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The health-economic studies of HPV vaccination in Southeast Asia Countries: A Systematic Review

Abstract

Introduction: The cervical cancer-related burden is an important problem in Southeast Asia (SEA) Countries. However, only 3 out of 11 countries implement the comprehensive prevention program.

Areas covered: This is a retrospective review from all relevant studies until 2015 from two main databases, MEDLINE/Pubmed and Embase in order to provide an evidence on the health economics of HPV vaccination in the region.

Expert commentary: The implementation of HPV vaccination will generate substantial health and economic benefit in SEA countries since the number of cervical cancer cases in this region are generally high. Therefore, a clear recommendation on how HPV vaccination should be implemented in a country, for example on how many doses will be used, how much cost is required or is it a school based- or clinical based-delivery, is critically required.

Keywords: human papillomavirus, vaccine, pharmacoeconomic, cost analysis, ASEAN, Southeast Asia

1. Introduction

Cervical cancer is the fourth most common cancer in the world. (worldwidescience.org) The total incidence and mortality rate of cervical cancer in 2012 was more than 500,000 and 250,000 cases, respectively (1). notably, the incidence of (worldwidescience.org) cervical cancer was twice as high in developing countries as in the developed countries, and mortality is three times as high (1). Cervical cancer generates not only a clinical burden but also social and economic burdens, for example, reduction of social interaction, productivity and also income (2–4).

Cervical cancer burden is considerably preventable as the cause of cervical cancer is well understood. Sexually transmitted infection with high-risk Human Papillomavirus (hrHPV), (onlinelibrary.wiley.com) in particular, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 58, 59, and 68 are responsible for cervical cancer (5,6). Therefore, several factors, including the numbers of sexual partners and start age of sexual intercourse, are responsible for the transmission of HPV infections (7,8).

According to WHO position paper (9), several strategies should be undertaken in order to prevent cervical cancer. This comprehensive strategy should include education about sexual behavior, screening, diagnosis and treatment of both pre-cancer and cancer itself. In addition, training of health workers and providing an accessible screening and treatment should be included in the prevention of cervical cancer strategy. Ultimately, the introduction of HPV vaccine as primary prevention of cervical cancer should not remove the cervical screening activity since the vaccines do not protect people from HPV infection completely.

Two available HPV (bivalent and quadrivalent) vaccines have been approved and implemented as a national policy in most developed and some developing countries (9). Recently, a nonavalent HPV vaccine, has also been approved in the US, Canada and the European Union (10). Each vaccine has its own additional advantages beyond the main effect of preventing HPV16 and HPV18 infections, including prevention of genital warts for quadrivalent vaccine (11–13), cross protection on other

hrHPV types bivalent vaccines (14), and also protection for most of the types of hrHPV for the nonavalent vaccine (15).

Although HPV vaccines provide potentially high benefits for cervical cancer disease prevention, the implementation of HPV vaccine as a national vaccination program in a country is challenging. There may be social barriers, such as rejection from communities on vaccination or parents misunderstanding on vaccination (7,16). In addition, since HPV vaccine is generally expensive, most countries, especially developing countries, require strong evidence of vaccine benefit including not only on clinical but also economic benefits before implementing a vaccination program. In addition, improvement of the available infrastructure will be required in order to introduce HPV vaccine in the developing countries (17).

Compared to developed countries, budget allocation is considerably vital in developing countries as they have not only the more limited budget but also more cervical cancer incidence and mortality cases (18). On the other hand, higher potential benefits are possibly produced by the implementation of HPV vaccine in developing countries. The Southeast Asian (SEA) region consists of 11 different countries which have similar characteristic on its social and culture. Meanwhile, the economic level is considerably diverse as according to world bank, there are two high-income countries (Singapore and Brunei Darussalam), two higher middle-income countries (Thailand and Malaysia), 6 lower middle-income countries (Indonesia, Philippines, Vietnam, Laos, Timor Leste and Myanmar) and one low-income country (Cambodia) (19) in this region (19,20). As the incidence and mortality rate of cervical cancer in this region are on top 10 highest (1,21), the economic diversity may influence the implementation of HPV vaccination in the region.

