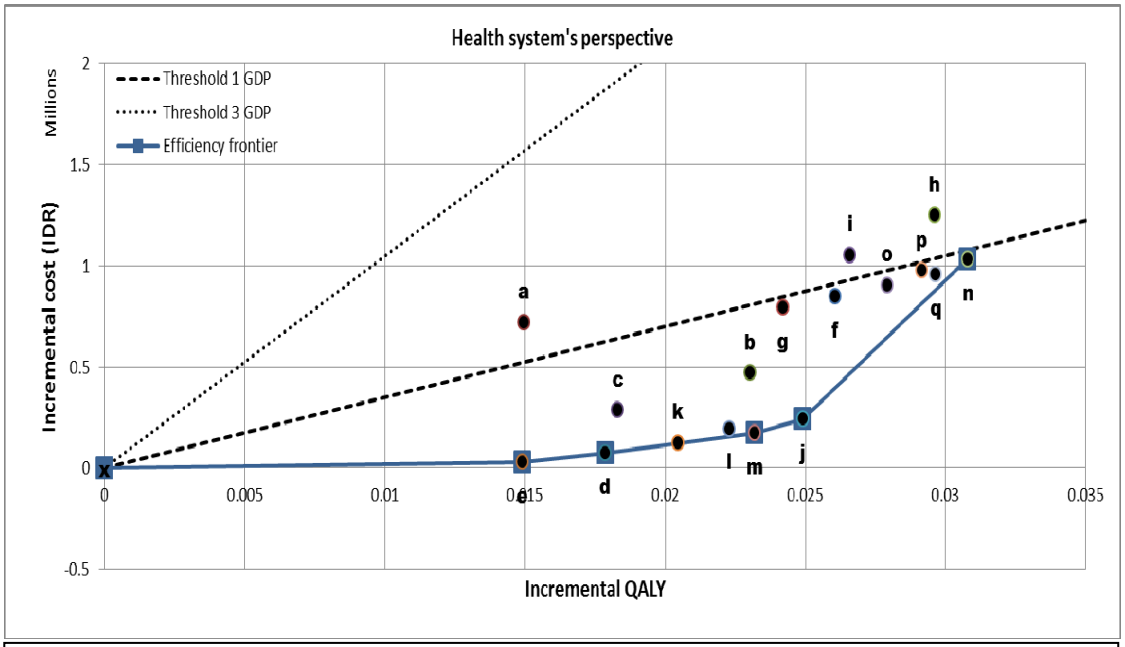


List of strategies

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.16 Cost effectiveness plane and efficiency frontier of strategies for cervical cancer prevention and control using scenario II; given 2 doses of HPV vaccine per fully immunized girl





List of strategies:

x = Do nothing	**i = Vac 12Y LT + Pap q5Y (30-65)**
a = Vac 12Y LT	**j = VIA q3Y (30-45) + Pap q3Y (48-63)**
b = Pap q3Y (30-63)	**k = VIA q5Y (30-45) + Pap q5Y (50-65)**
c = Pap q5Y (30-65)	**l = VIA q3Y (30-45) + Pap q5Y (50-65)**
d = VIA q3Y (30-45)	**m = VIA q3Y (30-45) + Pap q5Y (50-65)**
e = VIA q5Y (30-45)	**n = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**
f = Vac 12Y LT + VIA q3Y (30-45)	**o = Vac 12Y LT + VIA q5Y (30-45) + Pap q5Y (50-65)**
g = Vac 12Y LT + VIA q5Y (30-45)	**p = Vac 12Y LT + VIA q5Y (30-45) + Pap q3Y (48-63)**
h = Vac 12Y LT + Pap q3Y (30-63)	**q = Vac 12Y LT + VIA q3Y (30-45) + Pap q5Y (50-65)**

Figure 4.17 Cost effectiveness plane and efficiency frontier of strategies for cervical cancer prevention and control using scenario III; given 2 doses of HPV vaccine per fully immunized girl

4.3.5 Budget impact analysis

Long-term budget impact analysis

Table 4.24 presents the lifetime budget impact for providing several strategies for cervical cancer prevention and control in Indonesia. The budgets were separated into budget for prevention (vaccination or screening), budget for invasive cervical cancer treatment, and total budget. The incremental budgets for providing strategies relative to baseline intervention or doing nothing/treatment only were also presented. The budgets were projected for a 2015 cohort of girl aged 12 years old and simulated until age 100 years old. The strategies assigned were the best optimum strategies based on cost effectiveness analysis results, including VIA triennially, VIA pent-annually, combination of VIA triennially and sequential Pap smear triennially, and combination of vaccination and followed by VIA triennially and sequential Pap smear triennially. The different screening coverage rates and number of vaccine dose were also considered in the analysis.

Without any new intervention, a budget of IDR 968 billion was predicted to cost the national healthcare system for providing lifetime treatment of invasive cervical cancer. Implementing such strategies for cervical cancer prevention and control would reduce the budget for invasive cervical cancer treatment; however it would need additional budget for performing the program. The cumulative budget for performing program and treating the disease would result positive incremental budget when compared to treatment only. The incremental budget of those strategies ranged from IDR 7 billion for strategy of VIA pent-annually to IDR 3,337 billion for strategy of combination vaccination and screening with VIA and Pap smear triennially, at the screening coverage rate of 20%. Scaling up the screening coverage rates would decrease the budget for invasive cervical cancer treatment due to the increasing of effect; however it would also lead to increasing of budget for program performing and resulting more total budget about 10% greater in scenario II and III, gradually. The strategy involving vaccination was found to lead to a substantial increase in healthcare budget because of its high price.

Table 4.24 Life time budget impact for providing strategies for cervical cancer prevention and control*

Intervention	Budget (billions IDR)			
	Prevention	Treatment	Total	Incremental
Do nothing	0	968	968	Reference
VIA q3Y (30-45), 20% coverage	134	850	983	15
VIA q3Y (30-45), 50% coverage	330	714	1,044	76
VIA q3Y (30-45), 80% coverage	525	614	1,139	171
VIA q5Y (30-45), 20% coverage	90	885	975	7
VIA q5Y (30-45), 50% coverage	223	776	998	30
VIA q5Y (30-45), 80% coverage	354	682	1,037	69
VIA q3Y (30-45) + Pap q3Y (48-63), 20% coverage	273	785	1,058	90
VIA q3Y (30-45) + Pap q3Y (48-63), 50% coverage	674	588	1,262	294
VIA q3Y (30-45) + Pap q3Y (48-63), 80% coverage	1,068	450	1,518	550
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 20% screening coverage, 3 doses vaccine	3,251	497	3,748	2,780
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 50% screening coverage, 3 doses vaccine	3,640	371	4,010	3,042
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 80% screening coverage, 3 doses vaccine	4,024	281	4,305	3,337
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 20% screening coverage, 2 doses vaccine	2,255	497	2,752	1,784
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 50% screening coverage, 2 doses vaccine	2,643	371	3,014	2,046
Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63), 80% screening coverage, 2 doses vaccine	3,028	281	3,309	2,341

*Budget impact analysis was projected for a 2015 cohort of girl age 12 years

Short-term budget impact analysis

Table 4.25 describes the predicted budget required for providing such strategies for cervical cancer and prevention in Indonesia. The budgets were presented for each year period within 5 years along with the number target population receiving the intervention. The interventions assigned in this analysis were limited to single strategy because based on rationale assumption used in this study, the combination strategies were not suitable to be provided to the same target population within 5 years period. The strategies were selected to present each type of intervention and assigned in different scenarios of screening coverage rates and vaccine dose assumptions.

Table 4.25 Budget impact for 5 year program implementation

Strategies	Year				
	2015	**2016**	**2017**	**2018**	**2019**
Number of target population (women)					
Vac 12Y LT, 80% coverage, 2 doses	1,896,579	1,924,838	1,953,518	1,982,625	2,012,166
Vac 12Y LT, 80% coverage, 3 doses	1,896,579	1,924,838	1,953,518	1,982,625	2,012,166
Pap q5Y (30-65), 20% coverage	2,136,424	2,168,257	2,200,564	2,233,352	2,266,629
Pap q5Y (30-65), 50% coverage	5,341,060	5,420,642	5,501,409	5,583,380	5,666,573
Pap q5Y (30-65), 80% coverage	8,545,696	8,673,027	8,802,255	8,933,408	9,066,516
VIA q5Y (30-45), 20% coverage	1,475,554	1,497,540	1,519,853	1,542,499	1,565,482
VIA q5Y (30-45), 50% coverage	3,688,884	3,743,849	3,799,632	3,856,247	3,913,705
VIA q5Y (30-45), 80% coverage	5,902,215	5,990,158	6,079,411	6,169,995	6,261,928
Total budget (in billion IDR)					
Vac 12Y LT, 80% coverage, 2 doses	2,090	2,120	2,150	2,180	2,210
Vac 12Y LT, 80% coverage, 3 doses	3,130	3,180	3,220	3,270	3,320
Pap q5Y (30-65), 20% coverage	430	436	443	449	456
Pap q5Y (30-65), 50% coverage	1,070	1,090	1,110	1,120	1,140
Pap q5Y (30-65), 80% coverage	1,720	1,740	1,770	1,800	1,820
VIA q5Y (30-45), 20% coverage	163	166	168	171	173
VIA q5Y (30-45), 50% coverage	409	415	421	427	434
VIA q5Y (30-45), 80% coverage	654	664	674	684	694

The annual budget for providing interventions for cervical cancer prevention and control in first year of implementation ranged from IDR 163 billion to IDR 3,130 billion among all strategies in different scenarios. The lowest budget was in strategy of VIA pent-annually at 20% coverage rate and the highest budget was in strategy of vaccination with 3 doses at 80% coverage rate. The budget slightly increased by year due to population growth while keeping the unit cost of intervention constantly. Among different screening coverage rates, the increasing of budgets were in line with the addition of target population amount, which was about 30% for the greater coverage rate, gradually. In contrast, the budget for vaccination increased in the greater vaccine dose used due to the greater of vaccination cost only without any different of target population amount. Again, budget for vaccinations were substantially greater as compared to budget of screening due to its high price of vaccine.

In Figure 4.18 it is showed the comparison of total budget and target population receiving interventions in 5 years. It can be seen clearly that vaccinations required the higher budget as compared to screening, although given to smaller number of target population. When comparing VIA and Pap smear, VIA required lower budget due to the lower unit cost itself and smaller number of target population.

Finally, the additional budgets for new vaccination proposed was compared with other budget reference such as current budget of expanded program for immunization (EPI), and national health expenditure. Figure 4.19 illustrates the impact of annual additional budgets for HPV vaccinations using different vaccine price assumptions relative to current annual EPI budget (IDR 26,000 billion). The assumptions of vaccine prices per dose including programmatic costs were IDR 550,000 (USD 53.30) for market price; IDR 300,000 (USD 29.08) and IDR 450,000 (USD 43.61) for threshold price using 3 and 2 doses, respectively; IDR 180,000 (USD 17.45) for lowest public price; and IDR 80,000 (USD 7.75) for GAVI price. The annual additional budget was predicted for 2015 from budget analysis and reference was projected EPI budget in 2015 based on Comprehensive Multi-Year Plan of Immunization Program by Ministry of Health of Indonesia (115). Budgets for vaccinations ranged from 1 – 12% for all assumptions which the highest was if using current market price and the lowest was if using GAVI price. Current EPI budget

consumed about 10% from national health expenditure, then implementing HPV vaccination for cervical cancer prevention and control would lead to additional budget for national expenditure which ranged from 0.1 – 1.2% from current EPI budget.

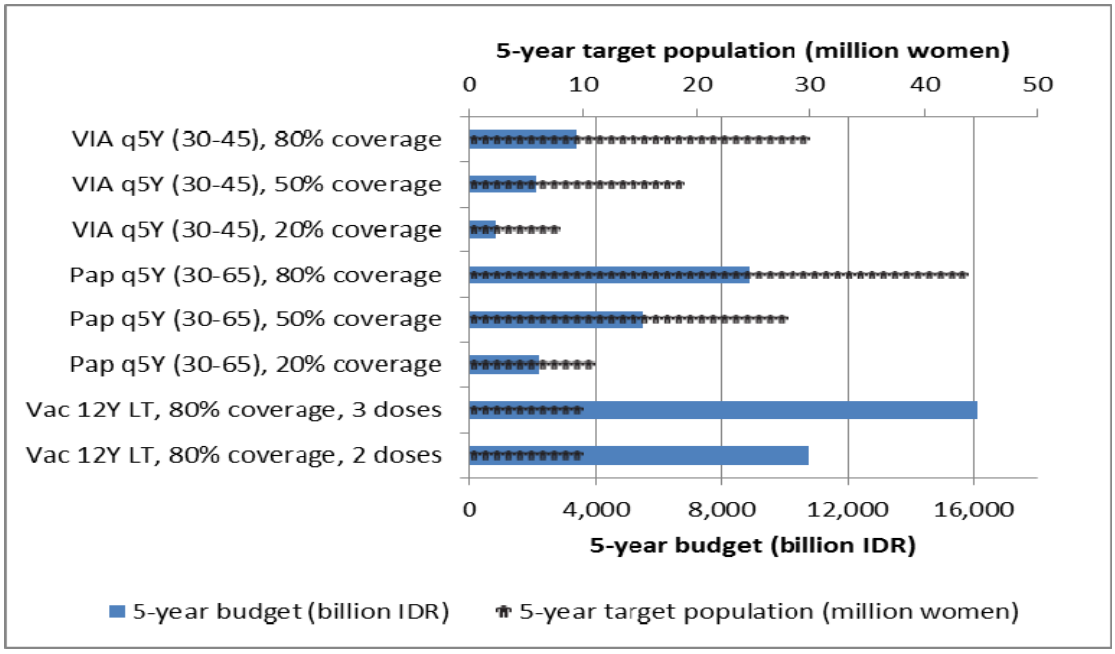


Figure 4.18 Five-year budgets for providing strategies for cervical cancer prevention and control

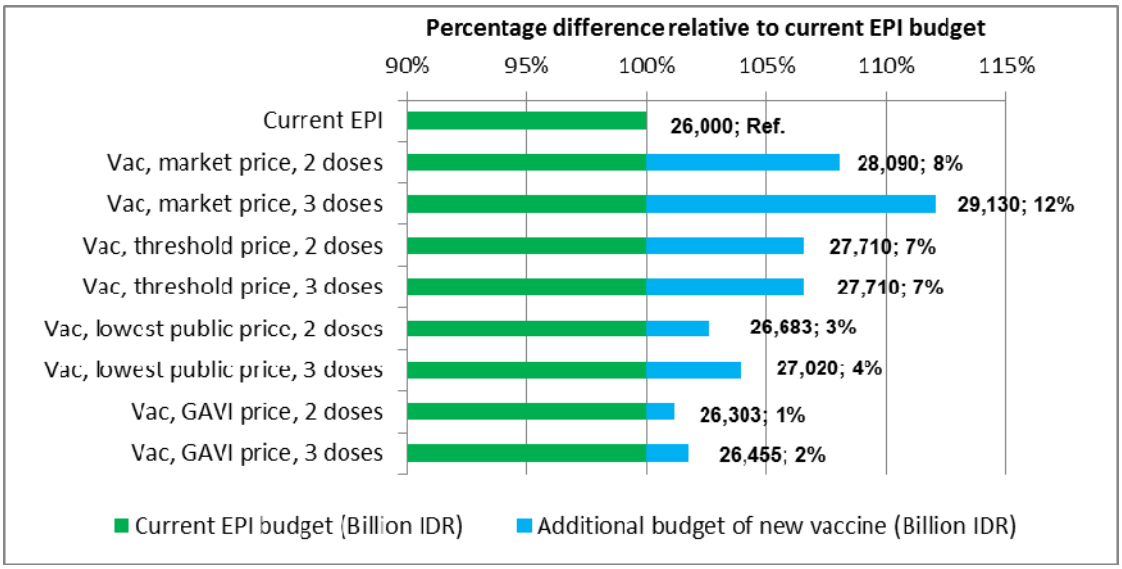


Figure 4.19 Comparison of annual budget of HPV vaccination with current EPI budget

4.4 Sensitivity analysis

4.4.1 One-way sensitivity analysis

Results of one way sensitivity analysis were presented as Tornado diagrams as were shown in Figure 4.20 to 4.23. Percent of changing ICERs for each tested parameter was calculated in comparison to baseline (do nothing). The analysis was conducted under societal perspective. Combination strategy of vaccination followed by VIA triennially plus sequential Pap smear triennially was selected to represent the effect of individual parameter changing on the final result of ICER per QALY. The analysis was also conducted to represent the situation of lowest screening coverage rate (scenario I/base case with 20% of screening coverage rate) and highest screening coverage rate (scenario III with 80% of screening coverage rate). The assumption of 2 vaccine doses was also assigned beside the 3 vaccine doses.

In general, it can be said that the base case ICER estimations were robust; the values were not influenced much by plausible changes in the most parameters of intervention effectiveness, costs, and utility. However, some parameters should be noticed. For instance, discount rate was the most sensitive parameter, as when applying discount rate of 0% and 6% the ICER changed about 100%. The next sensible parameter was direct medical cost of vaccination in which the ICER changed to -53% and 106% for the low and high value of parameter. However, the percentage of ICER changing was in line with percentage changing of parameter. When comparing the ICER changing due to changing of parameter values around 95% confidence interval, the utility was the most sensitive parameter, in which the ICER changed -12% and 16% for the lower and upper value of 95% confidence interval of base case utility. In case of relative risk of HPV vaccine parameter, the values for sensitivity analysis were varied from the estimation of the lowest and highest proportion of HPV type 16 and 18 to cause invasive cervical cancer in Indonesia setting.

The patterns of sensitivity analysis were relatively similar in situation of scenario III (highest screening coverage rate) and assumption of 2 vaccine dose used. Overall, none of parameters changed the ICER until crossed the cost effectiveness threshold of 3 times GDP, except only the parameter of direct medical

cost of vaccination at the base case scenario. The effect of vaccine price was further investigated in threshold analysis.

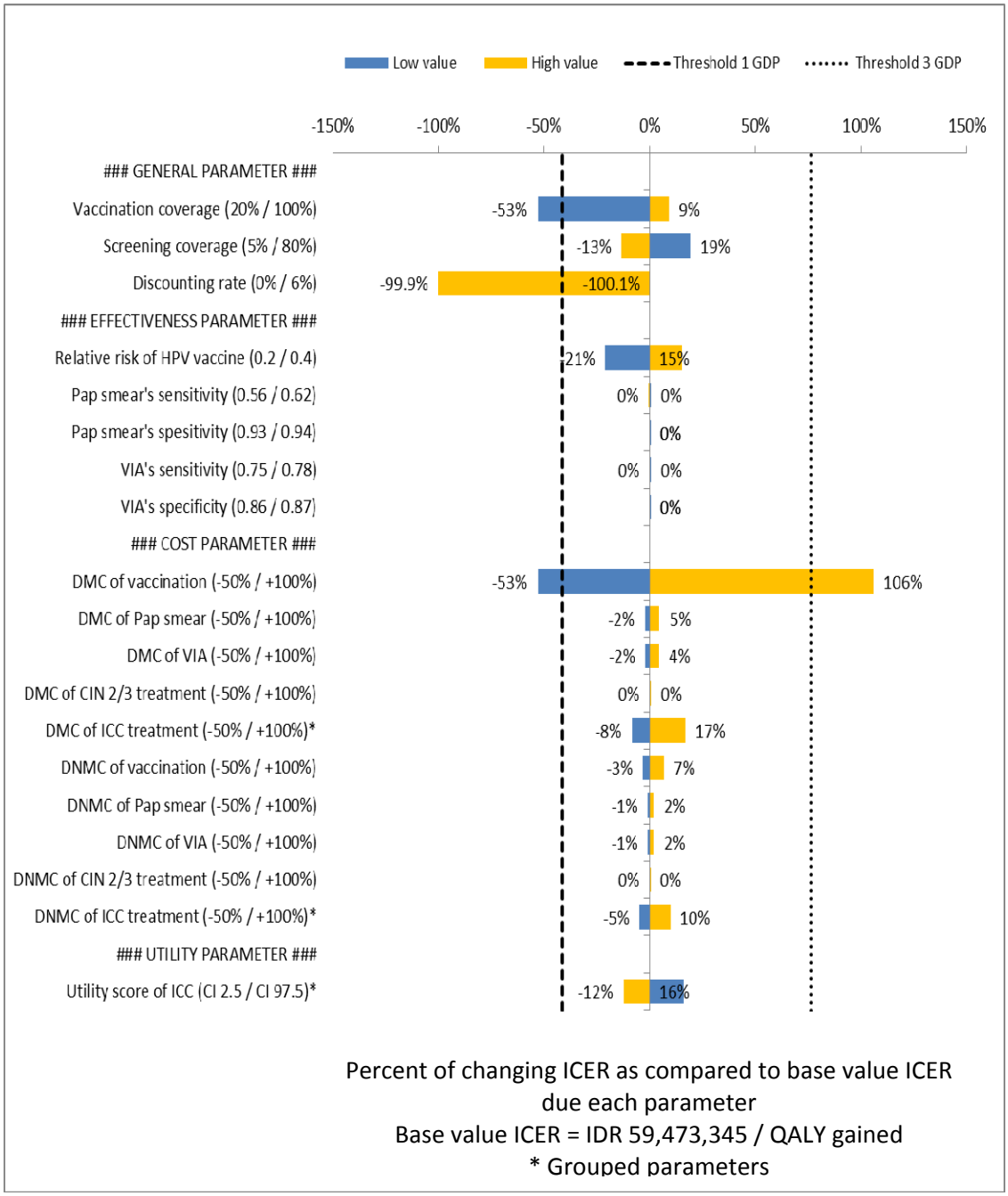


Figure 4.20 Tornado diagram of one-way sensitivity analysis for providing HPV vaccination at age 12 and followed by VIA every 3 years at age 30-45 plus sequential Pap smear every 3 years at age 48-63; following scenario I, given 3 doses of HPV vaccination, societal perspective, and do nothing as reference

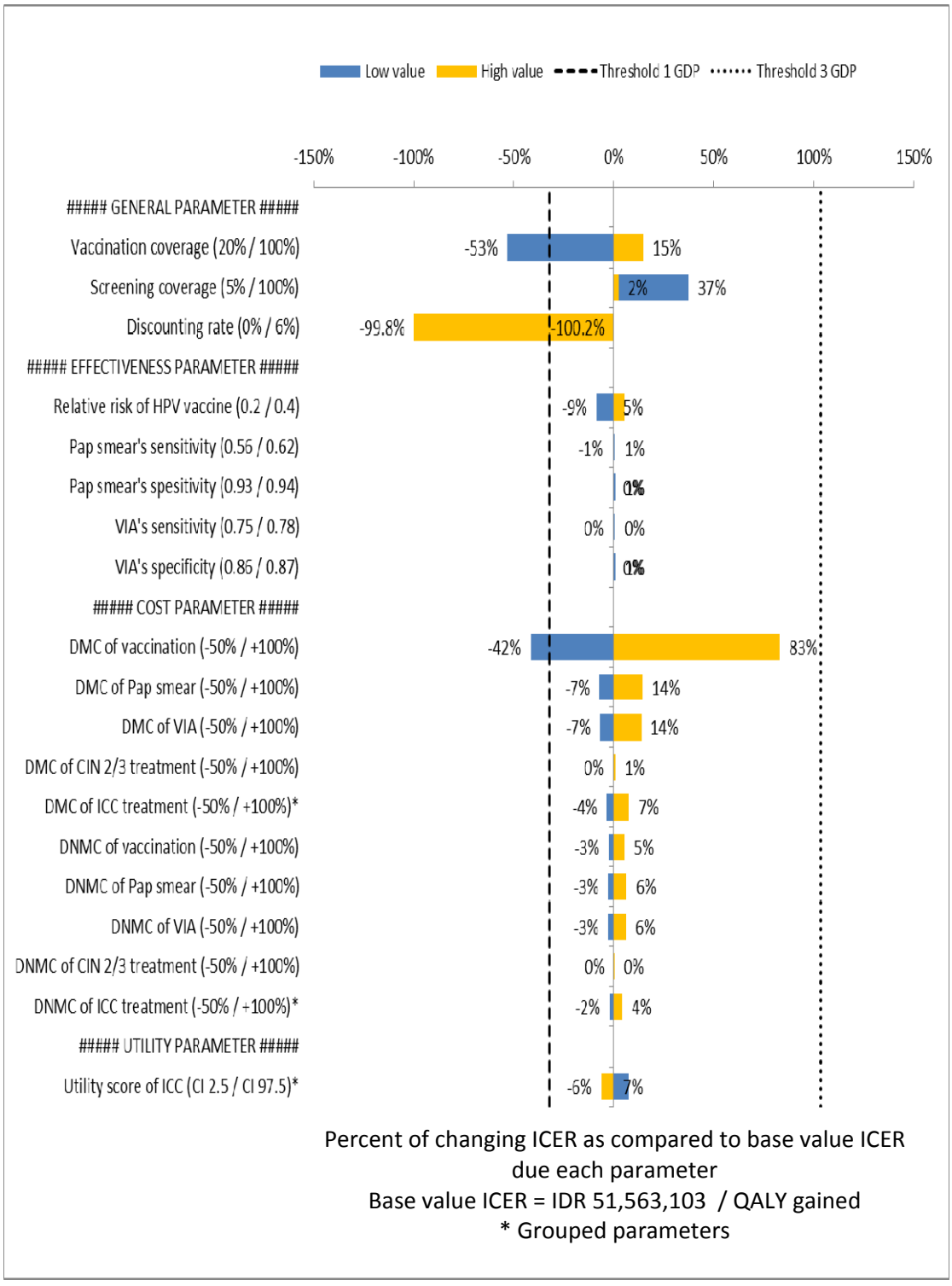


Figure 4.21 Tornado diagram of one-way sensitivity analysis for providing HPV vaccination at age 12 and followed by VIA every 3 years at age 30-45 plus sequential Pap smear every 3 years at age 48-63 in scenario III; given 3 doses of HPV vaccination, societal perspective, and do nothing as reference

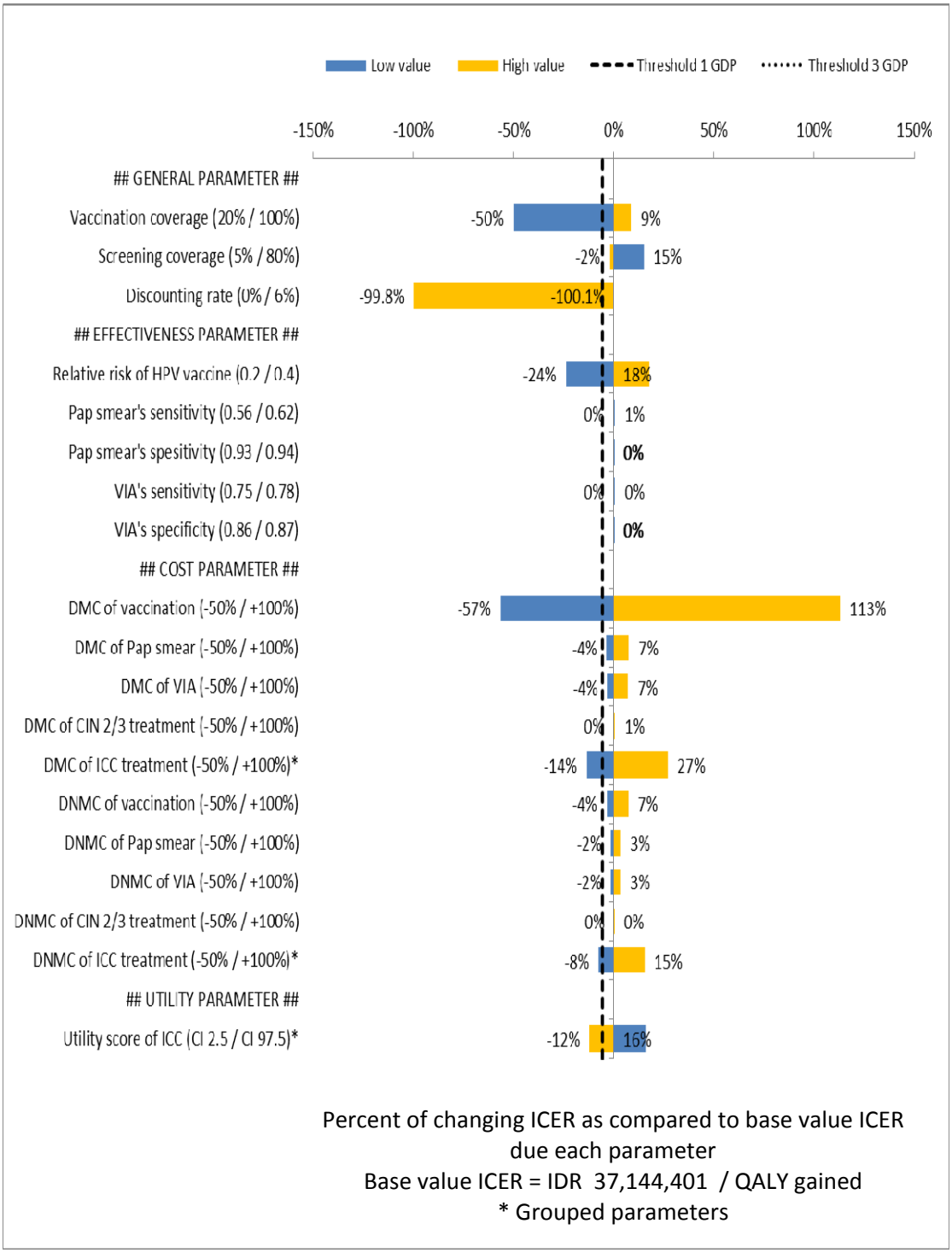


Figure 4.22 Tornado diagram of one-way sensitivity analysis for providing HPV vaccination at age 12 and followed by VIA every 3 years at age 30-45 plus sequential Pap smear every 3 years at age 48-63 in scenario I; given 2 doses of HPV vaccination, societal perspective, and do nothing as reference

4.4.2 Two-way sensitivity analysis

Two-way sensitivity analyses assigned the effect of sensitivity and specificity value on the value of ICER per QALY. The analysis was conducted in situation of screening coverage of 20% under societal perspective and for selected intervention of VIA pent-annually and Pap smear pent-annually. The results were presented in Table 4.26 and Table 4.27 with rows described the range of sensitivity from 0 to 1 and columns described the range of specificity from 0 to 1. The value of ICER resulted from certain value of sensitivity and specificity could then be found at the point by tracing a line from the certain row and column. This results allowed to predict in which value of sensitivity and specificity of VIA or Pap smear that the ICER would be very cost effective, or not cost effective given the cost effectiveness threshold of 1 and 3 times GDP.

