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02. Cost Utility Analysis of Human Papillomavirus Vaccination and Cervical Screening on Cervical cancer Patient in Indonesia

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Cost Utility Analysis of Human Papillomavirus Vaccination and Cervical Screening on Cervical cancer Patient in Indonesia

Abstract

Background Although cervical cancer is a preventable disease, the clinical and economic burdens of cervical cancer (worldwidescience.org) are still substantial issues in Indonesia.

Methods We developed a population-based Markov Model, consisting of three health states (susceptible, cervical cancer and death) to assess future costs, health effects and the cost-utility of cervical cancer (worldwidescience.org) prevention strategies in Indonesia. We followed a cohort of 100,000 women from 12 to 100 years old and compared Visual Inspection with Acetic acid (VIA) screening (worldwidescience.org) alone with the addition of Human Papillomavirus (HPV) vaccination on (orwh.od.nih.gov) top of the screening to no intervention.

Results The implementation of VIA screening alone and in combination with HPV vaccination would reduce the cervical cancer incidence (orwh.od.nih.gov) by 7.9% and 58,5%, corresponding to 25 and 98 deaths avoided within the cohort of 100,000, respectively. We also estimated that HPV vaccination combined with VIA screening apparently yielded a lower incremental cost-effectiveness ratio (ICER) at I\$1,863/QALYs, compared to VIA screening alone (I\$3,126/QALYs). Both strategies could however be definitely labeled as very cost-effective interventions, based on a threshold suggested by the World Health Organization. The ICER was sensitive to the discount rate, cervical cancer treatment costs and quality of life as part of the QALY.

Conclusion The addition of HPV vaccination on top of VIA screening could be a cost-effective strategy in Indonesia even if relatively conservative assumptions are applied. This population-based model can be considered as an essential tool to inform decision makers on designing optimal strategies [for cervical cancer \(www.science.gov\)](#) prevention in Indonesia.

Keywords: Cost utility analysis, cervical cancer, human papillomavirus, vaccination, Indonesia

Introduction

[first level header]

Cervical cancer is the second most common [cancer among women in Indonesia](#). The age-standardized [cervical cancer incidence and mortality rates \(www.science.gov\)](#) per 100,000 women in 2012 were 17.3 and 8.1, respectively (1). The long onset of cervical cancer development (2,3) enables the application of cervical screening to prevent and control cervical cancer. Despite the poor sensitivity of Visual Inspection with Acetic acid (VIA) screening (4), it is the most commonly recommended screening strategy for countries with limited resources (5). Well-organized VIA screening programs definitely decrease the burden of cervical cancer at relatively low costs (6,7). The Ministry of Health, Republic of Indonesia launched a cervical cancer control program in 2007 and started a campaign recommending VIA screening for all susceptible women (8–10). Yet, several studies reported various barriers on the implementation of this program, such as limited screening coverage, poor quality of services and subsequent poor cryotherapy performance (11).

In addition to the screening program, the introduction of prophylactic HPV vaccination of girls against two high-risk HPV types (16 and 18) (12), which together are responsible for the large majority of cervical cancer development, offers primary prevention of cervical cancer (5,7). There are two available

HPV vaccines in the market and their efficacies against HPV infections and Cervical Intraepithelial Neoplasm (CIN) have been demonstrated in numerous clinical trials (13–17). Next to the efficacy and safety of vaccines, the available national budget for vaccination and affordability present other main considerations for a country to implement a vaccination program. Although the cost-effectiveness of HPV vaccination has been proven in many studies (18–22), those findings not necessarily apply to Indonesia as many differences in clinical profiles, patient- and population characteristics and health-care systems among countries exist.

Although a new health insurance system has been implemented from 2014 onwards in Indonesia, pharmacoeconomic studies have not yet been incorporated as a criteria into the decision-making process. However, cost-utility studies on cervical cancer prevention can provide valuable information for the decision maker to design the most cost-effective strategy to reduce the clinical and economic burdens of HPV-related disease among Indonesian women, within the limited budget. The main purpose of this study is to model the costs, clinical benefits and cost-utility of both VIA screening alone and HPV vaccination in addition to VIA screening in Indonesia. To interpret the findings from this study, we applied the WHO's threshold on cost-effectiveness of immunization programs (23,24).

