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Systematic Review

Economic evaluation of hepatitis A vaccines by income level of the country: A systematic review

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***Background & objectives*: Although several reviews of economic evaluation (EE) studies on hepatitis A virus (HAV) vaccine exist, there remains a need to corroborate such data from time to time. This study aimed to systematically review the literature for reports on EE of HAV vaccination by type of population, characteristics of intervention and income level of the country.**

***Methods*: PubMed and Scopus were searched to identify relevant studies from inception up to May 2021 using topic-specific key words in various combinaiton. Full EE studies comparing HAV vaccination to no vaccine or immunoglobulin were included. The risk of bias was assessed by using the ECOBIAS checklist.**

***Results*: Among the 1984 identified studies, 43 were found eligible. Of these, 27 were from high-income countries (HICs), 15 from middle-income countries (MICs), and one from low income country. Majority of the studies used Markov model and/or decision tree (n=26). Eight studies used a dynamic model. The discount rate, perspective and time horizon varied across the studies. Universal HAV vaccination without screening was cost-effective among children (14/16, 87.5%) and adolescents (1/5, 20%) but not in adults (0/4, 0%). Analysis by the level of income found that universal HAV vaccination among children without screening was cost-effective in 81.8 per cent of the studies conducted in MICs (9/11) as compared to 66.7 per cent in HICs (4/6). About one-third of the studies conducted among children found that screening and HAV vaccination were cost-effective compared to no vaccination.**

***Interpretation & conclusions*: The finding of this review suggest that universal vaccination of children without screening was likely to be cost-effective, especially in MICs. Nevertheless, it should be noted that the methodology varied across studies. Several aspects should also be considered in transferring the EE results across jurisdictions.**

Key words Cost-effectiveness - economic evaluation - hepatitis A virus - vaccination - vaccine - systematic review

Hepatitis A is a liver disease caused by hepatitis A virus (HAV) infection, which belongs to the *Picornaviridae* family[1]. HAV is transmitted through the ingestion of contaminated food and water or even by close physical contact with an infected person[2]. Once a person gets infected with HAV, lifelong immunity develops[3,4]. A person with hepatitis A infection may have an asymptomatic state, or may develop symptoms such as fever, nausea or vomiting, abdominal discomfort, jaundice and acute liver failure. Nevertheless, it does not progress to chronic hepatitis[2]. Unlike hepatitis B and C, hepatitis A is rarely fatal[2].

The World Health Organization (WHO) estimates have suggested an increase in the number of acute hepatitis A cases from 117 million in 1990 to 126 million in 2005 with increase in deaths due to hepatitis A from 30,283 (in 1990) to 35,245 (in 2005)[5,6]. A global seroprevalence study on hepatitis A estimates an intermediate or low, level of endemicity in middle-income countries (MICs) from Asia, Eastern Europe, Latin America and the Middle East[6]. On the other hand, high-income countries (HICs) generally have low levels of HAV endemicity[7].

The severity of hepatitis A infection increases with age, leading to a higher rate of severe disease and death in adults[2]. In low-income countries (LICs), which usually have a high level of endemicity, nearly all children get infected at an early age and are usually asymptomatic[2].

In regions with intermediate endemicity, improved sanitary conditions may lead to the accumulation of adults who have never been infected, hence, have no immunity. These individuals in older age groups, therefore, are at a high risk of symptomatic hepatitis A infection[8]. Recently, the increasing burden of hepatitis A disease is noted in the regions with intermediate endemicity; thus, the countries in these regions may benefit from new/expanded vaccination programmes[8].

HAV vaccination is considered as an effective and safe method to prevent hepatitis A infection[2]. Worldwide, two types of HAV vaccines (formaldehyde inactivated and live attenuated vaccines) are available[2]. The WHO recommends HAV vaccination to be integrated into the national immunization schedule for children aged more than one year based on the incidence of hepatitis A, change in endemicity from high to intermediate and considering the cost-effectiveness of the vaccination strategy[8].

Economic evaluation (EE) is the comparative analysis of two or more interventions in terms of their costs and consequences[9]. Three main types of EE methods are cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA)[9]. In CEA, cost of each intervention is measured against its effectiveness (*e.g.* cost per case prevented, cost per life year gained). For CUA, cost incurred in the intervention is measured against the common unit, called quality-adjusted life year (QALY) (*e.g.* cost per 1 QALY gained). One QALY means one year in full health. For CBA, both cost and consequences of an intervention are expressed in monetary units. Then, the net benefit can be calculated as the difference between cost and consequences[9].

To compare the alternative intervention over a long timeframe, modelling techniques have been adopted. Modelling offers several advantages including extrapolation beyond data generated through a trial, synthesizing head-to-head comparisons wherever relevant and linking intermediate endpoint to final outcomes. The most common modelling approaches used in EE studies are decision tree and Markov model[10]. Unlike decision tree model, Markov model is suitable when timeframe is long, process of disease is complex and events may repeat[10].

Evidence generated through EE is important to inform effective healthcare resource allocation. Nevertheless, the capacity to conduct economic studies in many countries is limited[11]. To date, three systematic reviews on EE of HAV vaccination have been published[12-14]. The most comprehensive study[12] published in 2018 included four studies from MICs and 27 studies from HICs. Another systematic review included nine studies conducted in MICs, which were published till 2012[13]. The other identified 11 EE studies, were published between 1995 and 2010[14]. It should also be noted that methodological characteristics were not fully described in the previous reviews, making it challenging to assess the transferability of the results. Therefore, the aim of this study was to systematically review evidences on cost-effectiveness of hepatitis A vaccination along with epidemiologic parameters and methodological characteristics. Cost-effectiveness evidences were also summarized by the types of population, intervention and income level of the countries.

Material & Methods

This systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[15]. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018105279).

Search strategy: Relevant studies were identified from PubMed and Scopus database without language restriction from inception to May 31, 2021. For studies other than the English language, help of the language translator from Mahidol University, Bangkok, Thailand was sought. Reference lists of the included studies and previous systematic reviews[12-14,16] were also screened. Search terms were constructed based on intervention (I), outcome (O) and study design (S). These were combined using Boolean operators 'OR', 'AND' for within the same and between the domains, respectively. Both keywords and MeSH terms were used. The full details of search terms and strategies are given in Supplementary Appendix I.

Selection criteria: Duplicate articles were removed by EndNoteX9 software [Camelot UK Bidco Lmtd. (Clarivate analysis), Bangalore, Karnataka, India]. Study selection was performed independently by two authors. Titles and abstracts were screened for potential eligibility. The following criteria were used for screening: (*i*) full EE comparing HAV vaccine (inactivated or attenuated) to no vaccine or immunoglobulin and, (*ii*) reported findings in terms of cost per case prevented or incremental cost-effectiveness ratio (ICER) or benefit-to-cost ratio. Studies were excluded if HAV vaccine was investigated in combination with other vaccines, animal studies or studies which reported only clinical effectiveness or disease burden or outbreak investigations or if their fulltext were unavailable. In addition, narrative reviews, systematic reviews, editorial publications, and conference proceedings were also excluded.

Data extraction and quality assessment: Data were extracted independently by two authors using a predesigned data extraction form (Supplementary Appendix II). Any disagreement was resolved by discussion and consensus with a third author. The data extracted included were study and population characteristics, vaccination and comparator details (*i.e*. vaccine efficacy, vaccination approach), epidemiological parameters (*i.e*. incidence of HAV), methodological details (*i.e*. perspective, time horizon, discounting and sensitivity analysis) and EE results.