At the base case value of sensitivity and specificity of VIA, the strategy resulted ICER of IDR 0 per QALY, which was considered as very cost effective. When the sensitivity decreased to 0.7 at any value of specificity, the ICERs results were still considered of very cost effective. The threshold of VIA sensitivity value to result the ICER which not be considered as not cost effective was about 0.2 at any value of specificity. As for the specificity, the threshold of value to result the ICER which not be considered as not cost effective was about 0.7 at any value of sensitivity.

In similar way, at the base case value of sensitivity and specificity of Pap smear, the strategy resulted ICER of IDR 15,000,000 per QALY, which was also considered as very cost effective. The threshold of Pap smear sensitivity value to result the ICER which not be considered as not cost effective was about 0.6 at any value of specificity. Meanwhile, for the specificity, the threshold of value to result the ICER which not be considered as not cost effective should be above 0.9 at any value of sensitivity.

Table 4.26 Incremental cost effectiveness ratio (ICER) per QALY for providing VIA every 5 years at age 30-45; scenario I, from societal perspective [a]

SENSITIVITY OF VIA	SPECIFICITY OF VIA											
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.87	0.8	0.9	1
0	248	227	206	186	165	144	123	102		81.6	60.8	40
0.1	147	134	121	108	95.6	82.8	70	57.2		44.4	32	19
0.2	102	93	83.7	74.5	65.2	55.9	46.7	37.4		28	19	10
0.3	77.3	70	62.7	55.4	48.1	40.8	34	26.2		19	12	4
0.4	61.3	55.3	49.2	43.2	37.2	31	25	19		13	7	1
0.5	50.2	45	39.9	34.7	30	24	19	14		9	4	-1
0.6	42	37.5	33	29	24	20	15	11		6	2	-3
0.7	35.7	31.7	28	24	20	16	12	8		4	0	-4
0.77									0			
0.8	30.7	27.1	24	20	16	13	9	6		2	-2	-5
0.9	27	23	20	17	14	10	7	4		0	-3	-6
1	23	20	17	14	11	8	5	2		-1	-4	-7

[a]Number presented in this table were ICER per QALY (in million IDR); [b] ICER per QALY of base case.

ICER per QALY < 35 = the strategy was very cost effective; ICER per QALY between 35 – 105 = the strategy was cost effective; ICER per QALY > 105 = the strategy was not cost effective.

Table 4.27 Incremental cost effectiveness ratio (ICER) per QALY for providing Pap smear every 5 years at age 30-65; scenario I, from societal perspective [a]

SENSITIVITY OF PAP SMEAR	SPECIFICITY OF PAP SMEAR											
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.94	1
0	448	412	377	342	306	271	236	200	165	130		94.2
0.1	278	255	233	211	188	166	143	121	98.6	76		54
0.2	200	184	167	151	134	118	101	85	69	52		36
0.3	156	143	130	117	104	91	77	64	51	38		25
0.4	127	116	106	95	84	73	62	51	40	29		18
0.5	107	98	89	79	70	60	51	42	32	23		14
0.59											15	
0.6	93	84	76	68	60	51	43	35	27	18		10
0.7	81	74	66	59	52	44	37	30	22	15		7
0.8	72	65	59	52	45	39	32	25	19	12		5
0.9	65	59	53	46	40	34	28	22	16	10		4
1	59	53	47	42	36	30	25	19	13	8		2

[a]Number presented in this table were ICER per QALY (in million IDR); [b] ICER per QALY of base case.

ICER per QALY < 35 = the strategy was very cost effective; ICER per QALY between 35 – 105 = the strategy was cost effective; ICER per QALY > 105 = the strategy was not cost effective.

4.4.3 Threshold analysis

Figure 4.23 illustrated findings from threshold analysis. The situation of analysis was strategy of vaccination alone, under the societal perspective. Both 2 and 3 vaccine doses assumptions were assigned. With the assumption of 3 vaccine doses used per fully immunized girl, the base case price of vaccine at IDR 550,000 per dose resulted ICER about IDR 78 million per QALY, which was considered as cost effective. The vaccine price could not over than IDR 750,000 per dose to keep the strategy as cost effective. Reduction of vaccine price until below IDR 300,000 per dose would result the ICER to be very cost effective.

Meanwhile, at the assumption of 2 vaccine doses used per fully immunized girl, the ICER of base case vaccine price was about IDR 46 million per QALY, which also was considered as cost effective. To achieve very cost effective result, the vaccine price should be reduced to about IDR 450,000 per dose. In addition, the highest price of vaccine for strategy which not be considered as not cost effective was about double from the base case price of IDR 550,000 per dose.

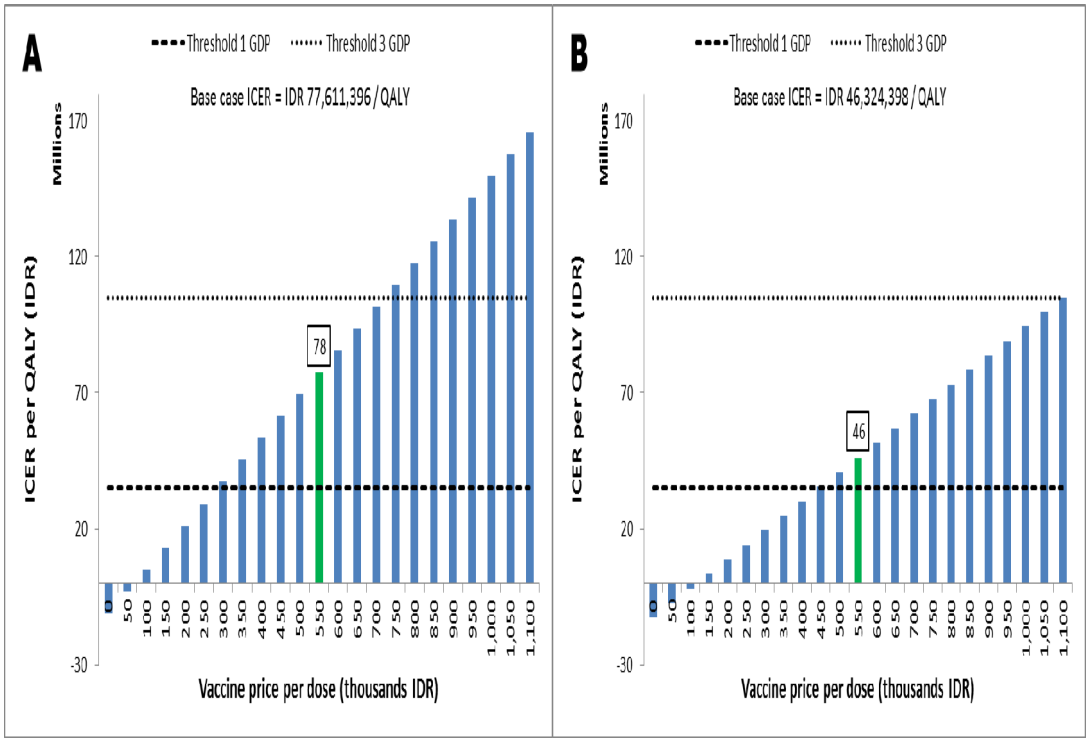


Figure 4.23 Threshold analyses of HPV vaccine price; (A): given 3 doses per fully immunized girl, and (B): given 2 doses per fully immunized girl

4.4.4 Probabilistic sensitivity analysis

Figure 4.24 to 4.26 report the results of probabilistic sensitivity analysis (PSA) in cost effectiveness acceptability curves (CEAC). Only the best optimum choice of strategies based on efficiency frontier in cost effectiveness plane were assigned in PSA. At the base case scenario, the CEAC illustrated the probability being cost effective of 5 strategies: VIA pent-annually, VIA triennially, combination of VIA triennially and Pap smear triennially, combination of vaccination and followed by VIA triennially and Pap smear triennially, and do nothing. Meanwhile, for scenario II and III, the CEAC illustrated the probability being cost effective of 6 strategies which were the same strategies as were of base case scenario and plus strategy of combination of VIA triennially and Pap smear pent-annually. The analysis also considered the assumptions of vaccine dose used.

At the base case scenario, when considering either cost effectiveness threshold of 1 times GDP or 3 times GDP, combination strategy of VIA triennially and PAP smear triennially was the strategy with the highest probability of being cost effective which probabilities were 0.787 and 0.571, respectively, with the assumption of 3 vaccine doses for strategy involving vaccination. Reducing the vaccine dose from 3 to 2 doses per fully immunized girl might cause increasing of probability of strategy involving vaccination. For instance, at the base case with the assumption of 2 vaccine doses, when considering threshold of 3 times GDP, the strategy with highest probabilities of being cost effective was combination of vaccination and followed by VIA triennially and Pap smear triennially, which probability was 0.778.

It can be noted that in all scenarios under the cost effectiveness threshold of 1 time GDP, combination strategy of VIA triennially and PAP smear triennially was the strategy with the highest probabilities of being cost effective among other strategies. Scaling up the acceptance rate of screening (in scenario II and III) might cause higher probability of strategies of screening and in opposite way reducing the probability of strategies involving vaccination. This can be seen in figure B, in which at the best case when considering cost effectiveness threshold of 3 times GDP, the probability of vaccination and followed by VIA triennially and Pap smear triennially being cost effective was 0.417; this probability gradually decreased in scenario II and III to be 0.153 and 0.046, respectively. This also occurred in Figure B for the

assumption of 2 doses, in which at the best case when considering cost effectiveness threshold of 3 times GDP, the probability of the strategy being cost effective was 0.778; this probability gradually decreased in scenario II and III to be 0.485 and 0.229, respectively.

The PSA gave information that when considering 1 time GDP as the cost effectiveness thresholds, the combination of VIA triennially and sequential Pap smear triennially was the most favorable strategy among other strategies in all scenarios and all vaccine dose assumptions. However, reducing vaccine doses and increasing the cost effectiveness threshold on 3 times GDP might cause the probability of strategy involving vaccination increased and even more favorable as compared to screening strategy at lower coverage rate of screening. Scaling up the coverage rate of screening strategy might increase the probability of being cost effective and would be more favorable as compared to vaccination strategy at lower dose and higher cost effectiveness threshold.

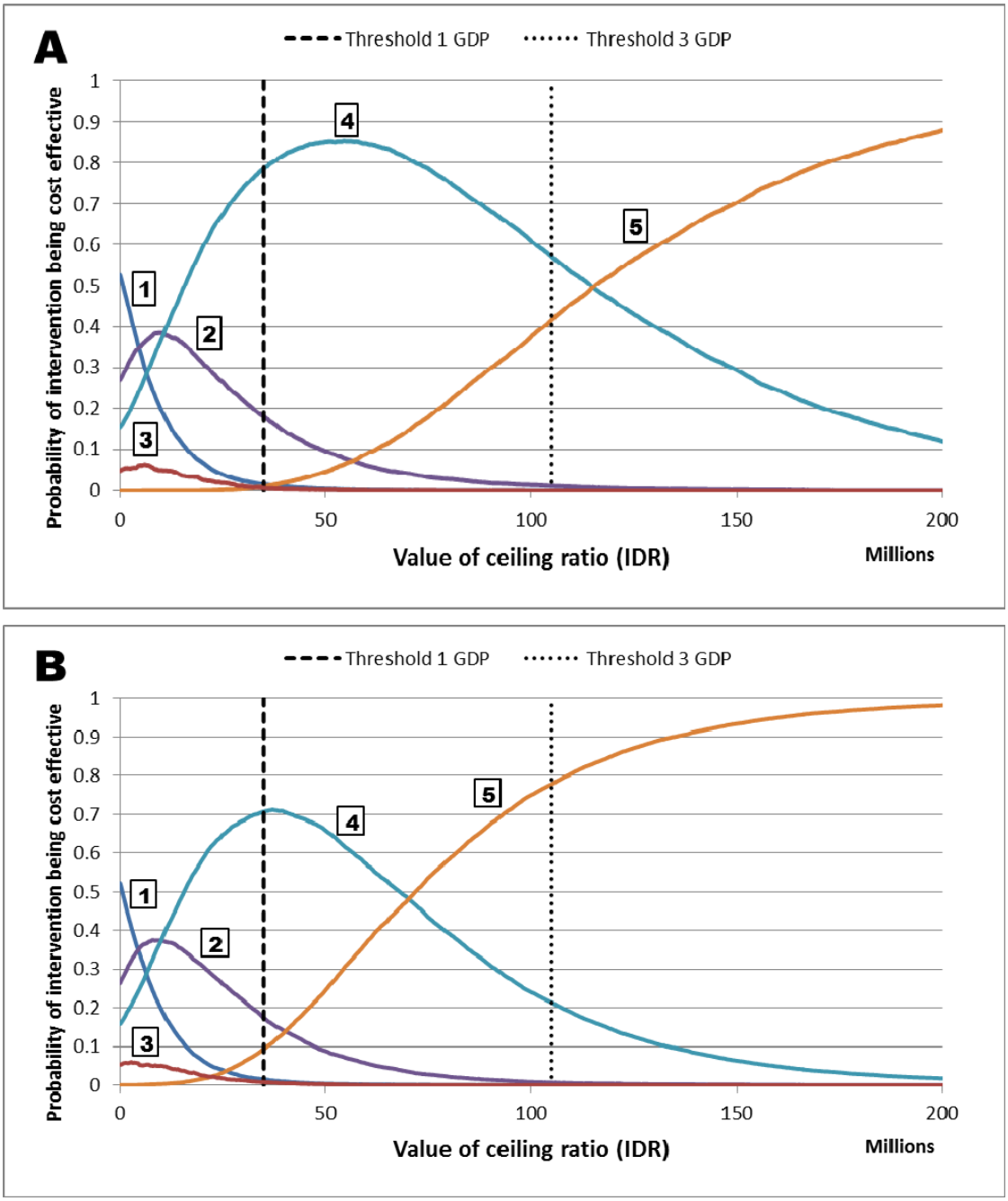
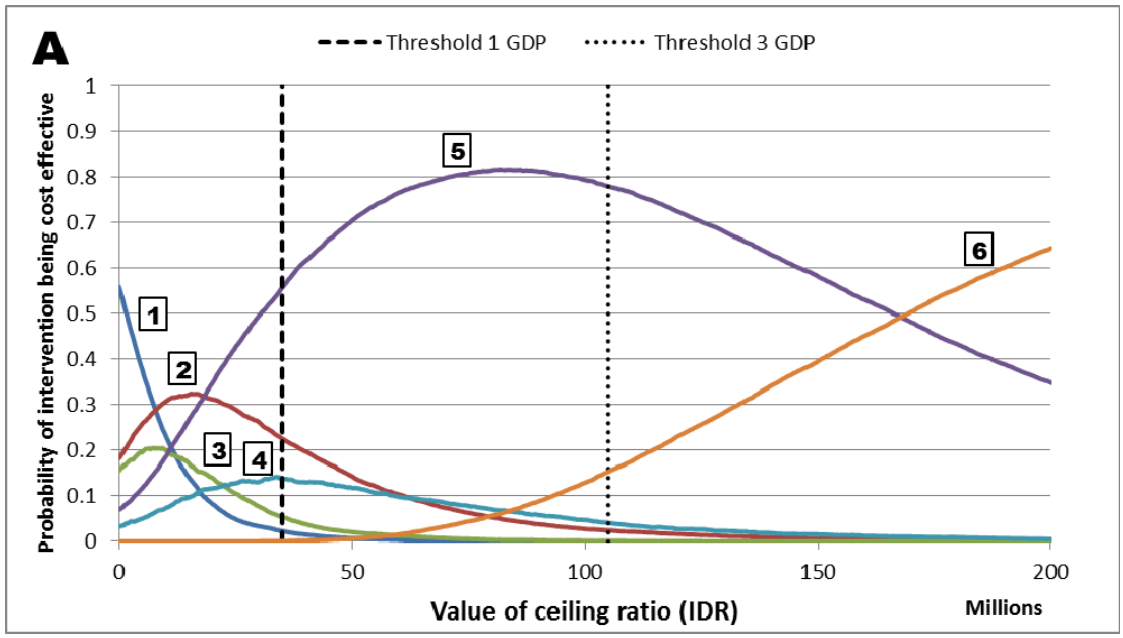
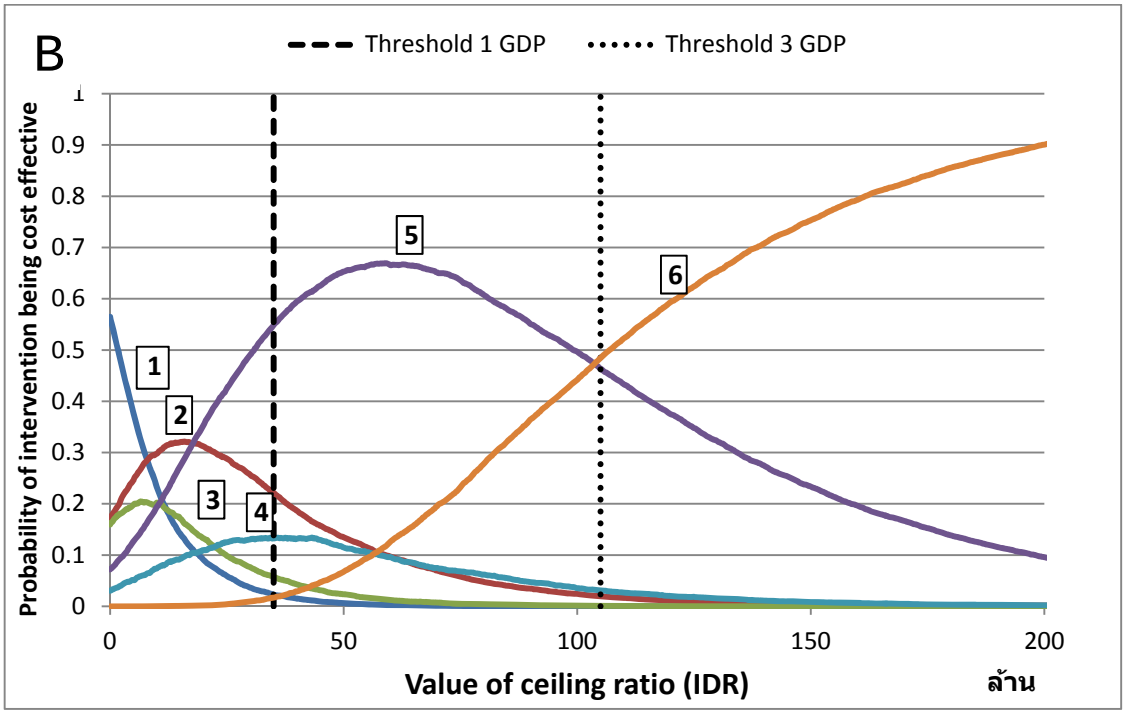


Figure 4.24 Cost effectiveness acceptability curve of best optimum strategies in scenario I; (A): given 3 doses of HPV vaccine per fully immunized girl and (B) given 2 doses of fully immunized girl

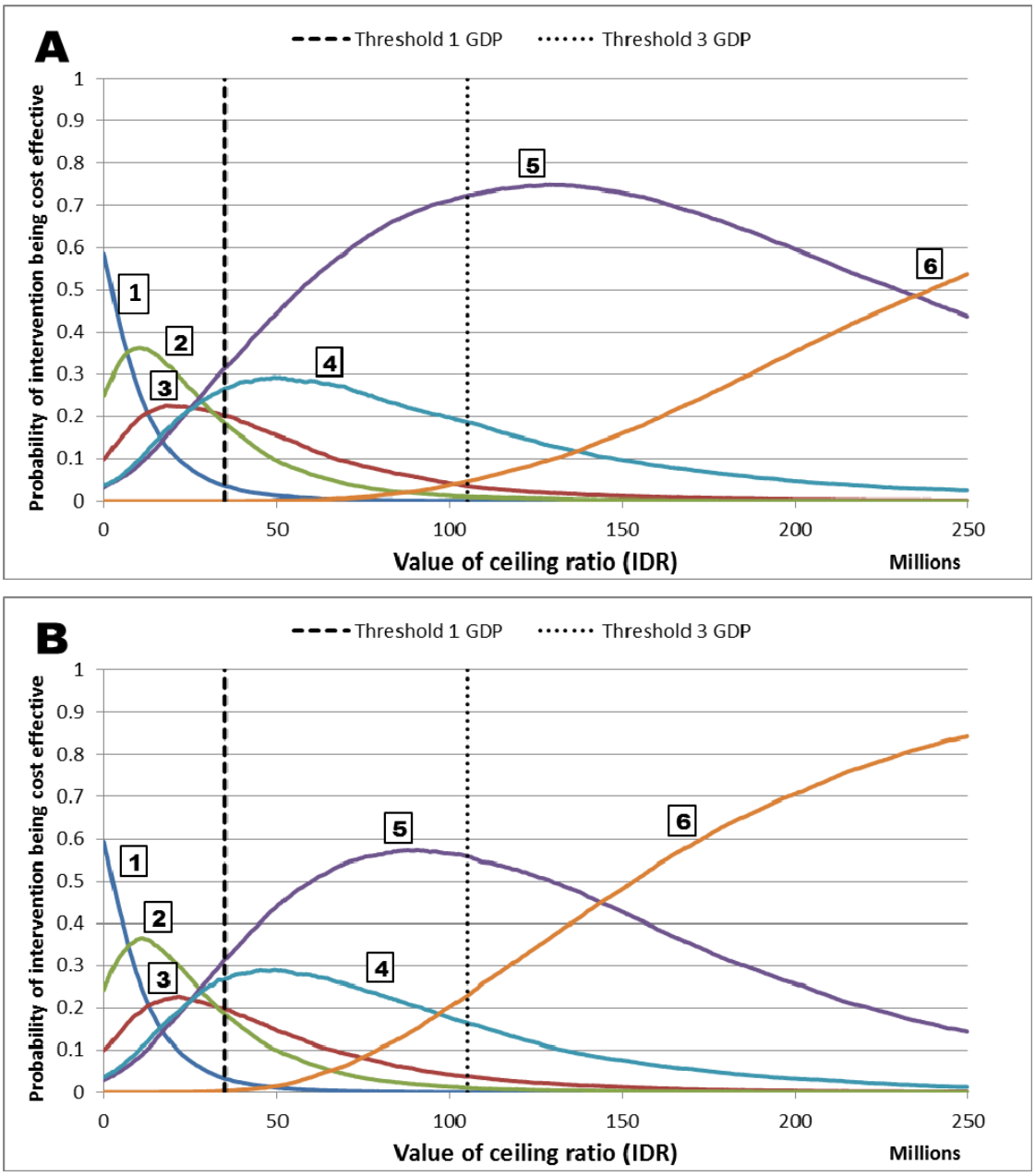




List of strategies:

1 = Do nothing	**4 = VIA q3Y (30-45) + Pap q5Y (50-65)**
2 = VIA q3Y (30-45)	**5 = VIA q3Y (30-45) + Pap q3Y (48-63)**
3 = VIA q5Y (30-45)	**6 = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**

Figure 4.25 Cost effectiveness acceptability curve of best optimum strategies in scenario II; (A): given 3 doses of HPV vaccine per fully immunized girl and (B) given 2 doses of fully immunized girl



List of strategies:

1 = Do nothing	**4 = VIA q3Y (30-45) + Pap q5Y (50-65)**
2 = VIA q3Y (30-45)	**5 = VIA q3Y (30-45) + Pap q3Y (48-63)**
3 = VIA q5Y (30-45)	**6 = Vac 12Y LT + VIA q3Y (30-45) + Pap q3Y (48-63)**

Figure 4.26 Cost effectiveness acceptability curve of best optimum strategies in scenario III; (A): given 3 doses of HPV vaccine per fully immunized girl and (B) given 2 doses of fully immunized girl

CHAPTER V
DISCUSSIONS

The discussion chapter consists of following part:

1. Methodological issue
2. Cost effectiveness result
3. Uncertainty analysis
4. Study limitation and strength

5.1 Methodological issue

This study performed economic analysis of strategies for cervical cancer prevention and control in Indonesia using different techniques of analysis, which are cost effectiveness analysis, cost benefit analysis, cost utility analysis, and budget impact analysis. The purpose of using these different techniques is to provide the economic evidence regarding strategies for cervical cancer prevention and control in Indonesia to the different stake holders who might have different interests. For instance, CEA provides value of money over life years saved which might be of interest of health care provider, CUA provides value of money over QALY that reflect people's preferences and thus can be used to assess allocative efficiency within the health care sector, CBA can address how a government budget should be distributed between different interventions and inter-sector, and lastly BIA provides an estimate of impact of new intervention on health care use and costs (65). The cost utility analysis was the main analysis performed in this study since it measures the health outcomes in term of QALY which is the preferred outcome measure in economic evaluation. Its advantage stems from the fact that it combines morbidity and mortality or health-related quality of life and length of life into a single metric. Hence, this

method allows for the comparison among broad healthcare interventions which effectiveness measurement using the same unit of QALY (60).

