Review Article

Pharmacoeconomic Studies of Vaccination in Southeast Asian Countries: A Systematic Review

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ABSTRACT

This review aimed to explore the research situation in Southeast Asian countries on the pharmacoeconomic studies of vaccination. A systematic literature search was conducted in July 2013 using the Medline electronic database with the PubMed interface. The methodological quality of the study was assessed against the CHEC criteria list for good reporting of economic evaluation and WHO recommendation for appraising of economic evaluation of vaccination program. Thirty two eligible articles were retrieved and reviewed. Most of articles met the selected recommendations for good reporting of economic evaluation of vaccination program. Published pharmacoeconomic studies of vaccination in Southeast Asian countries appeared since the year 2001; the number of articles tended to increase over the time. The studies had been conducted in seven of eleven countries in the region; Thailand had the greatest number of publications (11). Most of studies dealt with rotavirus vaccination (7), and followed by HPV vaccination (6) and Hib vaccination (4); in accordance with the concerning issues in the region. The contribution of the researchers from local settings appears significant. There is considerable number of pharmacoeconomic studies of vaccination program conducted in Southeast Asian countries indicating such economic information is gaining importance in policy decision making. More pharmacoeconomic studies need to be conducted in the absence of some evidences from the available studies to complete the evidence for considerations of policy decision making.

Keywords: pharmacoeconomics, cost analysis, vaccination, Southeast Asia, systematic review.

INTRODUCTION

Nowdays, vaccines are available to protect against more than 26 infectious diseases. WHO mentioned major vaccine preventable diseases included tuberculosis, diphteria, tetanus, pertussis, measles, rubella, yellow fever, haemophilus influenza type b, hepatitis b, polio, rotavirus, pneumococcus, meningococcus, and japanese encephalitis. While cervical cancer is another vaccine preventable disease that need to be considered.[1] Routine vaccination is an effective, safe, and economical intervention that has brought about dramatic improvements in health.[2]

A rational technical decision on a vaccine requires information on disease burden, vaccine safety and effectiveness, vaccine cost, and net impact (on immunization programme as well as health sector).[3,4] The information on these four areas can be combined by economic analysis that allows comparison of new vaccine introduction with alternative government investments. Pharmacoeconomics or economic evaluation is a tool to help priority setting. It compares the consequences of an intervention such vaccination program with the costs and guides policy makers wishing to maximise the benefits produced by the scarce resources available to them.[5,6]

In the South-East Asia Region childhood immunizations against polio, diphtheria, pertussis, tetanus, measles and tuberculosis have been given since the 1970s.[2] The other types of vaccine have been also added into the expanded program of immunization of the countries over time. Economic evaluation of both ex-ante and ex-post evaluation of vaccination program are needed to give a feedback and input to the government regarding vaccination program.[1] The methodology employed in the economic evaluations and the results of the studies both can be useful to be adopted in other setting[5]; supporting the ASEAN community achievement in the region which is expected soon.[7] In this study, we conducted systematic review of pharmacoeconomic studies of vaccination to describe the situation of the published research report on pharmacoeconomic studies of vaccination in Southeast Asia countries as well as to explore the methodology applied on pharmacoeconomic studies of vaccination in Southeast Asia countries.

METHODS

Searching method

A systematic literature search was conducted in July 2013 using the Medline electronic database with the PubMed interface.

A combination of MeSH terms and text keyword was employed. The search used variations of the following terms: (("Costs and Cost Analysis"[Mesh]) OR ("Economics, Pharmaceutical"[Mesh]) OR (economic evaluation)) AND (("Vaccines"[Mesh]) OR ("Vaccination"[Mesh])) AND ("Asia, Southeastern"[Mesh]). Inclusion criteria are the study of pharmacoeconomic studies comparing both cost and

outcome related to vaccination program; and available in full-text version. While exclusion criteria are review articles. Articles found by hand searching were also included if they meet the inclusion criteria.

Data extraction

The following information was obtained from each study included in the review: year of study and setting; capacity of local researcher on the studies (number of study by year, number of local researchers compare to outside researchers, number of local researchers as the first/correspondence author); affiliation of researchers; research funding support; type of vaccine; study objective and type of intervention (ex-ante or ex-post evaluation); interventions and comparators; study population; type of analysis (cost effectiveness analysis (CEA), cost utility analysis (CUA), cost benefit analysis (CBA)); perspective; economic evaluation technique (decision tree, Markov model, dynamic model); time horizon and discounting rates; cost elements and outcome expressions; analytic method (cost per outcome expression); cost effectiveness threshold and primary results of the studies.

Assessment of methodological quality of economic evaluation

The methodological quality of economic evaluation of each article was assessed against the selected lists recommended by the Consensus on Health Economic Criteria (CHEC) on reporting of economic evaluation study[8] and WHO on appraising economic evaluation of vaccination program.[1] Items assessed included study question, study population, competing alternatives, performed CUA, model structure or/and type, perspective, time horizon, discounting rates for cost or/and outcome, ICER (incremental cost effectiveness ration) conducted, cost-effectiveness threshold, sensitivity analysis and funding sources.

