EXECUTIVE SUMMARY

HEPATITIS B VACCINATION: AN UPDATED SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS IN LOW AND MIDDLE INCOME COUNTRIES

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KEY FINDINGS

- Since the introduction of HBV only 19 CEA studies in LMICs have been identified.
- HBV vaccination in LMICs has favorable cost-effective results in almost all published studies using per GDP per capita cost-effectiveness thresholds.
- This systematic review highlights that vaccine price, prevalence of HBV, discount rate, cost component, wastage rate of vaccine, and vaccine efficacy are the key drivers and play influential role in the decision to implement HBV immunization program in LMIC.
- In addition to cost-effectiveness results, decision makers should consider feasibility, affordability and sustainability of vaccination programs to ensure equitable access of vaccine when deciding whether to include HBV vaccination in national immunization program.

ABSTRACT

BACKGROUND

Hepatitis B virus (HBV) is blood-borne virus which is one of the major causes of liver diseases and hepatocellular carcinoma. HBV caused an important public health problem worldwide particularly in developing countries where the prevalence of disease is generally high. Although, in 1992, WHO recommended that all countries should include universal HBV vaccination in national immunization, this has not been fully implemented across the world possibly due to budget limitation. Therefore, information about economic evaluation of HBV vaccination is crucial for policy makers. In Low and Middle Income Countries (LMICs), so far, little is known about economic evaluation of HBV vaccination.

OBJECTIVES

To systematically review the evidence for economic evaluations of HBV vaccination in LMICs.

METHODS

The following databases were systematically searched: MEDLINE (PubMed), EMBASE (OVID), National Health Service Economic Evaluation Database (NHS EED), EconLit, CEA Registry, Scientific Electronic Library Online (SciELO), World Bank - e-Library, WHOLIS, WHO Global index medicus, Cochrane Library and LILCAS for HBV economic evaluation studies published from 2008 to September 2016 since the previous review of economic evaluations on HBV vaccination in LMICs was made through 31st January 2008 [1]. Literature search was

performed using the broad combined search of (hepatitis b) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (cost OR cost-effective* OR cost-utility* OR cost-benefit* OR pharmacoeconomics) AND (analysis OR "economic evaluation*"). To be included, studies must be a full economic evaluation of HBV in LMICs. No language restrictions were applied. Editorials, reviews and publications with abstract only without a full paper were excluded. Parameters extracted included: 1) study overview or characteristics of the study, 2) key drivers or parameters of economics evaluation, and 3) major area of uncertainty.

RESULTS

A total of 2,202 studies was screened, out of which 386 remained after duplicates were removed, 23 studies were eligible for inclusion and a final total of 19 studies [2-20] was included in this review.

Study Characteristics

Ten of the 19 studies evaluated the cost-effectiveness universal HBV vaccination while the remaining focused on risk-groups. Of 19 included studies, 16 [3, 5-13, 15-20] used static economic models to evaluate cost-effectiveness of Hep B vaccine in LMICs. Eight studies [2, 8, 11, 13-16, 18] performed a cost-effectiveness analysis (CEA), while five [5-7, 10, 12] and three [3, 19, 20] studies performed cost-utility analysis (CUA) and cost-benefit analysis (CBA), respectively. One each performed cost-minimization analysis (CMA) and CEA [4], CBA and CUA [9], and CEA and CUA [17]. Among the studies using CEA or CUA, 12 considered disability-adjusted life years (DALYs) or quality-adjusted life years (QALY) as a measure of health outcome. Five studies used decision-tree analytic model [5, 7, 8, 11, 19], while two studies used Markov model for analysis [6, 15]. Both decision tree and Markov models were used in five studies [13, 16-18, 20]. Type of static model of the other three studies were not specified [9, 10, 12].

A cost-effective threshold of one times Gross Domestic Product (GDP) per capita was clearly stated based on cost per DALY averted in five studies [5, 7, 8, 14, 15]. Seven studies [6, 9, 10, 13, 16, 17] estimating ICER as cost per QALY or LY gained and used one times GDP as threshold [6, 9, 10, 13, 16-18]. Of these, three studies used cost per QALY and one times Gross national product (GNP) per capita as threshold [6, 9, 10]. In CBA studies, benefit-to-cost ratio (BCR) ≥ 1 was used as threshold in three studies [3, 19, 20] (Table 1).

