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REVIEW

Economic Evaluations of HPV Vaccination in Targeted Regions of Low- and Middle-Income Countries: A Systematic Review of Modelling Studies

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Background: In countries with limited resources, a targeted HPV vaccination strategy by focusing in selected regions is preferable to be implemented than a nationwide vaccination strategy.

Objective: This study aimed to review articles on economic evaluations of HPV vaccination in countries over the world that applied targeted vaccination strategies.

Methods: Approximately 1769 articles were obtained from two databases (1242 and 527 articles from PubMed and ProQuest, respectively). The inclusion criteria in this systematic review were studies about full economic evaluations of HPV vaccination in targeted area or sub-national level and written in English. Full-text screening was applied to evaluate the eligibility. Final articles obtained were referred to the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist. Finally, we included only 4 articles that met all inclusion and exclusion criteria.

Results: Included studies in this review focused in different targeted regions, such as Punjab State in India, Vientiane in Lao PDR, Southern Vietnam in Vietnam, and Brazilian Amazon in Brazil. From 24 criteria in the CHEERS checklist, all included studies could meet 21 criteria (87.5%). All included studies in this review applied modeling approaches, which can estimate the number of cases and treatment costs averted. Applying various settings, the results of this study showed that HPV vaccination could potentially reduce the number of cervical cancer cases by 20–72%. Taking cervical cancer screening into account, this study showed that targeted HPV vaccination was cost-effective or even cost-saving.

Conclusion: Implementation of HPV vaccination in sub-national level as the initial step before nationwide vaccination is more favorable to be implemented in countries with limited budget.

Keywords: cost-effectiveness, cervical cancer, vaccine, immunization, screening

Introduction

As the leading cause of women's death, the case fatality rate of cervical cancer was reported to increase gradually.[1] The annual number of new cases related to cervical cancer would be 569,847 cases, as reported by WHO in 2018.[2] Representing regions with high number of cases, the incidence rate of cervical cancer in Africa and Asia varied at 4.4–42.7 events per 100,000 population.[2] Approximately 84–90% of cervical cancer cases occurred in low- and middle-income countries (LMICs).[3] Costs for treating cervical cancer patients in low-, lower-middle, and upper-middle countries were estimated up to $3000, $8118, and $11,645 per patient, respectively, as reported in Tanzania, Vietnam and Brazil.[4–6] It can be highlighted that the high epidemiology burden of cervical cancer is associated with the high economic burden, specifically in LMICs.[3]

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To prevent cervical cancer, screening methods have been proven to be effective, such as pap smear or cytology test with its ability to reduce the incidence of cervical cancer by 80–90%.[7] Increasing public awareness was associated with the high rate of screening methods.[8] Next to screening, human papillomavirus (HPV) vaccination was also reported to be cost-effective or even cost-saving in many countries.[1,9] Despite the fact that the cost-effectiveness of HPV vaccination has been proven by several studies in various countries, many countries have not yet implemented HPV vaccination program through a nationwide vaccination strategy. This situation might be caused by countries' limited budget. Next to economic factors, other factors that could influence public acceptance and willingness-to-pay for HPV vaccines are social and cultural factors.[10] To deal with these barriers, a targeted vaccination strategy by focusing in selected regions is preferable to be implemented than a nationwide vaccination strategy.

It has been known that a systematic review can synthesize and extract important information among different studies, and can provide major conclusions from the topics discussed. Hence, it is necessary to conduct economic evaluations of HPV vaccination in countries over the world that applied targeted vaccination strategies through a systematic review.

Methods

Two investigators (DF and DS) searched two databases (PubMed and ProQuest) for all published studies on economic evaluations of HPV vaccination. The search used the following keywords: "economic evaluation" OR "cost minimization" OR "cost-effectiveness" OR "cost utility" OR "cost benefit" AND "human papillomavirus" OR "HPV" AND "vaccine" OR "vaccination" OR "immunization". To increase the sensitivity of the literature search in the PubMed database, combinations of medical subject heading (MesH) and text word (tw) were used for each term. While at ProQuest, the double quotes (") were used to get specific words with keywords/terms to be searched. The inclusion criteria in this systematic review were full economic evaluation studies of HPV vaccination in targeted area or sub-national level and written in English.