This study applied modeling based economic evaluation using Markov model. The initial and most important phase in building decision model is to explicitly define its structure (140). The model structure was constructed based on firmly established of natural history of cervical cancer disease and similar to many other previous studies in many settings such as US (82), Thailand (85), Singapore (141), Netherland (142), and Latin American countries (88). The transitional probability of health states in the model mostly used the data from other setting and few data in respect with country specific data of Indonesia. Therefore, a calibration process was required. Calibration is a necessary component of models that simulate an unobserved disease process because it helps to ensure the validity and credibility of inferences drawn from model predictions (143). Without any calibration, the model was not fit with the empirical data for Indonesia. After calibrating some value of transitional probabilities, the model validation analysis showed good comparison between model prediction and empirical data of age specific prevalence, age specific incidence, age specific mortality, and stage distribution of cervical cancer in Indonesia. Although the calibration process used trial and error searching, but the results provided satisfied goodness of fit from both visual graphics and percentage deviation of predicted output from empirical data. Moreover, the method also was used by many other published studies (143). Nevertheless, further investigation might be necessary to compare the results with other more scientific and sophisticated methods of calibration, such as the use of mathematical approach and application of computer program techniques (144). In addition, the model was calibrated and validated based on the empirical data that available to cover population age 0-74 years old, while the model was simulated until age 100 years. The model fitting from age 75-100 years was not considered; however the proportion of population aged >75 years was tiny as compared to the whole population.

The model analysis adopted an existing computer-based Excel integrated with Visual Basic Application (VBA) which was developed by other researcher and used to analyze the cost effectiveness of HPV vaccination and screening with VIA and Pap smear in Thailand (85). Few changes from original spreadsheets were made for

adjustment in accordance with the model construction and assumption used in this study. In addition, development from main spreadsheets for further analysis of sensitivity analysis and budget impact analysis were conducted.

The comparators in this study were selected from the available and practicable modalities of cervical cancer management in Indonesia. Two types of HPV vaccine, bivalent (Cervarix) and quadrivalent (Garsasil and Silgard) has been licensed in Indonesia (145). HPV vaccination is currently available for voluntary practice, while Pap smear tests are served for limited target population for instance those who covered by particular health insurance providing the test in benefit package. Screening with VIA for women aged 30 – 50 years old has been implemented as national pilot program since 2007; the program has reached the coverage rate about 24.4% of the total female population in the target age group in the catchment area (121). As for HPV DNA test, the method might be hampered with limited resources and costs that make the test not affordable for population screening. All interventions were compared to existing practice for management of cervical cancer which is treatment for invasive cervical cancer.

The coverage rate for vaccination was set on 80%, considering the approximate coverage rate of current national immunization program through school based immunization program (85%) (115) and school participation rate (95%) (116). Moreover, given the disparity of Indonesian population and geographical situation, it seems impossible to reach 100% coverage rate. For screenings, the coverage rates were set on 20%, considering coverage rate of screened women in the catchment area of national VIA pilot program in Indonesia (121); this is also the average of screening coverage rate in developing countries (122). A gradually increased screening coverage rate in 50% and 80% also were assigned to explore the model simulation if the situation was the same with developed country (122) or achieved the optimistic coverage rate given the situation in Indonesia.

In order to interpret the results of economic analysis, perspective of study is one of important factor to be considered. The study perspective is the viewpoints from which costs and consequences of an intervention are evaluated. Economic analysis could be conducted from many perspectives, including patient’s perspective, institutional perspective (hospital), health care payer’s perspective (health insurance

provider), healthcare system, and societal perspective (146). This study used two perspectives to conduct analysis, which were health system and societal perspective. Health care system perspective included direct medical cost of intervention and treatment for cervical cancer at tertiary hospital for main therapy and cost of seeking treatment related to the disease at other health facilities. Societal perspective also estimated broader costs to society including productivity losses of patient and care giver. The societal perspective represents the public interest rather than that of any particular group. Hence, this is the most appropriate perspective to use when economic analysis was conducted with the intention of assist to guide public policy decision making for healthcare resource allocation (110).

It is recommended to apply discounting in economic evaluation model, which indicates that costs and outcomes occurring at different points in time are valued differently. Discount rate is a simple exponential model to represent this time preference in standard model of economic evaluation of health intervention (147). It allows adjustment for time preference of cost and outcome of decision by providing present values. Discount rate is not universal; it is varied according to the setting, location, and perspective of the analysis (146). Given no country-specific data of discount rates, this study employed an annual rate of 3% for both costs and outcomes as used in WHO-CHOICE project (148).

The reported ICER has limited value to decision makers without a reference to value it. Therefore, ICER/cost effectiveness threshold is set a reference to value whether such healthcare intervention is affordable and acceptable to be performed in particular setting (60). There is no single threshold exists for deciding the acceptance of cost effectiveness ratio; a variety of considerations would dictate the type of thresholds that might be affordable for a particular setting/country (111). There are three methods for estimating cost effectiveness thresholds as follows: human capital approach which is established based around the average income of individuals within the society; preference approach which is established by state (national threshold) or by revealed preferences of individuals within the society for the outcome of interest (for example willingness to pay per QALY); and league table approach which is based on the cost effectiveness ratio of the last intervention (149). In the absence of specific cost effectiveness threshold set for economic evaluation study in

Indonesia setting, the use of GDP as threshold following recommendation of WHO Commission on Macroeconomics and Health (150) is applied in this study. This Commission suggested that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country or region. The commission justified this threshold on the basis of expected direct and indirect benefits to national economics; the recommendation also targeted for low-income countries. However, it is controversial as this approach may unrealistic in assuming that a country is willing to allocate its whole GDP to healthcare (151). Regardless, the cost effectiveness thresholds of GDP per capita were used in all economic evaluation studies in Indonesia (152-157). This study adopted these thresholds and assumed that what society's willingness to pay (WTP) for one DALY is equivalent to its WTP for one QALY.

Alongside to disease natural progression or health state transitional probabilities, cost effectiveness model of cervical cancer requires information of many other input parameters, including effectiveness of interventions, cost/resource use, and health state/utility data. The evidence base informing economic evaluation model is rarely derived from a single source, but most likely using combine available data to inform the estimation of model parameters (140). Good-quality RCT evidence is the preferred data source for estimating clinical effects of interventions. Whereas, cost and utility outcome data are country specific, which in many cases it is almost impossible to find the specific RCT evidence on these parameters. Hence, data on cost and utility were usually obtained from observational studies (140). The best study design for quantifying cost includes prospective data collection within a long-term naturalistic trial setting. If it is not available, the other sources are retrospective analysis of existing data sets, administrative data bases, routine data from hospital records, and the broader literature. QALY profile is calculated by converting utility values at each time point of assessment. Utility values are derived from preference-based measures or non-preference-based measures of health-related quality of life using mapping approach (140,146).

In this study, effectiveness of HPV vaccination and screening with VIA/Pap smear were adopted from meta-analysis studies of randomized control trial (RCT). Meanwhile, direct medical costs were estimated based on standard treatment of cervical cancer and related disease management, which was differed for each severity and stage by the treatment type and protocol. The unit costs of each treatment type were referred to INA-DRG tariff. Diagnosis Related Group (DRG) is an alternative for estimating costs in economic evaluation study in the absence of detailed cost of illness study, as has been used in US and some European countries. The rationale to use DRG for estimating cost in economic evaluation is that DRG costs are disease-specific that includes various components of health care costs, DRG approximates the economic cost of care and may represent opportunity costs which is preferred in economic evaluation study (158,159). As for the health outcome measure, this study used EQ-5D questionnaire, the most widely used instrument to measure utility as the health outcomes (140). Again, cost and utility data are specific settings that cannot be easily compared. Cost of vaccination was driven by vaccine price and programmatic cost. Vaccine price varied across countries. Programmatic costs of vaccination in Indonesia as estimated using WHO-C4P tool were comparable with other countries (93,94,160). To the best of our knowledge, there have been no previous studies specific to neither cost per episode of cervical cancer treatment nor cost of life time follow-up of cervical cancer. One study has been conducted to summarize unit cost of cervical cancer treatment by type of treatment. The study used cost at charges and concluded that the unit costs of cervical cancer treatment by type were higher compared to INA-DRG tariffs, indicating inefficiency in treatment of cervical cancer (99). As for utility data, no study was found to evaluate the utility of cervical cancer patients in Indonesia.

5.2 Cost effectiveness result

The model can predict the effect of healthcare interventions for cervical cancer prevention and control on epidemiological burden of cervical cancer disease. Performing vaccination to adolescent girls at age 12 years old significantly prevented the risk of HPV infection in entire lifetime and consequently reduced the incidence of

cervical cancer. Performing screening can detect un-symptomatic cervical cancer resulted higher incidence of cervical cancer in younger women but lower incidence cervical cancer in elder women. The reduction of cervical cancer incidence is correspondence to the screening coverage rates. These findings are obviously the same with other previous studies assigning the effect of healthcare interventions on cervical cancer disease. The model can also examine the health outcomes effect and costs related to the implementation of that healthcare intervention, therefore allows the analysis of economic evidence to provide the healthcare interventions of cervical cancer prevention and control.

Considering the cost effectiveness threshold of 1 and 3 times GDP of Indonesia in 2013, all screening strategies assigned in this study were considered as very cost effective, whereas almost all strategies involving vaccination were considered as cost effective. Screening with VIA every 5 years for women aged 30 – 45 was the most cost effective strategy among all strategies with incremental cost effectiveness ratio of IDR -204,000 per QALY (equal to USD -19.77 per QALY), in a societal perspective, resulted from an incremental QALY gained of 0.0044 and a minuscule incremental cost saving of IDR 2,000 as compared to do nothing. This strategy is the same strategy that currently is implemented as national pilot program in Indonesia; therefore this finding support for continuity of the pilot program with economic evidence. As for vaccination, the incremental cost effectiveness ratio for providing HPV vaccination as single intervention revealed from this study were IDR 77.6 million per QALY and IDR 46.3 million per QALY for 3 and 2 doses assumptions, respectively, in a societal perspective. These values were equal to USD 7,522 per QALY and USD 4,490 per QALY for 3 and 2 doses assumptions, respectively. In a health system's perspective, ICER of VIA every 5 years was IDR 634,000 per QALY (equal to USD 61.45 per QALY), while ICER for vaccinations were IDR 77.8 million per QALY (equal to USD 7,541 per QALY) and IDR 48.4 million per QALY (equal to USD 4,689 per QALY) for 3 and 2 vaccine dose strategies, respectively.

Results of analyses using different techniques of economic evaluation, CEA and CBA, were in line with the conclusion of the most cost effective strategy of cervical cancer prevention and control in Indonesia from CUA. ICER per LY of VIA

every 5 years was the lowest which the value of IDR 912,000 (USD 88.39) per LY saved, in a health system's perspective. In addition, benefit to cost ratio of strategy with VIA every 5 years was 16, the highest among all strategies, in a societal perspective. This study also provides information for policy makers regarding the budget for implement such interventions for cervical cancer prevention and control. The information is expected to give insight for policy makers to assign the affordability of government for providing the interventions.

There are three previous published economic evaluation studies that included Indonesia setting in the analysis of the effect of HPV vaccination and cervical cancer screening towards cervical cancer related disease (90,127,128). Goldie et al (127) conducted economic analysis of HPV vaccination in 72 countries including Indonesia. Using the companion population-based model that simplifies and not fully simulate the natural history of HPV infection and cervical cancer, with the assumption 70% vaccination coverage and 3 doses per fully immunized girl, the ICERs for providing HPV vaccination were I$90, I$360, and I$810 per DALY averted for vaccine price of I$10, I$25, and I$50 per vaccinated girl, respectively. Ginsberg et al (128) conducted global economic evaluation of HPV vaccination, screening with VIA, Pap smear and HPV DNA test in 14 WHO regions. The study used standardized WHO-CHOICE methodology and population state-transition model. The study found that all screening and vaccination program were mostly cost effective or very cost effective. Jit et al (90) conducted economic evaluation of HPV vaccination in 179 countries. The study applied Excel-based modeling study called PRIME (Papillomavirus Rapid Interface for Modelling and Economics). Assuming 100% coverage rate and 3 vaccine doses with cost of I$25, the ICER of providing HPV vaccination in Indonesia setting was I$929 per DALY prevented which was considered as very cost effective. Finding from this study is in line with those of previous studies for interventions with screening which mostly were very cost effective. However, result of intervention involving vaccination in this study is inferior to those of previous studies. This study found that HPV vaccination was cost effective. This could be due this study used the greatly higher price for vaccination as compared to that of those studies; however the price was reflected the market price in Indonesia.

Health economic studies must be interpreted within the appropriate geopolitical context, for instance by comparing the cost effectiveness ratios of the studies with those from previous studies of other interventions that were considered at clinical and policy levels (111). Several economic evaluation study regarding healthcare interventions in Indonesia had been conducted and published previously (152-157). All studies involved economic evaluation of vaccination programs. The study assigned the following healthcare interventions: Haemophilus influenza type B (Hib) vaccination (152,153), Japanese encephalitis (JE) immunization (154), rotavirus vaccination (155,156), and hepatitis A vaccination (157). The summary results are as follows: ICERs for Hib vaccinations were USD 67 per DALY averted in 2005 value or USD 114 in 2013 value (152) and USD 74 – 102 per DALY averted in 2007 value or USD 104 – 144 in 2013 value (153); ICER for JE immunization was USD 31 per DALY averted in 2001 value or USD 74 in 2013 value (154); ICER for rotavirus vaccinations were USD 120.46 per DALY averted in 2007 value or USD 170 in 2013 value (155) and USD 174 per QALY in 2011 value or USD 194 in 2013 value (156); ICER for hepatitis A was USD 4,933 and USD 7,421 per QALY in 2012 value for 1 and 2 doses, respectively, or USD 5,247 and USD 7,893 per QALY in 2013 value for 1 and 2 doses, respectively (157). The ICERs of providing HPV vaccination in Indonesia are greatly higher as compared to those of Hib, JE, and rotavirus. This could be caused by the greatly higher of HPV vaccine costs compared to other vaccines, which were USD 106.6 and USD 159.9 per immunized girl for 2 and 3 doses, respectively. Whereas, costs of vaccinations of Hib were USD 11.3 (152) and USD 4.7 – 5.3 per immunized child (153); costs of JE vaccination was USD 10.7 per immunized child (154); and costs of rotavirus vaccinations were USD 3.8 (155) and USD 17.3 (156). However the ICERs of HPV vaccinations are comparable to ICERs for providing hepatitis A vaccination with the substantially lower costs of hepatitis A, which were USD 3.4 and USD 6.8 per immunized child for 1 and 2 doses, respectively (157).

Generalizability of the results of this study should be made with some considerations. Given the disparity of population and such geographical situation, universal cervical cancer screening and HPV vaccination might not be easy to be implemented in the whole country of Indonesia as were assumed in this study. Further

feasibility study of such interventions for cervical cancer prevention and control should be demonstrated for prioritizing the pilot program initiation, for instance based on epidemiological, health systems, and socioeconomic factors. More information such as region-specific of cervical cancer epidemiology data, role of central and local government in the health care program related to cervical cancer prevention and control, availability of supporting facilities and resources, and other socioeconomics factors of Indonesian population living in different areas are necessary to be explored for synthesizing such recommendations for program implementation (161-163). Despite of that, screening with VIA has been introduced as pilot project for cervical cancer prevention and control in Indonesia. The project was started by Ministry of Health of Indonesia in 2007 with the main activities in development and dissemination of policy, service delivery, and training guidelines on cervical cancer screening and treatment that applicable nationwide. It was reported that by December 2011, the project has been implemented in 14 of 33 provinces across Indonesia. The acceptance rate in the selected sample area was 24.4% (121). It seems that strategy of VIA is a feasible strategy to be implemented as a universal organized program for cervical cancer prevention and control in Indonesia in the near future. As for Pap smear strategy, it might have obstacles for universal implementation such as inequity of program accessibility throughout the whole country (164). In addition for HPV vaccination, the strategy might mainly face with the affordability issue given the high price of vaccine and huge of target population.

5.3 Uncertainty analysis

In one way sensitivity analysis, it shows that the cost effectiveness results represented by ICER per QALY were insensitive to changes in the most input parameters. The most sensitive parameter was discount rate as was also found in many other studies (85,127,165-167). The magnitude of ICER due to different discount rate applied did not lead the conclusion to be “not cost effective”, yet it decreased the ICER value. Cost of vaccination is another input parameter that could lead the change of result conclusion. This is also similar with other studies (127,128,168). However, the vaccination cost in the sensitivity analysis was set in very wide range from the

base case of market price of single purchasing dose of vaccine. Normally, the vaccine price will be lower as compared to market price when purchasing made by public sector or in huge volume. The change of ICER value due to other input parameters did not change the conclusion of cost effectiveness result.

Two-way sensitivity analyses give information regarding the minimum of screening performance should be have for resulting the cost effective of interventions with VIA and Pap smear screening. The analysis showed relatively flexible combination of sensitivity and specificity value for resulting cost effective result. The values seem could be perform in Indonesia's practice; as reported performance screening in several hospital in Indonesia may approximate the values (124,125).

Threshold analysis gave information of vaccine price ceiling in which vaccination program would be very cost effective. The result may useful for price negotiation with vaccine producer when HPV vaccination would be considered to be included in NIP. The analyses reveal that vaccine price per dose for intervention to be very cost effective should be reduced to below IDR 300,000 (USD 29) for 3 doses of vaccination and IDR 450,000 (USD 44) for 2 doses of vaccination. The prices are not impossible to be approved considering the successful of GAVI negotiation with pharmaceutical industries to reduce the vaccine price to be USD 13 for the lowest public price and USD 4.5 for GAVI-eligible countries (169).

This study also conducted and presented probabilistic sensitivity analysis, which made it possible to explore in depth the uncertainty surrounding the input parameters and consequently the economic evidence that can be revealed from the analysis. At the lower ceiling ratio less than 1 GDP, strategy with VIA every 3 years was the favorable option. At the ceiling ratio of either 1 or 3 times GDP, combination of VIA every 3 years and sequential Pap smear every 3 years was the most favorable strategy. Vaccination would be the favorable strategy only if 2 doses was applied and compared with screening strategy at lower coverage rate (20% and 50%). When the screening coverage achieved the optimum rate (80%), combination of VIA and Pap smear would always lead to be the most favorable strategy.

5.4 Study limitation and strength

Economic evaluations in lower middle-income countries (LMICs) typically encounter different challenges from those in high-income countries (HICs). For example, economic evaluations in LMICs often face data availability and data quality problems (65). This study is not far from those difficulties. Several issues that limit this study are as follows:

First, the model was calibrated to empirical data of HPV infection prevalence, stage distribution of cancer, cervical cancer incidence, and cervical cancer mortality. The data of age-specific prevalence of HPV infection was obtained from population-based study in 3 regions of Indonesia The stage-specific of cancer distribution was obtained from hospital-based registry data. These two empirical data could represent country specific data of Indonesia. In contrast, the empirical data of cervical cancer incidence and mortality were obtained from GLOBOCAN report. The data based on estimation not purely from observational data in Indonesia. This might mislead the model prediction for representing the real epidemiology of cervical cancer disease in Indonesia.

Second, the analysis used cohort and static model that do not consider the beneficial effects such as herd protection, cross protection of other HPV type, and prevention of other genital wart in vaccination intervention. The method of choice to investigate that effect is through application of dynamic model; however it is more difficult to conducted as it is more complex and needs data such as transmission rate of disease that might not available. The study applying static model tends to under estimate the benefit of intervention thus resulting higher ICER as compared to dynamic model.

Third, despite the evidence of duration of protection of HPV vaccine towards HPV infection that is still obscure; this study took assumption of lifetime protective effect of vaccine. Hence, this study overestimates the result of cost effectiveness ratio if the assumption is not valid or consequently the strategy may less favorable. In contrast for strategies involving combination of vaccination and screening, this study might under estimate the effect of combination of vaccination and screening. For instance, this study used assumption of targeted age of strategy with screening following vaccination which was the same as targeted age of strategy

with screening without prior vaccination in the same target population (starting age of 30 years old). Although there has been no clear recommendation, the addition of HPV vaccination as a strategy for cervical cancer prevention and control program might be potential to lead to the modification of current screening strategy using VIA/Pap smear methods for which delaying the starting age of screening and reducing the frequency or prolonging the interval of screening (170).

Fourth, the use of GDP value as cost effectiveness threshold beyond the lack of alternative thresholds in Indonesia might come with caution for interpretation. The original purpose of the use of GDP thresholds in WHO-CHOICE were to evaluate a variety of health intervention at a sub-regional level and classify them into broad categories to help assist decision makers. GDP threshold is applied in WHO-CHOICE study as a normative cut-off point of what could be internationally be considered as being cost effective for instance in sector wide approach cost effectiveness study comparing country, but it is not intended to use it at country level. In other words, cost effectiveness results in this study which being considered as cost effective and very cost effective strategies under the GDP threshold might not be affordable for Indonesia setting given the budgetary constraints and the results also might not sufficient to lead to funding of the strategies implementation. Other criteria for understanding cost effectiveness results that relate to the budget available for allocation should be considered by the decision maker (149).

An important strength of this study is that the estimation of several input parameters for country specific data of Indonesia was obtained from primary data such as direct non-medical cost, indirect cost, and utility related to cervical cancer. This study is also more advantageous in included societal cost that missed-counted in the previous studies.

CHAPTER VI
CONCLUSIONS

This chapter concludes overall results of the study that could be summarized into parts as follows:

1. Additional value of study
2. Recommendation for policy decision
3. Recommendation for future studies

6.1 Additional value of study

This study provides the model for Indonesia setting to predict the impact of healthcare interventions such as HPV vaccination, screening with VIA, screening with Pap smear, and multi-types of combinations among those interventions. When analyzed, the model can produce the output of epidemiological characteristics of cervical cancer disease including prevalence of HPV infection, incidence of cervical cancer disease, and mortality rate related to cervical cancer disease. Besides, the model also can examine the health outcomes impact as results of implementation of those healthcare interventions in terms of life years gained and quality adjusted life years when certain sets of parameter inputted in the model. Moreover, by applying the cost data for performing healthcare intervention as well as cost of illness of cervical cancer related diseases, the model then can reveal the cost effectiveness ratio in respect to costs for providing intervention as compared to the consequence of certain health outcome gained. This economic evidence has beneficial in guiding policy maker to decide the healthcare interventions for cervical cancer prevention and control in Indonesia.

This study reveals the economic evidence of some strategies for cervical cancer prevention and control in Indonesia. The study concludes that strategy of

providing screening with VIA every 5 years to women aged 30 – 45 years old is the most cost effective strategy without ignoring other strategies which also were considered as very cost effective and cost effective intervention as compared to current cervical management of treatment only. The ICER for this strategy is IDR -204,000 per QALY (USD -19.77 per QALY), resulted from an incremental QALY gained of 0.0044 and incremental cost saving of IDR 2,000 as compared to doing nothing, in a societal perspective, and IDR 634,000 per QALY (USD 61.45 per QALY), in a health system's perspective. Strategies involving vaccinations are also promising since they result better health outcomes, but face greater incremental cost due to the high of current vaccine market price. The ICERs of providing vaccination program are IDR 77.6 million per QALY (USD 7,522 per QALY) and IDR 46.3 million per QALY (USD 4,490 per QALY) for 3 and 2 vaccine doses, respectively, in a societal perspective. Meanwhile, in a health system's perspective, ICER for vaccinations were IDR 77.8 million per QALY (USD 7,541 per QALY) and IDR 48.4 million per QALY (USD 4,689 per QALY) for 3 and 2 vaccine dose strategies, respectively. Scaling up the coverage rate of screening leads to gain better health outcomes which comparable to that of vaccination. Combining strategy of vaccination and followed by VIA and sequential Pap smear at suitable targeted age is the best option when the higher ceiling of cost effectiveness threshold is allowed.

The cost effectiveness results are presented as incremental cost effectiveness ratio with respect to additional cost to gain one quality adjusted life year (QALY), this allows for comparison with other healthcare interventions in broad sectors. This study also accompany previous studies whose presentation of cost effectiveness ratios in ICER per DALY with new presentation form of cost effectiveness ratio in term of ICER per QALY. Compared to DALY, QALY offer more favor to be used as health outcome measure in economic evaluation due to efficiency and equity reasons (171,172).

6.2 Recommendation for policy decision

The economic evidences revealed from this study might be useful when considering the choice of healthcare intervention for cervical cancer prevention and

control in Indonesia. The most cost effective strategy is in line with the current strategy of national pilot program for providing VIA every 5 years to women aged 30 – 50 years old. The pilot program which recently has achieved about 20% coverage rate among women in the catchment area of pilot program areas should be continued and expanded to whole country by gradually increasing the coverage rate.

When the budget is affordable, vaccination is a promising strategy to combat cervical cancer disease for its greater health outcome and probably higher acceptability among target population of 12 years old-school girls considering the successful of current EPI through school based immunization program as compared to screening for elderly women that might faces obstacles in program acceptability (121). However, with other considerations such as sustainability of funding and competition with other new vaccines including rotavirus, JE, hepatitis A, and PCV which probably more reasonable to be included in NIP; including HPV vaccination in national program for cervical cancer prevention may need further analysis in depth.

Furthermore, economic evidence is just one factor for consideration of healthcare decision. Other policy issues such as disease burden, other competing interventions, and public health priority should be made in consideration of evidence-based decision-making for healthcare program (65).

In general, it is still obscure about application of economic evidence from economic evaluation study on decision making of health care programs in Indonesia. There has been very few published economic evaluation studies involved Ministry of Health of Indonesia as decision maker of health care implementation. Nevertheless, 2 of the previous studies of economic evaluation involved the authors who affiliated with Ministry of Health of Indonesia (153,155)and Hib vaccination, one of the topic of those studies has been introduced in NIP in 2013. With the implementation of universal coverage starting in year 2014, the need of economic evidence in decision making of health care interventions is expected to gain.

6.3 Recommendation for further studies

This study still lacks of being good and complete study. Nevertheless, this study gives insights of additional knowledge regarding economic evaluation study in

general and modeling method in particular, moreover accompanies the study in the scope economic evaluation of cervical cancer related diseases and in specific setting of Indonesia country. Several further studies might be conducted based on the results of the study, as follows:

– Calibration of model using scientific and statistical method. Calibration should also be updated when there are new empirical epidemiological data available such as the country specific observational data of HPV infection prevalence, cervical cancer incidence and mortality.

– Costing study on cervical cancer related diseases using the method of longitudinal study to capture the real incidence cost of cervical cancer diseases.

– Study for valuation of EQ-5D health state to provide the EQ-5D value set which specific for Indonesia population. The value set will allow utility measurement more accurately for Indonesia population.

– Updating the model analysis when the new and more valid input parameters are available such as long term efficacy and safety of HPV vaccine, more valid costs and utility data, etc.

– Assigning the other healthcare interventions for cervical cancer prevention and control such as screening with HPV DNA test and prevention strategy using educational approach.

– In general, refinements of mathematical and economic models of healthcare interventions for cervical cancer prevention and control are necessary to better inform the healthcare decisions in the future.

– Feasibility study to assess the practicability of implementation of healthcare programs as recommended by this study results in specific area and the whole country of Indonesia setting.