RESULTS

Searching result

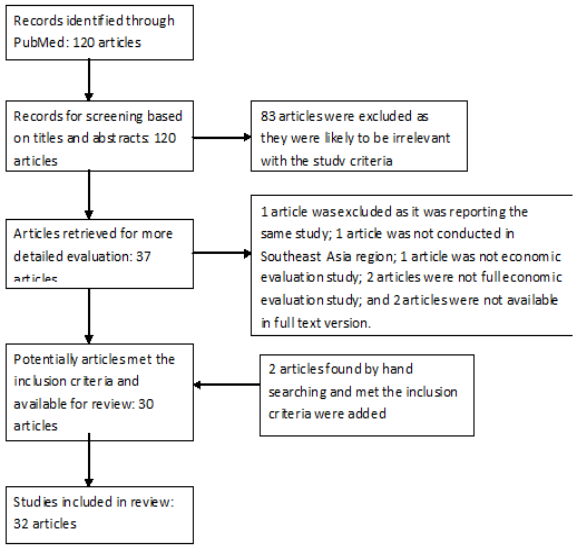

Figure 1: Flow chart of study selection process

The literature search found 120 records, 90 of which did not meet the iclusion criteria and were therefore excluded. Two articles found by hand-searching met the inclusion criteria and were therefore included. Thirty two eligible articles were retrieved and reviewed.[9-40] Flow chart of study selection process can be seen in **Figure 1**.

Articles mapping

We know from the review that published pharmacoeconomic studies of vaccination in Southeast Asian countries appeared since the year 2001. The number of articles tended to increase over the time. It has increased considerably starting in the year 2008 and has its peak number in the year 2011 with the total of 10 studies (**Figure 2**).

It was found that the studies had been conducted in seven of eleven countries in the region. Thailand had the greatest number of publications (11), followed by Singapore and Indonesia (5), Vietnam (4), Malaysia (2), and Cambodia and the Philippines (1). Three studies also conducted in multi-country including countries of Southeast Asia region; 1 study included Indonesia for cholera vaccination program, 1 study included Indonesia and Vietnam for Typhoid Vi vaccination program, and 1 study was conducted with the setting of the Southeast Asia region entirely for dengue vaccination program. The types of vaccination concerned in the studies were dengue, HPV (human papillomavirus), Hib (Haemophyllus influenza type b), HAV (hepatitis A), Hep B (hepatitis B), HIV (human immunodeficiency virus), influenza, JE (Japanese encephalitis), PCV (pneumococcal conjugate vaccine), rotavirus and varicella. Most of the studies dealt with rotavirus (7); and followed by HPV (6) and Hib (4).

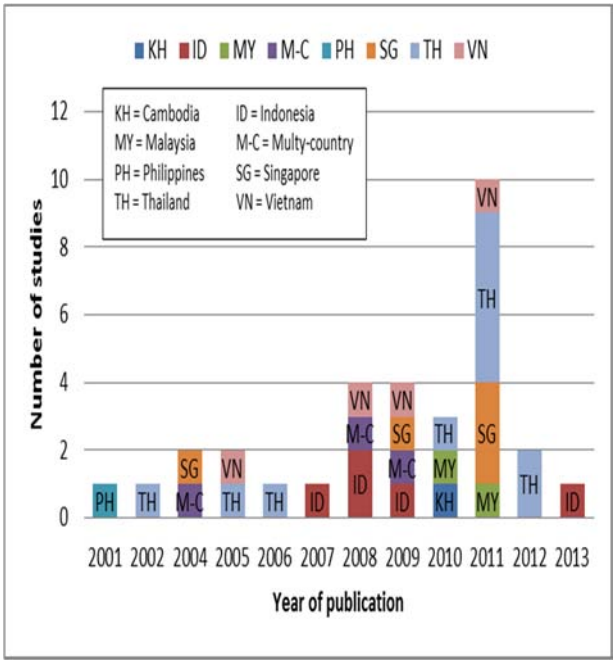

Figure 2: Distribution of studies by year of publication and study setting

Our review summarized that thirteen articles (41%) were written by local researchers, 7 articles (19%) by outside

researchers, and 12 articles (38%) in collaboration of both. Among the articles, 17 studies (53%) mentioned the name of a local researcher as the first or corresponding author. The authors of the reviewed articles were affiliated with the organization of university, government office (Ministry of Health), hospital, research institute and pharmaceutical company. Particularly, researchers from outside the countries were affiliated with university and/or research center. In general, most study was written by authors whom affiliated with university (11 studies); 5 studies written by collaborated authors whom affiliated with government and university, 4 studies written by collaborated authors whom affiliated with government, university and research institute, and another studies were written by collaborated authors whom affiliated with those various organization; only 1 study involved author from pharmaceutical company. Regarding the comparison number of researchers, local researchers had the total number which more than researcher from outside the countries, 103 and 89 respectively.

Out of 32 articles, 23 articles (72%) revealed their funding sources. Of these studies, 13 studies were supported by international non-profit organizations including Bill and Melinda Gates Foundation, World Bank, PATH (Program for Appropriate Technology for Health), GAVI (Global Alliance for Vaccine and Immunization) and US CDC (United States-Center for Disease Control and Prevention), The Rockefeller Foundation, and governments of Japan and Korea. Six studies were supported by domestic public funds, mostly by Ministry of Health, university, and national research center. The rest 4 studies were supported by pharmaceutical companies.

Adherence of methodological quality of economic evaluation studies to selected technical criteria

The methodological quality of economic evaluation of the articles reviewed has been assessed against the checklist of selected criteria of recommendations for good reporting of economic evaluation and particularly appraising for economic evaluation of vaccination program. **Table 1** shows the extent to which the thirty two articles meet the recommendations. Most of the studies meet almost all recommendations.