The search results were entered into the reference system application. All obtained titles and abstracts were read for initial screening to ascertain that the specified inclusion criteria were met. Furthermore, full-text screening was applied to evaluate the eligibility. Thus, final articles obtained were referred to the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist.[11] The following information was extracted from all eligible articles: authors, publication years, types of studies, methods, perspectives, vaccination strategies (schedule, cost, targeted area, and coverage of vaccination), screening methods of cervical cancer (type of screening, targeted age, coverage, and time interval), discounted values (cost and utility), clinical outcomes (incidence and death averted), incremental cost-effectiveness ratios (ICERs) and study conclusions. All costs were converted to US dollar in 2017 value by taking inflation rates into account.[12]

Results

Approximately 1769 articles were obtained from two databases (1242 and 527 articles from PubMed and ProQuest, respectively). From these numbers, 640 articles were excluded because of duplication. In particular, 1129 articles' titles and abstracts were screened. After the initial screening, 1091 articles were excluded because 72 articles were systematic reviews, 999 articles were not economic evaluations of HPV vaccination, and 20 articles were not written in English. Approximately 38 full-text articles were assessed for the eligibility. We excluded 34 articles because 32 articles were not full economic evaluations of HPV vaccination in targeted regions, 1 article was incomplete economic evaluation and 1 article was only available in abstract. Finally, we included only 4 articles that met all inclusion and exclusion criteria (see Figure 1).

Applying the CHEERS checklist, we assessed reporting quality of four included articles by focusing in six major parts: (i) title and abstract, (ii) background, (iii) methods (eg, targeted population, location, study perspective, time horizon, and discount rate), (iv) results of the study (eg, study parameters and ICER), (v) discussion, and (vi) others (eg, funding sources and conflicts of interest).[11]

Characteristics and Study Design

Four studies in this review focused in different targeted regions: Punjab State in India,[13] Vientiane in Lao PDR,[14] Southern Vietnam in Vietnam,[5] and Brazilian Amazon in Brazil.[6] All of these studies were conducted in the period of 2008–2016. Three studies were conducted in Asia,[5,13,14] and another study was conducted in South America.[6]

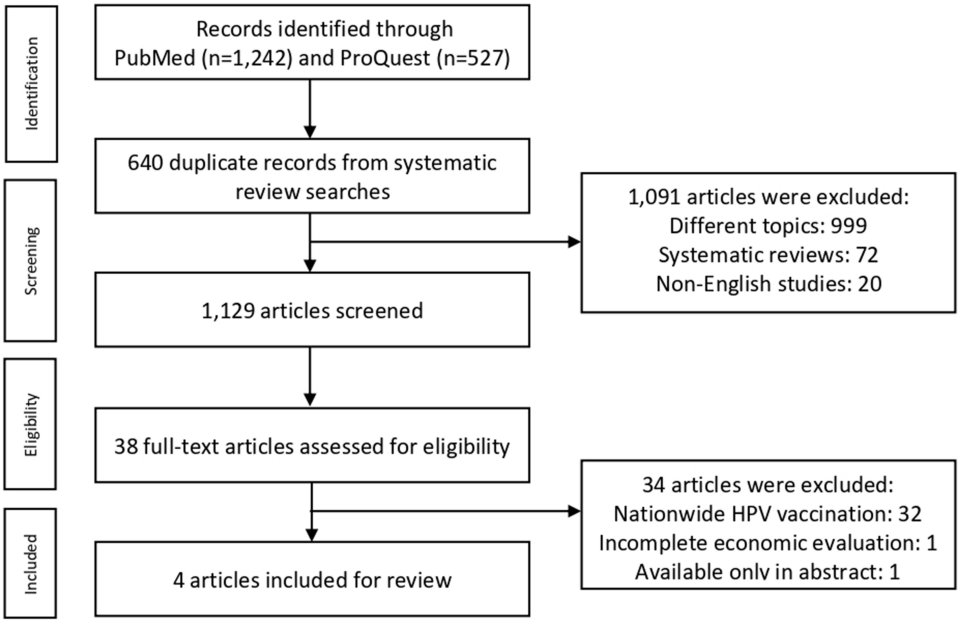

Figure 1 Flow chart for study selection.