Risk of bias assessment was performed using the ECOBIAS checklist, which was developed for assessing bias in EE studies[17]. This 22-item checklist consists of two parts. Part A is related to overall bias, while Part B focusses on model-specific aspects of bias. Results for each item were recorded as 'yes', 'partly addressed', 'unclear', 'no' and 'not applicable'.

Statistical analysis: Descriptive synthesis and narrative summary of study characteristics, participants, interventions, methodology and EE findings were reported according to the income level of the country studied as per the World Bank Report[18]. Countries were also classified into regions according to the WHO[19]. According to the World Bank Report 2017, the world's economies were classified into four income groups based on Gross National Income per capita (current US $) as: LICs (<1005 $), lower-middle-income countries (LMICs) (1006-3955 $), upper-middle income countries (3956-12,235 $) and HICs (>12,235 $)[18].

Results

Search results and study characteristics: Of the 1984 studies identified, a total of 43 eligible studies (40 English language and 3 Chinese language) were included in this review. The PRISMA flow diagram for study selection is shown in the Figure with preferred reporting items (Supplementary Appendix III). Selected studies were from 17 different countries: Argentina (2)[20,21], Belgium (3)[22-24], Brazil (1)[25], Canada (1)[26] Chile (2)[27,28], China (4)[29-32], France (1)[33], Germany (1)[34], Indonesia (1)[35], Israel (3)[36-38], Jordan (1)[39], Mexico (2)[40,41], Netherlands (2)[42,43], Spain (1)[44], Thailand (2)[45,46], United Kingdom (1)[47], USA (15)[25,48-61] and a multi-country study from developed countries[62]. One study[25] was conducted in the USA and Brazil (Table I). Among these, the majority (27/43, 62.8%) were from HICs, followed by MICs (15/43, 34.9%) and LICs (1/43, 2.3%) (Table I).

As per the WHO regions, the majority of the studies were from America (21/43, 48.8%) followed by Europe (9/43, 20.9%), Eastern Mediterranean (4/43, 9.3%), Western Pacific (4/43, 9.3%) and South-East Asia (3/43, 7.0%). It was not possible to classify a multi-country study from developed countries (1/43, 2.3%). Four studies were published before the licensure of hepatitis A vaccine in 1995 (Table I).

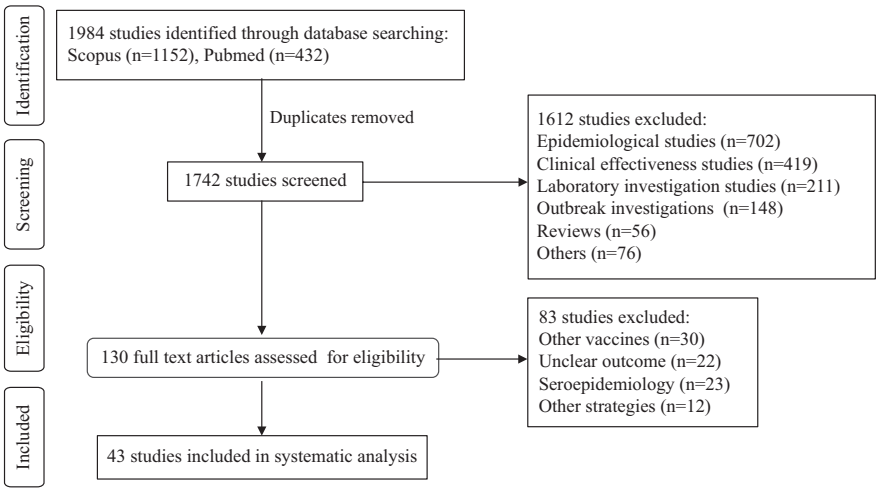

Figure. PRISMA flow diagram for study selection.

In terms of population, 27 studies were conducted in the general population while 16 were conducted in the specific risk group populations. Of those conducted in the general population, 19, five and three focused on children, adolescents and adults, respectively. Studies conducted among specific risk group population included military personnel (n=4), travellers (n=5), medical students (n=1), healthcare workers (n=3), people with hepatitis B infection (n=1), people with hepatitis C infection (n=2), day-care personnel (n=1), food-handlers (n=1) and homosexuals (n=1) (Table I).

Type of EE studies were CUA (18/43, 41.9%), CEA (14/43, 32.6%), both CUA and CEA (3/43, 7%), CBA (5/43, 11.6%) and CBA and CEA (3/43, 7%). Most studies used Markov model (13/43, 30.2%) followed by Markov model with decision tree (6/43, 14.0%), decision tree (7/43, 16.3%), dynamic model (6/43, 14.0%) and decision tree with dynamic model (2/43, 4.7%) (Table I). Most studies adopted societal (28/43, 65%) and healthcare provider perspective (14/43, 33%). However, nine studies (21%) did not mention the perspective.

Vaccine intervention: The summary of vaccination parameters is reported in Table II. All studies used attenuated hepatitis A vaccine as an intervention. Ten studies disclosed the name of the manufacturer. Vaccine efficacy ranged from 87.3 to 100 per cent (Table II).

Epidemiological parameters: As shown in Table II, the incidence of HAV was reported in about half of the studies (22/43), while the seroprevalence was reported in 12 studies. The incidence of HAV varied widely from 1.5 per 100,000[33] to 1130 per 100,000 population[53]. The seroprevalence varied from 0.1-4 per cent[44] to 91-94 per cent[24]. Only 10 studies considered herd immunity in the analysis[20,27,28,36,39,40,49,50,54,61].

Risk of bias assessment: The risk of bias assessment for this study is shown in Supplemantary Appendix IV. All included studies had adequate comparators. Only 23.3 per cent (10/43) of the studies adopted a lifetime horizon, while 27.9 per cent (12/43) did not specify a time horizon. In terms of perspective, only 67.4 per cent (29/43) adopted a societal perspective, while about 16.3 per cent (7/43) did not specify the perspective. The discounting rate was not specified in 18.8 per cent of the studies (8/43). Of the 20 studies that disclosed funding sources, 11 were funded by pharmaceutical companies. Eight studies were subjected to risk of bias related to sensitivity analysis. One-way sensitivity analysis was adopted in 72.1 per cent (31/43) of the studies, while probabilistic sensitivity analysis was conducted in only 16.3 per cent (7/43) of the studies. Among CUA studies, 85.7 per cent (18/21) had a partial risk of bias related to quality of life weight. Eleven studies (25.6%) had an unclear risk of double-counting biases. Double-counting occurred when a parameter was counted more than once. It usually occurs in CUA, when consequences of an intervention (*i.e*. productivity loss/time loss) get incorporated on the cost side (numerator) as well as on the consequences side, *i.e*. QALY (denominator). All studies in this review had an unclear risk of biases related to internal consistency.

Cost-effectiveness findings: These are summarized in Table III. Summary of cost-effectiveness results by income level of the country, type of population and vaccination strategies is shown in Table IV.