All articles described such recommendations as study question, study population, competing alternatives, perspective, and cost-effectiveness threshold. While most of articles also meet other recommendations of performing CUA in the analysis, describing model structure and/or type, time horizon, discounting rates for costs and/or outcomes, calculating and reporting ICER, sensitivity analysis, and disclosed funding sources.

Table 1: Methodological quality assessment of pharmacoeconomic studies of vaccination in Southeast Asia countries

Recommendation	Number of articles fulfilling recommendation[a]	Percentage (%)
Stated study question	32/32	100
Described study population	32/32	100
Described competing alternatives	32/32	100
Performed CUA	23/32	72
Described model structure and/or type	25/32	78
Stated time horizon	30/32	94
Specified perspective	32/32	100
Used discounting for cost and/or outcome	29/32	91
Calculated and reported ICER	26/28	93
Used cost-effectiveness threshold	27/27	100
Performed sensitivity analysis	31/32	97
Disclosed funding sources	23/32	72

[a] = Number of studies where the recommendation is applicable;
CUA = Cost utility analysis
ICER = Incremental cost-effectiveness ratio

Technical characteristics of pharmacoeconomic studies

We summarized the detail of study characteristics in **Table 2**, as well as the methodological characteristics of pharmacoeconomic studies of vaccination in Southeast Asia in **Table 3**.

Table 2: Study characteristics of pharmacoeconomic studies of vaccination in Southeast Asia

Study	Study objective	Competing alternatives	Study population	Method and technique of study
Jeuland[9], 2009	To conduct cost-effectiveness analysis of cholera vaccination in three coountries, including Indonesia.	(i) vaccination of young children, aged 1 to 4; (ii) vaccination school-aged children, 5 to 14 years; (iii) vaccination adults, ages 15 years and older; (iv) non-vaccination	Individual over than 2 years old, divided in three groups	Method: CUA Technique: Non-specified model
Carrasco[10], 2011	To performe an estimate of the economic impacts and disease burden of dengue illness in Singapore from 2000 to 2009	(i) vaccination; (ii) current vector control program	whole population	Method: CUA Technique: dynamic model
Lee[11], 2011	To evaluate the potential health and economic value of administering a dengue vaccine to an individual in Thailand	(i) vaccination; (ii) non-vaccination	A dengue-naive 1 year of age and less in Thailand	Method: CUA Technique: Markov model
Shepard[12], 2004	To ascertain the economic feasibility of a pediatric tetravalent dengue vaccine in Southeast Asia region	(i) vaccination; (ii) vector control program	Children at 15 months	Method: CUA Technique: Non-specified model
Ezat[13], 2010	To compare the cost-effectiveness of three programs in the prevention of cervical cancer in Malaysia	(i) screening with Pap smear; (ii) vaccination (HPV bivalent or quadrivalent); (iii) combined between screening and vaccination	A cohort of 15 years old girls	Method: CUA Technique: Non-specified model
Lee[14], 2011	To explore the cost-effectiveness of two HPV vaccines in Singapore	(i) vaccination with HPV bivalent; (ii) vaccination with HPV quadrivalent; (iii) non-vaccination	A cohort of 12-year old females	Methods: CEA, CUA Technique: Markov model
Sharma[15], 2011	To assess the health and economic outcomes of various screening and vaccination strategies for cervical cancer in prevention in Thailand	(i) vaccination; (ii) screening (VIA/HPV DNA/cytology); (iii) combined between vaccination and screening	Female cohort start at age 9 years	Method: CEA Technique: Markov model
Praditsitthikorn[16], 2011	To identify the optimum mix of interventions that are cost-effective for the prevention and control of cervical cancer in Thailand	(i) screening (Pap smear); (ii) screening (VIA); (iii) vaccination; (iv) non-vaccination	Female cohort start at age 15 years	Method: CEA, CUA Technique: Markov model
Temrungruanglert[17], 2012	To perform a cost-effectiveness evaluation of a prophylactic HPV vaccination program compared with the current management in Thailand	(i) vaccination (HPV quadrivalent); (ii) non-vaccination	a cohort of 12-year-old girls	Method: CUA Technique: Markov model
Kim[18], 2008	To assess the health and economic outcomes associated with cervical cancer prevention strategies in Vietnam	(i) vaccination; (ii)screening (cytology/HPV DNA); (iii) combined between vaccination and screening	Girls cohort start at age 9 years	Method: CEA Technique: Markov model
Broughton[19], 2007	To evaluate the cost-effectiveness of introducing Hib vaccine in Indonesia as an addition to the country's current DTP-Hb vaccination program	(i) vaccination; (ii) non-vaccination	A 1-year birth cohort (4,234 million children)	Method: CUA Technique: Decision tree model
Gessner[20], 2008	To estimate total vaccine-preventable disease burden and the cost-effectiveness of Hib conjugate vaccine in Indonesia	(i) vaccination (Hib monovalent); (ii) vaccination (Hib pentavalent); (iii) non-vaccination	2007 birth cohort	Method: CUA Technique: Decision tree model
Limcangco[21], 2001	To evaluate the costs and benefits of a 3-dose immunisation schedule of Hib in Manila, Philippines	(i) vaccination; (ii) non-vaccination	A birth cohort of 100,000 children	Method: CBA Technique: Decision tree model
Muangchana[22], 2011	To perform a CBA of a universal Hib vaccination program for	(i) vaccination; (ii) non-vaccination	Thai children born in 2006	Method: CBA