Considering countries' income classification, three studies were conducted in lower-middle income countries,[5,13,14] and another study was conducted in an upper-middle income country.[6] Various perspectives were applied by four included studies. A societal perspective was applied by two studies in Vietnam and India,[5,13] a healthcare perspective was applied by a study in Lao PDR,[14] and an insurance perspective was applied by a study in Brazil.[6]

Additionally, two different types of analyses were applied. A study in Brazil applied cost utility analysis,[6] while all studies in Asia applied both of cost-effectiveness and cost utility analyses.[5,13,14] Regarding mathematical modeling approach, a study in India combined decision tree and Markov models.[13] Two studies in Vietnam and Lao PDR applied dynamic models,[5,14] and a study in Brazil applied Markov model.[6] For both of cost and utility, three studies applied a discount rate of 3%,[5,13,14] and only one study in Brazil applied a discount rate of 5%.[6]

Cervical cancer screenings were conducted to find out someone at risk of cervical cancer.[15] Applying the Pap smear test, two studies in Vietnam and Brazil reported coverage rates of this test at 90% and 40%, respectively.[5,6] Applying visual inspection with acetic acid (VIA) test, a study in Lao PDR reported its coverage rate at 50%.[14] A study in India did not report a specific type of screening and its coverage rate.[4,13]

In the context of vaccine types, all studies used bivalent vaccines.[5,6,13,14] Related to time horizon analysis, four modeling studies applied lifetime.[5,6,13,14] All included studies targeted population at the age of ≤12 years old. Specifically, a study in Brazil targeted girls at the age of 12 years old.[6] Two studies in India and Lao PDR targeted girls at the age of 10–11 years old, respectively.[13,14] A study in Vietnam targeted girls and boys at the age of ≥9 years old.[5] More detailed information can be seen in Table 1.

Study Outcomes

A study in Punjab, India compared the existing policy (no screening and no vaccination) with vaccination. Clinical outcome of the intervention was estimated to be 54% of cervical cancer case averted, which concluded that HPV vaccination was highly cost-effective to be implemented in Punjab and cost-effective to be implemented in other parts of India.[13] A study in Vientiane, Lao PDR compared the current situation of cytology screening and no vaccination with three alternative scenarios: vaccination alone, vaccination with screening and screening only without vaccination. Considering various types of screening, HPV vaccination could reduce approximately 75% cervical cancer cases. In comparison with other types of screening, screening program once every three years for women with the age of 30–65 years old was more recommended.[14]

Table 1 Characteristic Study and Study Design

Study (Year)	Economic Classification	Targeted Area	Study Perspective	Methods	Type of Study	Incidence (Per 100.000 women)	Discount Rate		Screening		Vaccination		Time Horizon	Targeted Age
							Cost	Utility	Coverage	Type	Coverage	Type		
India, 2017	Lower middle income	Punjab State	Societal perspective	Markov Model and decision tree model	CEA and CUA	22	3%	3%	–	–	89%	Bivalent	Lifetime	Girl 11 years old
Lao PDR, 2016	Lower middle income	Vientiane	Public health care system perspective	Dynamic population-based model	CEA and CUA	11.4	3%	3%	50%	Visual inspection with acetic acid (VIA)	70%	Bivalent	Over 100 years	Girl 10 years old
Vietnam, 2015	Lower middle income	Southern Vietnam	Societal Perspective	Dynamic model	CEA and CUA	10.6	3%	3%	40%	Pap smear test	NR	Bivalent	Lifetime (100 years)	Girl and Boy ≥ 9 years old
Brazil, 2013	Upper middle income	Brazilian Amazon Region	Provider's Perspective	Markov cohort model	CUA	17.5	5%	5%	90%	Pap smear test	90%	Bivalent	Lifetime	Girl 12 years old

A study in Southern Vietnam took the addition of vaccination programs for boys into account by varying vaccination coverage and vaccine price. Applying the coverage of vaccination at 25–90%, HPV vaccination could reduce approximately 20–57% cervical cancer cases. Considering that vaccination programs for boys could be cost-effective only at low vaccine price, the study concluded that focusing vaccination on girls and increasing its vaccination coverage would be more efficient to be implemented in Southern Vietnam and other similar areas in Vietnam.[5]

In comparison with the baseline scenario of cytology screening, a study in Brazilian Amazon Region, Brazil focused on three alternative scenarios: HPV vaccination without and with screening (3- and 10-times), resulted that vaccination would reduce 50% cervical cancer cases if the coverage was higher than 70%. The study concluded that HPV vaccination could provide a favorable cost-effectiveness value by reducing the incidence and fatality rates due to cervical cancer in targeted region.[6] More detailed information can be seen in Table 2.