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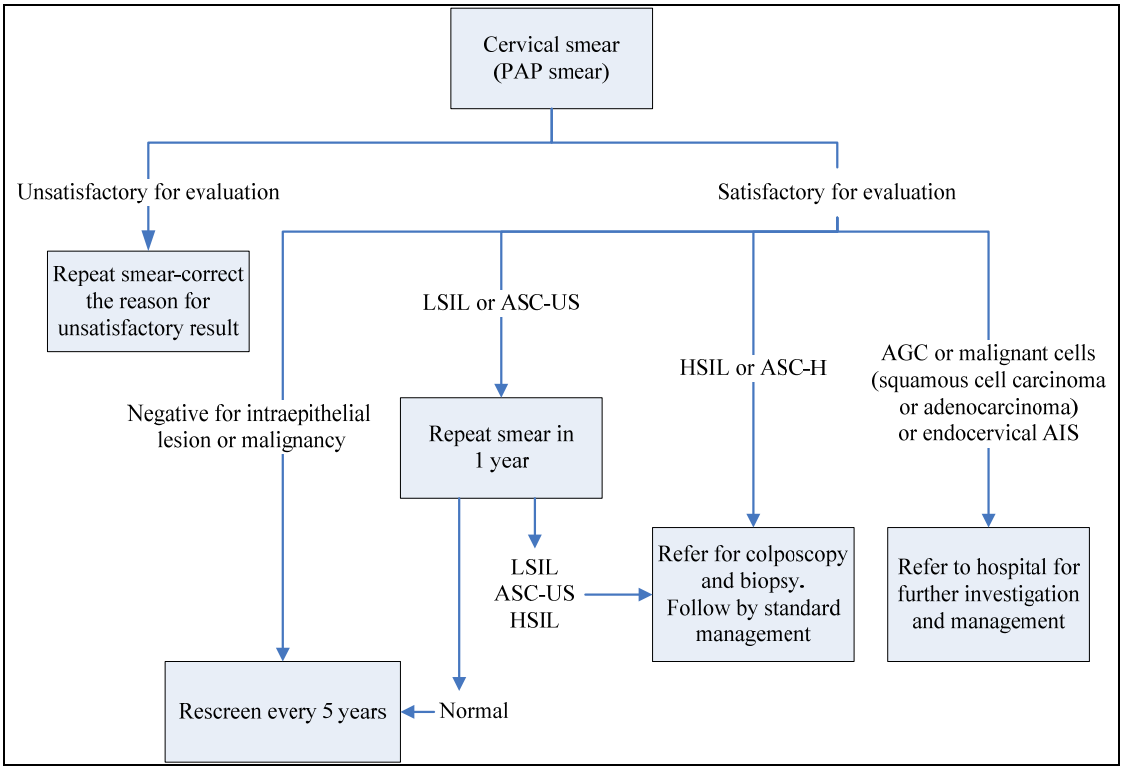
APPENDICES

APPENDIX A
GUIDELINES OF MANAGEMENT OF CERVICAL CANCER RELATED DISEASE

Flowchart for follow-up and management of patients according to pap smear as screening test



LSIL = low-grade squamous intraepithelial lesion

HSIL = high- grade squamous intraepithelial lesion

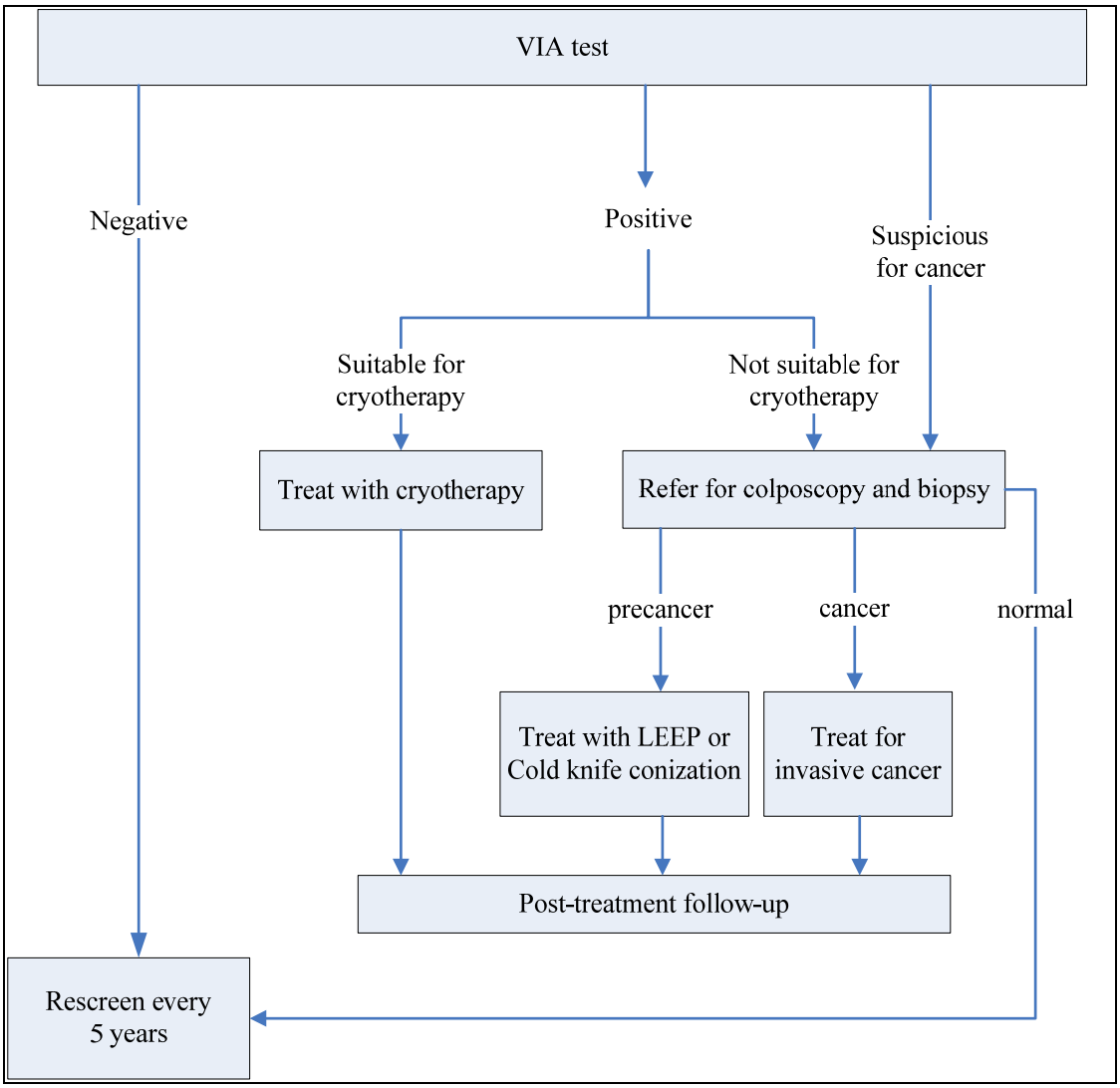
ASC-US = atypical squamous cells of undetermined significance

ASC-H = atypical squamous cells –cannot rule out HSIL

AGC = atypical glandular cells

AIS = adenocarcinoma in situ

Flowchart for follow-up and management of patients according to visual inspection with acetic acid as screening test



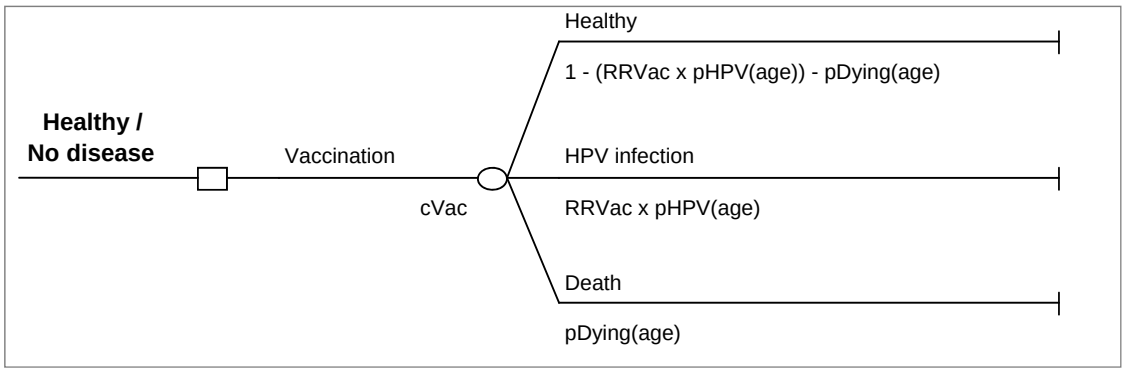
* Not suitable for Cryotherapy: lesion > 75% of cervical surface, extends onto vaginal wall or more than 2 mm beyond cryoprobe, or into the cervical canal beyond the probe tip. Pregnant women should also be referred.

APPENDIX B

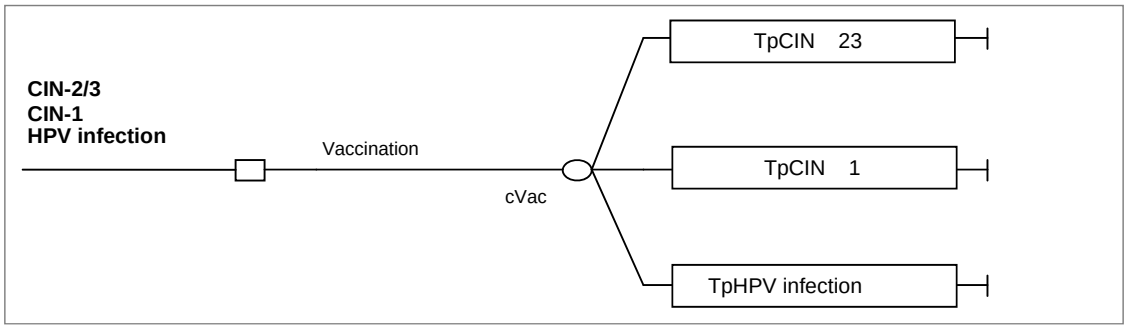
DECISION TREE USED TO EVALUATE EFFECTS OF INTERVENTIONS ON HEALTH STATES IN MARKOV MODEL

Decision tree used to evaluate effects of HPV vaccination on health states in Markov model (A - C) (Adopted from Praditsitthikorn, 201):

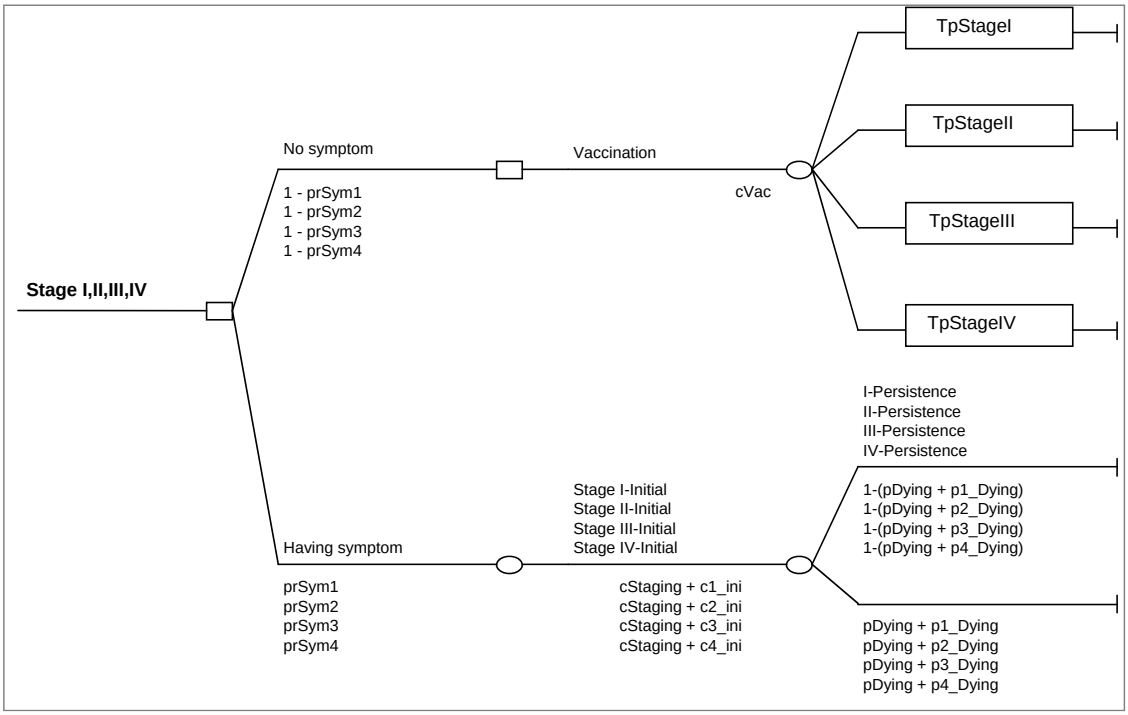
(A): effect of HPV vaccination on "Healthy"



(B): effect of HPV vaccination on "HPV infection" and "pre-invasive cervical cancer"

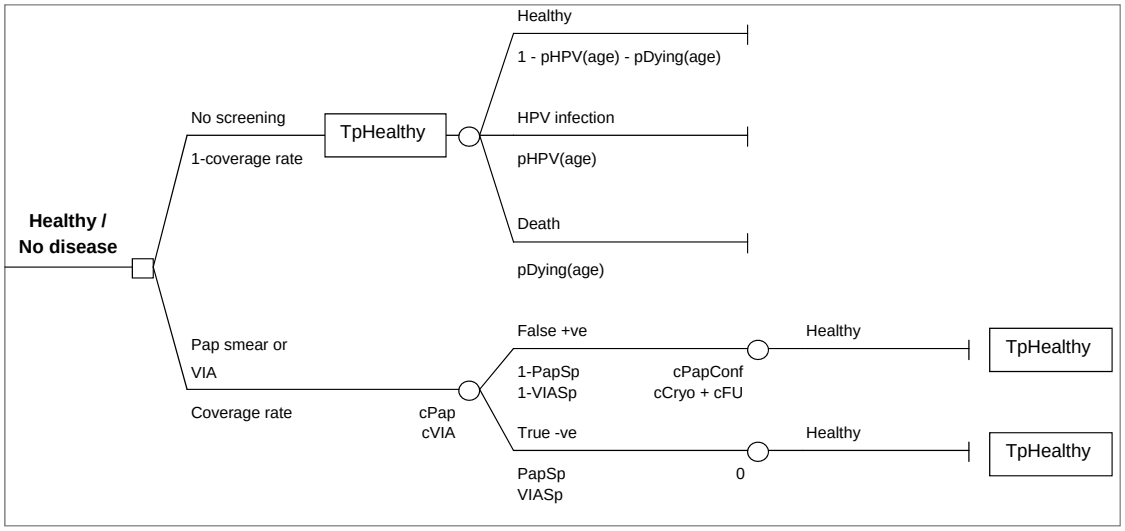


(C): effect of HPV vaccination on “invasive cervical cancer”

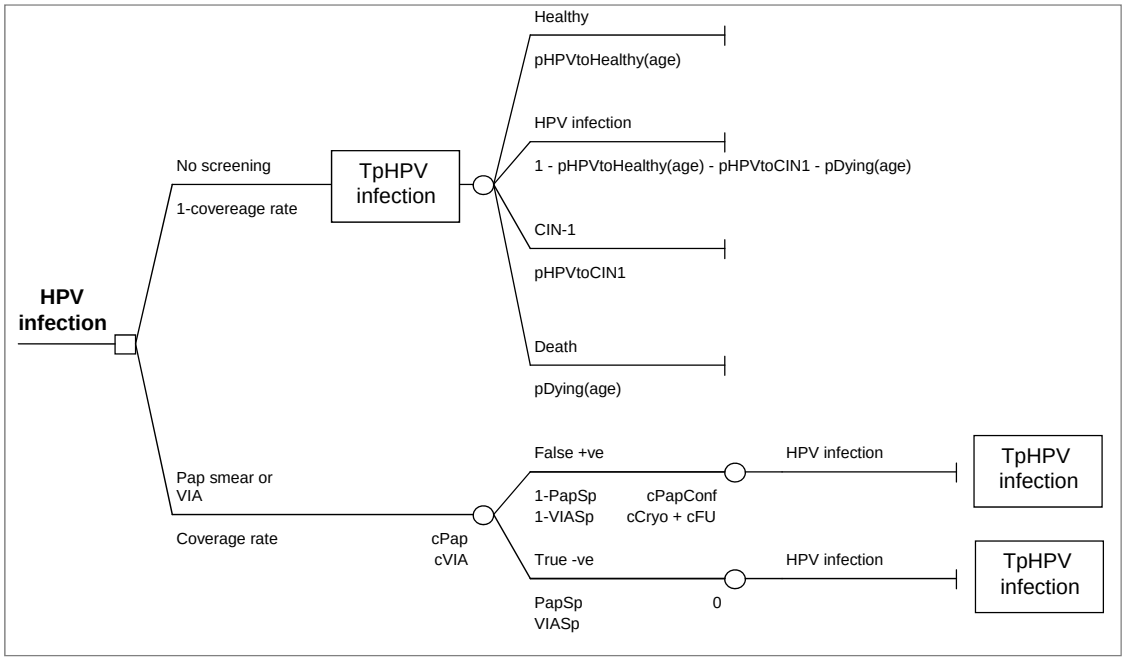


Decision tree used to evaluate effects of screening on health states in Markov model (A - J) (Adopted from Praditsitthikorn, 2010).

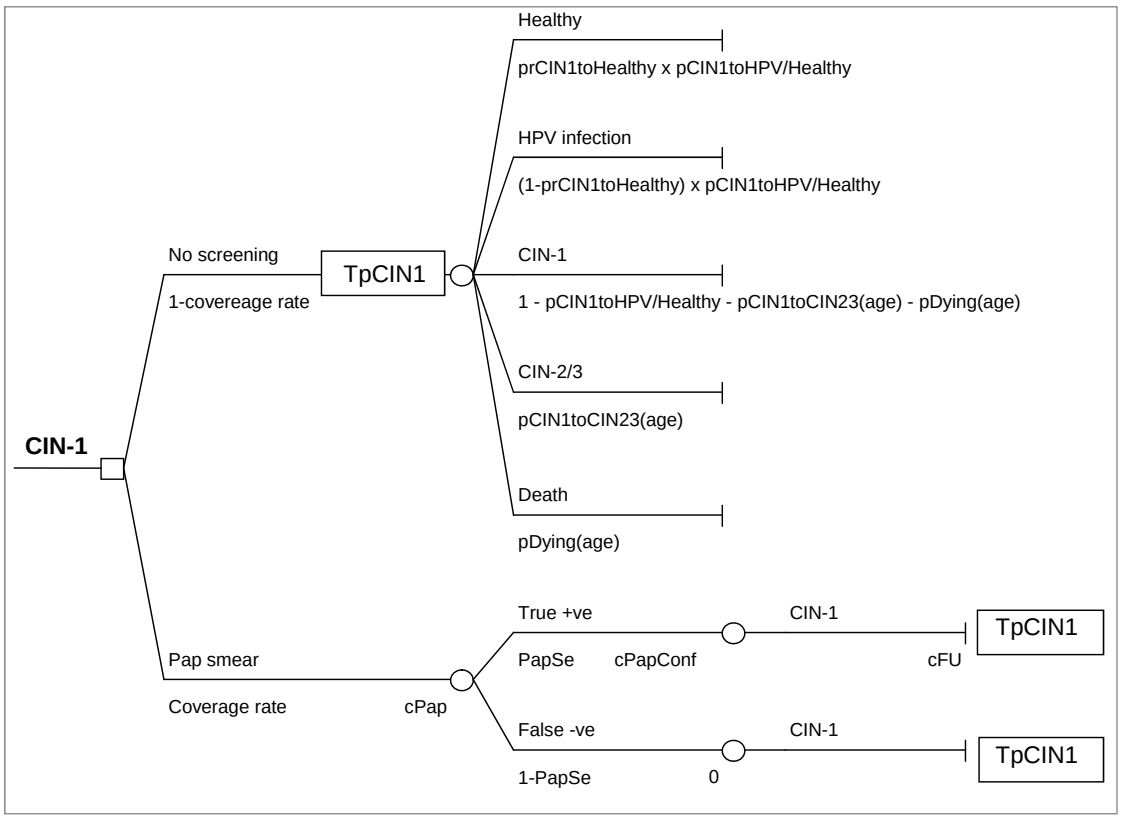
(A): effect of Pap smear and VIA on "Healthy"



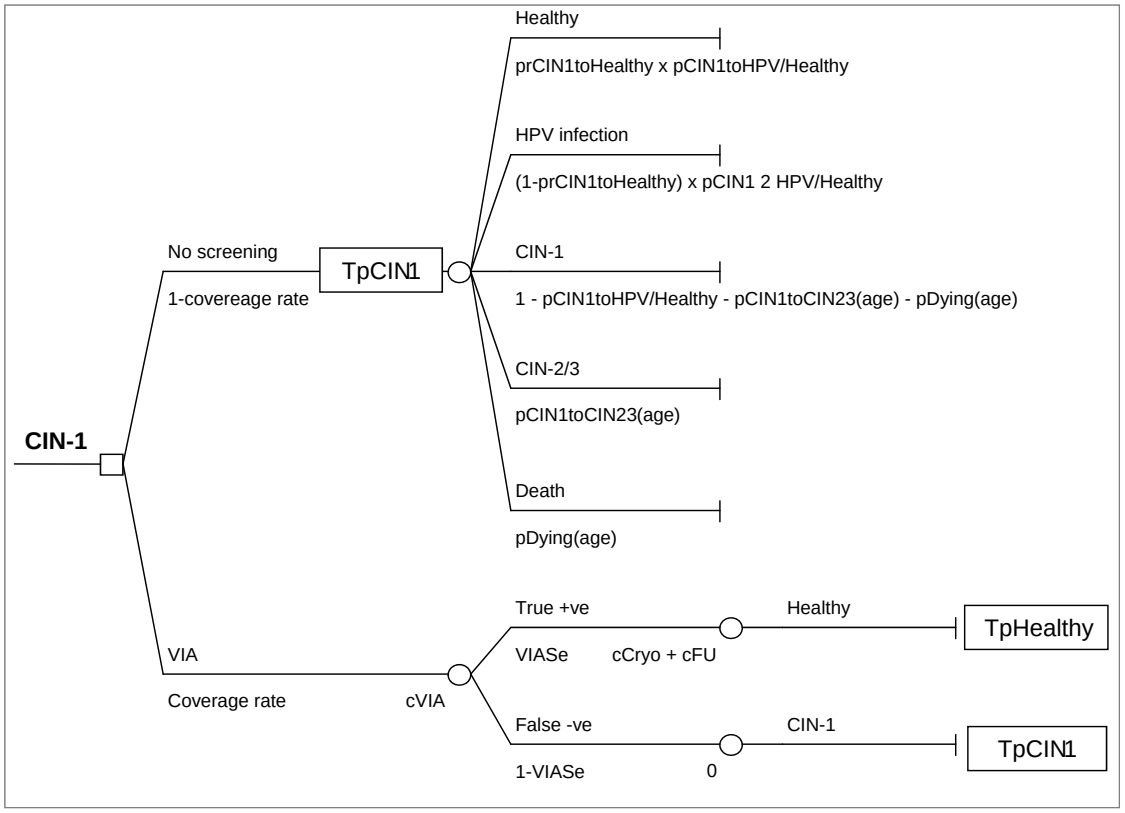
(B): effect of Pap smear and VIA on "HPV infection"



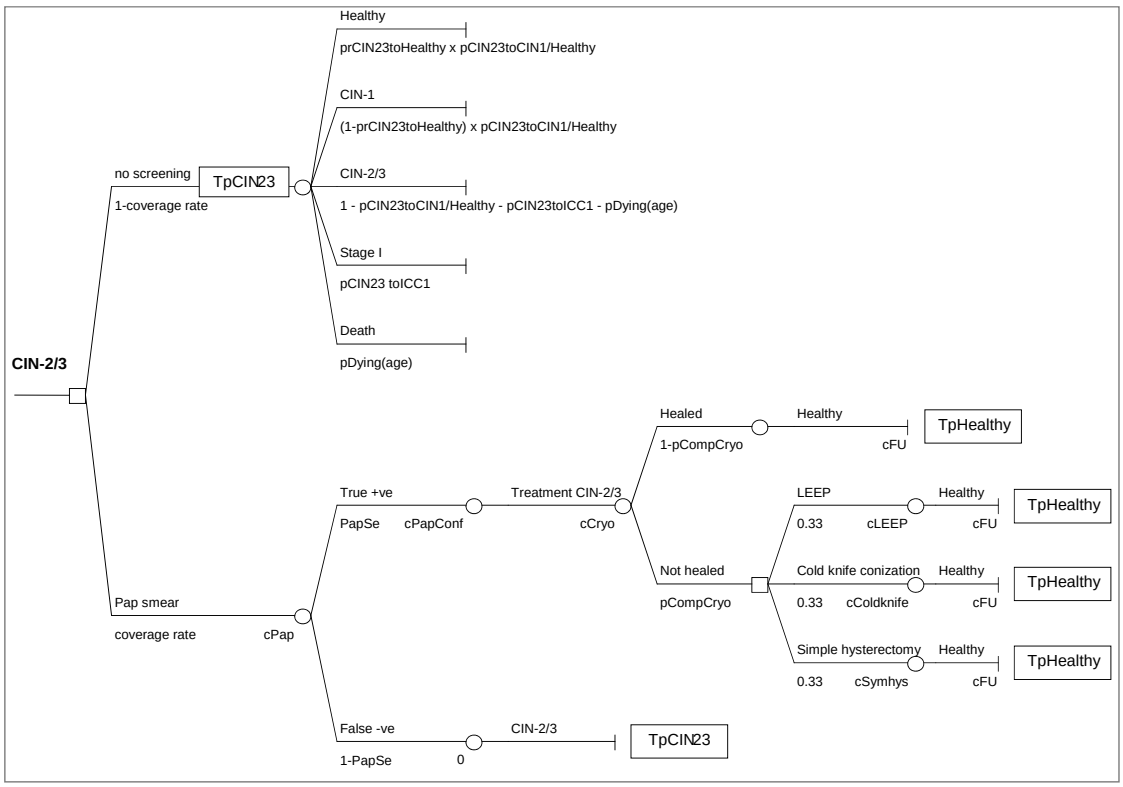
(C): effect of Pap smear on "CIN-1"