	decision making process			Technique: Decision tree model
Teppakdee[23], 2002	To determine the cost-benefit balance of hepatitis A vaccination strategies for the general population of Thailand	(i) vaccination without screening; (ii) vaccination after screening; (iii) non-vaccination	Population age 3-40 years divided into 3 groups	Method: CBA Technique: Markov model
Vimolket[24], 2005	To evaluate the cost-effectiveness of four infant vaccination strategies for protecting Thai population from Hepatitis B infection	(i) screening (HBsAg) and vaccination; (ii) screening (HBsAg and HBeAg) and vaccination; (iii) universal vaccination; (iv) non-vaccination	A hypothetical cohort of new borns	Method: CEA Technique: Decision tree model
Ono[25], 2006	To evaluate the cost effectiveness of three programs in the prevention of HIV/AIDS in Thailand	(i) vaccination; (ii)treatment (HAART); (iii) combined between vaccination and treatment	A cohort of 10 years children	Method: CUA Technique: Markov model
Leelahavarong[26], 2011	To estimate the costs and health outcomes of HIV prevention programs combined with HIV vaccination in comparison to the existing HIV prevention program without vaccination	(i) vaccination and current prevention program; (ii) current prevention program without vaccination	General population age 18-30 years, FSW, IDU, MSM, military conscript	Method: CUA Technique: Markov model
Lee[27], 2009	To compare the economic outcomes of vaccination with treatment with antiviral agents alone in the management of pandemic influenza in Singapore	(i) vaccination (immediate vaccination); (ii) vaccination (vaccine stockpilling); (iii) non-vaccination (treatment)	Singapore's 2007 mid-year local population	Method: CBA, CEA Technique: Decision tree model
Touch[28], 2010	To evaluate the cost and effectiveness of introducing a live, attenuated vaccine (SA 14-14-2) againts JE into in immunization program in Cambodia	(i) vaccination in 9 month-old-children; (ii) campaign among children aged 1-5 years/1-10 years and vaccination in 9-month-old children; (iii) non-vaccination	Theoretical cohort children age 1-15 years and 9 months	Method: CEA, CUA Technique: Decision tree model
Liu[29], 2008	To assess the cost-effectiveness of the vaccine for routine childhood JE immunization in Bali, Indonesia	(i) vaccination; (ii) non-vaccination	Two hypothetical birth cohort (each 100,000 healthy children)	Method: CUA Technique: Decision tree model
Aljunid[30], 2011	To estimate the disease burden of pneumococcal disease in Malaysia and to assess the cost effectiveness of routine infant vaccination with PCV7	(i) vaccination (PCV-7); (ii) non-vaccination	a hypothetical birth cohort of 550,000 infants	Method: CEA Technique: Decision tree model
Tyo[31], 2011	To estimate the costs and public health impacts of pneumococcal conjugate vaccine programs as part of NIP in Singapore	(i) vaccination (PCV-7/PHiD-10/PCV-13); (ii) non-vaccination	The vaccinated infant and child cohort	Method: CBA, CUA Technique: Markov model
Wilopo[32], 2009	To assess the potential for introducing rotavirus vaccine into Indonesia's National Immunization Program	(i) vaccination; (ii) non-vaccination	1 year birth cohort in 2008	Method: CUA Technique: Decision tree model
Suwantika[33], 2013	To assess the cost-effectiveness of rotavirus immunization in Indonesia by taking breastfeeding patterns into account	(i) vaccination; (ii) non-vaccination	Indonesia 2011 birth cohort infants (4,200,000 infants)	Method: CUA Technique: Decision tree model
Chotivitayatarakorn[34], 2010	To evaluate the cost-effectiveness of rotavirus vaccination as part of the national immunization program for Thai children	(i) vaccination; (ii) non-vaccination	The 2007 annual birth cohort (932,000)	Method: CUA Technique: Non-specified model
Muangchana[35], 2012	To provide information on the cost-effectiveness, cost–benefit and budget impact of incorporating the rotavirus vaccine into NIP	(i) vaccination; (ii) non-vaccination	a birth cohort of Thai children in 2009	Method: CBA, CUA Technique: Decision tree model
Fischer[36], 2005	To provide information to policy makers of an economic	(i) vaccination; (ii) non-vaccination	The 2003 Vietnamese birth	Method: CEA, CUA

	assessment of the cost and effectiveness of a rotavirus vaccination program in Vietnam		cohort	Technique: Non-specified model
Kim[37], 2009	To reflect additional features of rotavirus and assesing the influence of the features on the cost-effectiveness of rotavirus vaccination in Vietnam	(i) vaccination; (ii) non-vaccination	The 2004 Vietnamese birth cohort (start at age 5 years)	Method: CUA Technique: Markov model
Tu[38], 2011	To assess the cost-effectiveness analysis on rotavirus immunization in Vietnam focussing explicitly on the use of RotaTeq and assessing the affordability of implementing universal rotavirus immunization based on GAVI-subsidized vaccine price	(i) vaccination; (ii) non-vaccination	The 2009 birth cohort	Method: CUA Technique: Decision tree model
Cook[39], 2008	To evaluate the cost-effectiveness of Vi vaccination against typhoid in several sites	(i) vaccination school-aged children, aged 5 to 14 who attending school only; (ii) vaccination school-aged children, aged 2 to 14 years, who attending and no attending school; (iii) vaccination adults; (iv) non-vaccination	Individual over than 2 years old	Method: CUA Technique: Non-specified model
Jean-Jasmine[40], 2004	To assess the economic burden of varicella and the cost-benefit of adding a varicella vaccine to the existing immunization schedule in Singapore	(i) vaccination; (ii) non-vaccination	A cohort of 15 months infants	Method: CBA Technique: Non-specified model