Methods

[first level header]

Model overview

[second level header]

We developed a population-based Markov model for Indonesia by using Microsoft® Excel. The model (as shown in Figure 1) consists of 3 health states (susceptible, cervical cancer and death), which represents the major stages throughout the natural history of infection and cervical cancer. In citeseerx.ist.psu.edu our model, “susceptible for cancer” refers to healthy women, but also to infected women with CIN but (yet) without cancer. This simplification was made to accommodate with the

limited data availability in Indonesia; notably, more complicated models would lack the data to populate them. Additionally, in annual cycles, women may move through “cervical cancer” and citeseerx.ist.psu.edu “death” states. We hypothesized a cohort of 100,000 12-year-old girls before sexual debut as the initial situation in the model (25), followed until 100 years old. To estimate the natural history of cervical cancer, we applied the 2012 WHO’s life table on age-dependent incidence and mortality rate specific for cervical cancer in Indonesia (26,27). The transition from “cervical cancer” to “death” resulted from death caused by cancer as well as by other diseases. We performed our analysis from the payer’s perspective, based on national tariffs that were recently launched by the Ministry of Health for all treatments in primary care and hospitals (28).

We compared three strategies in the base-case: (i) without any intervention (reference); (ii) with VIA screening; (iii) with VIA screening and HPV vaccination. Both unvaccinated and vaccinated groups were followed in the model with differing risks until the potential screening process. Cryotherapy treatment was assumed to be performed among a part of positive individuals when pre-cancer stages would be detected. Specific proportions of deaths, cancer cases and recovered patients followed from VIA screening efficacies related to the prevention of cervical cancer (29). In addition, we assumed that 15.8% of new cervical cancer patients will have a recurrence and undergo an additional/recurrence treatment (30). The model parameters and baseline values specifically adopted for Indonesia can be seen in Table 1.

Screening and Vaccination

[second level header]

Despite the extensive communication and the introduction of the national VIA screening program in 2007, the performance of this program remains sub-optimal (11). In our study, we assumed implementation of the screening for 30- until 60-year-old women within an annual interval of 3 years if

the previous test was negative, according to the recommendation (8,9). We assumed that 63,6% of eligible (“susceptible” in the model) women would perform VIA screening every 3 years (29). We applied a detection rate of VIA screening of 69.4% (31) and an adherence rate to cryotherapy of 83.1% (11), based on previous studies in Indonesia. Furthermore, a study by Sankaranarayanan *et al.* showed that the incidence and mortality hazard ratios for screened women were 0.75 and 0.65, respectively, compared to unscreened women (29).

The vaccine efficacy against HPV type 16 and 18 infection was estimated from available clinical trials (13,32,33), without taking cross-protection against HPV types other than 16 and 18 into account in the base-case. The proportion of high-risk HPV (hrHPV) was estimated from three different studies in Indonesia (34–36). Although the duration of immunity induced by vaccination is formally unknown, we assumed lifelong vaccine-induced protection in the base-case similar with other studies (37–39). We also assumed that vaccination would be performed only at the start of followed cohort (i.e., at 12 years of age), with vaccination decreasing the transition probabilities from susceptible to cervical cancer. Vaccine coverage was assumed to be 76.6% based on the school enrollment rates (40) and the coverage of other vaccinations (measles, diphtheria and tetanus for 7-12 years old girls) in Indonesia (41).

Costs and Utilities

[second level header]

In this study, all costs were converted into 2013 International Dollars (I\$), using purchasing power parities conversion factors (42). With respect to the economic perspective, we only considered direct medical costs for cervical cancer treatment and all VIA screening-related activities, according to the national tariffs for primary and secondary healthcare services (28). Cervical cancer treatment costs (both initial and recurrent) were weighted by the cervical cancer treatment patterns for each stages of cervical cancer in Indonesia (34–36,43–46) and applied for every newly-detected cervical cancer patient. The

total costs for initial and recurrent treatments were I\$4,140 and I\$3,169, respectively. In the absence of a national vaccine price and availability of related relevant Indonesian information, we estimated all vaccine-related costs based on the Pan American Health Organization (PAHO) revolving fund, which consists of the price of a 3-dose vaccination (I\$39.71), revolving fund (I\$1.39), freight (I\$1.19), insurance and wastage cost (I\$1.99) (47). Thus, our assumption for the total vaccination costs would be I\$44.27.

We adopted utilities associated with cervical cancer patients based on the [Health and Activity Limitation Index \(HALex\)](#) (48), which allows to calculate [Quality-Adjusted Life Years \(www.who.int\)](#) (QALYs) by taking utilities and durations of health states into account. Finally, we systematically applied an annual discount rate of 3% for both future costs and utilities.

Model Outcome

[second level header]

We critically addressed the estimated epidemiologic and economic outcomes from each strategy. Predicted epidemiologic outcomes were the numbers of both prevented cervical cancer cases and deaths. Furthermore, as an economic outcome, we estimated the Incremental Cost Effectiveness Ratio (ICER) from the incremental costs divided by the incremental QALYs from preventive strategies, compared to no intervention. All outcomes were expressed for a cohort of 100,000 women through their lifetime in Indonesia.