Table I. Characteristics of the included studies

Study	Type of economic evaluation	Country classification	Country	Funding agency (name)	Population group	Time horizon (yr)	Discount rate of cost and effect (%)	Perspective	Type of model used (decision tree/Markov/ dynamic)	Sensitivity analysis
Ramsay *et al*[26], 2019	CUA	HIC	Canada	No funding	Traveller	Life time	1.5	Healthcare provider	Markov	One-way and probabilistic
Luyten *et al*[24], 2012	CUA	HIC	Belgium	Health care (Belgium)	High-risk adult (traveller, healthcare workers, soldiers, teachers)	100	3	Societal	Markov	Probabilistic
Chapko *et al*[50], 2010	CUA	HIC	USA	Veternas affairs (USA)	Adults with hepatitis C	NS	3	Payer and private sector, veteran affairs	Decision tree and Markov	One-way
Armstrong *et al*[49], 2007	CUA	HIC	USA	NS	Children	10	3	Societal	NS	Not mentioned
Hankin-Wei *et al*[60], 2016	CUA	HIC	USA	Government	Children (2-17 yr)	Life time	3 per cent	NS	Markov	One-way, probabilistic
Wilson *et al*[59], 2020	CEA	HIC	USA	NS	Adults	20	NS	Payer	Markov	One-way
Dhankhar *et al*[61], 2015	CEA	HIC	USA	No funding	Children	100	3	Societal	Dynamic	One-way and probabilistic
Ghildayal[25], 2019	CUA	HIC UMIC	USA Brazil	NS	All age group (general population)	20	3	Societal	Dynamic	One-way, two-way and three way
Rein *et al*[57], 2007	CEA/ CUA	HIC	USA	NS	Children	Life time	3	Societal	Markov	One-way
Postma *et al*[42], 2004	CEA	HIC	Netherlands	NS	Children of ethnic minorities	NS	NS	Societal	NS	NS
Jacobs *et al*[55], 2003	CEA/ CUA	HIC	USA	Pharma (GSK)	Children	Life time	3	Both societal and healthcare provider	Markov	One-way

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Study	Type of economic evaluation	Country classification	Country	Funding agency (name)	Population group	Time horizon (yr)	Discount rate of cost and effect (%)	Perspective	Type of model used (decision tree/Markov/ dynamic)	Sensitivity analysis
Arguedas *et al*[48], 2002	CUA	HIC	USA	NS	Adults with hepatitis B	Life time	3	Societal	Markov	One-way and two-way
Chodick *et al*[38], 2002	CUA	HIC	Israel	Government (National Institute of Health Policy, Israel)	Physicians, Nurses, Paramedical	Life time	3	Healthcare provider	Decision tree and Markov	One-way
Jacobs *et al*[54], 2000	CEA	HIC	USA	Pharma (SKB)	Adolescent	NS	3	Both societal and healthcare provider	Decision tree	One-way
Jacobs *et al*[52], 2002	CEA	HIC	USA	Pharma (SKB)	Chronic hepatitis C adults 30 yr, 45 yr, 60 yr	NS	3	Both societal and health care provider	Markov	One-way
Chodick *et al*[37], 2001	CBA	HIC	Israel	Non-government organization (full bright)	Day-care persons	20	5	Societal	Markov	One-way
Diel *et al*[34], 2001	CEA	HIC	Germany	NS	Children, adolescents	30	5	Societal	Other	One-way
Ginsber *et al*[36], 2001	CBA	HIC	Israel	NS	Children	45	4	Both societal and health care provider	Other	One-way
Jacobs *et al*[51], 2000	CEA	HIC	USA	Pharma (SKB)	Food handlers	NS	3	Both societal and healthcare provider	Decision tree	One-way
Jacobs and Meyerhoff[53], 1999	CEA	HIC	USA	Pharma (SKB)	Homosexuals	Life time	3	Societal	Decision tree	One-way
O'Connor *et al*[56], 1999	CEA	HIC	USA	NS	Adults >50 yr	Life time	3	Societal	Markov	One-way and two-way
Buma *et al*[43], 1998	CEA and CBA	HIC	Netherland	NS	Military personals	NS	NS	NS	Decision tree with Markov	NS

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Study	Type of economic evaluation	Country classification	Country	Funding agency (name)	Population group	Time horizon (yr)	Discount rate of cost and effect (%)	Perspective	Type of model used (decision tree/Markov/ dynamic)	Sensitivity analysis
Arnal *et al*[44], 1997	CEA	HIC	Spain	Government (Health Research Funds, Spain)	Children, adolescents, adults	NS	6	NS	Decision tree and Markov	One-way
Smith *et al*[58], 1997	CEA/ CUA	HIC	USA	NS	Medical students	Life time	5	Societal	Markov	One-way
Severo *et al*[33], 1995	CEA	HIC	France	NS	Military personals, travellers, healthcare workers	10	5	Societal	Decision tree	One-way
Van Doorslaer *et al*[23], 1994	CEA	HIC	Belgium	NS	Travellers	10	5	NS	Decision tree	One-way
Jefferson *et al*[47], 1994	CEA and CBA	HIC	United Kingdom	NS	Army personals	5	3	NS	NS	NS
Tormans *et al*[22], 1992	CEA	HIC	Belgium	Pharma (SKB)	Travellers	10	5	NS	Decision tree	One-way
Hayajneh *et al*[39], 2018	CUA	UMIC	Jorden	Pharma industry (MSDC)	Children	50	3	Societal	Dynamic	Probabilistic and deterministic
Curran *et al*[40], 2016	CUA	UMIC	Mexico	Pharma industry (GSK)	All ages (general population)	25	5	Health care provider	Dynamic and decision tree	Other
Carlos *et al*[41], 2016	CUA	UMIC	Mexico	Pharma (GSK)	Children	25	5	Mexican public health system and societal	Dynamic and dicision tree	One-way, probabilistic
Pan *et al*[32], 2012	CUA	UMIC	China	University (Henan)	Children	NS	3	Both societal and health care provider	Decision tree and Markov	One-way
Quezada *et al*[28], 2008	CEA	UMIC	Chile	NS	Children	100	3	Both societal and healthcare provider	Dynamic	One-way
Ellis *et al*[21], 2007	CUA	UMIC	Argentina	Pharma (GSK)	Children	50	3	Societal	Markov	One-way

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Study	Type of economic evaluation	Country classification	Country	Funding agency (name)	Population group	Time horizon (yr)	Discount rate of cost and effect (%)	Perspective	Type of model used (decision tree/Markov/ dynamic)	Sensitivity analysis
Lopez *et al*[20], 2007	CEA and CBA	UMIC	Argentina	NS	Children	100	3	Societal	Dynamic	One-way
Valenzuela *et al*[27], 2005	CUA	UMIC	Chile	Pharma (GSK)	Children	50	3	Both societal and healthcare provider	Markov	One-way
Das[62], 1999	CUA	UMIC	Developed countries	NS	Children	Life time	3	Societal	Decision tree with Markov	One-way and two-way
Suwantika *et al*[35], 2014	CUA	LMIC	Indonesia	NS	Children	70	3	Both societal and healthcare provider	Markov	One-way and probabilistic
Zhuang *et al*[31], 2008	CUA	LMIC	China	NS	Children	NS	5	Both societal and healthcare provider	Markov	Other
Soogarun and Wiwanitkit[45] 2002	CBA	LMIC	Thailand	NS	Adolescent	NS	NS	NS	NS	NS
Teppakdee *et al*[46], 2002	CBA	LMIC	Thailand	NS	Children, adolescent, adults	NS	NS	NS	NS	NS
Chen *et al*[30], 1999	CBA	LMIC	China	NS	General population	10	NS	NS	NS	NS
Li *et al*[29], 1998	CUA	LIC	China	Government (Chines Medical Foundation)	General population	NS	NS	Societal	NS	NS

CBA, cost benefit analysis; CDC, Centers for Disease Control; CEA, cost-effective analysis; CUA, cost utility analysis; GSK, GlaxoSmithKline Pharmaceuticals; HIC, high-income countries; LIC, low-income countries; LMIC, lower-middle-income countries; MSDC, Merck Sharp and Dohme Corp; NS, not specified; SKB, SmithKline Beecham pharmaceuticals; UMIC, upper-middle-income countries

Table II. Summary of epidemiological and vaccination parameters used in base case of economic evaluation studies