Table 3: Methodological characteristics of economic evaluation of vaccination in Southeast Asia

Study	Perspective	Cost elements			Outcome expressions	Time horizon (years)	Discounting rates (%)		Analytic methods	Cost-effectiveness threshold	Sensitivity analysis
		DMC	DNC	IC			Costs	Outcomes			
Jeuland[9], 2009	Healthcare	v	v	v	DALY	Lifetime	3	3	ICER per DALY	GDP per capita	Univariate
Carrasco[10], 2011	Societal	v	v	v	DALY	10 years	3	ND	Cost per DALY	GNI per capita	Univariate
Lee[11], 2011	Societal	v		v	DALY	Lifetime	3	ND	ICER per DALY	GDP per capita	Univariate
Shepard[12], 2004	Societal	v	v	v	DALY	Lifetime	3	3	ICER per DALY	GNI per capita	Univariate
Ezat[13], 2010	Healthcare	v			QALY	10	3	ND	ICER per QALY	GDP per capita	Univariate
Lee[14], 2011	Healthcare	v			LYS, QALY	Lifetime	3	3	ICER per LY, ICER per QALY	GDP per capita	Univariate
Sharma[15], 2011	Societal	v	v		LYS	Lifetime	3	3	Cost per LY	GDP per capita	Univariate
Praditsitthikorn[16], 2011	Healthcare Societal	v	v		LYS, QALY	Lifetime	3	3	ICER per QALY, ICER per LY	GDP per capita	PSA, Threshold analysis
Temrungruanglert[17], 2012	Healthcare	v			QALY	100	3	3	ICER per QALY	GDP per capita	PSA
Kim[18], 2008	Societal	v	v		LYS	Lifetime	3	3	ICER per LY	GDP per capita	Univariate
Broughton[19], 2007	Societal	v	v	v	DALY	66	3	3	ICER per DALY	GNI per capita	Univariate, Multivariate and PSA
Gessner[20], 2008	Healthcare Societal	v	v		DALY	5	3	3	ICER per DALY	GDP per capita	PSA

Limcangco[21], 2001	Healthcare Societal	v	v	v	Monetary unit	5	3	5	Net benefit	not applicable	Univariate
Muangchana[22], 2011	Healthcare Societal	v	v	v	Monetary unit	5	3	3	Net present value	not applicable	Univariate and Multivariate
Teppakdee[23], 2002	Societal	v	v	v	Monetary unit	Lifetime	ND	ND	Net benefit	not applicable	Univariate
Vimolket[24], 2005	Healthcare	v			Number of case prevented	ND	ND	ND	Cost per case prevented, ICER per case prevented	not applicable	Univariate
Ono[25], 2006	Healthcare	v	v		DALY	Lifetime	3	3	ICER per DALY	GDP per capita	Univariate
Leelahavarong[26], 2011	Healthcare	v			QALY	Lifetime	3	3	ICER per QALY	National threshold	Univariate
Lee[27], 2009	Healthcare	v		v	Monetary unit, LYS	Lifetime	3	3	Net benefit,cost per LYS	WTP (premium insurance)	Univariate
Touch[28], 2010	Healthcare Societal	v	v		Cases/Deaths averted, DALY	15	3	3	ICER per case averted, ICER per death averted, ICER per DALY	GNI per capita	Univariate
Liu[29], 2008	Healthcare	v	v		DALY	11	3	3	ICER per DALY	GNI per capita	Univariate
Aljunid[30], 2011	Healthcare	v			LYS	10	3	3	ICER per Life years gained	GDP per capita	Univariate
Tyo[31], 2011	Healthcare	v			Monetary unit, QALY	5	3	3	Net benefit, ICER per QALY	GDP per capita	Univariate
Wilopo[32], 2009	Healthcare Societal	v	v	v	DALY	5	3	3	ICER per DALY	GDP per capita	Univariate
Suwantika[33], 2013	Healthcare Societal	v	v	v	QALY	5	3	3	ICER per QALY	GDP per capita	PSA
Chotivitayatarakorn[34], 2010	Healthcare	v	v		DALY	5	3	3	ICER per DALY	GNI per capita	Univariate
Muangchana[35], 2012	Healthcare Societal	v	v	v	Monetary unit, DALY	5	3	3	Net present value, ICER per DALY	GDP per capita	Univariate
Fischer[36], 2005	Societal	v	v	v	LYS, DALY	5	3	3	ICER per life saved, ICER per DALY	World Bank's standard	Univariate and PSA
Kim[37],2009	Healthcare Societal	v	v		DALY	5	3	3	ICER per DALY	GDP per capita	Univariate and PSA
Tu[38], 2011	Healthcare Societal	v	v	v	QALY	5	3	3	ICER per QALY	GDP per capita	Univariate, Multivariate and PSA
Cook[39], 2008	Healthcare Societal	v	v	v	DALY	3	3	3	ICER per DALY	GNI per capita	Univariate and PSA
Jean-Jasmine[40], 2004	Societal	v		v	Monetary unit	ND	ND	ND	cost to benefit ratio	not applicable	Not performed