Scenario and Sensitivity Analysis

[second level header]

We investigated the robustness of the ICERs by developing several scenarios with regard to booster dosing at 30 years of age (scenario I), if the booster dose would be required to obtain lifelong effectiveness of the vaccine. We also investigated the effect of cross protection against HPV types 31/33/45/52/58 at 25% efficacy (scenario II: low cross protection) (33) and 53% efficacy (scenario III:

high cross protection) (13). Also, we considered limited duration of vaccine-induced protection, specifically at 10 years (scenario IV: short protection) and 20 years (scenario V: medium protection) and waning of vaccine-induced immunity at 95% efficacy for 10 years, followed by exponential decrease at 50% efficacy during each following period of 20 years (scenario VI: slow waning) or 5 years (scenario VII: fast waning).

We based the vaccine price on PAHO revolving fund for the base-case scenario (47). In sensitivity analyses, we also explored potential reductions of the market price (75%, 50%, 25% discounts on I\$125.17) (49,50), both with and without booster dosing. Price reductions indicate potential advantages of economic upscaling and tendering effects if widespread vaccination would be considered to be implemented.

Univariate sensitivity analyses were performed by estimating the ICERs based on changes of maximum and minimum values for each parameter and assumption, in order to investigate the most influential parameters or assumptions in the model. Parameters included in the univariate sensitivity analyses were vaccine efficacy, vaccine coverage, efficacy of VIA screening for cervical cancer incidence and mortality, screening coverage, utilities for cervical cancer patients, cryotherapy coverage and its costs.

Probabilistic sensitivity analysis (PSA) was (journals.plos.org) taken into account by drawing one value for each parameter from its respective distributions simultaneously and estimate the ICER for each strategy correspondingly. We repeated this process up to 1,000 times to provide a range for the ICER. We developed a cost-effectiveness acceptability curve (CEAC) to describe the relationship between potential Indonesian cost-effectiveness thresholds and the ICER, using the net monetary benefit approach. (journals.plos.org) Based on the WHO's criterion (24), a new intervention in Indonesia would

be deemed very cost-effective and cost-effective if the ICER would be <1x and 1-3x GDP per capita (51), respectively (2013 GDP per capita was I\$3,475).

Results

[first level header]

Clinical Outcomes

[second level header]

The projected annual reduction in cervical cancer cases and deaths as a consequence of VIA screening or in combination with HPV vaccination are presented in Figure 2. Since the cervical cancer progression increases strongly after the age of 40, the effect of cervical screening is most evident in those particular ages. All susceptible women in the VIA screening group have an equal risk again on cervical cancer to unscreened women when the screening program stops after the age of 60. Oppositely, women in the vaccination group remain protected by the effect of HPV vaccination until the end of the model analysis. Assuming an 3 yearly screening coverage of 63,6% (29), screening would reduce the total incidence of cervical cancer from 1,842 cases to 1,697 cases (7.9% reduction), compared to no intervention. In addition to the screening, the effectiveness of HPV vaccination in reducing the incidence of cervical cancer is high, as shown in the figure 2A. Specifically, it reduces the incidence of cervical cancer up to 58.5% and 55,0%, compared to no intervention and screening alone, respectively.

The effectiveness of VIA screening and HPV vaccination on mortality cases would increase gradually after 30 years and attain a peak at 65 years after introduction. Figure 2B shows that the addition of HPV vaccination on top of cervical cancer screening would prevent substantial mortality. Specifically, these strategies reduce cervical cancer-related death during lifetime with 24,58 and 97.49 cases per 100.000 women for screening alone and screening plus vaccination, respectively.

Costs, QALYs and ICERs

[second level header]

Discounted costs and QALYs from each strategy are presented in Table 2. Discounted costs and QALYs from VIA screening combined with HPV vaccination (I\$5,588,654 and 2,724,504) are higher than discounted costs and QALYs from VIA screening alone (I\$3,393,833 and 2,723,129), both compared to no intervention. We also estimated that the ICER of VIA screening combined with HPV vaccination (I\$1,863) would be slightly lower than the ICER of VIA screening alone (I\$3,126). Apparently, based on PAHO revolving fund policy, both ICERs were still lower than the GDP per capita of Indonesia in 2013 (I\$3,475).

