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Original Research

Cost effectiveness of cervical cancer prevention strategies in Indonesia

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Abstract

Background: The development of several HPV-related control techniques for the prevention of cervical cancer followed the identification of a link between high-risk human papillomavirus (HPV) infection and the occurrence of cervical cancer. **Objective:** The objective of the current study was to determine how cost-effective the different cervical cancer screening programs and HPV vaccinations in Indonesia. **Methods:** The lifetime costs and effects of vaccination among adolescent girls or screening with either the VIA, Papanicolaou, or HPV DNA test at various time intervals in a hypothetical cohort of 30-65 years-old women were estimated using a Markov model based on a societal perspective. **Results:** Based on statistics on transition probabilities, efficacy of HPV vaccination, and diagnostic accuracy of screening procedures. The findings of this study, specifically the cost-effectiveness of preventing cervical cancer with vaccination, revealed that each woman's vaccination cost was $16. The amount of disease-adjusted life years (DALYs) that may be saved was $213, and the averted cost per death was $1.438. **Conclusion:** Early cervical cancer screening using the IVA test method has a net cost of $576 for years of quality-adjusted life saved and costs $18 each examination for each woman, $1,532 for each preventable death. When the group of teenage girls who received the HPV, vaccine reaches the age of 30, the VIA screening frequency should be decided depending on the cohort's overall HPV vaccination coverage.

Keywords: IVA test; HPV vaccine; cost effectiveness; cervical cancer

INTRODUCTION

Cancer can be a significant cause of death and a factor that affects the life expectancy of a country. Cervical cancer is one of the leading causes of cancer in women and is in the fourth rank in the prevalence of cancer in women.[1] Cervical cancer is cancer that occurs in the cervix, which is one of the female reproductive organs. The cervix (cervix) is a pathway that leads into the uterus and is located between the uterus and the vaginal canal. Cervical cancer is only cancer caused by infection with the oncogenic sub-type *Human Papilloma Virus (HPV).* Cervical cancer can be transmitted through casual sexual intercourse, which is often changing partners. Transmission of this virus can occur through the genital organs to the genitals, orally to the genitals, or manually the genitals.[2]

The incidence of cervical cancer cases is estimated at 570,000 cases, with a death rate of around 311,000 cases in 2018.[3] In 2012, 528,000 new cases of cervical cancer were found, and as many as 266,000 cases of death from this disease were found. About almost 90% of them are in low to middle income countries.[4]

A major health problem that occurs in women in Indonesia namely cervical cancer because of the high incidence and one of the cancers which is the highest cause of death for women. The *World Health Organization* (WHO) states that in Indonesia in 2020, the incidence of cervical cancer cases will be 36,633 cases (9.2%) of the total cancer cases. Cervical cancer ranks second after breast cancer in the order of cancer incidence in Indonesia.[1] In 2020 there were 50,171 cases of cervical cancer and 5,847 suspected cervical cancer.[5] The high incidence of cervical cancer in Indonesia requires observation by implementing prevention and early detection. Prompt and appropriate treatment measures to achieve healing and increase life expectancy will be obtained if cervical cancer detection can be carried out at an early stage.[6]

The increase in the incidence and mortality of cervical cancer can be avoided by taking preventive measures and early detection. Preventive measures can be done by giving vaccines. Early detection aims to avoid delays in cervical cancer treatment so that it can increase healing in sufferers. Indonesia has implemented an early detection program using the Pap smear method, IVA (Visual Acetic Acid Infection) test, HPV (*Human Papilloma Virus*) test, coloscopy and pap net. Early detection of cervical cancer is often used, namely the IVA test, because it is the simplest method and can be carried out by basic health services.[6] In addition, the Indonesian government has included the provision of the HPV (*Human Papilloma Virus*) vaccine into the national immunization program targeting adolescent girls aged 9-14 years.[7]

All activities of prevention and early detection and treatment will cost money. All costs needed to carry out all cancer control

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activities are generally borne by insurance companies such as BPJS. In 2014 the cost of cancer was recorded at Rp.1.5 trillion and increased in 2015 to Rp.2.2 trillion. Until 2018, there was an increase in the burden of cancer costs by Rp.2.7 trillion with a total of 1.97 million cases. Cervical cancer is the type of cancer with the highest direct medical expenses, which is IDR 393 million (27.03%). Likewise, for the type of cancer in the female sex, cervical cancer is the highest direct treatment cost burden, which is Rp.392 million.[8]

The high burden of direct treatment costs for a disease is influenced by the high incidence and severity of the disease, including cervical cancer. Severity can occur due to delays in handling that can result in the length of the treatment process and have an impact on increasing the total cost required. The increase in the incidence of cervical cancer can be prevented by giving the HPV vaccine, and the severity can be avoided by early detection of cervical cancer so that treatment can be carried out quickly and precisely so that it can increase the rate of recovery of the sufferer. Therefore, prevention and early detection can reduce the burden of direct treatment costs for cervical cancer.