Recently, there are only three countries in the region which are implemented the HPV vaccination, there are Thailand, Malaysia and Lao PDR. The scale up plan of HPV vaccination in Thailand has been started since 2010 and the result from a pilot study was considerably promising since 88.1% of the study population received three doses of vaccination (22). In Malaysia, HPV vaccines are provided for free since 2010 for girls up to age 26 years old at any of the government clinics nationwide. Surprisingly, the vaccine coverage on 2011 was already high (87%) (20,23). Both countries have been successfully maintained the vaccine coverage among its target population (24). As the first SEAR country which has support from GAVI initiative, Lao People's Democratic Republic (25,26) was considerably succeed with about 26,000 girls were immunized in the Vientiane city and province (27). However, the sustainability of the program could not be guaranteed as it rely on external funding.

Cost-effectiveness analysis is a well-accepted method to provide evidence for decision makers in a country as it generally measures the clinical, economic and most importantly humanistic outcomes, particularly Quality of Life, from a health technology investment. This is also applied in guidelines for national immunization program (28). In addition to know cost-effectiveness of the intervention, threshold analysis is beneficial for price negotiation. For instance in Thailand, originally, HPV vaccine was not cost-effective based on market price at the time of the study. In the analysis, break-even price of the ICER at willingness-to-pay was explored. Then, as a result of the study, the market price has been decreased (23). This information are notably important for the decision maker in health policy as they have a limited budget for an enormous option of health technology (29,30). Therefore, the objective of this study is to systematically review the (worldwidescience.org) health economic studies in SEA countries in order to evaluate the (www.seeplatform.eu) cost-effectiveness of HPV vaccination.

2. Method

The inclusion criteria in this systematic review were health economic studies on HPV vaccination in young girls performed in SEA countries and that the articles were written in English. A systematic search (worldwidescience.org) in two main databases (PubMed and Embase) was performed on September 19th, 2015 using the four search terms: HPV, vaccine, economic, and ASEAN countries. To completely detect all country-specific studies in the region, each country of SEA region was included in the search term: Indonesia, Singapore, Malaysia, Vietnam, Cambodia, Laos, Philippines, Myanmar, Thailand, Timor Leste and Brunei Darussalam. In order to expand the sensitivity of the search term, a combination of medical subject heading (MesH) term and its text word (tw) were implemented in the PubMed database, (worldwidescience.org) while a combination of exploded (exp) and abstract- title (ab.ti) was implemented in the EMBASE database. The detailed search terms for this study are presented in Appendix 1. Additionally, we also performed a snowball search strategy to identify studies which is related to the topics but did not detected by both databases.

The screening of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (31). Firstly, a web-based reference management system, Refworks, was used to (bmcmusculoskeletdisord.biomedcentral.com) detect and automatically remove duplications. Furthermore, the initial screening process was performed by checking at title and abstract from each article which has been detected previously. Furthermore, final screening was performed by thorough reading on included articles.

Two reviewers (DS and MPO) independently extracted the information related to health economic analysis according to the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) statement (32). The information extracted from each study were first authors' name and year of publication, country, type of (www.wjgnet.com) health economic study, study objective, study method, perspective, time horizon, HPV vaccination methods (schedule, vaccine price, delivery and administration cost, age target, and coverage), cervical screening methods (type of screening, age target, coverage, interval), discount rate (cost and utility), cervical cancer prevention strategy observed, clinical outcome (incidence- and mortality averted), preferred strategy according to the study, Incremental cost-effectiveness ratio (ICER), study conclusion, and sensitivity analysis.

As there was no (www.seeplatform.eu) official cost-effectiveness threshold from each country in the region, a global normative recommendation from the Commission on Macroeconomic in Health was considered in this review (33). The commission recommends that an intervention is considered as a cost-effective strategy if the ICER lies below three times Gross domestic Product (GDP) in a country. Therefore, country specific-economic classification and -GDP in 2014 were collected from the world bank official website (20). The economic information, including vaccine price, delivery, and administration of the vaccine and the ICER, from each study, were updated to 2014 and transformed into International dollars (I$) using country-specific inflation rate and –purchasing power parity (PPP) index, respectively (20,34).