Sensitivity Analysis

[second level header]

The impact of all scenarios in costs and QALYs are presented in Table 3. An addition of a booster dose to achieve lifelong protection has a limited effect on the ICER (I\$3,040). Additionally, vaccine induced cross-protection against type 31/33/45/52/58 would increase the ICER up to I\$1,716 and I\$1,570 for low (scenario II) and high cross-protection (scenario III), respectively. Duration of vaccine-induced protection and waning immunity gives a significant effect on the ICER. Specifically, a short duration of vaccine-induced protection (scenario IV) affected the ICER strongly, raising it up to 5 times higher than the ICER in the base-case (I\$ 8,795).

We also investigated the influence of the vaccine price (compared to the assumed market price) for both with- and without booster dose scenarios (Figure 3). The implementation of HPV vaccination on top of VIA screening in Indonesia would not be cost-effective under the normal market price of HPV vaccine (I\$125.17) since the ICER would far above the Indonesian cost-effectiveness threshold of I\$10,425 per QALY gained (notably, I\$17,106 per QALY without a booster dose, and I\$27,092 per QALY with a booster dose). If a booster dose is not required to obtain lifelong protection, a 50% reduction

from the market vaccine price (I\$62.59) would achieve the ICER (I\$8,466) being below the threshold. With the booster dose taken into account, a 75% reduction (I\$31.29) keeps the ICER (I\$6,642) below the threshold (24,51).

We performed a PSA by running a Monte Carlo simulations to test the robustness of the model regarding the uncertainty surrounding the input parameters. A cost-effectiveness acceptability curve (CEAC) is presented in Figure 4. Applying a threshold of 1xGDP (I\$3,475), the probability to be cost-effective would be 72.2% and 99.8% for VIA screening alone and VIA screening combined with HPV vaccination, respectively. In addition, the full range of simulations fell below I\$7,200/QALYs and I\$3,150/QALYs for VIA screening alone and VIA screening combined with HPV vaccination, respectively.

We tested the influence of each parameter's changes on the cost-effectiveness ratio in a univariate sensitivity analysis. A minor change in a very sensitive parameter that alters the ICER strongly would be found in the top in the tornado diagram. We see that the most sensitive parameters in the VIA screening strategy are the utilities, the discount rate, and cervical cancer treatment costs. In addition, the ICER was mildly sensitive to cryotherapy coverage, detection rate of screening, cost of recurrence and VIA coverage (Figure 5A). The most sensitive parameters in the HPV vaccination in addition to VIA screening strategy were discount rates, utilities and cervical cancer treatment cost (Figure 5B).

Discussion

[first level header]

We developed a population-based Markov model to determine the cost-utility of cervical cancer prevention programs in Indonesia, including VIA screening with or without HPV vaccination. Our study revealed that either screening alone or screening in combination with HPV vaccination can relevantly decrease the incidence of cervical cancer and improve quality of life and survival. Since most of

developing countries, including Indonesia, have no explicit cost-effectiveness criteria to justify the implementation of a new intervention, we applied the WHO's recommendation on cost-effectiveness thresholds, stating that an intervention can be categorized as a cost-effective intervention if the ICER lies below three times the GDP per capita (24). As the GDP per capita of Indonesia in 2013 was approximately I\$3,475 (51), both VIA screening (I\$3,126) and VIA screening in combination with HPV vaccination (I\$1,863) compared to doing nothing can be considered as very cost-effective strategies. Specifically, the most cost-effective strategy is the combination of VIA screening and HPV vaccination. To our knowledge, **this is the first** cost-utility analysis of cervical cancer prevention strategies in Indonesia. However, the result of this study, that HPV vaccination on top of cervical screening could be a cost-effective intervention, is in line with **previous studies in other developing countries** (52–57).

We selected the payer's perspective for our study, which is in line with the new policy that has been implemented by the Indonesian government in early 2014 to cover almost all health-care services in primary and secondary settings (28,58). This method provides a clear picture of the average cost of cervical cancer treatment in Indonesia. Although, the cost of cervical cancer treatment in this study is estimated either lower (59) or higher (52,60) compared to other countries, the addition of HPV vaccination on top of VIA screening is considered as a cost-effective strategy as **in those other countries.** europe.theoil drum.com

As the long-term efficacy of the current HPV vaccination (www.bu.edu) has not been established, www.medicines.org.uk we investigated the possibility that a booster dose would be needed to achieve lifelong protection. As expected, the addition of a booster dose yielded a higher ICER, but the value itself remained below the GDP per capita of Indonesia. This finding is also **in accordance with** www.medicines.org.uk other studies in several settings (37,56,61). Moreover, the vaccine's

effectiveness [is not only \(europe.theoildrum.com\)](#) influenced by the implementation of a booster dose, but also by other variables such as vaccination coverage, the distribution of HPV types and adherence (29,56).