Implementation of an early detection and prevention program for cervical cancer will require substantial costs, especially in Indonesia, which is one of the countries with the highest population. Therefore, it is necessary to study the cost-effectiveness of the prevention strategy by vaccinating and early detection with the IVA method of cervical cancer testing with the aim of knowing the value of the *cost-effectiveness* of early detection by the IVA test and treatment of cervical disease so that it can be used as an evaluation material for the cost burden and control of cervical cancer for policymakers in Indonesia.

RESEARCH METHODS

Markov model development

In order to estimate the lifetime costs and effects in a hypothetical cohort of 30 years old women undergoing screening from a societal perspective, we conducted a model-based cost-utility study. The decision model specifically employed a sample of 11-year-old preadolescent girls for the HPV vaccine scenario. One year was chosen as the model's cycle length. From 30 years onwards for screening and 11 years onwards for immunization, future costs and effects were discounted at a rate of 3%. Reductions in cancer incidence, mortality, life years (LYs), and quality-adjusted life years were used to measure the results (QALYs). We created a markov model on the basis of the previously published and validated models for cervical cancer.

Intervention strategies

We compared the introduction of 2 screening strategies namely, VIA, and HPV vaccination, respectively at 3 different screening intervals every 5 years and 10 years among women in the 30-65 years age group, compared with no screening. Next, the cost-effectiveness of the 2 additional scenarios of HPV vaccination alone, and the combination of vaccination and screening (HPV vaccination at 11 years followed by screening of eligible women) for vaccination when they were adolescents with the most cost-effective screening strategy later in life) was assessed.

Model parameters

An annual incidence rate of 0.8% for HPV infection (HPV 16 and 18) among women aged 20-25 years immunized with 2 doses of HPV vaccine [28] and a vaccine efficacy of 93%, was used to calculate the incidence rate of HPV infection as 11 .6% among unvaccinated groups of the same age group. Furthermore, using the HPV. prevalence differential infection among other age groups relative to 20-25 years, calculated the age-specific incidence of HPV infection up to 50 years of age. Over the age of 50 years, prevalence HPV infection increased more than 2-fold. The prevalence of HPV infection, precancerous lesions and invasive cancer among 30 years old women is based on Indonesian registry data and other major studies. In particular, the likelihood of progression from HPV infection to precancerous or invasive cancer and regression to earlier or normal stages was based on the combined estimates of the 2 meta-analyses. The age-specific all-cause mortality probabilities were obtained from the Indonesian Census. The sensitivity and specificity of the respective screening and colposcopy strategies and the efficacy of the HPV vaccine were based on meta-analyses.

RESULTS

Prevention of cervical cancer can be done by conducting an early detection program. The early detection program is carried out to treat cervical cancer more quickly and precisely so that it can prevent an increase in the severity of the sufferer. The early detection program in Indonesia is carried out with several methods of diagnosing cervical cancer, including VIA, *Pap smear*, HPV test, *cryotherapy, colposcopy*, and LEEP. Each of these methods has different costs.

Costs for vaccine doses and service delivery were split into two categories for calculating vaccination unit costs. We thought about two vaccine pricing hypotheses in which we changed the vaccine's per-dose cost by Gavi and non-Gavi eligible price. We assumed that the cost of vaccines will not change under any of the scenarios from 2015 to 2024. We gathered information on HPV vaccination delivery costs per dose from the literature that has already been published, and we limited our estimates to economic costs, which we defined as the price of all resources used by the health sector to provide services, independent of payer. Using GDP deflators and exchange rates, all expenses were converted to 2022 US dollars. We anticipated that the cost of delivery did not change as vaccine coverage increased. To extrapolate stated costs for the delivery of the HPV vaccine from their initial conditions. Table 1 shows that the IVA method is an early detection method with the lowest cost, which is $4.87, followed by the *Pap smear method* at $5.38. The most expensive prevention method, the LEEP method, is $112.34.