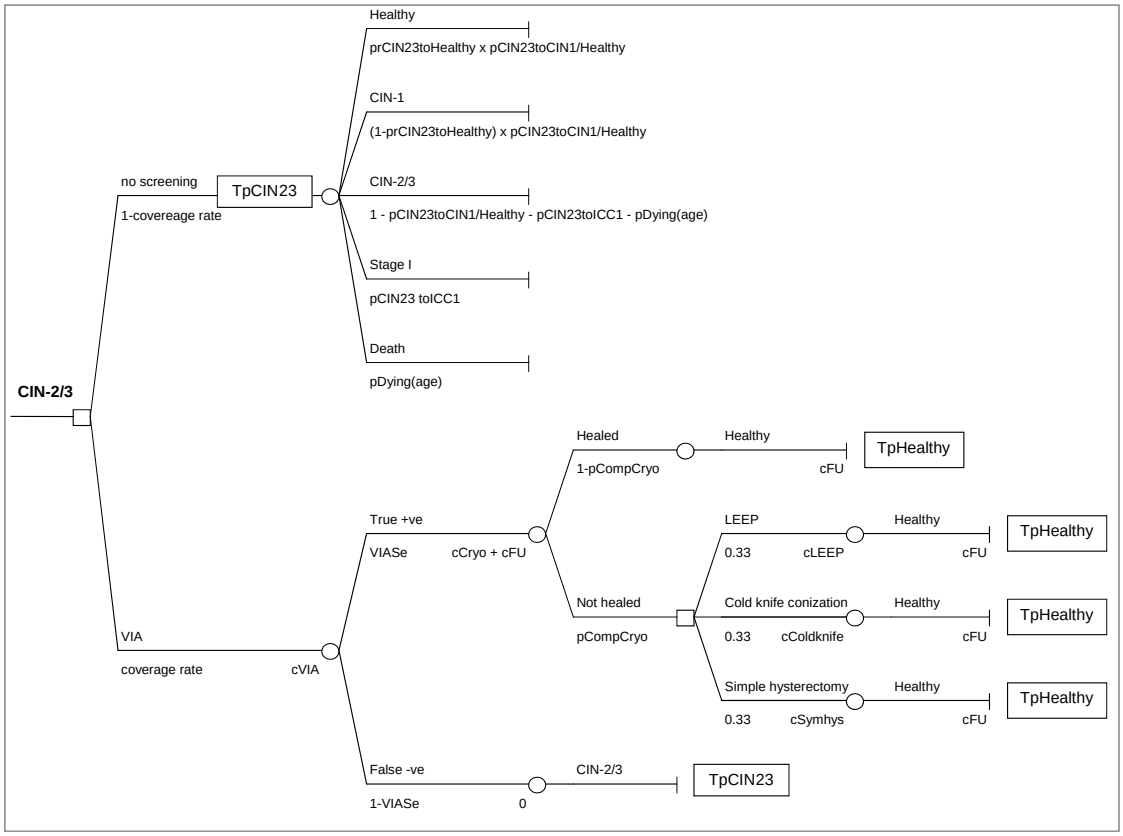
(D): effect of VIA on "CIN-1"



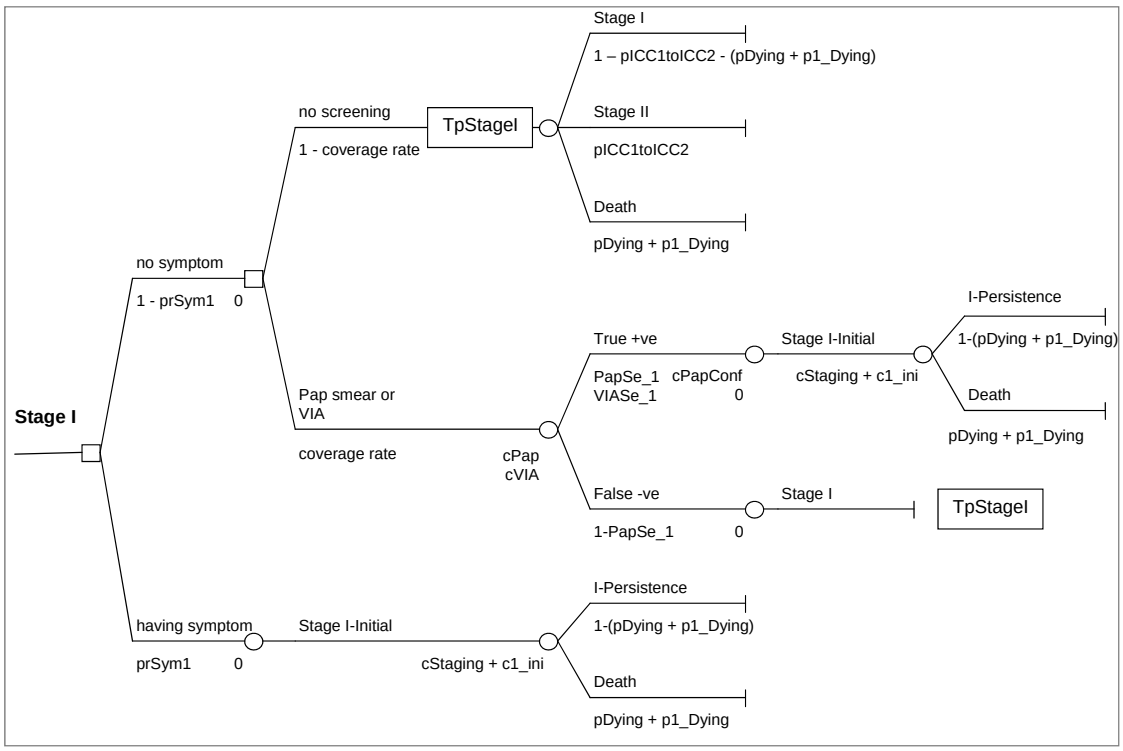
(E): effect of Pap smear on "CIN-2/3"



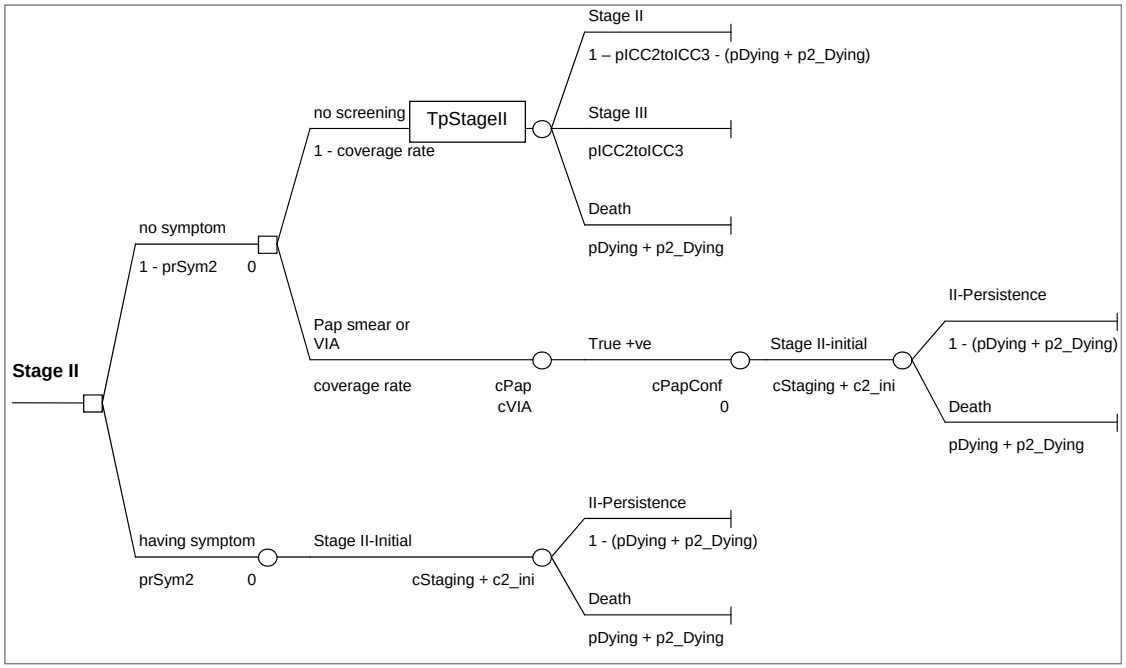
(F): effect of VIA on "CIN-2/3"



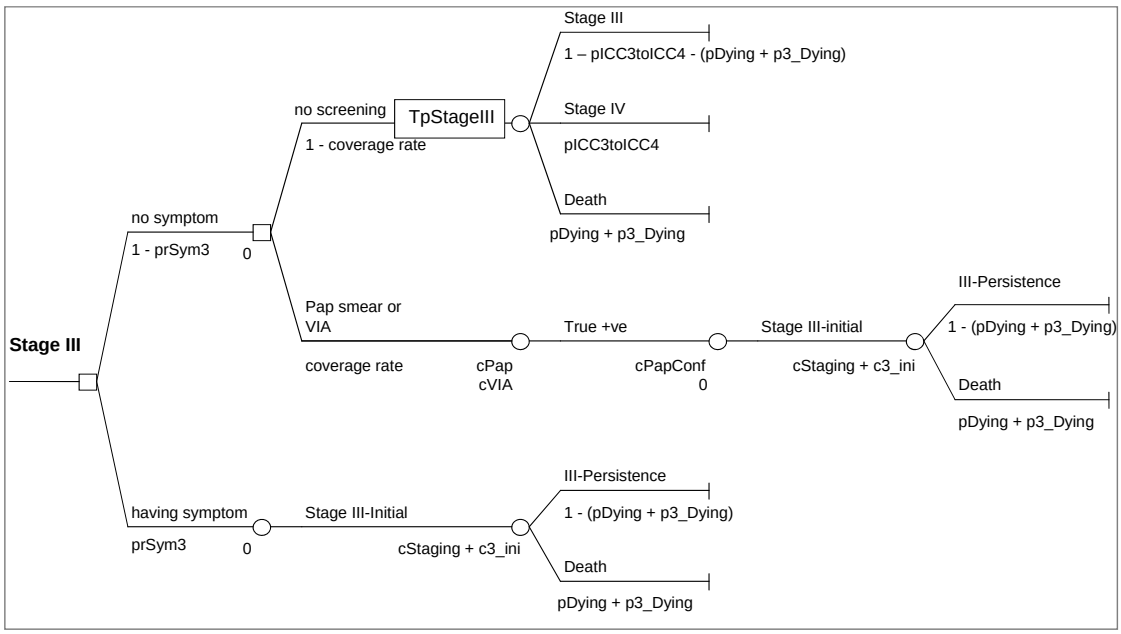
(G): effect of Pap smear and VIA on invasive cervical cancer "Stage I"



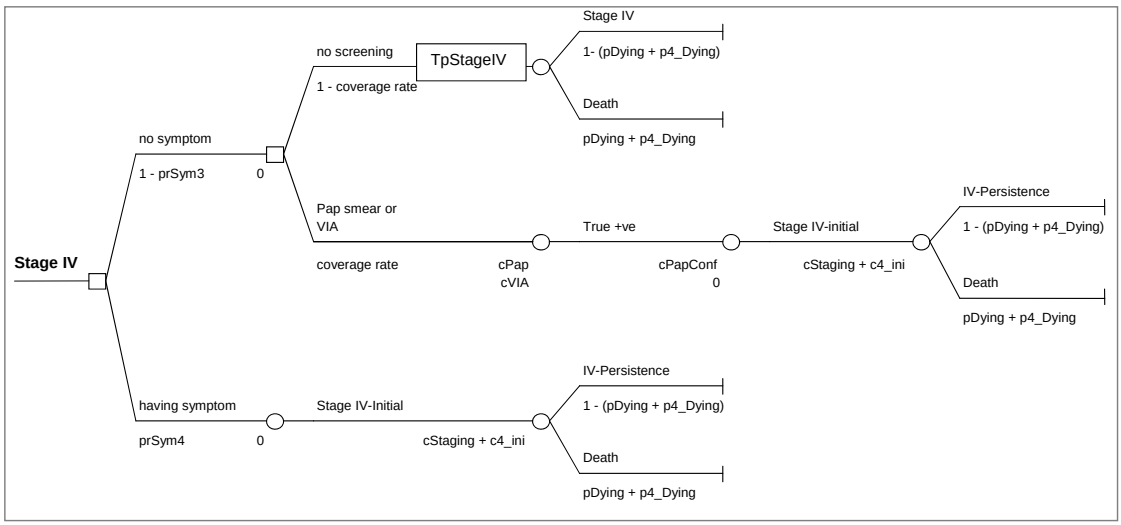
(H): effect of Pap smear and VIA on invasive cervical cancer "Stage II"



(I): effect of Pap smear and VIA on invasive cervical cancer “Stage III”



(J): effect of Pap smear and VIA on invasive cervical cancer “Stage IV”



APPENDIX C
QUESTIONNAIRE FOR COST AND UTILITY ASSESSMENT OF INVASIVE CERVICAL CANCER PATIENT

CONSENT STATEMENT FORM

I have received the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I understand if I need further information, I will ask the researcher.

Upon signing this form, I agree to participate in the study entitled "Economic analysis of strategies for cervical cancer and control in Indonesia".

Participant:

Name	Signature	Date

Witness:

Name	Signature	Date

Questionnaire for estimating direct non-medical and indirect costs

I.	**General information**	
1.	Code ID: …….. HN: …… Stage of cancer: …… Age: ……	
2.	Address/distance from home to hospital: …… / …….. km	
3.	Marital status:	
	a. Single, never married	b. Married
	c. Divorced	d. Widowed
4.	Education:	
	a. Never went to school	b. Elementary school
	c. Junior high school	d. Senior high school
	e. Bachelor degree	e. Graduate study degree
5.	Occupation before cancer diagnosed: …… Monthly income: ……..	
	a. Civil servant/military	b. Private company's employee
	c. Farmer/seller	d. Entrepreneur
	e. Retired	f. Unemployed
	g. Other, specify: ……...	
6.	Current occupation (if different from No. 5): ….. Monthly income: ……..	
	a. Civil servant/military	b. Private company's employee
	c. Farmer/seller	d. Entrepreneur
	e. Retired	f. Unemployed
	g. Other, specify: ……...	
7.	Scheme of health insurance:	
	a. Askes (civil servant insurance)	b. Askeskin (health insurance for poor people)
	c. Jamkesmas (universal coverage insurance)	d. Jamsostek (private employee health insurance)
	e. No insurance (self-paid)	e. Other insurance, specify: ……
8.	a. The first time diagnosed for cervical cancer: …….	
	b. First time got treatment for cervical cancer disease from hospital: ……	
	c. First time got treatment for cervical cancer disease from other health care facilities: ……	

II. Questions for assessing direct non-medical cost inside of hospital

9.	Within 1 year, how many times you visit this hospital or other hospitals for cervical cancer treatment? …… times							
	The following questions are related to each visit:	Visit No						
		1	2	3	4	5	6	
10.	Please specify time of visit (month/year)							
	Please specify name of hospital for each visit							
11.	For what purpose you visit the hospital?							
	a. OPD							
	b. IPD, how many days stay at hospital?							
12.	With whom do you go to the hospital?							
	a. Alone							
	b. Accompanied by relatives; how many person accompany you?							
	c. Did you go together or separate with them? (1=together; 2=separate)							
13.	If you go alone:							
	a. What kind of transportation that you used?							

	(1=Your own car/motor; 2=rental car; 3=taxi; 4=public bus; 5=other, specify ……)						
	b. How much cost for transportation?						
14.	If you are accompanied by relatives, and you go together:						
	a. what kind of transportation that you used? (1=Your own car/motor; 2=rental car; 3=taxi; 4=public bus; 5=other, specify ……)						
	b. How much cost for transportation?						
15.	If you are accompanied by relatives, and you go separate:						
	a. What kind of transportation that you used? (1=Your own car/motor; 2=rental car; 3=taxi; 4=public bus; 5=other, specify ……)						
	b. How much cost for transportation?						
	c. What kind of transportation that your relatives used? (1=Your own car/motor; 2=rental car; 3=taxi; 4=public bus; 5=other, specify ……)						
	d. How much cost for transportation?						
16.	How much cost that you spend for meal during visiting hospital?						
17.	How much cost that your relatives spend for meal during visiting hospital?						
18.	During hospital visiting for OPD, did you: (1=Not stay over-night, 2= Stay in hospital, but free of charge, 3= Stay in relative's house and free of charge, 4= Stay and pay; how many night and how much per night?)						
19.	While accompanying you to the hospital, did your relatives: (1=Not stay overnight, 2= Stay in hospital, but free of charge, 3= Stay in relative's house and free of charge, 4= Stay and pay; how many night and how much per night?)						
20.	How long you spend time for each OPD visit: (1= Less than half day, 2= More than half day, 3= More than one day, … days)						
21.	How long your relatives spend time to accompany you for each OPD visit: (1= Less than half day, 2= More than half day, 3= More than one day, … days)						
22.	Is there any other person accompany you while you are admitted in hospital for IPD? (1=no, 2=Yes, how many persons at the same time?)						
23.	How often they accompany you? 1=every day, 2=every two days, 3=how many days in a week?)						
24.	How long they accompany you for every visit? (1= Half day or less, 2= More than half day, 3= One day full)						
25.	While accompanying you, how long work time per day missed by them? (1= Less than 4 hours, 2= About 4-8 hours, 3=						

	More than 8 hours)						
26.	What is the occupation of persons accompanying you?						
	a. Person 1						
	b. Person 2						
	c. Person 3						
	d. Person 4						

III. Questions for accessing direct non-medical costs outside of hospital

Within 1 year:

27.	Did you get treatment from other health facilities instead from this hospital?						
	a. No						
	b. Yes, please specify in the following form:						
	Variables	Type of treatment or health facilities (1=primary healthcare, 2=private practice of physician, 3=OTC medicines, 4=herbal medicines, 5=alternative medicines, 6=others)					
		1	2	3	4	5	6
	How many visits?						
	How much cost pay for the treatment?						
	Did you accompany by other for seeking those treatments? How many persons accompany? What are their occupations?						
	How much time spent for the treatment?						
	How much cost for transportation?						
	How much cost for meal during the treatment?						
28.	Did you ever stop working due to the symptoms of your disease?						
	a. No						
	b. Yes, for how many days? ……..						
29.	Did you need some help from your family or other persons at home due to your symptoms of disease?						
	a. No						
	b. Yes, how many days? ……						
	c. How long they help you in a day? (1=full day, 2=half day, 3=how many hours ….)						
	d. What activities they help you? (1=healthcare activities, 2=daily living activities, 3=household activities, 4=traveling activities)						
30.	Did you pay other person for caring you at home?						
	a. No						
	b. Yes, how much you pay? ……..						
31.	Is there any renovation or modification in your house related to your disease?						
	a. No						
	b. Yes, please specify in the following form:						
	Type of renovation or modification	Price/cost					
	- Room						
	- Floor						
	- Bed						
	- Chair						
	- Stick						

Questionnaire for evaluate health related quality of life of cervical cancer patients

EQ-5D questionnaire English version used as reference

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

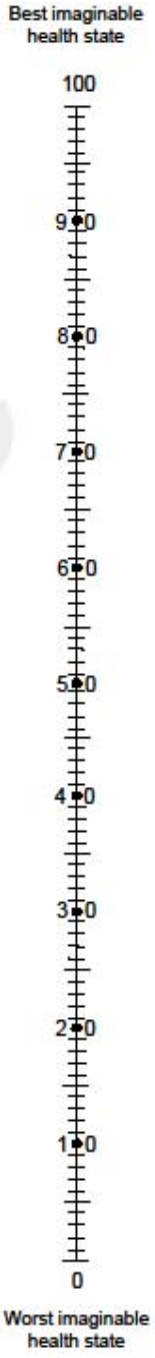
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



EQ-5D questionnaire Indonesian language version used in the study

Kuesioner Kesehatan

(Indonesian version for Indonesia)

Berilah tanda √ di dalam salah satu kotak di setiap kelompok pernyataan berikut yang paling sesuai dengan kondisi kesehatan anda hari ini.

Kemampuan Berjalan/Bergerak

Saya tidak mempunyai kesulitan dalam berjalan/bergerak ❑
Saya mempunyai kesulitan dalam berjalan/bergerak ❑
Saya harus selalu berada di tempat tidur ❑

Perawatan Diri

Saya tidak mempunyai kesulitan dalam merawat diri sendiri ❑
Saya mempunyai kesulitan untuk mandi atau berpakaian sendiri ❑
Saya tidak bisa mandi atau berpakaian sendiri ❑

Kegiatan yang Biasa Dilakukan *(misalnya bekerja, belajar, mengerjakan pekerjaan rumah tangga, kegiatan keluarga, atau bersantai/berekreasi)*

Saya tidak mempunyai kesulitan dalam mengerjakan kegiatan yang biasa saya lakukan ❑
Saya mempunyai kesulitan dalam mengerjakan kegiatan yang biasa saya lakukan ❑
Saya tidak bisa mengerjakan kegiatan yang biasa saya lakukan ❑

Rasa Kesakitan/Tidak Nyaman

Saya tidak merasa kesakitan/tidak nyaman ❑
Saya merasa agak kesakitan/tidak nyaman ❑
Saya merasa amat sangat kesakitan/tidak nyaman ❑

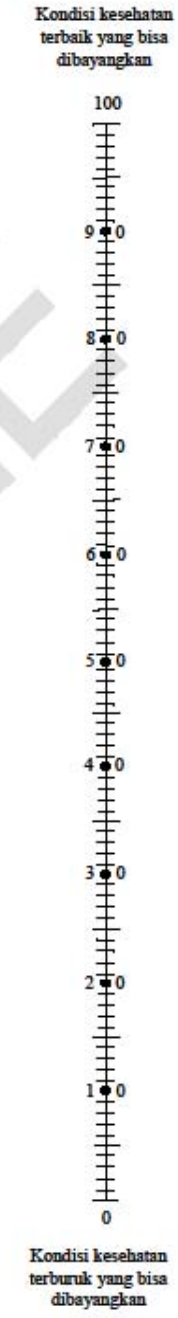
Rasa Cemas/Depresi (Sedih)

Saya tidak merasa cemas/depresi (sedih) ❑
Saya merasa agak cemas/depresi (sedih) ❑
Saya merasa amat sangat cemas/depresi (sedih) ❑

Untuk membantu menilai kondisi kesehatan seseorang, kami telah membuat sebuah skala (mirip sebuah termometer). Dalam skala ini, kondisi kesehatan terbaik yang dapat anda bayangkan diberi nilai 100 dan kondisi kesehatan terburuk yang dapat anda bayangkan diberi nilai 0.

Tolong tunjukkan pendapat anda tentang kondisi kesehatan anda hari ini pada skala yang ada. Tariklah garis dari kotak hitam di bawah ini ke titik yang ada pada skala di samping kanan yang menggambarkan kondisi kesehatan anda hari ini.

Kondisi Kesehatan Anda Hari Ini



APPENDIX D

WHO-LIFE TABLE

Age specific mortality for Indonesian population

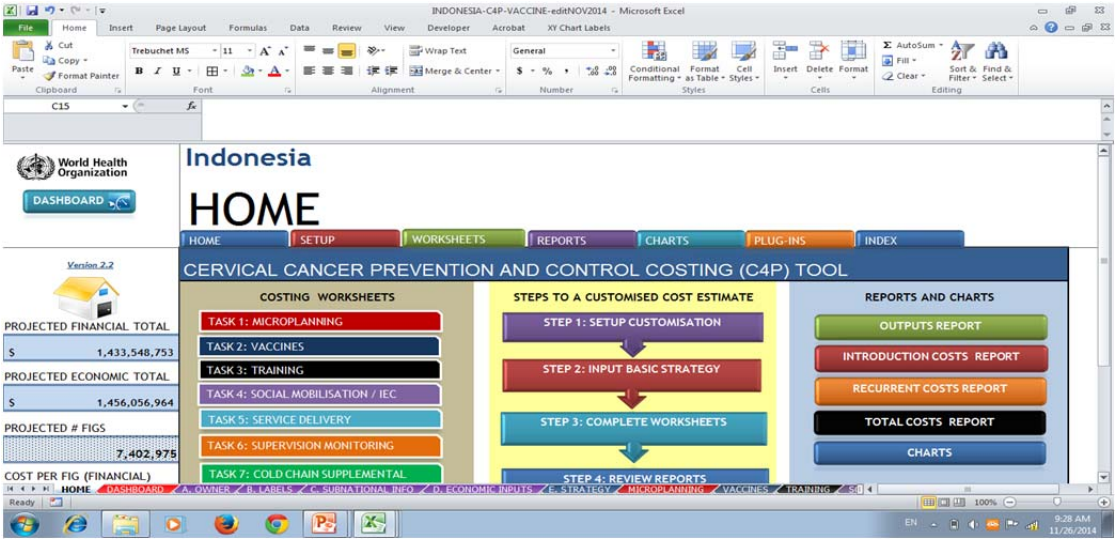
Age	Abridged probability of dying	Unabridged probability of dying	Age	Abridged probability of dying	Unabridged probability of dying
[10 – 14]/12	0.002	0.0004	57		0.0088
13		0.0004	58		0.0088
14		0.0004	59		0.0088
[15 – 19]/15	0.003	0.0006	[60 – 64]/60	0.068	0.0140
16		0.0006	61		0.0140
17		0.0006	62		0.0140
18		0.0006	63		0.0140
19		0.0006	64		0.0140
[20 – 24]/20	0.004	0.0008	[65 – 69]/65	0.113	0.0237
21		0.0008	66		0.0237
22		0.0008	67		0.0237
23		0.0008	68		0.0237
24		0.0008	69		0.0237
[25 – 29]/25	0.005	0.0010	[70 – 74]/70	0.189	0.0410
26		0.0010	71		0.0410
27		0.0010	72		0.0410
28		0.0010	73		0.0410
29		0.0010	74		0.0410
[30 – 34]/30	0.007	0.0014	[75 – 79]/75	0.303	0.0696
31		0.0014	76		0.0696
32		0.0014	77		0.0696
33		0.0014	78		0.0696
34		0.0014	79		0.0696
[35 – 39]/35	0.009	0.0018	[80 – 84]/80	0.465	0.1176
36		0.0018	81		0.1176
37		0.0018	82		0.1176
38		0.0018	83		0.1176
39		0.0018	84		0.1176
[40 – 44]/40	0.012	0.0024	[85 – 89]/85	0.638	0.1839
41		0.0024	86		0.1839
42		0.0024	87		0.1839
43		0.0024	88		0.1839
44		0.0024	89		0.1839
[45 – 49]/45	0.019	0.0038	[90 – 94]/90	0.79	0.2681
46		0.0038	91		0.2681
47		0.0038	92		0.2681
48		0.0038	93		0.2681
49		0.0038	94		0.2681
[50 – 54]/50	0.028	0.0057	[95 – 99]/95	0.889	0.3557
51		0.0057	96		0.3557
52		0.0057	97		0.3557
53		0.0057	98		0.3557
54		0.0057	99		0.3557
[55 – 59]/55	0.043	0.0088	100	1	1
56		0.0088			

APPENDIX E

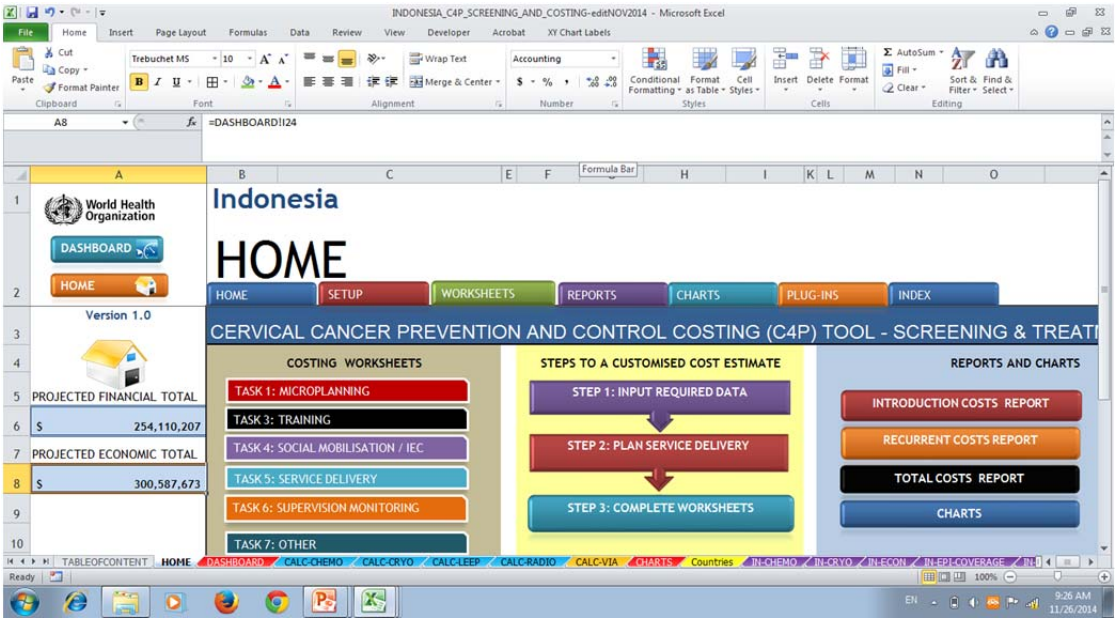
ESTIMATION OF UNIT COSTS OF HPV VACCINATION AND SCREENING FOR CERVICAL CANCER USING WHO-C4P TOOL