In this study, the effect of cross-protection against HPV types 31/33/45/52/58 is limited, as illustrated by limited reductions from I\$1,630 in the base-case to I\$1,488 and I\$1,346 for scenarios with low-and high effect of cross-protection, respectively. This finding is similar to several studies from other countries, that investigated the effect of cross-protection on cost-effectiveness (38,62). Despite [the fact that \(europe.theoildrum.com\)](#) the distributions of HPV types in various countries are evidently different (34–36) and that this considerably influences the overall vaccine effectiveness from a clinical perspective, cross-protection against other hrHPV types can be highly interesting in other settings in South-East Asia.

Based on a vaccine price derived from the PAHO revolving fund policy, the addition of vaccination yielded a cost-effective strategy in preventing cervical cancer. Yet, at the current market price of HPV vaccines it appears that the addition of HPV vaccination to VIA screening [is not a \(www.medicines.org.uk\)](#) cost-effective intervention in Indonesia. A range of 50-75% reductions from the vaccine market price is required to maintain HPV vaccination in combination with VIA screening as a cost-effective strategy. This result suggests that a reduction of HPV vaccine price, compared to market price will be essential for [the HPV vaccine \(www.bu.edu\)](#) to be included in the immunization schedule in Indonesia.

Notwithstanding [the fact that \(europe.theoildrum.com\)](#) a lack exists for data related to CIN or pre-cancer in Indonesia, our model can be considered to still validly and adequately estimate the natural history of cervical cancer patients in Indonesia based on actual epidemiological data from the WHO. For

example, the natural history of cervical cancer patients, [cervical cancer incidence \(www.bu.edu\)](#) and mortality rates for the population at risk could be described and implemented in the model. Notably, fewer assumptions were required in our model compared to a more complex Markov structure or even dynamic model, as we did not incorporate any transition to HPV infection or staging on pre-cancer and cancer stages. More complex modelling can be embarked upon if more data become available.

Despite the novelty of this study, it still has several limitations. Firstly, we did not take the vaccine protection for low risk HPV (type 6 and 11) into account. Although the data related to [the effectiveness of \(www.medicines.org.uk\)](#) both vaccines against other types of HPV is already available (63), the information related to the costs and QALYs caused by low-risk HPV (lrHPV) in Indonesia is scarce. Secondly, incorporation of genital warts as a consequence of HPV types 6 and 11 also will introduce further differences in clinical benefits (i.e. QALYs) between both available vaccines in the market. However to which extend this will be the case should be further investigated (64). Therefore, further research should be directed to the clinical burden and costs of genital warts in Indonesia to make a more precise comparison between both vaccines. Another limitation in this study is the potential benefit of HPV vaccines against non-cervical HPV-related cancers. Anal, vaginal, vulvar, and oropharyngeal, recurrent respiratory papillomatosis and other pre-cancerous lesion were not taken into account in the current model. The inclusion of these types of HPV-induced diseases [will increase the \(www.bu.edu\)](#) savings and quality of life gains of HPV vaccination and consequently improve the cost-effectiveness of HPV vaccination (65–69).

Although we assumed 3-yearly screening in this model, the efficacy of the screening on preventing [cervical cancer incidence \(www.bu.edu\)](#) and mortality are still considerably low. This can potentially be related to [the fact that \(europe.theoildrum.com\)](#) we did not incorporate the cumulative effect of

repeated screening in the model (29). Moreover, women who have negative results on their previous screening noticeably has lower risk of [cervical cancer incidence \(www.bu.edu\)](#) and mortality compared to unscreened women. In this model we assumed that they have equal risk since the straightforward static Markov model has no ability to remember where the patient has come from nor the exact timing of that transition (70). Yet, univariate sensitivity analysis showed that the influence of screening efficacy on the ICER is very low.

Notably, our results are consistent with previous studies from neighboring countries (20–22,38,53,56,57) by confirming that HPV vaccination [in addition to \(www.medicines.org.uk\)](#) screening can be a cost-effective intervention if it can be obtained at a price similar to, for example, the PAHO price. This finding may encourage the policy makers in Indonesia to further consider, decide and implement optimal cervical cancer prevention strategies.

Conclusion

[first level header]

The addition of HPV vaccination on top of VIA screening in Indonesia, even in the context of various conservative assumptions (need a booster dose to obtain full protection, low cross protection, short vaccine protection and fast waning immunity), is a very cost-effective strategy. Substantial clinical and economic benefits can be obtained by implementing an HPV vaccination program. Nevertheless, improvement of the screening program itself also remains important and provides further potentials to achieve optimal cervical cancer prevention strategies.

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