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Table 1. Types of cervical cancer prevention strategies and unit costs in Indonesia

Strategies	**Unit cost ($)**
IVA	4.87
PAP smear	5.38
HPV test	10.52
Cryotherapy	25.99
Colposcopy/biopsy	78.45
LEEP	112.34

Prevention of cervical cancer can be done by giving vaccines, namely the HPV vaccine with *the brand* Gardasil and Cervarix, at the cost of $4.55. The HPV vaccine can be given to women aged 10-26 years and given as many as 2 doses with a range of administration not more than 1 year. In addition, cervical cancer prevention can be done by early examination, one of the methods that are often used, namely VIA examination. Routine VIA examinations are carried out every 5 years, such as at the age of 35 years, 40 years, 45 years, and 50 years. Based on table 2, shows that the HPV vaccine with an increased vaccination program for 10 years has cost $10.32 Billion, and the cervical cancer screening using the IVA method has cost $12.34 Billion for 10 years.

Table 2. A 10-year program cost of scenarios for scaling up vaccination and screening and prevention in Indonesia

Screening program		**Program cost in 10 years (Billion $)**
Vaccinations*	2 doses	10.32
Screening using VIA**	screening every 5 years	12.34

*Gardasil or cervarix $4.55 (Gavi price)
**VIA or PAP at age 35,40,45,50

IVA test is a method of examination or early detection of cervical cancer, which is done by looking directly at the cervix after the cervix is smeared with 3-5% acetic acid solution. The IVA test is an early detection method that can be carried out by early-level health facilities because the IVA test method can be carried out by nurses, midwives or general practitioners at a reasonably affordable cost and only requires simple tools.[6]

Pap smear examination is an examination procedure to determine the presence or absence of potential cervical cancer to find abnormal cells that can develop into cancer cells. *Pap smear* examination can be done in hospitals, laboratories or institutions that provide *pap smear examinations*.[6]

Cryotherapy is a cervical cancer treatment procedure that can be performed in early-stage cervical cancer by destroying controlled cancer cells with the temperature reduction method.[9] *Colposcopy/biopsy* is a method used to examine cervical cancer using a colposcope in the form of a binocular microscope. The HPV test is an examination of cervical cancer with the aim of detecting the presence of HPV (*Human Papilloma Virus*) infection. LEEP (*Loop Electrosurgical Excision Procedure*) is an examination and treatment of cervical cancer patients by removing abnormal cells or cancer cells in the cervical area.[6]

Prevention of an infectious disease can be done by vaccinating, including cervical cancer. The implementation of HPV vaccine vaccination can reduce or prevent an increase in morbidity, mortality and disability due to cervical cancer.[10] Table 3 shows that cervical cancer prevention by giving the HPV vaccine can avoid cervical cancer treatment costs of $1.82 with a net cost of $1.18. The cost-effectiveness of vaccination on vaccination costs per woman is $16. In this study, vaccination prevention had an avoided cost per death of $1,438, and a total avoided cost-adjusted morbidity year (DALYs) of $213.

Table 3. HPV vaccination program costs, health outcomes, and cost-effectiveness

Program cost		**$**
Cancer treatment costs averted	discounted	1.82
	undiscounted	1.93
Cancer treatment costs averted		0.32
net cost		1.18
Treatmentsaving as a percentage of program costs		19.21
Health outcomes		
Vaccinated girls		4,250
Casesaverted		1,537
Death averted		1,238
DALYs averted		5,480
cost-effectiveness		
The program cost per vaccinated girl		16
The program cost per death averted		1,438
Net cost per DALYs averted		213

The early examination can be carried out to prevent an increase in severity in cervical cancer patients so that it can be handled quickly and appropriately to reduce mortality, disability and morbidity. Table 4 shows that early cervical cancer examination with the IVA test method can prevent cervical cancer treatment costs of $0.43. The cost of each examination per woman is $18. Early screening using the IVA test had an avoidable cost per death of $1,532 and a net cost per year of life adjusted for avoidable disability of $576.

DISCUSSION

The cost of vaccines is a significant contributor to the entire cost of cervical cancer prevention. In our 10-year roll-out scenario, if Indonesia, which was unable to join GAVI, had to pay double the F price (i.e., 2 x 13.79 per dose), the cost of vaccinations would increase globally by almost 50%, amounting to US$10.2

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Table 4. IVA program costs, health outcomes, and cost-effectiveness		
Program cost		**$**
Screening and lesion treatment	discounted	1.72
	undiscounted	1.92
Cancer treatment costs averted		0.43
net cost		1.21
Treatment saving as a percentage of program costs		23.43
Health outcomes		
Screening		6,590
Casesaverted		1,436
Death averted		1.125
DALYs averted		5,673
Cost-effectiveness		
The program cost per screening per woman		18
The program cost per death averted		1.532
Net cost per DALYs averted		576

billion over the course of 10 years. Naturally, over a longer time frame, it is realistic to anticipate a slight drop in vaccine prices as talks proceed, markets develop, and more significantly as patents expire and generic vaccines hit the market. However, these results highlight the significance of vaccine price negotiations in middle-income nations that are ineligible for the Gavi program.[11]