Most studies compared HBV vaccination with no vaccination except four studies compare with other strategy (Table 2). Two studies comparing catch-up program with *status quo* [13, 18], one study comparing additional birth dose of HBV vaccine with existing vaccination schedule administered at 6–10–14 weeks [15], and one study comparing vaccination without screening with screening-based vaccination [19].

Considering birth dose of HBV vaccine, only six of 19 studies provided information on birth dose vaccination [7, 9, 11, 15, 17, 20].

Cost-Effectiveness Findings

Out of 19 studies, 18 studies considered HBV vaccination cost-saving or cost-effective intervention, while only one study showed that it was unlikely to be cost-effective [9] (Table 3). All six studies investigating birth dose HBV vaccination showed that it was cost-effective.

Sensitivity Analysis Findings and Influential Parameters Reported

According to the Table 4, most studies conducted one-way sensitivity analysis. Probabilistic sensitivity analysis (PSA) was conducted in eight studies.

The influential parameters reported for each study of economic evaluations of HBV vaccination in LMICs were shown in Table 4. The most reported influential parameters were vaccine price (8 of 19 studies), prevalence of HBV (7 of 19 studies), discount rate (7 of 19 studies), cost component (5 of 19 studies), wastage rate of vaccine (3 of 19 studies), and vaccine efficacy (3 of 19 studies).

Key Findings and Implications

Our study found that only 19 economic evaluation studies of HBV vaccination in LMICs have been identified and most of them demonstrated that HBV vaccination program was a cost-effective intervention. The results are sensitive to vaccine price, prevalence of HBV, discount rate, cost component, wastage rate of vaccine, and vaccine efficacy. Decision makers should consider economic evaluation findings and affordability before the adoption of HBV vaccination.

SUMMARY OF FINDINGS: Table 1 Economics evaluation of Hepatitis B vaccination in LMICs

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach*	Effectiveness measure	Threshold
Hall, 1993	The Gambia	CEA	None	Society	Department for Co-operation and Development of the Ministry of Foreign Affairs of Italy. The vaccine for the study was donated by Merck, Sharp, and Dohme.	Universal	Death averted	US$2750 (year 1979)
Liu, 1995	China	CBA	Static model: Decision tree	Society	N/A	Universal	BCR	N/A
Edmunds, 2000	Ethiopia	CEA, CMA	None	Healthcare	University of Warwick's Research and Training Development Fund. Wellcome Health Services Research Fellowship.	N/A	Per fully vaccinated child	N/A
Hu, 2001	China	CUA	Static model: Decision tree	Society	N/A	Targeted*	DALY	N/A
Aggarwal, 2003	India	CUA	Static model: Markov	Society	N/A	Universal	LYG, QALY	GNP per capita (US$440 for year 1999)
Prakash, 2003	India	CUA	Static model: Decision tree	Society	N/A	Universal	DALY	N/A
Adibi, 2004	Iran	CEA	Static model: Decision tree	Society and Healthcare	Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University of Medical Sciences, Tehran, Iran	Targeted*	Per chronic infection prevented	GDP per capita (US$1641 for year 2002)
Sahni, 2004	India	CBA, CUA	Static model: -	Society	The Canadian International Development Authority (CIDA)	Universal	QALY	GNP per capita (US$466 for year 2001)
Griffiths, 2005	Mozambique	CUA	Static model: -	Society	N/A	Universal	QALY	GNP per capita (US$210 for year 2001)
Vimolket, 2005	Thailand	CEA	Static model: Decision tree	Society	The Center of Excellence Research Fund, Chulalongkorn University; and the Thailand Research Fund, Senior Research Scholar.	Universal	Per case adverted	N/A
Kim, 2007	The Gambia	CUA	Static model: -	Society and Healthcare	Supported in part by a Harvard Graduate Society Fellowship.	Universal	DALY	GDP per capita (US$300 for year 2002)
Hutton, 2010	China	CEA	Probability tree and Markov	Societal	N/A	Catch-up program	Death, HBV infections averted, and QALYs	GDP per capita (US$2,500 for year 2008)
Guo, 2012	China	CEA	N/A	N/A	The National Nature Science Foundation of China	N/A	DALY averted	N/A