Cost-Effectiveness Value

Vaccine price varied at $4.6-$23.5 from all included studies with the lowest and highest vaccine prices per dose were found in India and Brazil, respectively.[6,13] Program costs were reported to be $5.6-$13.4 per dose with the lowest and highest program costs per dose were found in Lao PDR and Brazil, respectively.[6,14] In particular, a study in India calculated treatment cost reduction due to vaccination at $1.6 million and cost-effectiveness value at $1.12 per QALY gained.[13] A study in Lao PDR estimated treatment cost of localized invasive cancer due to cervical cancer at $776. Treatment costs of regional invasive and metastatic cancer were reported to be the same at $877. Applying the combination of screening for every 5 years in 30–65 years old women and HPV vaccination, the ICER was calculated to be S1471 per DALY averted.[14] Considering the vaccine price at $9.1 per dose, a study in Vietnam highlighted that vaccination for girls only was considered to be cost-saving in the context of cancer and genital warts reduction.[5] Applying the highest vaccine price and program cost than other countries in the included studies, a study in Brazil estimated treatment cost for localized invasive, regional invasive and metastatic cancer would be $5120, $11,645 and $3631, respectively. In comparison with screening only, a scenario of 3 screenings lifetime that was coupled with

Table 2 Study Outcomes

No	Country	Strategy Observed		Clinical Outcome (Case Averted)	Conclusion
		Current Practice	New Intervention		
1	India, 2017	No screening and no vaccination	Vaccination	54%	HPV vaccination appears to be a very cost-effective strategy for Punjab state, and as is likely to be cost-effective for other Indian states.
2	Lao PDR, 2016	Cytology screening and no vaccination	Vaccination alone, vaccination with screening, and screening alone.	75%	A visual inspection with acetic acid (VIA) test in addition to a girl vaccination program was predicted to be the most attractive option in the healthcare context of Lao PDR. In comparison with other screening methods, VIA was the primary recommended method for combination with vaccination in Lao PDR.
3	Vietnam, 2015	Screening Pap smear and vaccination	Vaccination for girl only and Vaccination for girl and boy	20–57% (vaccination coverage at 25%-90%)	Vaccination for boys may be cost-effective at low vaccine costs but it would provide little benefit over-vaccinating girls only. Focusing on achieving high vaccine coverage of girls may be more efficient for southern Vietnam and similar low-resource settings.
4	Brazil, 2013	Cytology screening	No screening + vaccination, screenings (3x) + vaccination, and screenings (10x) + vaccination	50% (vaccination coverage at >70%)	Vaccination has a favorable profile in terms of cost-utility, and its inclusion in the immunization schedule would result in a substantial reduction in the incidence and mortality of invasive cervical cancer in the Brazilian Amazon region

Table 3 Cost-Effectiveness Value (US$ 2017)

Study (Year)	Vaccine price Per Dose	Program Cost	Treatment Cost	Cost-Effectiveness Value
India, 2016	$4.6	$2.1 million	• No vaccination scenario: $2.4 million • HPV vaccination scenario: $0.8 million	Incremental cost per QALY gained for HPV vaccination is $1.12
Lao PDR, 2013	$4.9	$5.6 per dose	• Localized invasive cancer: $775.6 • Regional invasive cancer: $877.3 • Metastatic cancer: $877.3	Visual inspection with acetic acid (VIA) screening + vaccination •VIA screening (30–65 years old, every 5 years) + vaccination o USD 1471/DALYs averted o USD 16,957/case reduction •VIA screening (30–65 years old, every 3 years) + vaccination o USD 2748/DALYs averted o USD 4825/case reduction •VIA screening (30–65 years old, annually) + vaccination o USD 7272/DALYs averted o USD 91,923/case reduction
Vietnam, 2008	$9.1	-	-	•Vaccination girl only (coverage: 25–90%) •$16.4 - $47.2 /QALY (cancer reduction) •Cost saving (cancer and genital warts reduction) •Vaccination girl and boy (coverage: 25–90%) o $1334 - $3750/QALY (cancer reduction) o $1039 -$3181/QALY (cancer and genital warts reduction)
Brazil, 2012	$23.5	$12.4 per dose	• Localized invasive cancer: $5120 • Regional invasive cancer: $11,645 • Metastatic cancer: $3631	In comparison with screening only: • 3 screenings lifetime + vaccination: $1141/QALY • 10 screenings lifetime + vaccination: $1763/QALY

vaccination resulted the most favorable cost-effectiveness value at $1141/QALY gained.[6] More detailed information can be seen in Table 3.