Screenshots of WHO-C4P generic tools

(A): WHO-C4P tool for vaccination



(B): WHO-C4P tool for screening and treatment of cervical cancer



Input and output information

(A): Basic assumptions for estimating cost of vaccination using WHO-C4P tool

Variable	Data	Justification/ Source
Country characteristics		
Country name	Indonesia	Factual
Start year	2015	Comprehensive multi-year plan of NIP Indonesia (2015-2019)/MOH
Administrative level	- Province - District - Subdistrict - Village	Indonesia administrative system/MOHA
Health facility level	- Top referral hospital - Referral hospital - Provincial hospital - District hospital - Health center - Integrated village post (Posyandu)	Indonesia health system/MOH
School type	- Public/government school - Private school	Indonesia education system/MOE

Variable	Data	Justification/ Source
Personnel type	Central (SubDirectorate of EPI, CDC MOH): - Head of SubDirectorate, 2 sections/ unit and a number of staffs - Cold chain/Logistics Manager Provincial Health Office: - Provincial EPI Manager - Cold chain/Logistics Manager - Supervised by Provincial EPI Manager District Health Office: - District EPI (Expanded Program for Immunization) Manager - Cold chain/Logistics Manager - Supervised by District EPI Manager Health Center: - Vaccinator (Midwife/Nurses) - Cold chain/Logistics Manager - Supervised by Head of health center	Indonesia health system/MOH
School personnel involved in immunization program	- Head of school - School health educator (teacher)	Interview with MOH staffs
Population information		
Number of region	33	MOHA
Number of district	497	MOHA
Number of elementary school	147,503	MOE
Estimated target population (girls 12 years old with proxy of sixth grade in elementary school)	2,342,900	NSB
Number of vaccination facilities	9,655	MOH
Number of health workers in vaccination facilities	99,263	MOH
Economic and Demographic variables		
Name of local currency	IDR (Indonesian Rupiah)	Factual
Exchange rate (USD to IDR)	12,364	UN operation rates
Annual Inflation Rate	4.29%	World Bank
Annual Discount Rate	3%	Assumption
Estimated Useful Life Years for Introduction Costs	5	Assumption
Annual Population Growth Rate	1.13%	World Bank
Strategy variables		
First Dose (HPV-1) Coverage rate	80%	Assumption based on current NIP coverage
Drop-out rate (between 1st and 2nd dose)	5%	Assumption
Drop-out rate (between 2nd and 3rd dose)	5%	Assumption
The proportion of vaccine delivered through health facilities	0%	Assumption
The proportion of vaccine delivered through school	100%	Assumption
The proportion of vaccine delivered through outreach clinics	0%	Assumption

Variable	Data	Justification/ Source
Area in which HPV vaccine will be introduced	1st year (4 province): Jawa Barat, NTB, Bali and DIY. 2nd year (13 province): Jawa Barat, NTB, Bali, DIY, Jawa Tengah, Jawa Timur, DKI Jakarta, Banten, Sulawesi Selatan, Bangka Belitung, Sumatera Utara, Jambi dan Lampung. 3rd year (33 province): all provinces in the whole country	Assumption based on current new vaccine-introduction in NIP
Vaccines variables		
Assumed wastage rate of each type of item procured	5%	Assumption
Planned buffer/reverse stock to have on hand	25%	Assumption
Planned doses to give to each fully immunized girl	3	Assumption based on regimen dose of HPV vaccine
Capacity of safety boxes in planned procurement (the number of syringes)	100	Estimation based on volume of 1L safety bos
Vaccine price per dose	$13	The lowest public price of HPV vaccine
	IDR 500,000	Market price of HPV vaccine in Indonesia
	$4.50	GAVI price
Injection syringe price per unit	IDR 2,000	MOH purchasing price
Safety box price per unit	IDR 21,000	
The amount of subsidy for each supply	0	Assumption based on GAVI status
Service delivery variables		
Average number of vaccinators per health facility offering vaccinations	2	Interview with MOH staffs
Average number of vaccinators per school visit	2	
Average number of teachers assisting per school visit	1	
Average number of people vaccinated per school visit	16	Estimation based on the number of schools and girls
Average number of minutes per person vaccinated in school	3	Assumption
Average number of length (in days) per school visit	0.5	Interview with MOH staffs
Number of visits to a school per year	3	Based on HPV vaccine dose regimen

Variable	Data	Justification/ Source
Average monthly salary and benefits of a health facility level vaccinator	IDR 2,515,536	Standard salary of government employer/MOF
Average cost of a R/T transport for a school vaccination visit (per person)	IDR 20,000	Interview with MOH staffs
Average per diem / allowance for a teacher assisting with school vaccination visit	IDR 20,000	
Supplemental cold chain variables		
The packaged volume per dose cm3	15	Assumption based on vaccine package of 0.5 ml vial per dose
Frequency of vaccines shipment from manufacturer to province	4	Interview with MOH staffs
Frequency of vaccines shipment from province to district	12	
Frequency of vaccines shipment from district to health facility	12	
Excess capacity at provincial level stores	sufficient	Assumption based on MOH report
Excess capacity at district level stores	sufficient	
Excess capacity at health facility	sufficient	
Meeting variables		
Micro-planning		
Number of micro-planning at country level	1	Interview with MOH staffs
Number of micro-planning per region	1	
Number of micro-planning per district	1	
Training		
Maximum number of participants per country level training of trainers workshop	25	Interview with MOH staffs
Maximum number of participants per training of district supervisors	25	
Maximum number of participants per training of health facility vaccinator	25	
The number of trainers per province	2	
The number of supervisors trained per district	5	
The number of vaccinators trained per health facility	2	
Social mobilization and IEC		
Number of sensitization events at republic level	1	Interview with MOH staffs
Number of sensitization events per region	1	
Number of sensitization events per district	1	
Number of sensitization events per school	0	
Supervision Monitoring and Evaluation		
Number of supervision visits by country level team per year	1	Interview with MOH staffs
Number of supervision visits by provincial level team per year	4	
Number of supervision visits by district	4	

Variable	Data	Justification/ Source
level team per year		
Monitoring record books per active facility per year (number of accounting for wastage)	1.1	Assumption
Vaccination tally sheet reporting form	USD 15.6	
Vaccination cards per HPV-1 (number of accounting for wastage)	USD 1.3	
Proportion of supervisory cost allocated to HPV vaccine	20%	

(B): Selected assumptions for estimating cost of screening for cervical cancer using WHO-C4P tool

Variable	Data	Justification/ Source
Country characteristics		
Country name	Indonesia	Factual
Start year	2015	Comprehensive multi-year plan of Indonesia (2015-2019)/MOH
Administrative level	- Province - District - Health catchment area	Indonesia administrative system/MOHA
Health facility level	- Referral hospital - Local referral hospital - Provincial hospital - District hospital - Health center - Health dispensary	Indonesia health system/MOH
Population information		
Number of region	33	MOHA
Number of district	497	MOHA
Number of health center facilities	9,655	
Number of referral hospital	56	
Number of local referral, provincial, and district hospital	2,301	
Estimated target population (women age 30-65 years at year 2015)	50,156,558	
Economic and Demographic variables		
Name of local currency	IDR (Indonesian Rupiah)	Factual
Exchange rate (USD to IDR)	12,364	UN operation rates; predicted for 2015 value
Annual Inflation Rate	4.29%	World Bank
Annual Discount Rate	3%	Assumption
Estimated Useful Life Years for Introduction Costs	5	Assumption
Annual Population Growth Rate	1.13%	World Bank
Strategy plan		
Number of active region	2015 – 2019: 100%	
Number of active district	2015 – 2019: 40%, 50%, 60%, 70%, 80%, respectively	Assumption
Number of active health center		

Variable	Data	Justification/ Source
Number of target population		
Coverage rate of screening in active region	20%	
Epidemiology and coverage		
Proportion of cervical cancer related disease		
Normal Cervix	97.37%	Previous study in Indonesia
Small Precancerous Lesions	1.30%	
Large Precancerous Lesions	1.15%	
Early Stage Invasive Cancer	0.04%	
Mid Stage Invasive Cancer	0.07%	
Late Stage Invasive Cancer	0.07%	
Contribution of each facility level to a region's screening coverage		
In-region referral hospital	1%	Assumption
Regional and district hospital	5%	
Health center	20%	
Health dispensary	0	
Drop-out rates		
Cryotherapy	25%	Assumption based on C4P tool template
LEEP	50%	
Radiotherapy	90%	
Chemotherapy	90%	
Palliative therapy	50%	

(C): Input data of meeting variables

Meeting variables	Data	Source
Micro-planning		
Number of micro-planning at country level	1	Interview with MOH staffs
Number of micro-planning per region	1	
Number of micro-planning per district	1	
Training		
Maximum number of participants per country level training of trainers workshop	25	Interview with MOH staffs
Maximum number of participants per training of district supervisors	25	
Maximum number of participants per training of health facility vaccinator	25	
The number of trainers per province	2	
The number of supervisors trained per district	5	
The number of vaccinators trained per health facility	2	
Social mobilization and IEC		
Number of sensitization events at republic level	1	Interview with MOH staffs
Number of sensitization events per region	1	
Number of sensitization events per district	1	
Number of sensitization events per school	0	
Supervision Monitoring and Evaluation		
Number of supervision visits by country level team per year	1	Interview with MOH staffs
Number of supervision visits by provincial level team per year	4	

Number of supervision visits by district level team per year	4	
Monitoring record books per active facility per year (number of accounting for wastage)	1.1	Assumption
Vaccination tally sheet reporting form	USD 15.6	
Vaccination cards per HPV-1 (number of accounting for wastage)	USD 1.3	
Proportion of supervisory cost allocated to HPV vaccine	20%	

(D): Input values of activities related to program introduction used to calculate activity costs in C4P tool

Activity	Number of personnel in each acitivity				Source
	Facilitator/ trainer	Moderator	Support staff	Participant	
Micro-planning					Assumption based on interview with MOH staffs
Micro-planning at country level	4	1	3	86	
Micro-planning at region level	4	1	3	45	
Micro-planning at district level	4	1	3	45	
Training					
Curriculum development	4	1	3	20	
Training at country level	4	1	3	66	
Training at region level	4	1	3	75	
Training at district level	4	1	3	40	
Social mobilization and IEC (SM-IEC)					
SM-IEC at country level	4	1	3	86	
SM-IEC at region level	4	1	3	45	
SM-IEC at district level	4	1	3	45	
Supervision -monitoring (SM) and Evaluation					
SM at country level	0	0	0	2	
SM at province level	0	0	0	2	
SM at district level	0	0	0	2	
Evaluation at country level	4	1	3	66	
Evaluation at province level	4	1	3	30	

Activity	Duration of meeting in each activity			Source
	Number of day	Number of session per day	Number of hours per day	
Micro-planning				Assumption based on interview with MOH staffs
Micro-planning at country level	1	4	8	
Micro-planning at region level	1	4	8	
Micro-planning at district level	1	4	8	
Training				
Curriculum development	3	4	8	
Training at country level	5	4	8	
Training at region level	5	4	8	
Training at district level	5	4	8	
Social mobilization and IEC (SM-IEC)				

SM-IEC at country level	1	4	8	
SM-IEC at region level	1	4	8	
SM-IEC at district level	1	4	8	
Supervision -monitoring (SM) and Evaluation				
SM at country level	2	0	8	
SM at province level	1	0	8	
SM at district level	1	0	8	
Evaluation at country level	1	4	8	
Evaluation at province level	1	4	8	

(E): Unit cost lists used to calculate activities costs

Cost component	Value	Source
Unit cost of salary		Ministry of Finance of Indonesia; cost in year 2014
Government employee level 1 (IDR per month)	1,926,726	
Government employee level 1 (IDR per day)	96,336	
Government employee level 2 (IDR per month)	2,515,536	
Government employee level 2 (IDR per day)	125,777	
Government employee level 3 (IDR per month)	3,174,667	
Government employee level 3 (IDR per day)	158,733	
Government employee level 4 (IDR per month)	3,827,763	
Government employee level 4 (IDR per day)	191,388	
Unit cost of per diem		
Per diem for meeting (IDR per day)		
- Half day/Full day meeting	98,088	
- Full board meeting	114,706	
- Full board meeting across-province	136,765	
Per diem for business trip (IDR per day)		
- Within province	161,765	
- Across province	406,765	
- Training	120,588	
Lodging cost for business trip		
Government employee level 3 (IDR per night)	489,353	
Government employee level 4 (IDR per night)	799,118	
Unit cost of transport allowance		
Local transport within district (IDR per meeting)	110,000	
Local transport across district within province (IDR per meeting)	156,088	
From capital to country side (IDR per meeting)	3,810,273	
Transport for vaccine delivery (IDR per person per school)	20,000	
Unit cost of honorarium		
Facilitator/trainer (IDR per hour)		
- Country level meeting	900,000	
- Province and district level	700,000	
Moderator (IDR per session)		
- Country level meeting	700,000	
- Province and district level	500,000	
Resource personnel/committee (IDR per meeting)	400,000	
Unit cost of meeting package		
Half-day (IDR per person per day)	182,624	
Full day (IDR per person per day)	281,853	
Full board (IDR per person per day)	619,059	
Unit cost of meeting material (IDR per	60,000	Interview with

package/person)		MOH staffs
Cost for IEC support		
Poster/leaflet (IDR per package per year)		
- Country level	500,000,000	
- Region level	45,000,000	
TV and radio airing (IDR per package per year)	195,000,000	
Unit cost of equipment and supply for SME (IDR per province per year)	1,000,000	
Car rental (IDR per day)	709,118	Ministry of Finance

(F): Unit cost of activities for estimating cost of HPV vaccination and screening for cervical cancer using WHO-C4P tool

Meeting variables	Data	Justification/ Source
Micro-planning		
Financial cost per event of micro-planning at country level	USD 29,936	Calculation output from C4P tool
Financial cost per event of micro-planning at region level	USD 4,968	
Financial cost per event of micro-planning at district level	USD 3,030	
Economic cost per event of micro-planning at country level	USD 31,156	
Economic cost per event of micro-planning at region level	USD 5,661	
Economic cost per event of micro-planning at district level	USD 3,723	
Training		
Financial cost of curriculum development workshop	USD 9,835	Calculation output from C4P tool
Financial cost per event of country level training of trainers workshop	USD 46,428	
Financial cost per event of province level training of supervisors workshop	USD 29,380	
Financial cost per event of district level training of vaccinator workshop	USD 18,169	
Economic cost of curriculum development workshop	USD 10,953	
Economic cost per event of country level training of trainers workshop	USD 51,244	
Economic cost per event of province level training of supervisors workshop	USD 34,774	
Economic cost per event of district level training of vaccinator workshop	USD 21,316	
Social mobilization and IEC		
Financial cost per event of country level sensitization event	USD 29,936	Calculation output from C4P tool
Financial cost per event of province sensitization event	USD 4,968	
Financial cost per event of district sensitization event	USD 3,030	
Economic cost per event of country level sensitization event	USD 31,156	
Economic cost per event of province sensitization event	USD 5,661	
Economic cost per event of district sensitization event	USD 3,723	
Supervision Monitoring and Evaluation		
Financial cost per event of supervision visit by country level team	USD 1,121	Calculation output from C4P tool
Financial cost per event of supervision visit by a province team	USD 233	
Financial cost per event of supervision visit made by a district team	USD 15.87	

Meeting variables	Data	Justification/ Source
Financial cost of post-introduction evaluation (country)	USD 29,046	
Financial cost of post-introduction evaluation (province)	USD 3,719	
Economic cost per event of supervision visit by country level team	USD 1,183	
Economic cost per event of supervision visit by a province team	USD 264	
Economic cost per event of supervision visit made by a district team	USD 46.83	
Economic cost of post-introduction evaluation (country)	USD 30,009	
Economic cost of post-introduction evaluation (province)	USD 4,220	

*costs were presented for year 2015 value

(G): Summary results of estimation of HPV vaccination cost using WHO-C4P tool

Summary of expected output of introducing HPV vaccine in Indonesia at projected year or 2015-2019

Output	2015	2016	2017	2018	2019
% National target population fully immunized	17%	55%	74%	75%	75%
Fully immunized girls	389,045	1,674,946	3,403,218	5,149,249	6,912,648
Doses used	1,229,642	5,293,943	10,756,431	16,275,050	21,848,565
Vaccinator trained	2,898	10,756	19,310	19,310	19,310
Health center mobilized	1,449	5,378	9,655	9,655	9,655
School vaccination sites added	44,784	89,159	147,503	147,503	147,503

Five-year predicted cost for introducing HPV vaccine in Indonesia based on activities

Activity	Total 5 Years		Total 5 Years	
	Financial Cost (USD)	%	Economic Cost (USD)	%
Microplanning	339,908	0.03%	451,643	0.04%
Vaccines	1,057,953,590	97.46%	1,057,953,590	95.73%
Training	3,418,606	0.31%	4,383,446	0.40%
Social Mobilization/IEC	2,315,262	0.21%	3,136,575	0.28%
Service Delivery	8,392,312	0.77%	25,984,948	2.35%
Supervision Monitoring Evaluation	10,940,025	1.01%	11,091,930	1.00%
Other	2,184,856	0.20%	2,184,856	0.20%
Total	1,085,544,560	100%	1,105,186,989	100%

Five-year predicted cost for introducing HPV vaccine in Indonesia based on activities

Type of cost	5-year financial cost (USD)	5-year economic cost (USD)
Introduction cost		
Microplanning	339,908	451,643
Training	3,418,606	4,383,446
Social mobilization (initial)	479,266	603,790
Total introduction cost	4,237,780	5,438,879
% introduction cost	0.39%	0.49%
Recurrent cost		
Vaccines	1,057,953,590	1,057,953,590
Social mobilization (continue)	1,835,996	2,532,785
Service delivery	8,392,312	25,984,948
Monitoring	10,940,025	11,091,930
Waste management	2,184,856	2,184,856
Total reccurent cost	1,081,306,780	1,099,748,110
% reccurent cost	99.61%	99.51%
Total all costs	1,085,544,560	1,105,186,989

Financial and economic cost per dose and per fully immunized girl without and with vaccine costs

	3-doses vaccine		2-doses vaccine	
	Cost per dose (USD)	**Cost per FIG (USD)**	**Cost per dose (USD)**	**Cost per FIG (USD)**
Without vaccine				
Financial cost	1.26	3.99	1.80	3.70
Economic cost	2.16	6.83	3.12	6.40
With vaccine (at market price) (base case)				
Financial cost	49.68	157.04	50.22	103.09
Economic cost	50.58	159.88	51.54	105.79
With vaccine (at lowest public price)				
Financial cost	16.98	53.68	17.52	35.96
Economic cost	17.88	56.52	18.84	38.66
With vaccine (at GAVI price)				
Financial cost	6.85	21.66	7.39	15.17
Economic cost	7.75	24.50	8.71	17.87

(H): Summary results of estimation of cost of screening for cervical cancer using WHO-C4P tool

Summary of expected output of providing VIA screening in Indonesia at projected year or 2015-2019

Output	Value
Number of eligible women	50,156,558
Number of screened women	21,284,591
Number of women treated for pre-cancer	329,911
Number of women treated for cervical cancer	3,193

Five-year predicted cost for screening of cervical cancer in Indonesia based on activities

Activity	Total 5 Years		Total 5 Years	
	Financial Cost (USD)	**%**	**Economic Cost (USD)**	**%**
Micro-planning	980,952	0.71%	1,311,763	0.73%
Training	1,919,532	1.39%	2,434,109	1.36%
Social Mobilization/IEC	3,857,925	2.80%	4,043,701	2.26%
Service Delivery	104,059,427	75.48%	144,041,277	80.50%
Supervision Monitoring Evaluation	27,051,954	19.62%	27,112,114	15.15%
Total	137,869,791	100%	178,942,964	100%

Five-year predicted cost for screening of cervical cancer in Indonesia based on activities

Type of cost	5-year financial cost (USD)	5-year economic cost (USD)
Introduction cost		
Micro-planning	980,952	1,311,763
Training	1,919,532	2,434,109
Social mobilization (initial)	1,070,769	1,256,545
Total introduction cost	3,971,254	5,002,417
% introduction cost	2.88%	2.80%
Recurrent cost		
Social mobilization (continue)	2,787,156	2,787,156
Service delivery	104,059,427	144,041,277
Monitoring	27,051,954	27,112,114
Total recurrent cost	133,898,537	173,940,547
% recurrent cost	97.12%	97.20%
Total all costs	137,869,791	178,942,964

Financial and economic cost per screened woman

	Financial cost (USD)	Economic cost
Total cost per screened woman	6.48	7.51
Programmatic cost per screened woman (without cost of service delivery of screening and follow-up treatment)	1.59	1.64

APPENDIX F

ESTIMATION OF COSTS OF HEALTHCARE PROGRAM FOR CERVICAL CANCER PREVENTION AND CONTROL

Basic assumptions to estimate costs of healthcare program

Variable	Description
HPV vaccine service	Vaccination was held in the school. Costs regarding transportation and time loss were same as if vaccine was given in primary healthcare
VIA service	VIA was provided at primary healthcare
Pap smear service	Pap smear was provided at primary healthcare
Pre-cancer treatment	Cryotherapy was conducted at primary health center
	Confirmation with colposcopy and biopsy was conducted at secondary health center
	LEEP, cold knife conization, and simple hysterectomy were conducted in secondary health center
	Cryotherapy and LEEP were performed as outpatient procedures
	Cold knife conization and simple hysterectomy were performed as inpatient procedures
Follow-up visits after pre-cancer treatment	Cryotherapy needed one follow-up visit; LEEP, cold knife conization, and simple hysterectomy needed two follow-up visits
	Cost of follow-up for cryotherapy was the same as cost a cervical cytology test
	Cost of follow-up for LEEP, cold knife conization, and simple hysterectomy were the same as the cost of colposcopy-biopsy visit and the same as the cost of a cervical cytology test, for the first and second visit, respectively
Complication from cryotherapy	The rates of complication from cryotherapy were 1% and 5% for minor and major complication, respectively
	Minor complication required a clinic visit; Major complication required a hospital admission
Probability of patient receiving pre-cancer treatment by lesion and treatment type*	
Probability of CIN 1 patient receiving Cryosurgery	1
Probability of CIN 1 patient receiving LEEP	0.050
Probability of CIN 1 patient receiving Cold knife conization	0.050
Probability of CIN 1 patient receiving Simple hysterectomy	0.050
Probability of CIN 2/3 patient receiving Cryosurgery	1
Probability of CIN 2/3 patient receiving Cold knife conization	0.125
Probability of CIN 2/3 patient receiving Simple hysterectomy	0.125

*values were obtained from Goldie et al, 2005

List of costs of selected procedures related to cervical cancer disease for estimating direct medical cost of healthcare program

Procedure	Value	Justification/Source
Unit cost (IDR)		
HPV vaccination; per dose including programmatic cost	550,000	Output of WHO-C4P tool
Pap smear	125,000	INA-CBG 2014
VIA	25,000	
Programmatic cost of screening	15,000	Output of WHO-C4P tool
Cytology test	205,301	Estimated from INA-DRG 2008[a,b]
Colposcopy	507,476	
Biopsy	208,804	
Cryosurgery	208,804	
Cauterization (LEEP)	208,804	
Conization (cold knife conization)	3,454,425	
Simple hysterectomy	6,327,947	
Treating cryosurgery complication		
- minor complication	224,376	
- major complication	4,293,559	
F/U of Cryosurgery	205,301	c
F/U of LEEP	921,582	
F/U of Cold knife conization	921,582	
F/U of Simple hysterectomy	921,582	d

[a]Costs were based on INA-DRG tariffs of four different classifications of hospital and calculated using weighted average. Weighted factors were estimated from 4,129 admission records of cervical cancer patients based on database claims of PT Askes (health insurance provider) in Indonesia. The weighted factors for hospital classification of top referral, A, B, and CD were 0.07, 0.53, 0.23, 0.17; respectively.
[b]Costs were adjusted from year of 2008 to 2013 value using CPI; CPI 2008=91, CPI 2013=117.
[c]Cost including costs of cytology test
[d]Cost including costs of cytology test, colposcopy, biopsy

Utilization of hospital by its classification*

Hospital classification	Number of admission	Proportion
A	2207	0.53
B	928	0.22
C	667	0.16
D	44	0.01
Top referral	283	0.07

* Estimated from admission records of cervical cancer patients based on database claims of PT Askes (health insurance provider) in Indonesia in year 2011

Input to estimate direct non-medical cost of healthcare program

Variable	Value	Justification/Source
Patient time for receiving service by procedure type (minutes)		
Vaccine	5	Assumed
VIA	15	Goldie et al., 2005; Supplementary Appendix p. 17, referred to Thailand data
Pap smear	15	
Colposcopy/biopsy	20	
Cryosurgery	20	
LEEP	30	
Cold knife conization	45	
Simple hysterectomy	130	
F/U visit	15	
Patient time for waiting at health center (minutes)		
Primary health facility	30	Goldie et al., 2005; Supplementary Appendix p. 18, referred to Thailand data
Secondary health facility	35	
Tertiary health facility	50	
One-way transportation time to health center (minutea)		
Primary health facility	15	Goldie et al., 2005; Supplementary Appendix p. 18, referred to Thailand data
Secondary health facility	44	
Tertiary health facility	53	
Unit cost of transportation to health center (IDR)		
Primary health facility	15,556	Results of cost of illness study conducted by researcher
Secondary health facility	37,069	
Tertiary health facility	190,184	
Wage rate (IDR/hour)	17,758	Calculated from GNI per capita of Indonesia in 2013
Hospitalization days of specific treatment (number of days)		
Conization	6	INA-DRG 2008
Simple hysterectomy	8	
Clinical staging for cervical cancer	6	Assumption based on cost of illness study conducted by researcher

Identification and valuation of cost of healthcare program

Cost category and components	Resource identification	Valuation
Cost of HPV vaccination (cVac)		
Direct medical cost		IDR 1,650,000
Vaccine + programmatic cost	3 x vaccine cost per dose	3 x IDR 550,000
Direct non-medical cost		IDR 104,382
Travel by public/own transportation	3 visit x Patient traveling cost for a visit of 1°facility	3 x IDR 15,556
Time loss while transport	6 x Patient one-way traveling time to 1°facility x Patient wage rate	(6 x 15 minutes x IDR 17,758)/60
Time loss while waiting for 1°facility	3 visit x Patient waiting time at 1°facility x Patient wage rate	(3 x 30 minutes x IDR 17,758)/60
Time loss while receiving vaccine	3 visit x Patient time spent for receiving vaccine x Patient wage rate	(3 x 5 minutes x 17,758)/60
Cost of Pap smear (cPap)		
Direct medical cost		IDR 140,000
Programmatic + Service	1 unit cost of Pap smear procedure + programmatic cost per screened woman	IDR 125,000 + 25,000