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach*	Effectiveness measure	Threshold
		HBIG						
Klingler, 2012	Mozambique	CEA	Markov	Payer	N/A		DALY averted	GDP per capita (US$441 for year 2008)
Tu, 2012	Vietnam	CEA	Decision tree and Markov	Societal, healthcare, and payer	The Dutch Higher Education Foundation (NUFFIC)	Universal	LYG and QALY	GDP per capita (US$440 for year 2002)
Lu, 2013	China	CEA, CUA	Decision tree and Markov	Societal and healthcare payer	N/A	Universal	New infections, HCC, deaths, LYG, and QLAY	GDP per capita (US$1,136 for year 2002)
Jia, 2014	China	CEA	Decision tree and Markov	Societal	National Health and Family Planning Commission and Minister of Science and Technology	Catch-up program	QLAY	GDP per capita (US$5,414 for year 2013)
Zheng, 2015	China	CBA	Decision tree	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Screening based vaccination for 21-59 years old	NPV, BCR	BCR $\geq$1
Chen, 2016	China	CBA	Decision tree and Markov	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Combine with one dose of HBIG for infants with HBsAg +ve mothers	NPV, BCR	BCR $\geq$1

* Universal = Immunization given to the whole general population or to all within a certain age group of the population (newborns, adolescents, adults, and so on), Targeted and catch-up = Immunization programs selectively targeting individuals at risk of hepatitis B virus

BCR: Benefit cost ratio; CBA: Cost–benefit analysis; CEA: Cost–effectiveness analysis; CMA: Cost–minimization analysis; CUA: Cost–utility analysis; DALY: Disability-adjusted life year; GNP: Gross national product; GDP: Gross domestic product; HBIG: Hepatitis B immunoglobulin; HCC: Hepatocellular carcinoma; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable; NPV: Net present value

SUMMARY OF FINDINGS: Table 2 Vaccine strategy in each included studies

Study	Birth dose HBV	Group	Vaccine Strategy	
			Vaccine	Comparator
Hall, 1993	N/A	Newborns (Universal)	HBV vaccination	No vaccination
Edmunds, 2000	N/A	Children	HBV vaccination	No vaccination
Aggarwal, 2003	N/A	Newborns (Universal)	Received three doses of HB vaccine in early life	No vaccination
Prakash, 2003	●	Newborns (Universal)	HBV vaccination	No vaccination
Adibi, 2004	N/A	Targeted	2 groups*	No screening and no prevention.
Sahni, 2004	●	Newborns (Universal)	HBV vaccination	No vaccination
Griffiths, 2005	N/A	Newborns (Universal)	HBV vaccination	No vaccination
Vimolket, 2005	●	Newborns (Universal)	3 groups**	No vaccination
Kim, 2007	Not	Newborns (Universal)	HBV vaccination	No vaccination
Hutton, 2010	Not	Children under age 5 years and aged 5 to 19 years	Catch-up program	No catch-up program
Klingler, 2012	●	Newborns (Universal)	Additional birth dose of Hepatitis B (HBV) vaccine	Existing vaccination schedule administered at 6–10–14 weeks.
Gou, 2012	N/A	N/A	HBIG on the mother group includes pregnant women who were injected with HBIG during pregnancy, but not their children	3 groups***
Tu, 2012	N/A	Newborns (Universal)	Vaccination against HBV	No vaccination
Lu, 2013	●	Newborns (Universal)	Birth dose (HepB1) with a three-dose vaccination (HepB3)	No vaccination
Jia, 2014	N/A	8‐15 y old	Catch-up program	*Status quo* (no catch-up program)
Zheng, 2015	N/A	21–59-years-olds	Vaccination without screening	Screening-based vaccination.
Chen, 2016	●	Newborns (Universal)	HBV vaccination combined with HBIG	No vaccination

 = Got birth vaccine, HBV = Hepatitis B virus

* 1. Screening all premarriage individuals for HBsAg and then performing the following prevention protocol for HBsAg negative individuals whose would-be spouse is HBsAg positive, 2 Screening all premarriage individuals for HBsAg followed by rescreening of the HBsAg negative spouses of HBsAg positive persons for HBcAb and finally performing the prevention protocol only for HBcAb (and HBsAg) negative individuals whose would-be spouse is HBsAg positive.