Numerous other studies have demonstrated that, overall, vaccination and screening offered very good value for money.[12-15] According to our study, a vaccination program with the favorable baseline 2-tier pricing scenario will avoid 1.5 million cases and 1.3 million cervical cancer deaths over the lifetimes of the 4250 women who received the vaccine during the decade of the program's scale-up (2015-2024). The program also has the advantage of avoiding the expense of cervical cancer therapy. A third of the expense of the immunization program was actually covered by avoided treatment expenditures. After deducting the cost of therapy, the vaccination program would typically cost $5480 to prevent a disability-adjusted life year (DALY). This was a really good deal that was far less than the threshold of 1 times GDP per capita.

Additionally, the IVA screening scenario offer considerable value. Similar to HPV vaccination, cost savings from reduced treatment expenses cover at least one-third of the program's expenses. The IVA screening program provides primary screening to 6590 women over the course of a decade, preventing 1,4 thousand cases and 1,1 thousand deaths from cervical cancer during the course of these women's lifetimes. The cost per DALY averted is a very favorable $5673, which shows that even the IVA screening program, which uses HPV testing in all but low-income settings and screening is every five years between the ages of 30 and 49, also appears to be a very good value in comparison to GDP-based cost-effectiveness benchmarks.

Our analysis did not consider HPV testing more frequently than every five years, and our current models are not calibrated to foretell the effects of cervical screening on women who are HIV-positive in terms of their health. In a few hyper-endemic areas, we anticipate that the costs and benefits of targeted high frequency screening among women with known HIV infection could be significant. Despite the moderately increased risk of cervical cancer associated with HIV, a policy of frequent screening among HIV-infected women who are identified and receiving HIV care is not anticipated to significantly increase the global cost estimates we have calculated because the proportion of women in Indonesia who are HIV-infected is low.

We concentrated on the screening and triage methods advised by WHO recommendations.[16,17] Therefore, we evaluated an HPV-based screening strategy with VIA triage for HPV-positive women in nations with sufficient resources to offer a series of tests. The WHO recommendations advise either continuing with Pap testing or recommending an HPV test followed by colposcopy for nations with Pap programs that already exist and meet quality standards.[16]

The costs of delivering the HPV vaccine that we took into consideration were mostly based on demonstration programs, which may have underestimated the expenses if national scale-up were to occur. However, it is important to highlight that extrapolated HPV vaccine delivery costs in this research appear to be close to recent estimates of the typical delivery costs related to the conventional EPI vaccines. We extrapolated these costs using the WHOCHOICE tool to take advantage of the correlation between healthcare costs and GDP per capita across settings since published and primary cost data on HPV vaccine delivery, cervical cancer screening, and preventive treatment are only available for a small number of settings.[17] We cannot be positive that the published and primary data cost estimates we used contain comparable components due to differences in cost reporting throughout the literature. In order to address this, we considered all information that was accessible and sufficiently stated, and we used the projected values' average to adjust for variability and uncertainty.

This analysis has a number of limitations, including assumptions and restrictions related to epidemiologic data. We assumed that the Globocan estimates of cancer incidence and mortality would remain steady during the lifetimes of 10-year-old girls and women who were screening-eligible during the intervention period due to the paucity of data on long-term disease patterns.[19] In many settings, where there was a lack of country-specific epidemiologic data,[20] we relied on model-based extrapolation techniques. For example, we predicted the prevalence of HPV based on cancer incidence using a multivariate regression and the prevalence of lesions using a microsimulation model calibrated to the Indonesian setting.[21] In order to account for outliers, we looked at extrapolated estimates of the HPV prevalence. Additionally, we estimated the effectiveness of screening in terms of cancer incidence using the microsimulation models.

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CONCLUSION

Both HPV vaccine and IVA screening offer excellent value for public health, however, whereas the advantages of screening can be seen immediately in terms of health, those of HPV vaccination won't be felt for several years.

For the foreseeable future, HPV vaccination and IVA screening will be necessary for the prevention of cervical cancer on a comprehensive scale. These initiatives offer chances to enhance primary healthcare systems and lessen cancer disparities. We anticipate that our study will stimulate the ongoing policy debate to swiftly secure the required funding and to facilitate national-level discussions on the implementation of healthcare delivery strategies to rapidly scale up HPV vaccination and cervical cancer screening.

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