DMC = direct medical cost; DNC = direct non-medical cost; IC = Indirect cost; DALY = disability adjusted life year; QALY = quality adjusted life years; LYS = life year saved; ND = not described; ICER = incremental cost effectiveness ratio; GDP = gross domestic product; GNI = gross national income; PSA = probabilistic sensitivity analysis

Type of intervention of pharmacoeconomic studies

All articles clearly stated the study questions and objectives to which the studies were purposed. All studies conducted the ex-ante evaluation (the studies undertaken before vaccination implementation which the objective was to provide the economic feasibility data of vaccination to be included into the country setting); except only one study conducted the ex-post intervention of economic evaluation (the studies undertaken after the vaccination implementation which the objective was to evaluate a vaccination program that was included in the NIP of the particular country) which was economic evaluation of PCV vaccination in in Singapore. This study was conducted in the year 2011 to do the revised analysis of cost effectiveness of PCV vaccination in Singapore; and compared with the original analysis in the year 2008 before PCV vaccination being part of NIP.[31] In contrast, one study in Thailand also conducted economic evaluation of intervention related to Hep B vaccine which already being part of NIP. This study assessed the different modified interventions of Hep B vaccination program from the existing Hep B vaccination program.[24] Regarding the primary results of the studies, 30 studies assessed the cost effectiveness of program; while only 2 studies estimated the vaccine price for the programs being cost effective.

Program interventions and comparators

The interventions to control infectious diseases were including various vaccination programs and other interventions such as screening in HPV infection and hepatitis cases, prevention program in HIV and dengue cases, immediate or stock pilling intervention in influenza case, and campaign intervention in some cases. Thirteen studies compared vaccination with no vaccination intervention; 5 studies compared vaccinations with various types of vaccines (e.g. PCV-7/PCV-10/PCV-13, HPV-bivalent/quadrivalent, Hib-monovalent/pentavalent), as well as varying the target populations for the same type of vaccination with no vaccination; and the other 14 studies compared vaccination with both non vaccination scenario and other interventions such as screening for HPV infections and hepatitis cases, non-vaccination prevention programs/vector control programs in HIV and dengue, and additional campaign programs.

Study population

Study population was derived from targeted population (the population that was tended to receive the vaccination). It could be general/whole population or specific population. Most of studies covered birth cohort of infant or children (e.g. Hib, hepatitis B, japanese encephalitis, PCV, rotavirus, and varicella). Some studies covered specific population as the study population (e.g. HPV recruited female cohort start at age 9/12/15 years old, hepatitis A recruited the population aged 3-40 years old, cholera and typhoid recruited all population over than 2 years old which was divided into several groups; while dengue and influenza covered the whole population in all age group.

Method and technique of pharmacoeconomic studies

CUA has become the predominant method of economic evalution employed in the studies reviewed which accounted for 23 studies (72%), followed by CEA (18 studies/56%) and CBA (9 studies/28%). Among those studies, few studies employed combination of economic evaluation methods which were CEA-CUA (4 studies), CUA-CBA (2 studies), and CEA-CBA (1 study). Practically, all studies employed modeling; the decision tree model used in 13 studies (41%), Markov model used in 11 studies (54%), and one study employed dynamic model, however 2 studies failed to explicitly state the specific model used.

Study perspectives, cost elements and outcome expressions

Perspective in the economic evaluation study determines which costs and outcomes should be incorporated in the study. Our review found that all authors explicitly stated the perspective of study in their articles. The health care provider was the most perspective adopted in the studies (12), followed by societal perspective (9), and multiple viewpoint from the perspective of both societal and health care provider (11).

The perspectives drove the cost elements included in the analysis. Seven studies considered only direct medical cost; 9 studies considered direct medical and non-medical cost; 3 studied included direct medical cost and indirect cost; finally, 13 studies covered both direct medical and non-medical cost as well as indirect cost.

The effectiveness/outcomes of the analysis were expressed in several different types based on the economic evaluation methods. CEA studies expressed the outcomes in the form of percentage of effectiveness, number of cases or diseases averted, number of death averted, and years of life saved/years of life gained. Effectivenesses in CUA studies were expressed as DALY (disability adjusted life years) and QALY (quality adjusted life years). While CBA studies expressed the outcome in term of monetary unit.

DALY was used in 15 studies, QALY was used in 8 studies, LYS/LYG (life years saved/life years gained) and monetary unit were used in 7 studies respectively, while cases averted and death averted were only used in 2 studies and 1 study respectively.

Time horizon and discounting rate

Practically all studies used long time-time horizon (more than one year). The time horizons in the study could be grouped into 3 as follow: 3 to 5 years (Hib, PCV, rotavirus, varicella); 10 to 15 years (PCV, dengue, Japanese encephalitis); and life time or life time-nearly (HPV, dengue, Hib, Hepatitis, HIV). In summary, 1 study used 3

years of time horizon, 11 studies used 5 years of time horizon, 3 studies used 10 years of time horizon, 2 studies used 11 and 15 years of time horizon respectively, 2 studies used long time-time horizon (66 and 100 years), and 11 studies mentioned life time as the time horizon, finally 2 studies did not mention the time horizon.