3. Results

From the initial search, we found 33 and 87 articles from the PubMed and Embase databases, respectively. After removing 22 duplicated articles, the remaining 98 articles were screened based on title and abstract. There were 79 articles excluded in the screening process, of which 56 articles were not health economic studies, 19 articles were performed outside the SEA countries, 1 article was not about HPV, 2 articles were meeting reports and 1 article was not written in English. Furthermore, a thorough reading of the articles the allowed exclusion of 10 articles: 7 articles were abstracts of poster presentations, 2 articles were not in Southeast Asian countries, and 1 article was about HPV vaccination in boys. A snowball search strategy found 1 study evaluating the cost-effectiveness of HPV vaccination in 72 GAVI eligible countries including several countries in the region, however, only one country, which is Vietnam, that has complete information about the (www.seeplatform.eu) study. Finally, 10 articles were included in this study (worldwidescience.org) (figure 1).

FIGURE 1 HERE

3.1. Study characteristics

In this review, ten included studies were from 5 different countries: the (www.seeplatform.eu) Philippines (n=1) (35), Thailand (n=3) (36–38), Singapore (n=1) (39), Malaysia (n=3) (40–42), and Vietnam (n=2) (43,44) (Table 1). The Philippines and Vietnam represented lower-middle income countries (GPD per capita:US$1,046 to US$4,125) (19,35,43,44), while Thailand and Malaysia represented upper-middle income countries (GPD per capita:US$4,125 to US$12,734) (36–38,40–42), and Singapore represented high income countries (GPD per capita: >US$4,125) (39). A cost-utility analysis (CUA), adopting Quality Adjusted Life Years (QALYs) as the main (www.seeplatform.eu) study outcome, was performed by 2 different studies (35,37), while cost-effectiveness analysis, adopting clinical parameters as the study outcome, was implemented by 3 studies (38,43,44). Additionally, 4 studies performed CUA and CEA simultaneously (36,39,41) and 1 study performed cost-minimization analysis (CMA) to compare all attributable cost of two available vaccines in the market (40). As also shown in Table 1, one studies compared HPV vaccines against no vaccination(37), 2 studies looked at quadri versus bivalent vaccines (39,40), and 7 studies looked at vaccination in combination with screening against screening alone(35,36,38,41–44).

TABLE 1 HERE

3.2. Study design

Since the clinical outcomes of HPV vaccination, such as reduction in cervical cancer incidence and mortality are difficult to obtain from clinical trials, a mathematical model is commonly used in the cost-effectiveness analysis of HPV vaccination. Seven studies implemented modelling: 5 Markov models (35–37,39,43), 2 mathematical model (38,44) and 1 prevalence-based model using 1-year cross-sectional data (40). Two studies from Malaysia were performed using three-year cross-sectional data from tertiary and teaching hospitals that provide oncology services in Malaysia (41).

In health-economic studies, study perspective plays an important role as it not only influences the data required in the analysis but also the conclusion generated from the studies. Various perspectives were implemented in the studies performed in the (www.seeplatform.eu) SEA countries including societal (5 studies) (36,38,40,43,44), patients (2 studies) (41), provider (2 studies) (36,37), payer (1 study) (40) and health care system (2 studies) (35,39). In order to obtain a complete description of the cost-effectiveness of HPV vaccination, (kce.fgov.be) the implementation of

(docplayer.net) lifetime horizon is important as the cost and effectiveness of HPV vaccination as cancer incidence and mortality reduction will only be shown several decades after vaccination. Most studies included in this (www.researchgate.net) review modeled a lifetime horizon for their studies (35–39,43,44), however, there were 1 and 2 studies modeled 1 (40) and 10 years (41) as their time horizon, respectively.

There were several strategies of HPV vaccination which is identical among included studies: 3 doses of administration (35–38,41,43,44), vaccination of young age girls (11 to 15 years old) (35–41,43,44), and vaccine coverage of 70% or higher (35–41,43,44). The vaccine price used across included studies, which is ranged from I$12 to I$1,463, were considerably wide. Furthermore, only 3 studies reported the delivery and administration costs and it ranged from the lowest of IS6 to the highest of I$40 (35,36,43). Those costs were obtained from (kce.fgov.be) different sources: from previous vaccination program implementation (35), from the national vaccine committee office (36) and assumption (43). In addition to (kce.fgov.be) HPV vaccination, cervical screening for older women is also important strategy on preventing cervical cancer disease. Cytology-based screening/pap smear (n=7) was implemented in most of included studies (35,36,38,39,41,43) followed by VIA screening (n=3) (35,36,38). The cervical screening was targeted for women ages 25 years old until 65 years old and most countries have so far faced low coverage (n=6) (35,36,38,39,43). Three studies implemented 5 years screening interval (35,36,43) and one study from Singapore implemented 3 years screening interval (39). Additionally, a study from Thailand varied several screening interval (from 1 year to 5 years) in their study (38).