Study	Hepatitis A		Vaccination approach	Vaccine type	Vaccine brand	Vaccine efficacy	Herd effect	Vaccine price/dose (currency)	Vaccination coverage
	Incidence per 100,000 population	Sero-prevalence (%)							
Ramsay *et al*[26], 2019	NS	5	Targeted	Inactivated	NS	93.5 per cent	No	45.5 (USD)	NS
Luyten *et al*[24], 2012	NS	91-94	Targeted	Inactivated	Havrix	95 per cent	No	46.7 (euro)	95 per cent, 95 per cent (2-dose)
Chapko *et al*[50], 2010	17.5-34.9 per 100,000	NS	Targeted	Inactivated	Vaqta	99 per cent	Yes	24.9-58.2 (USD)	64 per cent, 16 per cent (2-dose)
Armstrong *et al*[49], 2007	NS	NS	Universal	Inactivated	NS	NS	Yes	NS	NS
Hankin-Wei *et al*[60], 2016	NS	NS	Targeted	NS	NS	NS	No	No	50 per cent
Wilson *et al*[59], 2020	NS	NS	Universal	Inactivated	NS	NS	No	NS	NS
Dhankhar *et al*[61], 2015	1.8-8.9 per 100,000	NS	Universal	NS	NS	100 per cent	Yes	NS	64.4 per cent
Ghildayal[25], 2019	25-132 per 100,000	NS	Universal	Inactivated	NS	94 per cent	No	17 (USD) 60 (USD)	90 per cent, 77 per cent
Rein *et al*[57], 2007	6.7-22.7 per 100,000	NS	Universal	Inactivated	NS	91-100 per cent	No	55.5 (USD)	93 per cent, 87 per cent (2-dose)
Postma *et al*[42], 2004	NS	NS	Targeted	Inactivated	Havrix	90 per cent	No	21 (euro)	NS
Jacobs *et al*[55], 2003	NS	3	Universal	Inactivated	NS	98-99 per cent	No	14.2 USD	69 per cent, 20 per cent (2-dose)
Arguedas *et al*[48], 2002	NS	34	Targeted	Inactivated	NS	NS	No	NS	NS
Chodick *et al*[38], 2002	21.7-87.6 per 100,000	NS	Targeted	Inactivated	Havrix	95 per cent	No	35 (USD)	90 per cent
Jacobs *et al*[54], 2000	NS	NS	Universal	Inactivated	NS	94 per cent	Yes	NS	NS
Jacobs *et al*[52], 2002	17.7-109 per 100,000	NS	Targeted	Inactivated	NS	93-95 per cent	No	11.8 (USD)	80 per cent
Chodick *et al*[37], 2001	66.7-98.9 per 100,000	NS	Targeted	Inactivated	Havrix	95 per cent	No	35 (USD)	89 per cent
Diel *et al*[34], 2001	7 per 100,000	NS	Universal	Inactivated	NS	99 per cent	No	158 (DM)	20-80 per cent
Ginsber *et al*[36], 2001	54 per 100,000	NS	Universal	Inactivated	Havrix	94-95 per cent	Yes	7.47 (USD)	95 per cent, 92 per cent (2-dose)
Jacobs *et al*[51], 2000	157 per 100,000	NS	Targeted	Inactivated	NS	93-95 per cent	No	43 (USD)	100 per cent, 50 per cent (2-dose)
Jacobs and Meyerhoff[53] 1999	210-1130 per 100,000	NS	Targeted	Inactivated	Havrix	90-95 per cent	No	43 USD	70 per cent

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Study	Hepatitis A		Vaccination approach	Vaccine type	Vaccine brand	Vaccine efficacy	Herd effect	Vaccine price/dose (currency)	Vaccination coverage
	Incidence per 100,000 population	Sero-prevalence (%)							
O'Connor *et al*[56], 1999	5 per 100,000	63	Universal	Inactivated	NS	94-99 per cent	No	57 (USD)	100 per cent, 80 per cent (2-dose)
Buma *et al*[43],1998	3.2-70.3 per 100,000	NS	Targeted	Inactivated	NS	95 per cent	No	35 (USD)	100 per cent
Arnal *et al*[44], 1997	NS	0.1-4	Universal	Inactivated	NS	90 per cent	No	NS	70 per cent
Smith *et al*[58], 1997	9 per 100,000	NS	Targeted	Inactivated	Havrix	94 per cent	No	40 (USD)	NS
Severo *et al*[33], 1995	1.5-39.6 per 100,000	NS	Targeted	Inactivated	Havrix	NS	No	115 (FF)	100 per cent
Van Doorslaer *et al*[23], 1994	NS	20-45	Targeted	Inactivated	NS	90-99 per cent	No	15 pound	100 per cent
Jefferson *et al*[47], 1994	21 per 100,000	NS	Targeted	Inactivated	NS	NS	No	11.7 (pounds)	100 per cent
Tormans *et al*[22], 1992	NS	NS	Targeted	Inactivated	NS	90 per cent	No	24 (USD)	NS
Hayajneh *et al*[39], 2018	NS	NS	Universal	Inactivated	NS	97-99 per cent	Yes	NS	NS
Curran *et al*[40], 2016	NS	NS	Universal	Inactivated	NS	87.3-100 per cent	Yes	10 (USD)	95 per cent, 70 per cent (2-dose)
Carlos *et al*[41], 2016	NS	NS	Universal	Inactivated	Havrix	97 per cent (1st dose), 99 per cent (2nd dose)	No	194.5 MXN (per dose)	80 per cent, 85 per cent (2nd dose)
Pan *et al*, 2012[32]	15 per 100,000	NS	Universal	Inactivated	NS	90-100 per cent	No	69 (USD)	80 per cent (2-dose)
Quezada *et al*[28], 2008	NS	92.3	Universal	Inactivated	NS	95 per cent	Yes	11 (USD)	95 per cent
Ellis *et al*[21], 2007	NS	2-60	Universal	Inactivated	NS	98 per cent	No	8.50 (USD)	95 per cent, 80 per cent (2-dose)
Lopez *et al*[20], 2007	NS	NS	Universal	Inactivated	NS	95 per cent	Yes	7 (USD)	95 per cent
Valenzuela *et al*[27], 2005	10-90 per 100,000	NS	Universal	Inactivated	NS	96-99 per cent	Partially	11 (USD)	96 per cent
Das[62], 1999	NS	0.01	Universal	Inactivated	Havrix	NS	No	55.6 USD	80 per cent
Suwantika *et al*[35], 2014	11-81 per 100,000	NS	Universal	Inactivated	NS	93-95 per cent	No	3.21 (USD)	80 per cent
Zhuang *et al*[31], 2008	NS	50-90	Universal	Inactivated	NS	93-95 per cent	No	30 (RMB Yuan)	80 per cent
Soogarun and Wiwanitkit[45], 2002	NS	8	Universal	Inactivated	NS	98-100 per cent	No	1430 (BHT)	NS

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Study	Hepatitis A		Vaccination approach	Vaccine type	Vaccine brand	Vaccine efficacy	Herd effect	Vaccine price/dose (currency)	Vaccination coverage
	Incidence per 100,000 population	Sero-prevalence (%)							
Teppakdee *et al*[46], 2002	9.4-70 per 100,000	NS	Universal	Inactivated	NS	94-100 per cent	No	920 (BHT)	97 per cent
Chen *et al*[60], 1999	10-101 per 1,000,000	NS	Universal	Inactivated	NS	NS	No	18 (RMB Yuan)	NS
Li *et al*,[29] 1998	17-93 per 100,000	NS	Universal	Inactivated	NS	NS	No	NS	NS

BHT, Baht from Thailand; DM, Deutsche Mark from Germany; Euro, European Euros; FF, French Franks; MXN, Mexican pesos; NS, not specified; ND, not done; RMB, RMB Yuan from China; USD, US dollar; Pound, UK Pound

For universal vaccination strategy, 70 (7/10), 86.7 (13/15) and 100 per cent (1/1) of the studies conducted respectively, in HICs, MICs and LICs were found to be cost-effective. When examining the types of population, universal vaccination among children was more likely to be cost-effective than the other age groups. About 63 per cent (17/27) of the studies conducted in HICs found that universal vaccination more cost-effective as compared to no vaccination, *i.e.* 86.7 per cent (13/15) in MICs in contrast to the adult population where, universal vaccination was not found to be cost-effective in both HICs (0/3) and MICs (0/1). Only 50 per cent (1/2) of the studies, comparing screening and vaccination to no vaccination among children in MICs, were found to be cost-effective. On the other hand, screening and vaccination among children in HICs were not cost-effective (0/1).