The study with time horizon over 1 year needs to adjust the costs and outcomes by employing the discount rate in the calculation. Majority of the studies (26) used discount rates to accommodate the issue on translating future values of costs and outcomes to current ones. In detail for discounting of costs, 28 studies used 3% discount rate, 1 study used 5% discount rate, and 3 studies did not mention about discounting rates in the papers. Regarding the discount rates for outcomes, 25 studies used 3% discount rates, 1 study used 5% discount rate, and 6 studies did not mention discount rate.

Analytic methods and valuations

The summary measure for CEA and CUA were average cost effectiveness ratio and incremental cost effectiveness ratio (ICER). The study employing CUA method used summary measure of cost per DALY, ICER per DALY, and ICER per QALY. The CEA used ICER per life years saved, ICER per case averted, cost per life years saved, cost per case averted, cost per % of effectiveness. While CBA used net benefit summary measure. ICER per DALY and ICER per QALY were the most analytic methods used in the studies which accounted for 14 and 7 studies respectively.

The valuation to present the cost-effectiveness results used several threshold, including WHO's recommendation standard for health care intrevention (compare to GDP per capita of the country), World bank's standard (compare to GNI/GNP per capita of the country or other recommended value of threshold), and national threshold.

The other studies employed CBA used net benefit or net present value to assess the cost effectiveness of the programs, and were not applicable using the threshold.

Most studies used GDP per capita and GNI per capita which accounted for 17 and 7 studies respectively.

Sensitivity analysis

Sensitivity analysis is important to assess the robustness of the results to changes in assumptions of key parameters.

All studies, except one, performed sensitivity analysis mostly using the method of univariate sensitivity analysis solely (21 studies), the others using combined of univariate, multivariate, and probabilistic sensitivity analysis.

Cost effectiveness results

Table 4 summarizes the cost effectiveness of vaccination program in Southeast Asia countries resulted from the studies reviewed. It also shows the comparisons of the cost effectiveness results between country setting and type of vaccine. All studies gave favorable results of cost effectiveness ratios of vaccination programs in Southeast Asia country setting, except two studies conducted in Thailand for HPV vaccination[16] and HAV vaccination[23] which conclude that the vaccinations were not cost effective for their settings.

DISCUSSION

This review explored the studies on economic evaluation of vaccination in Southeast Asia countries that were published in international journals before July 2013 at the time the review done. For maximum usefulness, systematic reviews of economic evaluations should be transparent, that is, all relevant methodological information from the included studies should be described in a systematic way. Therefore to understand the quality of economic evaluation of vaccination in Southeast Asia, we assessed the quality of papers against selected technical criteria recommended by CHEC[8] and WHO.[1]

Most of the studies has met the selected criteria for good reporting of economic evaluation particularly economic evaluation of vaccination program. It can be said that the economic evaluations of vaccination in Southeast Asia published in international journal had a good quality based on the selected recommendation, although few studies did not meet those criteria.

Our review suggested that economic evaluations specifically conducted in vaccination interventions have the better quality than economic evaluations of healthcare in general, as were performed in Thailand[41] and Bangladesh.[42] Economic evaluations of vaccinations in Southeast Asian countries have better methodological quality than of those studies.

Other study conducting economic evaluation of Hepatitis B immunization did not intense assess the quality of study reporting, however this study finally recommend the need of specific guidelines for economic evaluation of the prevention of infectious diseases to guarantee the relevance of and to improve the comparability between studies.[43]

Table 4: Cost effectiveness of vaccinations program in Southeast Asia

Study	Type of vaccine	Setting	Cost effectiveness resulted from studies
Jeuland[9], 2009	Cholera	Multi-country (including Indonesia)	Cost effective
Carrasco[10], 2011	dengue	Singapore	Estimation of vaccine price
Lee[11], 2011	dengue	Thailand	Cost effective
Shepard[12], 2004	dengue	Multi-country (Southeast Asia region)	Cost effective
Ezat[13], 2010	HPV	Malaysia	Cost effective
Lee[14], 2011	HPV	Singapore	Cost effective
Sharma[15], 2011	HPV	Thailand	Cost effective
Praditsitthikorn[16], 2011	HPV	Thailand	Not cost effective
Temrungruanglert[17], 2012	HPV	Thailand	Cost effective
Kim[18], 2008	HPV	Vietnam	Cost effective
Broughton[19], 2007	Hib	Indonesia	Cost effective
Gessner[20], 2008	Hib	Indonesia	Cost effective
Limcangco[21], 2001	Hib	Philippines	Cost effective
Muangchana[22], 2011	Hib	Thailand	Cost effective
Teppakdee[23], 2002	HAV	Thailand	Not cost effective
Vimolket[24], 2005	Hep B	Thailand	Cost effective
Ono[25], 2006	HIV	Thailand	Cost effective
Leelahavarong[26], 2011	HIV	Thailand	Cost effective
Lee[27], 2009	Influenza	Singapore	Cost effective
Touch[28], 2010	JE	Cambodia	Cost effective
Liu[29], 2008	JE	Indonesia	Cost effective
Aljunid[30], 2011	PCV	Malaysia	Cost effective
Tyo[31], 2011	PCV	Singapore	Cost effective
Wilopo[32], 2009	Rotavirus	Indonesia	Cost effective
Suwantika[33], 2013	Rotavirus	Indonesia	Cost effective
Chotivitayatarakorn[34], 2010	Rotavirus	Thailand	Cost effective
Muangchana[35], 2012	Rotavirus	Thailand	Estimation of vaccine price
Fischer[36], 2005	Rotavirus	Vietnam	Cost effective
Kim[37], 2009	Rotavirus	Vietnam	Cost effective
Tu[38], 2011	Rotavirus	Vietnam	Cost effective
Cook[39], 2008	Typhoid Vi	Multi-country (including Indonesia and Vietnam)	Cost effective
Jean-Jasmine[40], 2004	Varicella	Singapore	Cost effective