** 1. Screening for HBsAg, and vaccination; 2. Screening for HBsAg, then HBeAg, and vaccination; 3. Universal vaccination of all neonates

*** 1. HBIG on the infant group includes children who were injected with HBIG and HBV vaccines within 24 h after birth (active and passive immunization), 2. HBIG on the mother and infant group includes both pregnant women and their children who were injected with HBIG (united maternal and child immunization), 3. no-HBIG group comprises pregnant women and their children who were not injected with HBIG

SUMMARY OF FINDINGS: Table 3 Vaccine coverage, efficacy duration, price, discounting, and results

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US$)*		Discounting rate (%)		Results (US$, at costing year)
			Price	Costing year	Cost	Effect	
Hall, 1993	10%-15%	99% (95%CI 91-100)	3	1998	6	N/S	**Cost-effective** US$150-200 per death averted
Liu, 1995	100%	50% (HBsAg+ by 3 doses of 10µg) 90% (HBsAg+ by 3 doses of 30µg) 90% (HBsAg-)	6.53 (for 3 doses of 10µg) 12.37 (for 3 doses of 30µg)	1990	-	-	**Cost saving** With screening 30µg X3 for HBsAg+ and 10µg X3 for HBsAg-: BCR = 42.41 30µg X3 for HBsAg+ and no vaccination for HBsAg-: BCR = 48.01 Without screening 10µg X3 for both HBsAg+ and HBsAg-: BCR = 43.64
Edmunds, 2000	60%	N/A	0.35-1.69	1996	6	N/S	**Cost-effective** US$7.83 per fully vaccinated child (Extrapolate the cost-effectiveness in terms of outcome measure such as life years gained relative to The Gambia)
Hu, 2001	100%	90%	2.97	2001	3	-	**Cost-effective** Without screening: CER = 392.7 With screening: CER = 251.9
Aggarwal, 2003	75% (40% - 95%)	95%	3	2002	3	0	**Cost-effective** US$16.27/LYG and US$13.22/QALY
Prakash, 2003	52%	95%	0.75	1993	3	0 or 3	**Cost-effective** US$27.36/DALY
Adibi, 2004	100%	N/A	4.8	2003	3	0	**Cost-effective** US$202 per chronic infection prevented (no HBcAb screening) US$197 per chronic infection prevented (with HBcAb screening)
Sahni, 2004	N/A	100%	4.2	2001	3	0	**Not cost-effective** US$2909/QALY (US$8894/ discounted QALY)
Griffiths, 2005	80% (70% - 85%)	95% (90% - 99%)	0.27 for monovalent vaccine and 1.2 for DTP-Hepatitis B	2001	3	0 or 5	**Cost-effective** Undiscounted US$436 per death averted, US$15/DALY (monovalent), and US$36/DALY (combination vaccine) Discounted US$1833 per death averted, US$19/DALY (monovalent),, and US$47/DALY (combination vaccine)
Vimolket, 2005	N/A	N/A	3.75	2004	N/S	N/S	**Cost-effective** US$2201 per case averted (screen for HBsAg, then vaccination) US$464 per case averted (screen for HBsAg, HBeAg, then vaccination) US$152 per case adverted (universal vaccination) (Based on funds presently available in Thailand, universal vaccination should certainly be continued)
Kim, 2007	94% (85% - 100%)	95% (90% - 100%)	0.32	2002	3	3	**Cost-effective** US$28/DALY (societal perspective) US$47/DALY (healthcare perspective)
Hutton, 2010	100% (catch up for those who missed newborn vaccination)	95%	0.34	2008	3	3	**Cost-saving**
Guo, 2012	N/A	N/A	30.93, HBIG	N/A	N/A	N/A	**Cost-effective** US$118.61/DALY averted
Klingler, 2012	55%	88%	0.71	2008	3	3	**Cost-effective** US$250.95/DALY averted