Cost category and components	Resource identification	Valuation
Direct non-medical cost		IDR 71,068
Travel by public/own transportation	2 visit x Patient traveling cost for a visit of 1°facility	2 x IDR 15,556
Time loss while transport	4 x Patient one-way traveling time to 1°facility x Patient wage rate	(4 x 15 minutes x IDR 17,758)/60
Time loss while waiting for 1°facility	2 visit x Patient waiting time at 1°facility x Patient wage rate	(2 x 30 minutes x IDR 17,758)/60
Time loss while receiving pap smear	1 visit x Patient time spent for pap smear x Patient wage rate	1 x 15 minutes x IDR 17,758)/60
Cost of VIA (cVIA)		
Direct medical cost		IDR 40,000
Programmatic + Service delivery	1 unit cost of VIA procedure + programmatic cost	IDR 25,000 + 15,000
Direct non-medical cost		IDR 37,754
Travel by public/own transportation	1 visit x Patient traveling cost for a visit of 1°facility	1 x IDR 15,556
Time loss while transport	2 x Patient one-way traveling time to 1°facility x Patient wage rate	(2 x 15 minutes x IDR 17,758)/60
Time loss while waiting for 1°facility	1 visit x Patient waiting time at 1°facility x Patient wage rate	(1 x 30 minutes x IDR 17,758)/60
Time loss while receiving VIA	1 visit x Patient time spent for VIA x Patient wage rate	1 x 15 minutes x IDR 17,758)/60
Cost of confirmation test of pap smear (cPapConf)		
Direct medical cost		IDR 716,281
Colposcopy + biopsy	1 unit cost of colposcopy + 1 unit cost of biopsy	IDR 507,476 + 208,804
Direct non-medical cost		IDR 152,867
Transportation cost	2 visit x Patient traveling cost for a visit of 2°facility	2 x IDR 37,069
Time loss while transport	2 visit x 2 x Patient one-way traveling time to 2°facility x Patient wage rate	(2 x 2 x 44 minutes x IDR 17,758)/60
Time loss while waiting for 2°facility	2 visit x Patient waiting time at 2°facility x Patient wage rate	(2 x 35 minutes x IDR 17,758)/60
Time loss while receiving diagnosis test	1 visit x Patient time spent for colposcopy/biopsy x Patient wage rate	1 x 20 minutes x IDR 17,758)/60
Cost of cryosurgery (cCryo)		
Direct medical cost		
Cost of treatment + cost of follow-up + cost of complication	(no hospitalization, 1 F/U visit, 5% minor complications, 1% major complications)	IDR 208,804 + 205,301 + (5% x 224,376) + (1% x 1,899,887)
Direct non-medical cost		
Transportation cost	2 visit x Patient traveling cost for a visit of secondary facility	2 x IDR 37,069
Time loss while transport	2 visit x 2 x Patient one-way traveling time to secondary facility x Patient wage rate	(2 x 2 x 44 minutes x IDR 17,758)/60
Time loss while waiting for 2°facility	2 visit x Patient waiting time at secondary facility x Patient wage rate	(2 x 35 minutes x IDR 17,758)/60
Time loss while receiving cryosurgery	1 visit x Patient time spent for cryosurgery x Patient wage rate	1 x 20 minutes x IDR 17,758)/60
Cost of LEEP (cLEEP)		
Direct medical cost		
Cost of treatment + cost of follow-up	(no hospitalization, 2 F/U visit)	IDR 208,804 + 921,582
Direct non-medical cost		
Transportation cost	3 visit x Patient traveling cost for a visit of	3 x IDR 37,069

Cost category and components	Resource identification	Valuation
	secondary facility	
Time loss while transport	3 visit x 2 x Patient one-way traveling time to secondary facility x Patient wage rate	(3 x 2 x 44 minutes x IDR 17,758)/60
Time loss while waiting for 2°facility	3 visit x Patient waiting time at secondary facility x Patient wage rate	(3 x 35 minutes x IDR 17,758)/60
Time loss while receiving LEEP	1 visit x Patient time spent for LEEP x Patient wage rate	1 x 30 minutes x IDR 17,758)/60
Time loss while follow-up	2 visit x Patient time spent for FU x Patient wage rate	2 x 15 minutes x IDR 17,758)/60
Cost of cold knife conization (cColdknife)		
Direct medical cost		
Cost of treatment + cost of follow-up	(6 hospitalization days, 2 F/U visit)	IDR 3,454,425 + 921,582
Direct non-medical cost		
Transportation cost	3 visit x Patient traveling cost for a visit of secondary facility	3 x IDR 37,069
Time loss while transport	3 visit x 2 x Patient one-way traveling time to secondary facility x Patient wage rate	(3 x 2 x 44 minutes x IDR 17,758)/60
Time loss while waiting for 2°facility	3 visit x Patient waiting time at secondary facility x Patient wage rate	(3 x 35 minutes x IDR 17,758)/60
Time loss while receiving cold knife conization	6 hospital patient day x minimum daily wage rates	6 x IDR 17,758
Time loss while follow-up	2 visit x Patient time spent for FU x Patient wage rate	2 x 15 minutes x IDR 17,758)/60
Cost of simple hysterectomy (cSimhys)		
Direct medical cost		
Cost of treatment + cost of follow-up	(8 hospitalization days, 2 F/U visit)	IDR 6,327,947 + 921,582
Direct non-medical cost		
Transportation cost	3 visit x Patient traveling cost for a visit of secondary facility	3 x IDR 37,069
Time loss while transport	3 visit x 2 x Patient one-way traveling time to secondary facility x Patient wage rate	(3 x 2 x 44 minutes x IDR 17,758)/60
Time loss while waiting for 2°facility	3 visit x Patient waiting time at secondary facility x Patient wage rate	(3 x 35 minutes x IDR 17,758)/60
Time loss while receiving simple hysterectomy	8 hospital patient day x minimum daily wage rates	8 x IDR 17,758
Time loss while follow-up	2 visit x Patient time spent for FU x Patient wage rate	2 x 15 minutes x IDR 17,758)/60
Cost of Pap smear with negative result		
Direct medical cost	DMC of Pap smear screening	IDR 140,000
Direct non-medical cost	DNMC of Pap smear screening	IDR 71,068
Cost of Pap smear with positive result		
Direct medical cost	DMC of Pap smear + DMC of confirmation	IDR 856,280.73
Direct non-medical cost	DNMC of Pap smear + DNMC of confirmation	IDR 223,935
Cost of VIA with negative result		
Direct medical cost	DMC of VIA	IDR 40,000
Direct non-medical cost	DNMC of VIA	IDR 37,754
Cost of VIA with positive result		
Direct medical cost	DMC of VIA + Cryotherapy + F/U cryotherapy	IDR 454,105.63
Direct non-medical cost	DMC of VIA + Cryotherapy + F/U cryotherapy	IDR 81,427

Cost category and components	Resource identification	Valuation
Cost of pre-cancer treatment		
DMC of CIN-1	(Probability of treatment with cryotherapy for CIN-1 x DMC of treatment with cryotherapy for CIN-1) + (Probability of treatment with LEEP for CIN-1 x DMC of treatment with LEEP for CIN-1) + (Probability of treatment with conization for CIN-1 x DMC of treatment with conization for CIN-1) + (Probability of treatment with simple hysterectomy for CIN-1 x DMC of treatment with simple hysterectomy for CIN-1)	IDR 1,106,056
DMC of CIN-2/3 (after VIA)	(Probability of treatment with conization for CIN-2/3 x DMC of treatment with conization for CIN-2/3) + (Probability of treatment with simple hysterectomy for CIN-2/3 x DMC of treatment with simple hysterectomy for CIN-2/3)	IDR 1,507,346
DMC of CIN-2/3 (after Pap smear)	(Probability of treatment with cryotherapy for CIN-2/3 x DMC of treatment with cryotherapy for CIN-2/3) + (Probability of treatment with conization for CIN-2/3 x DMC of treatment with conization for CIN-2/3) + (Probability of treatment with simple hysterectomy for CIN-2/3 x DMC of treatment with simple hysterectomy for CIN-2/3)	IDR 1,921,452
DNMC of CIN-1	(Probability of treatment with cryotherapy for CIN-1 x DNMC of treatment with cryotherapy for CIN-1) + (Probability of treatment with LEEP for CIN-1 x DNMC of treatment with LEEP for CIN-1) + (Probability of treatment with conization for CIN-1 x DNMC of treatment with conization for CIN-1) + (Probability of treatment with simple hysterectomy for CIN-1 x DNMC of treatment with simple hysterectomy for CIN-1)	IDR 212,605
DNMC of CIN-2/3 (after VIA)	(Probability of treatment with conization for CIN-2/3 x DNMC of treatment with conization for CIN-2/3) + (Probability of treatment with simple hysterectomy for CIN-2/3 x DNMC of treatment with simple hysterectomy for CIN-2/3)	IDR 386,260
DNMC of CIN-2/3 (after Pap smear)	(Probability of treatment with cryotherapy for CIN-2/3 x DNMC of treatment with cryotherapy for CIN-2/3) + (Probability of treatment with conization for CIN-2/3 x DNMC of treatment with conization for CIN-2/3) + (Probability of treatment with simple hysterectomy for CIN-2/3 x DNMC of treatment with simple hysterectomy for CIN-2/3)	IDR 309,273

APPENDIX G

ESTIMATION OF COSTS OF ILLNESS OF CERVICAL CANCER

Standard treatment of invasive cervical cancer by cancer stage*

Cancer stage	Treatment	Description	Probability of patient receiving treatment
IA1	Surgery	If fertility is not desired (>45 years old): simple hysterectomy	90%
		If fertility is desired (<45 years old): cone biopsy:	10%
IA2	Surgery, if fertility is not desired	radical hysterectomy	90%
	Surgery, if fertility is desired	large cone biopsy	5%
		radical trachelectomy/cervicectomy	5%
IB1	surgery (plus adjuvant therapy post-surgery)/	radical hysterectomy + (5 radiotherapy and chemotherapy)	80%
	radiotherapy	4 weeks external pelvic irradiation + 4 weeks brachytherapy	20%
IB2 - IIA	chemoradiation	5 weeks chemotherapy + radiotherapy	20%
	Surgery and adjuvant radiation	radical hysterectomy + 5 weeks radiotherapy	40%
	neoadjuvant chemotherapy, surgery, and adjuvant post operatif radiation or chemoradiation	chemotherapy (3 weeks) + radical hysterectomy + (5 weeks radiotherapy)	20%
		chemotherapy (3 weeks) + radical hysterectomy + (5 weeks chemotherapy and radiotherapy)	20%
IIB - IVA	Irradiation and concurrent chemotherapy	6 weeks chemotherapy + radiotherapy	100%
IVB	palliative chemotherapy	chemotherapy (6 weeks)	50%
	chemoradiotherapy	radiotherapy + chemotherapy (5 weeks)	50%
Recurrence/ metastasis	chemotherapy	chemotherapy (6 weeks)	46.25%
	chemoradiotherapy	radiotherapy + chemotherapy (5 weeks)	46.25%
	pelvic exenteration	pelvic exenteration	7.50%

*Based on FIGO

Probability of recurrence in each stage*

Cancer stage	Probability of recurrence
I	11.60%
II	20.8%
III	30.0%
IV	13.0%

*Based on Ginsberg et al, 2009

Distribution of cervical cancer patients in Indonesia by stage*

Stage	Number of patient	Proportion among all stage	Proportion within each stage of I, II, III, and IV
IA1	68	0.66	0.047
IA2	15	0.15	0.010
IB1	878	8.50	0.610
IB2	478	4.63	0.332
IIA1	996	9.64	0.290
IIA2	103	1.00	0.030
IIB	2338	22.64	0.680
IIIA	243	2.35	0.050
IIIB	4625	44.78	0.950
IVA	311	3.01	0.533
IVB	273	2.64	0.467
Total	10,328	100.00	

***** Based on INASGO

List of costs of selected procedures for estimating direct medical cost of invasive cervical cancer

Procedure	**ALOS**	**Cost (IDR)**	**Source/ Justification**
Gynecological examination/observation	1	131,884	Estimated from INA-DRG 2008[a,b]
Abdominal ultrasound	1	220,780	
Chest x-ray	1	224,376	
Skeletal x-ray/bone scan	1	288,369	
Cytology test	1	205,301	
Conization	6	3,454,425	
Radiotherapy	6	2,386,286	
Chemotherapy	5	2,124,572	
Simple hysterectomy	6	3,454,425	
Radical hysterectomy	9	7,423,555	
Pelvic exenteration	9	7,423,555	
Physical and pelvic examination	1	131,884	
OP visit for cxca	1	224,376	
Unit cost of hospitalization at tertiary facility		313,172	WHO-CHOICE 2011
Cost of clinical staging for cervical cancer	6	3,457,218	c

[a]Costs were based on INA-DRG tariffs of four different classifications of hospital and calculated using weighted factors. Weighted factors were estimated from 4,129 admission records of cervical cancer patients based on database claims of PT Askes (health insurance provider) in Indonesia. The weighted factors for hospital classification of top referral, A, B, and CD were 0.07, 0.53, 0.23, 0.17; respectively.
[b]Costs were adjusted from year of 2008 to 2013 value using CPI; CPI 2008=91, CPI 2013=117.
[c]Cost of staging including costs of vaginal examination, abdominal ultrasound, colposcopy, cytology test, chest x-ray, skeletal x-ray/bone scan, and 6 days-hospitalization at tertiary facility.

Identification and valuation of direct medical cost of invasive cervical cancer

Cancer stage	Treatment type	Resource identification	Valuation
Initial therapy of invasive cervical cancer			
IA1	Simple hysterectomy (>40y)	pStage x pTreatment x Cost of simple hysterectomy	0.047 x 0.9 x IDR 3,454,425
	Cone biopsy (<=40 y)	Proportion of stage x Probability of receiving treatment x Cost of cone biopsy	0.047 x 0.1 x IDR 3,454,425
IA2	Radical hysterectomy (>40y)	pStage x pTreatment x Cost of radical hysterectomy	0.010 x 0.9 x IDR 7,423,555
	Large cone biopsy (<=40y)	Proportion of stage x Probability of receiving treatment x Cost of cone biopsy	0.010 x 0.05 x IDR 3,454,425
	Trachelectomy (radical hysterectomy)	pStage x pTreatment x Cost of radical hysterectomy	0.010 x 0.05 x IDR 7,423,555
IB1	Radical hysterectomy + chemoradiotherapy	pStage x pTreatment x (Cost of radical hysterectomy + 5 x (cost of chemotherapy + cost of radiotherapy))	0.610 x 0.8 x (IDR 7,423,555 + 5 x (IDR 2,124,572 + IDR 2,386,286))
	Radiotherapy + brachytherapy	pStage x pTreatment x (4 x Cost of radiotherapy + 4 x cost of brachytherapy)	0.610 x 0.2 x 8 x IDR 2,386,286
IB2	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.332 x 0.2 x 5 x (IDR 2,124,572 + 2,386,286)
	Radical hysterectomy + radiotherapy	pStage x pTreatment x (Cost of radical hysterectomy + 5 x cost of radiotherapy)	0.332 x 0.4 x (IDR 7,423,555 + 5 x IDR 2,386,286)
	Chemotherapy + radical hysterectomy + radiotherapy	pStage x pTreatment x (3 x Cost of Chemotherapy x Cost of Radical Hysterectomy + 5 x cost of Radiotherapy)	0.332 x 0.2 x (3 x IDR 7,423,555 + 5 x IDR 2,386,286)
	Chemotherapy + radical hysterectomy + chemoradiotherapy	pStage x pTreatment x (3 x Cost of Chemotherapy x Cost of Radical Hysterectomy + 5 x (cost of chemotherapy + cost of radiotherapy))	0.332 x 0.2 x (3 x IDR 7,423,555 + 5 x IDR 2,124,572 + IDR 2,386,286))
IIA	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.320 x 0.2 x 5 x (IDR 2,124,572 + 2,386,286)
	Radical hysterectomy + radiotherapy	pStage x pTreatment x (Cost of radical hysterectomy + 5 x cost of radiotherapy)	0.320 x 0.4 x (IDR 7,423,555 + 5 x IDR 2,386,286)
	Chemotherapy + radical hysterectomy + radiotherapy	pStage x pTreatment x (3 x Cost of Chemotherapy x Cost of Radical Hysterectomy + 5 x cost of Radiotherapy)	0.320 x 0.2 x (3 x IDR 7,423,555 + 5 x IDR 2,386,286)
	Chemotherapy + radical hysterectomy + chemoradiotherapy	pStage x pTreatment x (3 x Cost of Chemotherapy x Cost of Radical Hysterectomy + 5 x (cost of chemotherapy + cost of radiotherapy))	0.320 x 0.2 x (3 x IDR 7,423,555 + 5 x IDR 2,124,572 + IDR 2,386,286))
IIB	Chemoradiotherapy	pStage x pTreatment x 6 x (cost of chemotherapy + cost of radiotherapy)	0.680 x 1 x 6 x (IDR 2,124,572 + 2,386,286)

Cancer stage	Treatment type	Resource identification	Valuation
III	Chemoradiotherapy	pStage x pTreatment x 6 x (cost of chemotherapy + cost of radiotherapy)	1 x 1 x 6 x (IDR 2,124,572 + 2,386,286)
IVA	Chemoradiotherapy	pStage x pTreatment x 6 x (cost of chemotherapy + cost of radiotherapy)	0.533 x 1 x 6 x (IDR 2,124,572 + 2,386,286)
IVB	Chemotherapy	pStage x pTreatment x 6 x cost of Chemotherapy	0.467 x 0.5 x 6 x IDR 2,124,572
	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.467 x 0.5 x 5 x (IDR 2,124,572 + 2,386,286)
Treatment of recurrence invasive cervical cancer			
I	Chemotherapy	pStage x pTreatment x 6 x cost of Chemotherapy	0.116 x 0.4625 x 6 x IDR 2,124,572
	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.116 x 0.4625 x 5 x (IDR 2,124,572 + 2,386,286)
	Pelvic exenteration	pStage x pTreatment x cost of Pelvic exenteration	0.116 x 0.075 x IDR 7,423,555
II	Chemotherapy	pStage x pTreatment x 6 x cost of Chemotherapy	0.208 x 0.4625 x 6 x IDR 2,124,572
	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.208 x 0.4625 x 5 x (IDR 2,124,572 + 2,386,286)
	Pelvic exenteration	pStage x pTreatment x cost of Pelvic exenteration	0.208 x 0.075 x IDR 7,423,555
III	Chemotherapy	pStage x pTreatment x 6 x cost of Chemotherapy	0.3 x 0.4625 x 6 x IDR 2,124,572
	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.3 x 0.4625 x 5 x (IDR 2,124,572 + 2,386,286)
	Pelvic exenteration	pStage x pTreatment x cost of Pelvic exenteration	0.3 x 0.075 x IDR 7,423,555
IV	Chemotherapy	pStage x pTreatment x 6 x cost of Chemotherapy	0.13 x 0.4625 x 6 x IDR 2,124,572
	Chemoradiotherapy	pStage x pTreatment x 5 x (cost of chemotherapy + cost of radiotherapy)	0.13 x 0.4625 x 5 x (IDR 2,124,572 + 2,386,286)
	Pelvic exenteration	pStage x pTreatment x cost of Pelvic exenteration	0.13 x 0.075 x IDR 7,423,555
Treatment of follow up in subsequent year of invasive cervical cancer			
I to IV	physical and pelvic examination	pStage x pTreatment x cost of physical and pelvic examination	1 x 1 x IDR 131,884
	cytology	pStage x pTreatment x cost of cytology	1 x 1 x IDR 205,301
	OP visit for cxca	pStage x pTreatment x cost of OP visit for cervical cancer	1 x 1 x IDR 224,376
	Total cost per year	2 x cost of follow up	2 x (IDR 131,884 + 205,301 + 224,376)

pStage = proportion of patient in each certain stage; pTreatment = probability of patient in certain stage receiving certain treatment

Estimation of direct non-medical cost of invasive cervical cancer

Direct non-medical cost at hospital side

Variable	Stage of cancer				Source/ Justification
	I	II	III	IV	
Average cost of transportation per visit (IDR)	218,713				a*
Average cost of meal per person per day (IDR)	27,069				b*
Average number of IP visit for initial treatment per year	7.29	6.64	6.00	6.23	c**
Average number of OP visit for initial treatment per year	0	0	0	0	d**
Average number of IP visit for subsequent year per year	5.16	5.16	5.16	5.16	e**
Average number of OP visit for subsequent year per year	2	2	2	2	f**
Average LOS for initial treatment per patient within duration of treatment	61	60	61	55	g**
Average LOS for recurrence treatment per patient within duration of treatment	40	40	40	40	h**
Cost valuation					
Cost of transportation per patient per year (initial)	1,593,942	1,452,145	1,312,276	1,363,396	a x (c + d)
Cost of meal per OP visit per year (initial)	-	-	-	-	b x d x 2
Cost of meal of care giver per IP admission per year (initial)	1,655,115	1,635,627	1,651,207	1,493,034	b x g
Cost of meal per year (initial)	1,655,115	1,635,627	1,651,207	1,493,034	(b x d x 2) + (b x g)
Cost of transportation per patient per year (follow-up)	568,401	672,279	776,156	584,209	a x (e + f)
Cost of meal per OP visit per year (follow-up)	108,276	108,276	108,276	108,276	b x f x 2
Cost of meal of care giver per IP admission per year (follow-up)	125,561	225,143	324,726	140,715	b x h
Cost of meal per year (follow-up)	233,837	333,419	433,002	248,990	(b x f x 2) + (b x h)

* Based on primary data of patients' interview

** Estimated in respect to stage distribution of cervical cancer, probability of receiving certain treatment type, and ALOS of certain treatment type from INA-DRG

Direct medical and direct non-medical cost out of hospital side

Variable	Valuation	Stage of cancer			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
*Average number of visit per patient by health facility type (a)**					
alternative healing		0.08	0.02	0.17	0.25
hospital 1st level		1.58	0.83	1.27	0.75
hospital 2nd level		0.08	0.10	0.10	0.00
Midwife		0.00	0.05	0.03	0.00
Physician		0.58	0.20	0.40	0.25
Primary healthcare		0.25	0.15	0.27	0.25
*Average direct medical cost per visit by health facility type (IDR)(b)**					
alternative healing	5,154,000				
hospital 1st level	1,072,435				
hospital 2nd level	175,000				
Midwife	150,000				
Physician	626,300				
Primary healthcare	5,154,000				
Direct medical cost per patient by cancer stage (IDR)	**a x b**	**2,509,047**	**1,162,575**	**2,492,144**	**2,251,001**
*Average transportation cost per visit by health facility type (IDR)(c)**					
alternative healing	75,714				
hospital 1st level	37,069				
hospital 2nd level	28,875				
Midwife	20,000				
Physician	15,714				
Primary healthcare	15,556				
Transportation cost per patient by cancer stage (IDR)	**a x c**	**80,464**	**41,722**	**73,561**	**54,548**
Average meal cost per day (IDR)(d)	27,184				
Average OP visit per patient (e)		0.67	0.49	0.83	0.25
Average IP visit per patient (f)		1.92	0.85	1.33	1.25
Average LOS per IP admission (day) (g)		9	4	5	5
Cost of meal per patient by cancer stage (IDR)	**(d x e x 2) + (d x f x g)**	**497,724**	**122,914**	**224,720**	**183,491**
Direct non-medical cost per patient by cancer stage (IDR)	**Transportation + meal cost**	**578,189**	**164,636**	**298,282**	**238,039**

* Based on primary data of patients' interview

Indirect cost of invasive cervical cancer

Variable	Source/ Justification	Cancer stage			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
Indirect cost per patient for initial treatment of invasive cervical cancer					
Variable for estimation the cost					
Average OP visit at hospital	a*	0	0	0	0
Average OP visit at out of hospital side	b*	0.67	0.49	0.83	0.25
Average IP visit at hospital	c*	7.29	6.64	6.00	6.23
Average IP visit at out of hospital side	d*	1.92	0.85	1.33	1.25
Average LOS of IP at hospital for the whole treatment (day)	e*	61	60	61	55
Average LOS per IP visit at out of hospital side (day)	f*	9	4	5	5
Average of patient's time loss per OP visit (day)	g#	0.79	0.83	0.83	0.75
Average of caregiver's time loss per OP visit (day)	h#	0.79	0.83	0.83	0.75
Average of caregiver's time loss per day for patient's IP admission (day)	i#	0.94	0.89	0.93	0.88
Proportion of patient absent from work after treatment	j#	0.58	0.39	0.47	0.50
Number of day patient out of healthcare facility	k	286	301	297	303
Proportion of patient need informal care after discharge from hospital	l#	0.75	0.61	0.77	1.00
Time for providing informal care within a day (day)	m	0.17	0.17	0.17	0.17
Wage rate per day (IDR)	n	101,199			
Valuation					
Productivity loss of patient for OP visit at hospital	a x g x n = o	0	0	0	0
Productivity loss of patient for OP visit out of hospital side	b x g x n = p	53,410	40,937	70,277	18,975
Productivity loss of caregiver for OP visit at hospital	a x h x n = q	0	0	0	0
Productivity loss of caregiver for OP visit out of hospital side	b x h x n = r	53,410	40,937	70,277	18,975
Productivity loss of patient for IP admission at hospital	e x n = s	6,187,734	6,114,878	6,173,124	5,581,787
Productivity loss of patient for IP admission out of hospital side	d x f x n = t	1,717,969	358,847	667,912	632,492
Productivity loss of caregiver for IP admission at hospital	e x i x n = u	5,801,001	5,443,733	5,761,582	4,884,064
Productivity loss of caregiver for IP admission out of hospital side	d x f x i x n = v	1,610,596	319,462	623,384	553,431
Productivity loss of patient from work absent	j x k x n = x	16,895,886	11,869,055	14,005,683	15,348,983
Cost of informal care after discharge from hospital	k x l x n = y	3,620,547	3,090,900	3,834,889	5,116,328
Productivity cost of caregiver	q + r + u + v + y	**11,085,554**	**8,895,031**	**10,290,133**	**10,572,797**
Morbidity cost per patient	o + p + s + t + x	**24,855,000**	**18,383,718**	**20,916,995**	**21,582,237**

Variable	Source/ Justification	Cancer stage			
		Stage I	**Stage II**	**Stage III**	**Stage IV**
Indirect cost per patient for follow-up treatment of invasive cervical cancer in subsequent year					
Variable for estimation the cost					
Average OP visit at hospital	a*	2.0	2.0	2.0	2.0
Average IP visit at hospital	b*	5.2	5.2	5.2	5.2
Average LOS of IP at hospital for the whole treatment (day)	e*	40	40	40	40
Average of patient's time loss per OP visit (day)	g#	0.79	0.83	0.83	0.75
Average of caregiver's time loss per OP visit (day)	h#	0.79	0.83	0.83	0.75
Average of caregiver's time loss per day for patient's IP admission (day)	i#	0.94	0.89	0.93	0.88
Proportion of patient absent from work after treatment	j#	0.58	0.39	0.47	0.50
Number of day patient out of healthcare facility	k	323	323	323	323
Proportion of patient need informal care after discharge from hospital	l#	0.75	0.61	0.77	1.00
Time for providing informal care within a day (day)	m	0.17	0.17	0.17	0.17
Wage rate per day (IDR)	n	101,199			
Valuation					
Productivity loss of patient for OP visit at hospital	a x g x n = o	160,231	167,842	168,665	151,798
Productivity loss of caregiver for OP visit at hospital	a x h x n = q	160,231	167,842	168,665	151,798
Productivity loss of patient for IP admission at hospital	e x n = s	469,415	841,711	1,214,006	526,069
Productivity loss of caregiver for IP admission at hospital	e x i x n = u	440,077	749,328	1,133,072	460,310
Productivity loss of patient from work absent	j x k x n = x	2,211,919	2,653,346	4,576,385	2,124,750
Cost of informal care after discharge from hospital	k x l x n = y	473,983	690,976	1,253,058	708,250
Productivity cost of caregiver	q + u + y	**1,074,291**	**1,608,145**	**2,554,794**	**1,320,359**
Morbidity cost per patient	o + s + x	**2,841,566**	**3,662,899**	**5,959,055**	**2,802,617**