Sensitivity Analysis

Dealing with uncertainty is a critical issue in economic evaluation studies, specifically in mathematical modeling studies. Studies in Vietnam and Brazil applied one-way sensitivity analysis by taking several parameters into account, such as cost of vaccination, effectiveness of vaccination, vaccination coverage, time of immunity, annual discount rate, and characteristics of cytology test.[5,6] In addition to one-way sensitivity analysis, a study in Lao PDR conducted multi-way and probabilistic sensitivity analysis (PSA) by considering natural history progression of HPV infection, proportion of people receiving treatment, monthly remission rates of pre-cancerous lesions and cancer treatment, screening sensitivity and specificity, screening coverage, vaccination coverage, vaccine-induced immunity, effectiveness vaccine, disability weight, and discount rate, and cost.[14] Considering three major parameters of lifetime risk of developing cervical cancer, vaccine price, and vaccine efficacy, a study in India conducted PSA.[13]

Discussion

Given countries' limited budget, a targeted HPV vaccination strategy is more preferable to be implemented than a nationwide vaccination strategy. It should be highlighted that an economic evaluation of targeted health-care

interventions has several advantages and disadvantages. Despite its ability to produce local evidence, the conclusion can not be generalized for other regions in the context of national policy. Five studies in this review focused in selected regions, such as Punjab in India, Vientiane in Lao PDR, Southern Vietnam in Vietnam, and Brazilian Amazon in Brazil, with several major reasons.[5,6,13,14] Initiated by a well-established group of experts, a cost-effectiveness study of HPV vaccination for adolescent girls in Punjab, India, was carried out by considering the implications of this program for India's universal immunization program.[13] As the capital of Lao PDR, access to health-care facilities in Vientiane was considered to be better than other regions. Hence, the initial implementation of cervical cancer screening and vaccination was more feasible to be focused in this region.[14] Considering Southern Vietnam is a region with more liberal sexual behavior attitudes and higher premarital sex relations than Northern Vietnam, a study by Sharma et al took the addition of vaccination programs for boys into account by varying vaccination coverage and vaccine price.[5] Furthermore, the high prevalence of cervical cancer in Brazilian Amazon was the major reason for Da Fonseca et al to conduct a cost-effectiveness analysis of HPV vaccination in a selected region in Brazil.[6]

All included studies in this review applied modeling approaches, which can estimate the number of cases and treatment costs averted. Applying various settings, the results of this study showed that HPV vaccination could potentially reduce the number of cervical cancer cases by 20–72%. This finding is similar with the result of a previous study, which reported that HPV vaccination could reduce approximately 70% incidence of cervical cancer.[16]

The World Health Organization (WHO) has developed the global strategy to eliminate cervical cancer by 2030. The purpose of this strategy is 90% of girls (<15 years old) have been vaccinated, 70% of women (35–45 years old) have been screened for cervical cancer, and 90% of women identified with cervical cancer have been treated.[17] Taking cervical cancer screening into account, this study showed that targeted HPV vaccination was cost-effective or even cost-saving to be implemented.

Using the implementation of HPV vaccination in the sub-national level as the initial step before nationwide vaccination, a targeted HPV vaccination strategy is currently being considered by several countries in Asia and Africa.[18] More economic evaluation studies in these regions are urgently required to assist decision-making process. In addition, all included studies in this review focused in LMICs by targeting population at the age of ≤12 years old. In these countries, a school-based vaccination program is highly recommended to optimize the vaccination coverage. Even in high-income countries, such as Singapore, a school-based HPV vaccination strategy is more favorable to be implemented.[19]

Even though this is the first systematic review that highlighted economic evaluations of HPV vaccination in targeted regions from various countries in the world, it has a major limitation in the limited number of included studies. Considering countries' income classification, all included studies in this review represent the implementation of targeted HPV vaccination in LMICs. Despite the healthcare spending of LMICs (6% of GDP) was reported to be higher than high-income countries (4% of GDP), the majority of cervical cancer cases occurred in LMICs.[20] Therefore, priority-setting for cervical cancer prevention in LMICs is very critical by enhancing the alignment of budgeting and planning practices.[21] Given LMICs' limited resources, it is important to take into account the sub-national setting with regard to availability of key data, role of various stakeholder groups, organizational and leadership capacity, and sustainable financing for public programs.

Conclusion

Applying various settings, the results of this study showed that HPV vaccination could potentially reduce the number of cervical cancer cases by 20–72%. Taking cervical cancer screening into account, this study showed that targeted HPV vaccination was cost-effective or even cost-saving. Considering many factors (eg, budgeting, acceptance, infrastructure, and human resources), implementation of HPV vaccination in sub-national level as the initial step before nationwide vaccination is more favorable to be implemented in countries with limited budget, such as LMICs.

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Disclosure

The authors report no conflicts of interest in this work.

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