Hepatitis A vaccine was proven to be cost-effective as compared to no immunization among hepatitis C virus patients, food handlers and the homosexual population in studies conducted in high-income nations that used a targeted vaccination strategy. The results from travellers, healthcare staff and military personnel were mixed. In studies comparing the cost-effectiveness of vaccines *vs*. no vaccine among travellers, healthcare workers and military people, 40, 33 and 75 per cent were shown to be cost-effective, respectively. In studies comparing screening and vaccination versus no vaccination, 50, 50 and 66.7 per cent were found to be cost-effective among the same categories, respectively (Table IV).

Discussion

The present study revealed that universal hepatitis A vaccination without screening among children, especially in MICs, was more likely to be cost-effective than no vaccine strategy. This finding was consistent with that of earlier studies[12,14]. This might probably be due to the fact that countries such as Argentina[20], Brazil[25], Chile[28], China[30-32], and Indonesia[35] have intermediate endemicity. Only half of the studies with data from MICs found that screening and vaccination among children were cost-effective. However, only two such studies were identified in this review. Because of the high seroprevalence of HAV infection among children in MICs, the cost-effectiveness of screening and immunisation was less favoured. In both HICs and MICs, universal hepatitis A vaccination among adults either with or without screening was less likely to be cost-effective. Consistent findings as that was seen in the previous study[12], cost-effectiveness evidences

among specific risk group populations varied widely depending on the risk of HAV infectivity. It was found that among people with greater risk of acquiring an infection due to a particular occupation or lifestyle, hepatitis A vaccination was found to be economically attractive[22,23,43,44,51-53,63,64].

Vaccine considered in the analysis, it should be noted that all studies used inactivated hepatitis A vaccine. However, live-attenuated hepatitis A vaccine has been developed in China since 2007[65]. The vaccine is mainly marketed in China and India[65]. It was shown to have similar efficacy to that of inactivated vaccine[66], but only one dose was required. With the assumption of similar price per dose and similar efficacy, cost-effectiveness evidence would likely favour live-attenuated vaccine.

The present review found that the most common biases identified were related to internal inconsistency in terms of methodological quality. This is similar to other studies[67,68], which found that mathematical logic was not evaluated in most of the investigations. Although experts generally recommend using societal perspective, as it is more comprehensive[69], a societal perspective was adopted only in 68 per cent of the studies; hence, the direct non-medical cost was not included in the analysis. In addition, we found that only 23 per cent of the studies adopted lifetime horizons. Furthermore, probabilistic sensitivity analysis was rarely conducted.

It should be noted that most of the studies did not use a dynamic model. Furthermore, herd immunity was not taken into account. In fact, a dynamic model was a necessity in deciding on implementing realistic universal vaccination strategies[70]. However, due to the unavailability of large epidemiological parameters in a local context, complex study design and lack of expertise, the dynamic models were not used widely by researchers. In addition, it should be noted that when herd immunity is not taken into account, cost-effectiveness evidences of vaccine may be underestimated.

Our review found that most included studies had partial bias related to quality of life weight. This was because most of the studies used secondary data with limited information on the methods used to estimate utility weight, as well as characteristics of the sample. In addition, data on utility weights for symptomatic and asymptomatic hepatitis A infection were limited.

It should be noted that cost-effectiveness studies need to be conducted using locally available epidemiological data as such data from other settings have low transferability[13]. Although the age-specific incidence of hepatitis A infection had a significant impact on cost-effectiveness finding[12], we found that many included studies[20,21,27,28,31] adopted such data from the US study[54,55,71]. However, it was suggested that if the hepatitis A incidence data were not available, seroprevalence data of the country could be used to estimate the incidence[71,72]. In the absence of local data, it is recommended that data from countries with similar endemicity may be used cautiously[73]. On the other hand, some parameters could be adopted from other countries or other studies. As the natural history of hepatitis A infection is similar across the countries, the probability of symptomatic infection (presented with jaundice) among infected individuals may be transferable from other studies[13]. Since the efficacy of HAV vaccination was not affected by ethnicity variation, vaccine efficacy data could be adopted from other studies.

In terms of study perspective, most of the studies with societal perspective indicated that HAV vaccination was cost-effective. Studies with societal perspectives, in which HAV vaccination was not found to be cost-effective, were conducted in HICs[24,34,42,56,58]. For the studies that used both societal perspective and healthcare provider perspective, the results from societal perspective were more favourable towards cost-effectiveness or even cost-saving.

The present systematic review could not identify any EE study on HAV conducted in India. India is considered as a LMIC with wide variation in terms of socio-economic status. Due to rapid improvement in sociodemographic development in India during the past decade, there is evidence of a shift from high to intermediate endemicity, especially in the high-income region. In such region, with the decreasing number of adolescents with prior exposure to HAV, several hepatitis A outbreaks have been reported[74-76]. According to our review, almost all studies conducted among children in MICs, which were also facing improvement in sociodemographic development, found that HAV vaccination was cost-effective. Therefore, it is likely that HAV vaccination would be cost-effective in India, especially in the regions with reported shift from high to intermediate endemicity. In these regions, policymakers working on HAV vaccination may consider inclusion of HAV vaccination in public insurance schemes.

Table III. Summary of economic evaluation studies results

Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Ramsay *et al*[26], 2019	Two doses versus no vaccination (Status Quo)	Canadian $, 2017	$50,000	$ 3,391,504 per QALY	ND	Expanded vaccination for traveller was not cost-effective
Luyten *et al*[24], 2012	Two dose vaccination versus no vaccination	€, 2008	€50,000	€ 203,454 per QALY € 231,227 per LYs	€ 192,338 per QALY € 218,580 per LYs	Expanded vaccination strategies to adult traveller were not cost-effective for all three strategies
	Screening and vaccination versus no vaccination			€ 2,048,623 per QALY € 282,041 per LYs	€ 237,507 per QALY € 269,394 per LYs	
	Two dose versus screening and vaccination			€ 103,649 per QALY € 117,651 per LYs	€ 92,533 per QALY € 110,462 per LYs	
Chapko *et al*[50], 2010	Screening and vaccination versus no vaccination	$, 2006	$100,000	$ 82,022 per QALY (private sector cost) $ 184,088 per QALY (veterans affairs cost)	ND	Not cost-effective
Armstrong *et al*[49], 2007	Vaccination versus no vaccination	$, 2005	GDP per capita	ND	$ 1000 per QALY saved $ -29,000 per Lys saved	Cost-effective
Hankin-Wei *et al*[60], 2016	Catch up versus no catch up vaccination	$, 2015	$50,000	ND	$ 189,000 per QALY gained at age 12 yr	Catch up vaccination campaign was not cost-effective, given low incidence
Wilson *et al*[59] 2020	Vaccination versus no vaccination	$, NS	$50,000	$ 1,208,660 per LYs	ND	Not cost-effective
Dhankhar *et al*[61], 2015	Regional versus universal	$, NS	GDP per capita	ND	$ 21,223 per QALY	Cost saving
Ghildayal[25], 2019	Vaccination versus no vaccination	$, NS	$100,000	$ 55,778.5 per QALY saved for USA $ 8193.6 per QALY saved for Rio de Janerio	ND	Cost-effective
Rein *et al*[57], 2007	Two doses versus no vaccination	$, 2005	GDP per capita	ND	$ 28,000 per QALY $ 199,000 per LYs	Cost-saving
Postma *et al*[42], 2004	Vaccination versus no vaccination	€, 1999	GDP per capita	ND	€ 13,500 per averted HAV infection	Not cost saving
Jacobs *et al*[55], 2003	Two doses versus no vaccination	$, 2002	GDP per capita	$ 9100 per QALY gained $ 14,100 per LYs saved	$ 1400 per QALY gained $ 2200 per LYs saved	Cost-effective