* Estimated in respect to stage distribution of cervical cancer, probability of receiving certain treatment type, and ALOS of certain treatment type from INA-DRG
# Based on primary data of patients' interview
k: calculated
m: assumed based on time of providing informal care for household work activity was 4 hours per day
n: calculated based on GNI per capita in 2013

Mortality cost

Age (year)	Life expectancy (year)	PVLE (IDR)	Age (year)	Life expectancy (year)	PVLE (IDR)
12	65	2,726,064,771	61	19	738,110,415
13	65	2,726,064,771	62	19	738,110,415
14	65	2,726,064,771	63	19	738,110,415
15	60	2,622,701,824	64	19	738,110,415
16	60	2,622,701,824	65	15	576,183,964
17	60	2,622,701,824	66	15	576,183,964
18	60	2,622,701,824	67	15	576,183,964
19	60	2,622,701,824	68	15	576,183,964
20	55	2,369,260,095	69	15	576,183,964
21	55	2,369,260,095	70	12	457,077,131
22	55	2,369,260,095	71	12	457,077,131
23	55	2,369,260,095	72	12	457,077,131
24	55	2,369,260,095	73	12	457,077,131
25	50	2,122,756,562	74	12	457,077,131
26	50	2,122,756,562	75	9	339,937,543
27	50	2,122,756,562	76	9	339,937,543
28	50	2,122,756,562	77	9	339,937,543
29	50	2,122,756,562	78	9	339,937,543
30	46	1,930,421,421	79	9	339,937,543
31	46	1,930,421,421	80	6	224,732,707
32	46	1,930,421,421	81	6	224,732,707
33	46	1,930,421,421	82	6	224,732,707
34	46	1,930,421,421	83	6	224,732,707
35	41	1,695,931,492	84	6	224,732,707
36	41	1,695,931,492	85	4	148,988,544
37	41	1,695,931,492	86	4	148,988,544
38	41	1,695,931,492	87	4	148,988,544
39	41	1,695,931,492	88	4	148,988,544
40	36	1,467,860,937	89	4	148,988,544
41	36	1,467,860,937	90	3	111,430,669
42	36	1,467,860,937	91	3	111,430,669
43	36	1,467,860,937	92	3	111,430,669
44	36	1,467,860,937	93	3	111,430,669
45	32	1,289,908,183	94	3	111,430,669
46	32	1,289,908,183	95	2	74,080,720
47	32	1,289,908,183	96	2	74,080,720
48	32	1,289,908,183	97	2	74,080,720
49	32	1,289,908,183	98	2	74,080,720
50	27	1,072,952,882	99	2	74,080,720
51	27	1,072,952,882	100	0	-
52	27	1,072,952,882			
53	27	1,072,952,882			
54	27	1,072,952,882			
55	23	903,672,840			
56	23	903,672,840			
57	23	903,672,840			
58	23	903,672,840			
59	23	903,672,840			
60	19	738,110,415			

APPENDIX H
ESTIMATION UNIT COST OF SCREENING AND VACCINATION FOR USED IN BUDGET IMPACT ANALYSIS

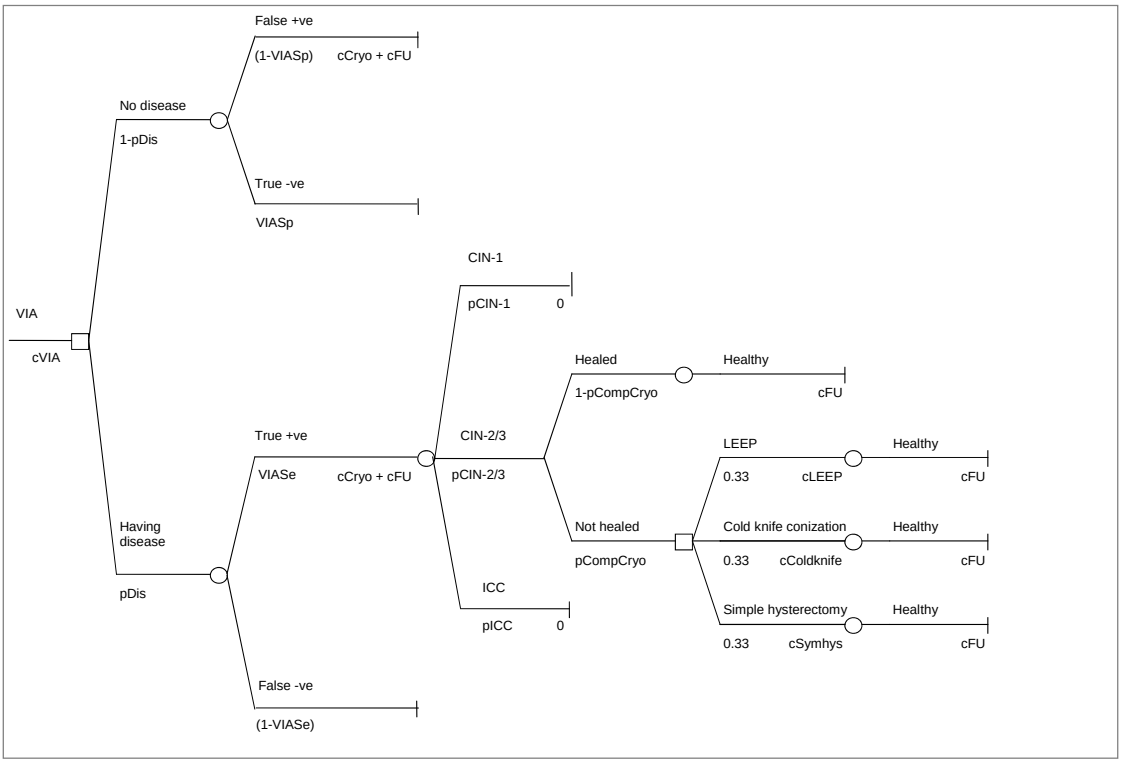
Valuation of unit cost of vaccination and screening

Cost of vaccination program	**2 doses**	**3 doses**	**Source/ Justification**
Cost of HPV vaccination per individual target (IDR)	**1,100,000**	**1,650,000**	WHO-C4P tool output
Cost valuation of screening program	**Value**		**Source/ Justification**
	VIA	**Pap smear**	
Variable for costs valuation based on decision tree			
Sensitivity	0.77	0.59	Previous study by Chen et al, 2012
Specificity	0.87	0.94	
Probability of false positive	0.13	0.06	Calculation based on sensitivity and specificity
Probability of true negative	0.87	0.94	
Probability of true positive	0.77	0.59	
Probability of false negative	0.23	0.41	
Proportion of having disease	0.03	0.03	Previous study by Vet et al, 2012
Proportion of disease free	0.97	0.97	
Proportion of having CIN-1	0.013	0.013	
Proportion of having CIN-2/3	0.012	0.012	
Proportion of having ICC	0.005	0.005	
Cost of providing screening	40,000	140,000	Calculation based on Decision tree model; See Appendix D
Cost of follow up for false positive	414,106	716,281	
Cost of follow up for False negative	0	0	
Cost of follow up for True negative	0	0	
Cost of follow up for True positive CIN-1	414,106	716,281	
Cost of follow up for True positive CIN-2/3	1,561,501	1,975,606	
Cost of follow up for True positive ICC	28,473,635	28,473,635	*
Cost valuation			
Cost of screening per cohort	40000	140,000	Calculation based on Decision tree model
Cost of F/U screening for pre-cancer treatment per cohort	70,792	61,169	
Cost of F/U screening for ICC treatment per cohort	96,313	73,798	
Total cost of screening per individual target (IDR)	**207,105**	**274,967**	

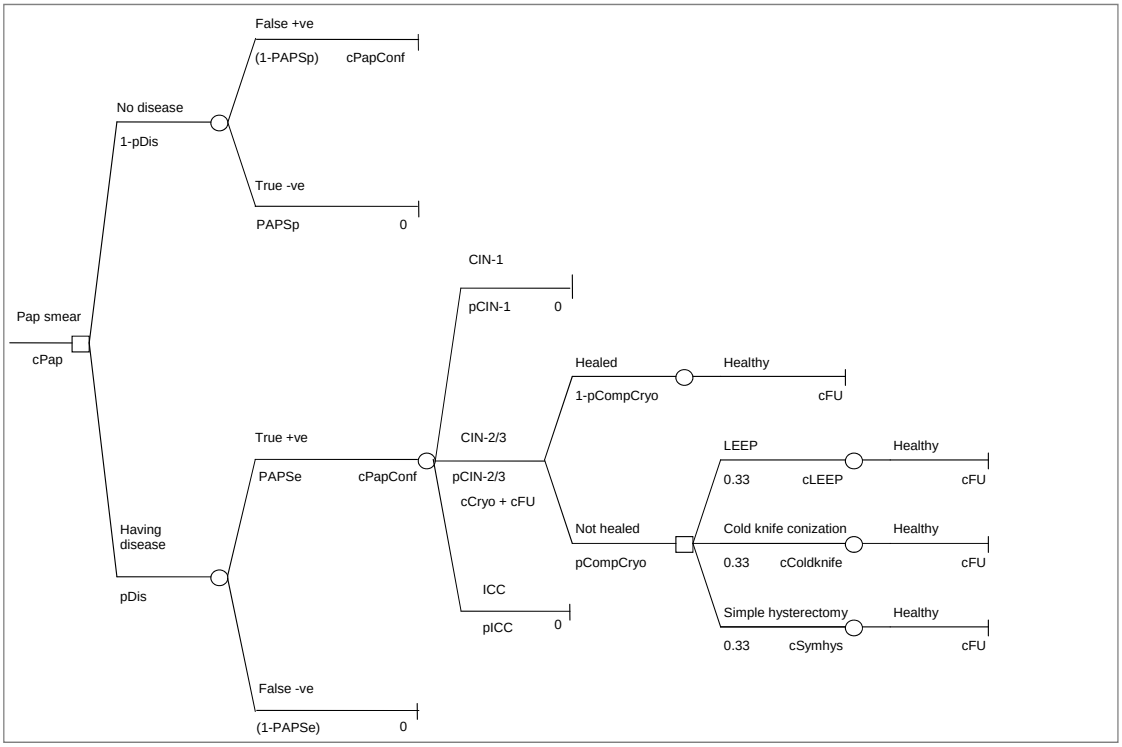
*Average cost of invasive cervical cancer treatment stage I to IV and cost of staging; calculated using weighted average of stage distribution

The decision tree used to estimate the unit cost of screening per individual target

(A): Cost of screening with VIA



(B): Cost of screening with Pap smear



APPENDIX I

EVALUATION OF HEALTH RELATED QUALITY OF LIFE OF CERVICAL CANCER PATIENT IN INDONESIA

Comparison of utility calculation methods using the different value sets of Malaysia, Thailand, Singapore, and UK*

Value sets	Malaysia	Thailand	Singapore	UK
Full health (health state 11111)	1	1	1	1
Starting value	1	1	1	1
Constant (at least one level 2 or 3)	-0.067	-0.202	0	-0.081
N3 (at least one level 3)	-0.116	-0.139	-0.2905	-0.269
Mobility level 2	-0.084	-0.121	-0.1678	-0.069
Mobility level 3	-0.191	-0.432	-0.3040	-0.314
Self-Care level 2	-0.097	-0.121	-0.1615	-0.104
Self-Care level 3	-0.16	-0.242	-0.3465	-0.214
Usual Activity level 2	-0.053	-0.059	-0.2555	-0.036
Usual Activity level 3	-0.122	-0.118	-0.3209	-0.094
Pain and discomfort level 2	-0.054	-0.072	-0.1462	-0.123
Pain and discomfort level 3	-0.127	-0.209	-0.2291	-0.386
Anxiety and depression level 2	-0.081	-0.032	-0.1501	-0.071
Anxiety and depression level 3	-0.086	-0.110	-0.2784	-0.236

Notes: *adapted from[7-10]

Patients' characteristics

Characteristic		N (%)
Age (year)	Mean ± SD	51 (8.9)
Duration of illness (month)	Mean ± SD	6.7 (9.0)
Cancer stage (N=87)	I	12 (13.8%)
	II	44 (50.6%)
	III	27 (31.0%)
	IV	4 (4.6%)
Education level (N=80)	Not attending school	13 (16.2%)
	Elementary school	34 (42.5%)
	Junior high school	9 (11.3%)
	Senior high school	19 (23.8%)
	University degree	5 (6.2%)
Employment status (N=86)	Unemployed	25 (29.1%)
	Part-time job	12 (14.0%)
	Self-employed	34 (39.5%)
	Paid-employed	15 (17.4%)
Marital status (N=86)	Married	71 (82.6%)
	Single	15 (17.4%)

Frequency of EQ-5D-3L health states

EQ-5D health states	Number of patients	Percentage (%)
11111	12	13.8
11112	11	12.6
11121	15	17.2
11122	13	14.9
11221	3	3.5
11113	2	2.3
11223	2	2.3
21222	3	3.5
22221	2	2.3
33333	1	1.2
Others (23 different health states)	23	26.4
Total	87	100

Patients' responses to EQ-5D descriptive system in each dimension

Dimension	No problem		Moderate problem		Severe problem	
	n	%	n	%	n	%
Mobility	67	77.0	14	16.1	6	6.9
Self-care	73	83.9	9	10.3	5	5.8
Usual activity	58	66.7	25	28.7	4	4.6
Pain	28	32.2	48	55.2	11	12.6
Anxiety	37	42.5	36	41.4	14	16.1

Descriptive statistics of EQ-5D VAS scores by cancer stages

Stage of cancer	**Mean**	**SD**	**95% CI of mean**	**Median**	**Range**
I	84.17	15.79	74.14–94.20	90	50–100
II	76.41	14.76	71.92–80.90	80	50–100
III	72.04	20.49	63.93–80.14	75	10–100
IV	70	13.54	48.46–91.55	75	50–80
All stages	75.83	17.03	72.20–79.46	80	10–100

Abbreviations: EQ-5D VAS, EuroQol five-dimensional visual analog scale; SD, standard deviation; 95% CI, 95% confidence interval.

Descriptive statistics of utility scores calculated using the Malaysia, Thailand, Singapore and UK value sets

Value set	**Mean***	**SD**	**95% CI**	**Median**	**Range**
Malaysia	0.757	0.202	0.714–0.800	0.793	0.131–1
Thailand	0.595	0.326	0.525–0.664	0.693	-0.454–1
Singapore	0.537	0.464	0.438–0.636	0.704	-0.769–1
UK	0.608	0.384	0.526–0.689	0.727	-0.594–1

Notes: *Friedman test between utility scores derived from value sets of Malaysia, Thailand, Singapore and UK: $p<0.001$. Wilcoxon signed rank test between Malaysia and Thailand/Singapore/UK: $p<0.001$; Singapore and UK: $p<0.001$; Singapore and Thailand: $p<0.05$; Thailand and UK: $p=0.111$.

Agreement of EQ-5D VAS and EQ-5D Index scores derived from different value sets using intra-class correlation coefficients (r, 95% r)

Value set	Malaysia	Singapore	Thailand	UK	VAS
Malaysia	1	0.712 (0.591–0.802) **	0.879 (0.820–0.919) **	0.785 (0.689–0.854) **	0.512 (0.339–0.652) **
Singapore	0.712 (0.591–0.802) **	1	0.912 (0.868–0.941) **	0.947 (0.921–0.965) **	0.343 (0.144–0.515) *
Thailand	0.879 (0.820–0.919) **	0.912 (0.868–0.941) **	1	0.959 (0.937–0.973) **	0.420 (0.230–0.578) **
UK	0.785 (0.689–0.854) **	0.947 (0.921–0.965) **	0.959 (0.937–0.973) **	1	0.362 (0.165–0.537) **
VAS	0.512 (0.339–0.652) **	0.343 (0.144–0.515) *	0.420 (0.230–0.578) **	0.362 (0.165–0.537) **	1

*p<0.01; **p<0.001. ICC, intra-class coefficient correlation; 95% CI, 95% confidence interval; EQ-5D VAS, EuroQol five-dimensional visual analog scale.

Convergent validity of patients' characteristics and EQ-5D Index scores calculated using Malaysia, Singapore, Thailand, and UK value sets

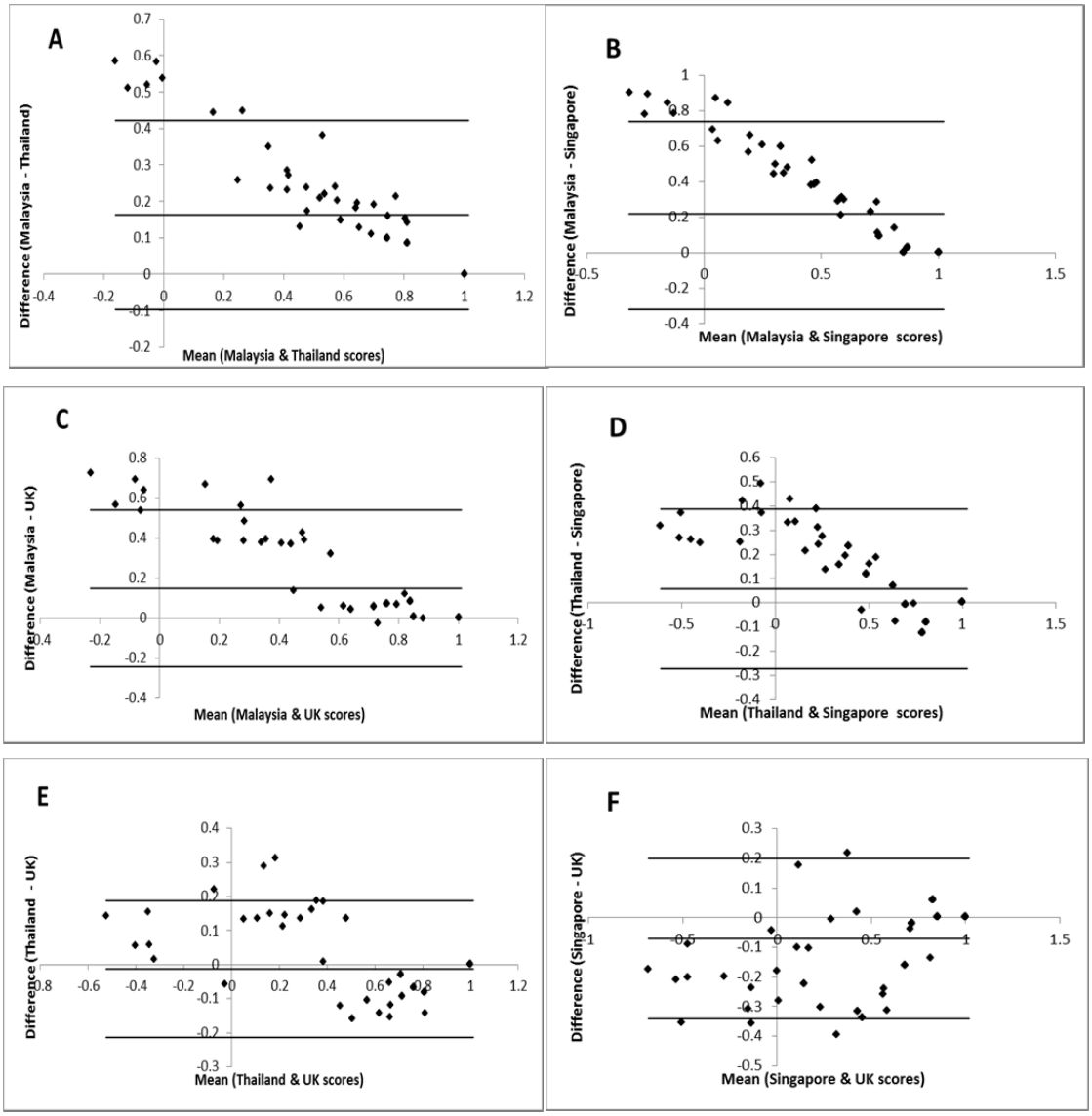
Characteristic	Spearman's rho correlation coefficient			
	Malaysia	Singapore	Thailand	UK
Age (year)	0.116	0.118	0.083	0.072
Marital status (2 level[#])	-0.074	-0.092	-0.108	-0.122
Education level (5 level[#])	-0.037	-0.064	-0.034	-0.059
Cancer stage (4 level[≠])	-0.242*	-0.249*	-0.237*	-0.222*
Duration of illness (month)	-0.225*	-0.251*	-0.222*	-0.222*

Known-group validity of EQ-5D Index scores calculated using Malaysia, Thailand, Singapore and UK value sets

Value set		EQ-5D Index scores classified by cancer stage		
		Stage I (n=12)	Stage II (n=44)	Stage III (n=27)
Malaysia	Median (range)	0.879 (0.267 - 1)	0.793 (0.131 - 1)	0.793 (0.136 - 1)
	p-value	0.032[a*]; 0.042[b*]; 0.011[c*]; 0.300[d]		
Singapore	Median (range)	0.854 (-0.576 - 1)	0.704 (-0.769 - 1)	0.598 (-0.641 - 1)
	p-value	0.017[a*]; 0.024[b*]; 0.005[c*]; 0.300[d]		
Thailand	Median (range)	0.726 (-0.316 - 1)	0.693 (-0.454 - 1)	0.666 (-0.375 - 1)
	p-value	0.054[a]; 0.064[b]; 0.018[c*]; 0.289[d]		
UK	Median (range)	0.796 (-0.371 - 1)	0.725 (-0.595 - 1)	0.725 (-0.429 - 1)
	p-value	0.071[a]; 0.076[b]; 0.022[c*]; 0.372[d]		

[a] p-value of Kruskall-Wallis test of EQ-5D utility scores between cancer stage of I, II, and III; [b] p-value of Man-Whitney U test of EQ-5D utility scores between stage of cancer I and II; [c] p-value of Man-Whitney U test of EQ-5D utility scores between stage of cancer I and III; [d] p-value of Man-Whitney U test of EQ-5D utility scores between stage of cancer II and III. EQ-5D, EuroQol five-dimensional; SD, standard deviation. *significant at p<0.05

Bland-Altman plots* of agreement between utility scores derived from a pair of value sets.



Notes: *The Bland-Altman plot shows the agreement of EQ-5D index score between each pair of value sets. The limits of agreement, indicated by the dotted lines in the graph, were obtained by using the formula as follow: d ± 1.96*SD of d. While d was the mean differences between EQ-5D utility scores of two value sets and SD was the standard of deviation of it. The more spot felt between the agreement lines represented the more agreement between two value sets [26].

A: Agreement between EQ-5D Index scores derived from MY and TH value sets; B: Agreement between EQ-5D Index scores derived from MY and SG value sets; C: Agreement between EQ-5D Index scores derived from MY and UK value sets; D: Agreement between EQ-5D Index scores derived from TH and SG value sets; E: Agreement between EQ-5D Index scores derived from TH and UK value sets; F: Agreement between EQ-5D Index scores derived from SG and UK value sets.

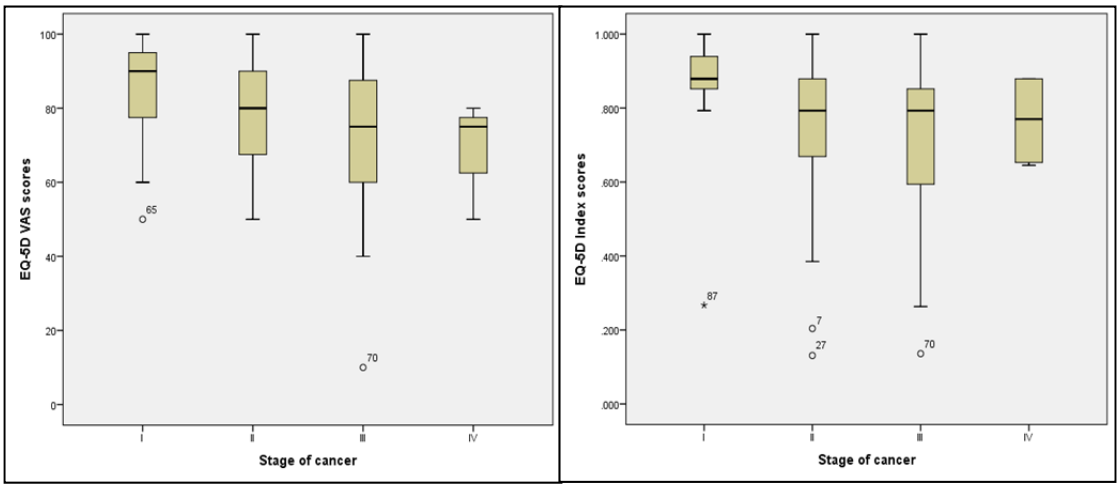
The bland-Altman plot of MY and TH, MY and SG, and MY and UK indicated that 91.95% of the difference scores were between the limits of agreement. While the proportion of the difference utility scores distributed between the limits of agreement for TH and SG, TH and UK, and SG and UK were 96.55%, 96.55%, and 95.40%, respectively.

Descriptive of EQ-5D VAS score and EQ-5D index score classified by cancer stage

Cancer stage	EQ-5D VAS scores					EQ-5D index scores*				
	Mean	SD	95% CI of mean Lower	Upper	SE	Mean	SD	95% CI of mean Lower	Upper	SE
I	84.2	15.8	74.1	94.2	4.56	0.85	0.19	0.73	0.97	0.06
II	76.4	14.8	71.9	80.9	2.23	0.76	0.20	0.70	0.83	0.03
III	72.0	20.5	63.9	80.1	3.94	0.71	0.21	0.63	0.79	0.04
IV	70.0	13.5	48.5	91.6	6.77	0.77	0.13	0.56	0.97	0.07
All stages	75.8	17.0	72.2	79.5	1.83	0.76	0.20	0.71	0.80	0.02

*calculated using Malaysia value set

Box plots of the distribution of EQ-5D VAS scores and EQ-5D index scores by cancer stage. The horizontal line is the median, the ends of the box are the upper and lower quartiles, and the vertical lines are the full range of values in the data.



APPENDIX J

ETHICAL APPROVAL

MINISTRY OF EDUCATION AND CULTURE
FACULTY OF MEDICINE GADJAH MADA UNIVERSITY
MEDICAL AND HEALTH RESEARCH ETHICS COMMITTEE (MHREC)

ETHICS COMMITTEE APPROVAL

Ref : KE/FK/ 369 /EC

Title of the Research Protocol	:	Economic Analysis of Strategies for Cervical Cancer Prevention and Control in Indonesia
Documents Approved	:	1. Study Protocol versi 01 2013 2. Information for Subjects versi 02 2013 3. Informed consent form versi 02 2013
Principle Investigator	:	Dwi Endarti
Name of supervisor	:	ASSOC. Prof. DR. Arthorn Riewpaiboon
Date of Approval	:	17 APR 2013
		(Valid for one year beginning from the date of approval)
Institution(s)/place(s) of research	:	RSUP Dr Sarjito Yogyakarta and PT Askes Jakarta

The Medical and Health Research Ethics Committee (MHREC) states that the above protocol meets the ethical principle outlined in the Declaration of Helsinki 2008 and therefore can be carried out.

The Medical and Health Research Ethics Committee (MHREC) has the right to monitor the research activities at any time.

The investigator(s) is/are obliged to submit:
□ Progress report as a continuing review : Annually
□ Report of any serious adverse events (SAE)
√ Final report upon the completion of the study

Prof.dr.Muhammad Hakimi, Sp.OG (K),Ph.D
Chairman

Dr. dr. Eti Nurwening Sholikhah, M.Kes
Secretary

Attachments:
□ Continuing review submission form (AF 4.3.01-014.2012-02)
□ Serious adverse events (SAE) report form (AF 6.1.01- 019.2012-02)

Recognized by Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP)
15-Apr-13

BIOGRAPHY

NAME	Mrs Dwi Endarti
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