As there is only few guideline available on how to perform a cost-effectiveness analysis in SEA countries (45,46), a recommendation from the Commission on Macroeconomic in Health on 3% discounting for both cost and effect in the cost-effectiveness analysis is usually adopted. Almost all included studies (N=7) applied 3% discounting for both future cost and effect in the analysis (36–39,41,43,44). Only 1 study, from the Philippines, used a 3.5% discount rate (35) and 1 study did not incorporate discounting as the time horizon was 1 year (40) (Table 2).

TABLE 2 HERE

3.3. Study outcomes

With regard to (docplayer.net) cervical cancer (kce.fgov.be) prevention strategies observed in the study, there were 6 studies that explored the combination of screening and vaccination in a country (35,36,38,41–43), 1 study analyzed the addition of vaccination on top of screening only (37) and 2 other studies compared the cost-effectiveness of both bivalent and quadrivalent vaccines (39,40). Since not all studies reported the clinical outcomes, including cancer related incidence and mortality, as the results of cervical cancer prevention strategies, there were only 5 studies reported the percentage of cervical cancer incidence averted by HPV vaccination (37–40,43,44) and the highest prevention of cervical cancer (kce.fgov.be) incidence was generated by the implementation of (docplayer.net) bivalent vaccine in Malaysia (89.4% of efficacy) (40). Vaccine efficacy on preventing cervical cancer-related mortality was reported by 3 studies (37,39,41) and there was high efficacy was reported by the addition of bivalent vaccine over pap smear in Singapore (39) and the combination of quadrivalent over pap smear in Malaysia (41).

The main information provided by health economic studies is the ICER which explains the cost-effectiveness of a (kce.fgov.be) new intervention in comparison with (www.researchgate.net) a gold standard, previous recommendation or existing intervention. Only 7 studies provided the value of ICER from their base case analysis (35–37,39,41,44), since 2 studies, from Thailand and Vietnam, explored various scenarios of HPV vaccination and/or screening (38,43), and 1 study from Malaysia reported Cost Minimization Analysis (CMA) (40). Studies from Philippines, Singapore, and Malaysia showed that HPV vaccination was considered as a very cost-effective intervention (35,39,41) since the ICER generated from the study lies below 1x GDP. Two studies from Thailand showed that HPV vaccine was a cost-effective intervention since the ICER lies below 3x Thailand's GDP (36,37).

Two studies exploring the combination of HPV vaccination and screening generated different recommendations on cervical cancer prevention strategies. A Study from Thailand proposed that HPV vaccination in addition to (kce.fgov.be) screening five times over lifetime was an effective strategy if the vaccine price is low (I$2 per dose) (38). A study from Vietnam considered HPV vaccination as a promising strategy if several requirements were met including high vaccination coverage, low vaccine price (<IS5 per dose), and screening has to be performed for older women (35-45 years old) (43). A cost minimization study from Malaysia, comparing the bivalent and quadrivalent vaccines, showed that clinical and economic benefits provided by bivalent vaccine were notably higher than the quadrivalent vaccine (40).

TABLE 3 HERE

3.4. Sensitivity analysis

As the mathematical model has been widely used in health economic studies, there are several issues regarding the model-related uncertainties. Therefore, a sensitivity analysis is needed to compensate the uncertainties. There are two main sensitivity analyses, univariate and probabilistic sensitivity analysis (PSA). Univariate sensitivity analysis is able to detect the most influencing parameters from the model (kce.fgov.be) conclusion, while PSA provides the probability of the intervention to be a cost-effective intervention based on a countries willingness to pay. Almost all studies (N=9) performed univariate sensitivity analysis (35,37–41,43,44), while the PSA was only performed in two studies (35,36) (Table 4). The ICER generated from the included studies were sensitive to various parameters including discount rate, the cost of treatment, the cost of screening, vaccine price, vaccine efficacy, and vaccine coverage.