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Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Arguedas *et al*[48], 2002	Screen and vaccinate versus no vaccination	$, 1999	GDP per capita	ND	$ 51,000 per QALY	Cost-effective
	Universal vaccination versus screening and vaccination				$ 3,900,000 per QALY	
Chodick *et al*[38], 2002	Vaccination versus no vaccination	$, 2001	$60,000	ND	$ 318,418 per QALY (physicians); $ 717,056 per QALY (nurses); $323, 283 per QALY (paramedical staff)	Selective vaccination is cost-effective
	Screening and vaccinate (selective vaccination) versus no vaccination				$ 39,619 per QALY (physicians); $ 70,531 per QALY (nurses); $50,166 per QALY (paramedical staff)	
Jacobs *et al*[54], 2000	Vaccination versus no vaccination	$, 1997	GDP per capita	$ 13,722 per YOLS	<0 per YOLS	Cost-effective
Jacobs *et al*[52], 2002	Vaccination versus no vaccination	$, 2000	GDP per capita	$ 22,266 per LY saved (age 30 yr); $50,391 per LY saved (age 45 yr); $ 102,064 per LY saved (age 60 yr)	ND	Cost-effective at younger age (30 and 45 yr)
Chodick *et al*[37], 2001	Screening and vaccination versus immunoglobulins	$, 2000	GDP per capita	ND	1.50 benefit to cost ratio	Selective vaccination is cost-effective
	Vaccination versus immunoglobulins				0.04 benefit to cost ratio	
Diel *et al*[34], 2001	Vaccination versus no vaccination	DM, 1998	GDP per capita	ND	53,052 DM per case averted for children 83,247 DM per case averted for adolescent	Not cost effective among children and adolescent
Ginsber *et al*[36], 2001	Vaccination versus no vaccination	$, 1997	GDP per capita	ND	2.54:1 benefit to cost ratio	Cost-effective
Jacobs *et al*[51], 2000	Vaccination versus no vaccination	$, 1997	GDP per capita	ND	$ 13,969 per LYs saved	Cost-effective
Jacobs and Meyerhoff[53] 1999	Vaccination versus no vaccination	$, 1997	GDP per capita	ND	−213 yr of life lost and ratio of cost reduction to vaccination is 10.72:1	Cost-effective
O'Connor *et al*[56], 1999	Vaccination versus no vaccination Screening and vaccination versus no vaccination	$, 1997	GDP per capita	ND	$ 20,119,000 per extra LY $ 230,113 per extra LYs	Not cost-effective for both strategies

Contd...

Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Buma *et al*[43], 1998	Vaccination versus no vaccination Immunoglobulin versus no vaccination Screening and vaccination versus no vaccination	$, 1998	GDP per capita	ND	Cost saving $295 Cost saving	Cost-saving with two or more missions per 10 yr in all interventions Vaccination without prior screening was the most optimum strategy
	Mass vaccination versus no vaccination					
Arnal *et al*[44], 1997	Immunoglobulins versus no vaccination	ECU, 1994	GDP per capita	ND	Cost per prevented infection ECU 6394 (children), ECU 6394 (adolescent)	
	Screening and vaccination versus no vaccination				Cost per prevented infection ECU 18,863 (adolescent), ECU 9169 (young adults), 3696 (adults) Cost per prevented infection ECU 6701 (adolescent), ECU 2264 (young adults), 2986 (adults)	All strategies were not cost-effective among children, adolescents and adults
Smith *et al*[58], 1997	Vaccination versus no vaccination Screening and vaccination versus no vaccination	$, 1994	GDP per capita	ND	$ 22,000 for case prevented, $ 58,000 per LY saved and $ 47,000 per QALY saved $ 34,000 per case prevented $ 92,000 per LY save, $ 75,000 per QALY saved	Routine vaccination was cost-saving. Screening versus vaccination was not cost-effective
	Vaccination versus no vaccination				Cost saving 4.72 million FF (military staff); 278,263 FF cost per case avoided travellers); 107,910 FF per case avoided (hospital worker)	
Severo *et al*[33], 1995	Immunoglobulins versus no vaccination	FF, 1993	GDP per capita	ND	Cost saving of - 2.89 million FF (military staff)	Both systemic and selective vaccination is cost-effective among military personals
	Screening and vaccination (selective) versus no vaccination				Cost saving 4.17 millions FF (military staff); 174,412 FF cost per case avoided (travellers); 59,303 FF per case avoided (hospital worker)	

Contd...

Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Van Doorslaer *et al*[23], 1994	Vaccination/versus no vaccination	£, 1994	GDP per capita	ND	£ 4705-£ 556 per infection prevented by Havrix 720 and Havrix 1440	Cost-effective among passive immunization
	Immunoglobulins versus no vaccination				£ 304 per infection prevented	
	Screening and vaccination versus no vaccination				£ 470-£ 551 per infection prevented for Havrix 720 and Havrix 1440	
Jefferson *et al*[47], 1994	Vaccination versus no vaccination	£, 1994	GDP per capita	ND	Cost benefit ratio=7.2 (vaccine)	Vaccination is cost-effective
	Immunoglobulins versus no vaccination				Cost benefit ration=13.4 (immunoglobulin)	
Tormans *et al*[22], 1992	Vaccination (three doses) no vaccination	$, 1992	GDP per capita	ND	$ 4880 per case prevented	Vaccination cost-effective, Screening and vaccination more cost-effective, immunoglobulin not cost-effective
	Immunoglobulins versus no vaccination				$ 29,932 per case prevented	
	Screening and vaccination versus no vaccination				$ 5621 per case prevented	
Hayajneh *et al*[39], 2018	Vaccination versus no vaccination	$, 2015	GDP per capita	ND	$ 37,502 per QALY gained	Cost-effective
Curran *et al*[40], 2016	Vaccination versus no vaccination	MXN, 2012	GDP per capita	ND	MXN -2198 per QALY for single dose MXN -14,829 per QALY for two doses	Cost-effective in single dose vaccination
Carlos *et al*[41], 2016	Two doses versus no vaccination One dose versus no vaccination	MXN, 2012	1 GDP (132, 465 MXN)	2270 MXN per QALY 14,961 MXN per QALY	Dominant 3752 MXN per QALY	Routine vaccination among infants either with one dose or two doses was cost-effective
Pan *et al*[32], 2012	Vaccination versus no vaccination	RMB Yuan, 2009	GDP per capita	RMB Yuan 4,560,814 cost per case saved	RMB Yuan 5,840,430 cost per case saved	Cost-effective
Quezada *et al*[28], 2008	Vaccination versus no vaccination	$, 2009	GDP per capita	ND	$ 4984 per LYs gained; $ 18,665,808 incremental cost	Cost-effective