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US$)*		Discounting rate (%)		Results (US$, at costing year)
			Price	Costing year	Cost	Effect	
Tu, 2012	70%	84%	1	2008	0 or 3	0 or N/S	**Cost-effective** US$4.52/LYG and US$3.77/QALY
Lu, 2013	84.3% for HepB3 and 66.1% for timely HepB1	66% (HBsAg+ HBeAg+) 73% (HBsAg+ HBeAg-) 95% (HBsAg- HBeAg-)	3.6, vaccination cost	2008	3	3	**Cost-saving**
Jia, 2014	100% (catch up for those who missed newborn vaccination)	N/A	0.34	2013	3	0 or N/S	**Cost-effective**
Zheng, 2015	50% for direct vaccination and 75% for screening based vaccination	93% (21-29 years) 89% (30-39 years) 80 (40-49 years) 70 (50-59 years)	0.76	2014	3	3	**Cost saving for young adults (21-39 years)** Without screening: direct BCR = 1.06, societal BCR = 1.42 With screening: direct BCR = 1.19, societal BCR = 1.73 **Not cost saving for middle aged adults (40-59 years)** Without screening: direct BCR = 0.59, societal BCR = 0.59 With screening: direct BCR = 0.68, societal BCR = 0.43
Chen, 2016	99.6% for HepB3 and 95.88% for timely birth dose	83.1% for vaccine only and 91.0% for vaccine+HBIG (HBSAg+ HBeAg+)	0.5	2013	3	3	**Cost saving** HepB+HBIG compared with HepB vaccination without HBIG: direct BCR = 0.4, and societal BCR = 2.7

*The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Converter (http://eppi.ioe.ac.uk/costconversion/default.aspx)

CBA: Cost–benefit analysis; CEA: Cost–effectiveness analysis; CMA: Cost–minimization analysis; CUA: Cost–utility analysis; DALY: Disability-adjusted life year; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable, N/S: Not specified

SUMMARY OF FINDINGS: Table 4 Sensitivity analyses and influential parameters reported for each study of economic evaluations

Study	Sensitivity analyses				Influential parameters reported														
	1-way	PSA	Two way/ multi way	CEAC	Vaccine price	Wastage rate of vaccine	Vaccine efficacy	Vaccine coverage rate	Prevalence of HBV or HBsAg	Prevalence of HBcAb	HBV carrier rate	Spouse-to-spouse transmission rate	Efficacy of preventive intervention	Mortality rate	Health outcome cost	Administration cost	Cost of screening HBsAg or HBeAg	Discount rate	Cohort age
Hall, 1993	●				●	●								●				●	
Liu, 1995	●						●								●		●		
Edmunds, 2000	●				●	●												●	
Hu, 2001	●				●		●												
Aggarwal, 2003	●	●			●						●								
Prakash, 2003	●	●			●	●	●	●	●										
Adibi, 2004	●		●						●	●		●	●						
Sahni, 2004	●																	●	
Griffiths, 2005	●	●							●										
Vimolket, 2005	●																●		
Kim, 2007	●	●		●															
Hutton, 2010	●	●	●	●	●				●						●	●			●
Guo, 2012																			
Klingler, 2012	●		●																
Tu, 2012	●	●		●	●				●										
Lu, 2013	●	●							●									●	
Jia, 2014	●	●							●									●	
Zheng, 2015	●				●			●										●	
Chen, 2016	●														●	●		●	

● = Conducted such sensitivity analysis OR parameter reported that it influent the economic evaluation result

N/A: Not applicable, N/S: Not specified, PSA: probabilistic sensitivity analysis, HBV: Hepatitis B virus, HBsAg: hepatitis B surface antigen

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