TABLE 4 HERE

4. Discussion

The implementation of (docplayer.net) national HPV vaccination in a country is influenced by several factors including cervical cancer-related burden (1), pre-existing level of prevention strategies, such as the type of cervical screening and its performance (47–49), and most importantly, national budget (50,51). A Cost-effectiveness study provides a tool for decision-makers to justify whether the addition of HPV vaccination over cervical screening will generate higher health and economic benefits combined with an acceptable budget allocation (29,52). Our current study found that the addition of HPV vaccination on top of cervical screening is a cost-effective strategy for most countries in the SEA countries. These results seem (repositorium.sdum.uminho.pt) to be consistent with other

(one2oneheights.pbworks.com) studies from not only developing countries (37,53,54) but also developed countries (49,55–58).

Two studies, comparing the cost-effectiveness of two available HPV vaccines in Singapore and Malaysia (39,41), showed different results. The study from Singapore suggested that quadrivalent vaccine (contain HPV type 16, 18, 6 and 11) considerably more cost-effective than the bivalent vaccine (contain HPV type 16 and 18) while cost-minimization analysis from Malaysia suggested that bivalent vaccine prevents more cervical cancer incidence and cervical cancer-related cost than quadrivalent vaccine. Different findings on the comparison of two available vaccines are apparently found from other studies, for example, several studies performed in Colombia, Ireland, Canada and UK (53,59–61) showed the superiority of quadrivalent while studies from Italy and Taiwan showed that bivalent vaccine is more cost-effective (62,63). HPV vaccines are considered beneficial for not only preventing cervical cancer but also genital warts, genital cancer and oropharyngeal cancer (53,59,61). The inclusion of these additional outcomes in the analysis will considerably influence the results of this comparative study.

Two studies, from Thailand and Vietnam (38,43), explored the various scenario of HPV vaccination in combination with several types of screening and compared the ICER with the Commission on Macroeconomic in Health recommendation on cost-effectiveness threshold (33). In order to maintain the cost-effectiveness ratio of below the threshold, both studies proposed a significantly lower price of HPV vaccine if vaccination would be implemented as a policy in addition to cervical screening. The lower price of HPV vaccine apparently becomes an important issue when a country wants to implement a universal coverage of HPV vaccination as it is recommended by studies from not only developing countries (53) but also developed countries (55,64). Therefore, a reasonable price recommendation for acceptable HPV vaccine price according to countries' GDP could be an interesting information.

There is some discussion on the implementation of the Commission on Macroeconomic in Health recommendation on cost-effectiveness threshold in low and middle-income countries (LMICs). Several studies showed that this threshold was not suitable for all countries. therefore, a country-specific threshold should be soon decided using the various approach such as human capital approach, preference approaches or league table approach (65) as it provides a better language for the decision maker.

A budget impact analysis is also considered useful for decision maker as it generally provides the impact of HPV vaccination on the national budget for the health care. However, only one study from the Philippines performed budget impact analysis and it showed that the implementation of HPV vaccination on top of VIA screening was considerably challenging for the Philippines government as it required a mobilization of additional budget to ensure the implementation (35).

A dynamic model provides a better description on how infectious disease, in this context (one2oneheights.pbworks.com) HPV infection, is spread in a population since it also considers the impact of waning immunity in the population (59,66). However, none of the cost-effectiveness analysis, which is included in this study, (repositorium.sdum.uminho.pt) implemented dynamic model as their prediction tool. An explainable reason of this issues is that dynamic model requires more complex, large and rarely available information especially in SEA countries such as sexual contact matrix and force of infection, the rate at which individuals acquire an infectious disease, such

as HPV infection. Obtaining a specific number of the sexual contact for SEA countries is challenging as eastern society generally consider this information as a taboo (3,67). Therefore, a static model (known as Markov-model) is considerably sufficient on describing the natural history of cervical cancer in a population especially when the vaccination coverage is potentially high.