HPV = human papillomavirus; Hib = haemophyllus influenza type b; HAV = hepatitis A vaccine; Hep B = hepatitis B; HIV= human immunodeficiency virus; JE = Japanese encephalitis; PCV = pneumococcal conjugate vaccine

We then reported the reviews of all studies without filter the articles against any quality criteria. This also because we would like to describe the real situation of published economic evaluation of vaccination in Southeast Asia countries.

Finding from the review shows that the contribution of the researchers from local settings appears significant. In a fair number of articles, the local researchers appeared as the principal investigators or first/correspondence authors and as collaborative partners with the researchers from outside the country settings. However, it should be highlighted that few studies conducted solely by researchers from outside the settings without contribution from local researchers. It cannot be denied that collaboration with researchers from outside the setting who are more in expertise is also important.

The number of articles in Southeast asia countries tended to increase over the time. It shows that there is a good progress in economic evaluation studies in Southeast asia countries as one consideration in health care program policy. The trend of progress of economic evaluation studies in each country in Southeast asia was different. It may caused by the different supports from the government and international organisations or other parties that can be indicated by the funding sources revealed in most studies; as well as influence of the

activities of academic researchers as most of the researchers were affiliated with university. Most studies were conducted by local researchers, furthermore there is considerable number of them were affiliated with government office (Ministry of Health); it can be assumed that such economic information is gaining importance in setting priority of health-policy decision-making. Now days, economic evidences have been used as one criteria for considering the benefit package of insurance in country adopting universal coverage such as Thailand[44]; hence it is not surprising that most of studies were conducted in this setting. In addition, government of Thailand concerns to support economic evaluation studies in the country by establishing specific body, namely Health Intervention and Technology Assessment in 2007 which purposed to serve evidences for policy decision makers.[45]

Almost all studies were purposed for ex-ante evaluation; indicating the preparedness of new vaccination introduction in the settings. When considering the type of vaccination being concerned in the studies, these are in accordance with the majority health problem of vaccine preventable diseases in the region particularly rotavirus, HPV and Hib which become most concerned issues in the region.[46]

The review indicates that cost utility analysis was the most popular method used in economic evaluation of vaccination conducted in Southeast Asia countries. In accordance with WHO recommendation for economic evaluation of vaccination program that CUA is the preferred form of economic evaluation.[1] In addition, CUA which the outcome of interest is measured in a unit of utility (e.g. disability-adjusted life-years (DALYs) averted or quality-adjusted life-years (QALYs)) is more useful to decision-makers with abroad mandate than is CEA because of its broad applicability.[5] Other good point of economic evaluations of vaccination in Southeast Asia is that the calculating and presenting ICER which was adopted in almost all studies. With ICER, it is easy for the readers to make direct comparisons between interventions and conclude whether a new intervention is noteworthy compared to the existing one.[5]

Considering the results of cost effectiveness of vaccination programs in Southeast Asian countries, it is impressive that most studies served favorable cost effectiveness ratios of vaccination programs. These results indicate that such programs may be implemented in such setting, as well as may be adopted in other settings. However, some considerations should be concerned when adopting the economic evaluation results, such thing as the robustness of the findings.[5,47] To assess these, sensitivity analysis is a suitable tool to assess the robustness of findings to change in the value of key parameters. Fortunately, sensitivity analysis was conducted in almost all the studies. Readers need to concern the value of information providing by sensitivity of analysis as part of the studies. The variables such as incidence of disease, vaccine price, vaccination effectiveness, discount rates are potentially influenced the finding results.[1] Furthermore, it should be noted that economic evidence is not the only aspect to decide the introduction of vaccination program, other aspects such as social value and policy issues are also important.[1,48]

Finally, it is important to point out the limitation of this study. The study searched only published literature in one international data base. Other data base sources, as well as grey literatures may also possible to provide more number of economic evaluation of vaccination in Southeast Asian countries instead of this finding. However, the number of publications available can represent the situation of economic evaluation of vaccination in Southeast Asian countries; and therefore can give recommendations such as the need to conduct economic evaluation of vaccination in these settings for the absence of the evidence provide by these studies, the considerations to adopt the economic evidence for policy decision making in such setting or other settings in the region supporting the achievement of harmonized-ASEAN community.

CONCLUSION

In this review we explored that there is considerable number of pharmacoeconomic study of vaccination program conducted in Southeast Asian countries. It can be assumed that such economic information is gaining importance in policy decision making. Most of articles met the selected recommendations for good reporting of economic evaluation of vaccination program. Based on the review, we recommend that more pharmacoeconomic studies need to be conducted in the absence of some evidences from the available studies. Summary of available economic evidence may also be considered as one of consideration aspects of decision making in vaccination program.

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