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Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Ellis *et al*[21], 2007	Vaccination (one dose) versus no vaccination	$, 2004	GDP per capita	ND	$ 2481 per lost QALY for birth cohort vaccination $ 2402 per lost QALY for personal contact vaccination	Most cost-effective
	Vaccination (two dose) versus one dose vaccination			ND	$ 1137 per lost QALY for birth cohort vaccination $ 1150 per lost QALY for personal contact vaccination	Cost-effective
Lopez *et al*[20], 2007	Vaccination versus no vaccination	$, 2004	GDP per capita	ND	$ 3429 per LY gained	Cost-effective
Valenzuela *et al*[27], 2005	Vaccination [two doses (18-54 months)] versus no vaccination	$, 2004	GDP per capita	$ 460 per LY saved $ 281 per QALY gained	<0 per LY saved <0 per QALY gained	Cost-effective
	Vaccination [two doses (18 and 24 months)] versus no vaccination			882 per LY saved $ 503 per QALY gained	<0 per LY saved <0 per QALY gained	
Das[62], 1999	Vaccination versus no vaccination	$, 1999	GDP per capita	ND	12,833 marginal cost-effectiveness ratio	Screening of vaccination is cost-effective
	Screening and vaccination versus no vaccination				7267 marginal cost effectiveness ratio	
Suwantika *et al*[35], 2014	Vaccination (one dose) versus no vaccination	$, 2014	GDP per capita	$ 5025 per QALY gained	$ 4933 per QALY gained	One dose vaccination is cost-effective
	Vaccination (two dose) versus one dose vaccination			$ 7510 per QALY gained	$ 7421 per QALY gained	
Zhuang *et al*[31], 2008	Vaccination (two dose) versus no vaccination	RMB Yuan, 2005	GDP per capita	RMB Yuan 1673 per QALY gained RMB Yuan 21,955 per LY gained	RMB Yuan -2268 per QALY gained RMB Yuan -29,764 per LY gained	Cost-effective
Soogarun and Wiwanitkit[45] 2002	Vaccination (two dose) no vaccination	Baht, 2002	NS	ND	BHT -2866 total cost	Both strategies were not cost-effective
	Screening and vaccination versus no vaccination				BHT -3149 total cost	

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Study	Intervention versus comparator	Currency, yr	Threshold	ICER from base case with perspective		Conclusion
				Health care	Societal	
Teppakdee *et al*[46], 2002	Vaccination versus no vaccination	Baht, 2002	NS	ND	BHT -1258 benefits in children. BHT -1325 in adolescents and BHT -3255 in adults	Both strategies were not cost-effective among children, adolescent and adults
	Screening and vaccination versus no vaccination				BHT -1967 benefits in children. BHT -1871 in adolescents and BHT -1732 in adults	
Chen *et al*[30], 1999	Vaccination/screening and vaccination versus no vaccination	RMB Yuan, 1999	GDP per capita	ND	2.13 (cost benefit ratio)	Most cost-effective among screening and vaccination than only vaccination
	Vaccination/screening and vaccination versus no vaccination				NS	
Li *et al*[29], 1998	Vaccination versus no vaccination	RMB Yuan 1998	GDP per capita	ND	153,277 RMB Yuan per QALY	Cost-effective

*Study conducted in developed and developing country.BHT, Baht from Thailand; DM, Deutsche Mark from Germany; ECU, European currency unit; €, Euros; FF, French Franks; MXN, Mexican pesos; NS, not specified; ND, not done; RMB, Yuan from China; $, US dollar; £, UK Pound; YOLS, year of life saved; GDP, gross domestic product; QALY, quality-adjusted life year

Table IV. Summary of cost-effectiveness results by income level of the country, population and vaccination strategies

Variables (n=number of studies)	Cost-effective findings; number of cost effective studies/number of studies, n (%)		
	High income (n=27)	Middle income (n=15)	Low income (n=1)
Universal vaccination (n=26)	7/10 (70.0)	13/15 (86.7)	1/1 (100.0)
Children (n=19)	6/8 (75.0)	11/11 (100.0)	0
Vaccination *vs*. no vaccination (n=19)	5/7 (71.4)	10/12 (83.3)	0
Screening and vaccination *vs*. no vaccination (n=3)	0/1 (0)	1/2 (50.0)	0
Adolescents (n=5)	1/3 (33.3)	0/2 (0)	0
Vaccination *vs.* no vaccination (n=5)	1/3 (33.3)	0/2 (0)	0
Screening and vaccination *vs*. no vaccination (n=3)	0/1 (0)	0/2 (0)	0
Adult (n=4)	1/3 (33.3)	0/1 (0)	0
Vaccination *vs.* no vaccination (n=4)	0/3 (0)	0/1 (0)	0
Screening and vaccination *vs*. no vaccination (n=2)	0/1 (0)	0/1 (0)	0
Immunoglobulins *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
General population (n=4)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)
Vaccination *vs*. no vaccination (n=4)	1/1 (100.0)	1/2 (50.0)	1/1 (100.0)
Screening and vaccination *vs*. no vaccination (n=1)	0	1/1 (100.0)	0
Targeted vaccination (n=17)	13/17 (76.5)	0	0
Traveller (n=5)	3/5 (60.0)	0	0
Vaccination *vs*. no vaccination (n=5)	2/5 (40.0)	0	0
Screening and vaccination *vs*. no vaccination (n=4)	2/4 (50.0)	0	0
Vaccination *vs*. screening and vaccination (n=1)	0/1 (0)	0	0
Passive immunization *vs*. no vaccination (n=3)	2/3 (66.7)	0	0
Health care staff (n=3)	1/3 (33.3)	0	0
Vaccination *vs*. no vaccination (n=3)	1/3 (33.3)	0	0
Screening and vaccination *vs*. no vaccination (n=2)	1/2 (50.0)	0	0
Vaccination *vs*. screening and vaccination (n=1)	0/1 (0)	0	0
Military (n=4)	3/4 (75.0)	0	0
Vaccination *vs*. no vaccination (n=4)	3/4 (75.0)	0	0
Vaccination *vs*. screening and vaccination (n=1)	0/1 (0)	0	0
Screening and vaccination *vs*. no vaccination (n=3)	2/3 (66.7)	0	0
Immunoglobulins *vs*. no vaccination (n=3)	2/3 (66.7)	0	0
HCV adults (n=2)	1/2 (50.0)	0	0
Vaccination *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
Screening and vaccination *vs*. no vaccination (n=1)	0/1 (0)	0	0
Students (n=2)	1/2 (50.0)	0	0
Vaccination *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
Screening and vaccination *vs*. no vaccination (n=1)	0/1 (0)	0	0
Children of ethnic minority (n=1)	0/1 (0)	0	0
Vaccination *vs*. no vaccination (n=1)	0/1 (0)	0	0
Day care workers (n=1)	1/1 (100.0)	0	0
Immunoglobulin *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
Selective vaccination *vs*. immunoglobulins (n=1)	0/1 (0)	0	0

Contd...