There are several limitations in our study. Firstly, a complete overview on how the cost-effectiveness of HPV vaccine in SEA countries could not be obtained since the cost-effectiveness analysis of HPV vaccination had not been performed in all countries located in the region. A country-specific cost-effectiveness study is rarely performed since it has not been considered as an obligation in a drug registration system in all SEA countries. However, our review suggested that the implementation of HPV vaccination will generate the optimum health and clinical benefit if several conditions, including low vaccine price, high vaccination coverage, and availability of cervical screening, were achieved.

As the development of (one2oneheights.pbworks.com) cervical cancer disease generally requires several decades of time. A lifetime horizon is a necessary in the cost-effectiveness analysis of HPV vaccination as the cervical cancer prevention strategy. Since studies from Malaysia implemented 1 year and 10 years as the study periods, it is difficult to capture the complete cost and health-related information generated by cervical cancer disease (41). However, a general impression of how HPV vaccine will influence the cost and health-related outcome was clearly explained.

5. Expert Commentary

The implementation of HPV vaccination will generate substantial health and economic benefit in SEA countries since the number of cervical cancer cases in this region are generally high. However, an initial investment for promotion, infrastructure, human resources (68), and most importantly, HPV vaccine apparently requires a large proportion of the national budget. This investment could be an important issue as most of the (one2oneheights.pbworks.com) countries in SEA countries are included in the low- or middle-income country and having a limited health care budget. Consequently, a clear recommendation on how HPV vaccination should be implemented in a country, for example on how many doses will be used, how much cost is required or is it a school based- or clinical based-delivery, is critically required.

Another consideration of cervical cancer prevention strategy in SEA countries were low performances of cervical screening. Although a free-of-charge cervical screening has been provided in several countries, the adherence and coverage of the screening were considered as the main challenges. Additionally, the importance of (repositorium.sdum.uminho.pt) disease prevention has not been integrated completely in the society. A comprehensive health promotion is generally required in SEA countries especially in the rural area or in the population with low awareness of health.

6. Five Years Perspective

Recently, there are two main updates on HPV vaccination: the update version of quadrivalent vaccine “nonavalent HPV vaccine” (10,13) and two doses administration of the vaccine (66,69). Previously, each HPV vaccine, quadrivalent and bivalent vaccine, proposed their own advantages in addition to the main benefit on cervical cancer. The quadrivalent vaccine provides an additional benefit on genital warts prevention since the vaccine not only contains HPV16 and HPV18 but also HPV6 and

HPV11 (53,70). On the other hand, the bivalent vaccine provides a higher additional benefit of HPV-related cancer , including penile, vaginal, and oropharyngeal cancer than quadrivalent vaccine, as bivalent vaccine possess a cross-protection against another type of high-risk HPV: HPV31, HPV33, HPV45, HPV52, and HPV58 which are also responsible for the development of HPV-related cancer (14,71). The existence of nonavalent HPV vaccine noticeably propose even higher protection on HPV infection compared to the bivalent and quadrivalent vaccine, which means also HPV related cancer, into society (10,13). However, as the vaccine price is also higher than both available vaccines (72), the cost-effectiveness of the new vaccine has to be observed.

Key Issues

- Pooling cost-effectiveness data on HPV vaccination from a specific region allows the assessment of the health and economic aspects from different countries with considerably similar characteristics.
- In line with other studies from different regions, the addition of HPV vaccination on top of cervical screening is a cost-effective prevention strategy for most countries in SEA region.
- The threshold recommendation from The Commission on Macroeconomic in Health are commonly used by the countries which have not define their country-specific threshold. However, there are several other aspects to be considered in the decision-making process including budget impact
- a clear recommendation on how HPV vaccination should be implemented in a country is critically required
- A comprehensive health promotion is generally required in SEA countries especially in the rural area or in the population with low awareness of health.

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LEGENDS

Figure 1.Flow chart for study selection

Table 1. Study characteristics of the health economic studies of HPV vaccination in South East Asia Region

Table 2. Methodological aspects and the base-case parameters of health economic studies of HPV vaccination in South East Asia Region

Table 3. clinical and economic outcomes of health economic studies of HPC vaccine in South East Asian Region

Table 4. Sensitivity analysis of health economic studies of HPV vaccination in South East Asian Region