Variables (n=number of studies)	Cost-effective findings; number of cost effective studies/number of studies, n (%)		
	High income (n=27)	Middle income (n=15)	Low income (n=1)
Food handlers (n=1)	1/1 (100.0)	0	0
Vaccination *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
Homosexuals (n=1)	1/1 (100.0)	0	0
Vaccination *vs*. no vaccination (n=1)	1/1 (100.0)	0	0
HBV adults (n=1)	1/1 (100.0)	0	0
Universal vaccination *vs*. screening and vaccination (n=1)	1/1 (100.0)	0	0
Screening and vaccination *vs*.no vaccination (n=1)	1/1 (100.0)	0	0
Children (n=1)			
Catch up vaccine *vs*. no catch up vaccine (n=1)	1/1 (100.0)	0	0

HCV, hepatitis C virus; HBV, hepatitis B virus

In summary, our study provides updated cost-effectiveness evidences of hepatitis A vaccination. Based on the existing evidence, we found that universal vaccination among children was more likely to be cost-effective, especially in MICs. Nevertheless, our study had some limitations. First, evidences on LICs and live-attenuated vaccines were limited. Second, as the presented ICERs varied by type of currency, year of valuation and types of outcome, direct comparisons could not be made. Third, most studies had partial biases on both epidemiological parameters and quality of life weights; therefore, further studies that aim to estimate such parameters are warranted to ensure the accuracy of cost-effectiveness evidences. Finally, transferability of the cost-effectiveness findings of hepatitis A vaccine should be made after careful consideration of epidemiological parameters, resource utilization, unit cost data, as well as structure of healthcare delivery system, and country-level income.

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Supplementary file

Appendix I

Search terms in intervention and outcome domain for searching relevant papers for systematic review

Search terms used in PubMed

Domain	Intervention (I)	Outcome (O)
Search term	"Hepatitis A" "Hepatitis A"[MeSH Terms] Vaccination Vaccine Immunisation Immunisation [MeSH term] Immunisatization [MeSH term] Hepatitis A vaccine" "Hepatitis A immunization" "Hepatitis A immunisation" "Hepatitis A vaccination" Avaxim Havrix Havpur Vaqta Twinrix "Biovac A" Viatim Hepatyrix ViCPS Vivaxim	DALY "Disability adjusted life year" QALY "Quality adjusted life year" "Life year" "Life years" ICER "Incremental cost effectiveness ratio" "Cost benefit" "Cost effectiveness" "Cost utilit*" "Cost analysis" "Econom* evaluation" economics Economics [MeSH terms] "Economics assessment"

Search terms used in Scopus

Domain	Intervention (I)	Outcome (O)
Search term	"Hepatitis A vaccine" "Hepatitis A vaccination" "Hepatitis A immunisation" "Hepatitis A immunization" Avaxim Havrix Havpur Vaqta Twinrix "Biovac A" Viatim Hepatyrix ViCPS Vivaxim	DALY "Disability adjusted life year" QALY "Quality adjusted life year" "Life year" "Life years" ICER "Incremental cost effectiveness ratio" "Cost benefit" "Cost effectiveness" "Cost utilit*" "Cost analysis" "Econom* evaluation" economics Economics "Economics assessment"

Medline-PubMed search and strategies in intervention domain using Boolean operator “OR”

Intervention Domain:

Search number	Builder	Term
1	#1	Search “Hepatitis A”
2	#2	Search “Hepatitis A”[MeSH Terms]
3	#3	Search Vaccination
4	#1 OR#2 AND #3	Search ((“Hepatitis A”) OR “Hepatitis A”[MeSH Terms]) AND Vaccination
5	#4	Search Vivaxim
6	$5	Search ViCPS
7	#6	Search Hepatyrix
8	#7	Search “Biovac A”
9	#8	Search Viatim
10	#9	Search Twinrix
11	#10	Search Vaqta
12	#11	Search Havpur
13	#12	Search Havrix
14	#13	Search Avaxim
15	#4OR# 5 OR#6OR#7OR #8 OR#9 OR. #10 OR#11 OR#12 OR#13	Search (((((((((Vivaxim) OR ViCPS) OR Hepatyrix) OR Biovac A) OR Viatim) OR Twinrix) OR Vaqta) OR Havpur) OR Havrix) OR Avaxim
16	#14	Search immunisation
17	#15	Search immunisation[MeSH Terms]
18	#14 OR #15	Search (immunisation) OR immunisation[MeSH Terms]
19	#16	Search immunization[MeSH Terms]
20	#17	Search immunization

Medline-PubMed search and strategies in intervention domain using Boolean operator "OR" (cont.)

Intervention Domain

Search number	Builder	Term
21	#16 OR #17	Search (immunization[MeSH Terms]) OR immunization
22	#18	Search Vaccination
23	#19	Search Vaccine
24	Search 4 OR15 OR 18 OR 21 OR 22 OR 23	Search ((((((((((("Hepatitis A") OR "Hepatitis A"[MeSH Terms])) AND Vaccination) OR ((((((((((Vivaxim) OR ViCPS) OR Hepatyrix) OR Biovac A) OR Viatim) OR Twinrix) OR Vaqta) OR Havpur) OR Havrix) OR Avaxim)) OR ((immunisation) OR immunisation[MeSH Terms])) OR ((immunization[MeSH Terms]) OR immunization)) OR Vaccination) OR Vaccine) OR immunization) OR Vaccine) AND "Hepatitis A"

Medline-PubMed search and strategies in outcome domain using Boolean operator "OR"

Outcome domain

Search number	Builder	Term
1	#1	Search (((((((("Cost utility*") OR "Cost benefit") OR "Cost effectiveness") OR (("Incremental cost effectiveness ratio") OR ICER)) OR (("life years") OR "Life year")) OR ((DALY) OR "Disability adjusted life year")) OR ((QALY) OR "Quality adjusted life year")) OR (((((economics) OR economics[MeSH Terms]) OR economic) OR "Economic* evaluation") OR "economic assessment")
1	#1	Search "Cost utility*"
2	#2	Search "Cost benefit"
3	#3	Search "Cost effectiveness"
4	#4	Search "Incremental cost effectiveness ratio"
5	#5	Search ICER
6	#4OR#5	Search ("Incremental cost effectiveness ratio") OR ICER
7	#6	Search "life years"
8	#7	Search "Life year"
9	#6OR#7	Search ("life years") OR "Life year"
10	#8	Search DALY
11	#9	Search "Disability adjusted life year"
12	#8OR#9	Search (DALY) OR "Disability adjusted life year"
13	#10	Search QALY
14	#11	Search "Quality adjusted life year"

Medline-PubMed search and strategies in outcome domain using Boolean operator "OR" (cont.)

Outcome domain

Search number	Builder	Term
15	#10OR#11	Search (QALY) OR "Quality adjusted life year"
16	#12	Search economics
17	#13	Search economics[MeSH Terms]
18	#14	Search economic
19	#15	Search "Economic* evaluation"
20	#16	Search "economic assessment"
21	#12OR#13OR#14 #15OR#16	Search ((((economics) OR economics[MeSH Terms]) OR economic) OR "Economic* evaluation") OR "economic assessment"
22	1 OR 2 OR 3 OR 6 OR 9 OR 11 OR 15 OR 21	Search (((((("Cost utility*") OR "Cost benefit") OR "Cost effectiveness") OR (("Incremental cost effectiveness ratio") OR ICER)) OR (("life years") OR "Life year")) OR ((DALY) OR "Disability adjusted life year")) OR ((QALY) OR "Quality adjusted life year")) OR (((((economics) OR economics[MeSH Terms]) OR economic) OR "Economic* evaluation") OR "economic assessment")

Medline-PubMed search and strategies in intervention and outcome domain using Boolean operator "AND"

Search number	Builder	Term
1	#1 (From intervention domain)	Search ((((((((((("Hepatitis A") OR "Hepatitis A"[MeSH Terms])) AND Vaccination) OR ((((((((((Vivaxim) OR ViCPS) OR Hepatyrix) OR Biovac A) OR Viatim) OR Twinrix) OR Vaqta) OR Havpur) OR Havrix) OR Avaxim)) OR ((immunisation) OR immunisation[MeSH Terms])) OR ((immunization[MeSH Terms]) OR immunization)) OR Vaccination) OR Vaccine) OR immunization) OR Vaccine) AND "Hepatitis A"
2	#2 (outcome domain)	Search (((((("Cost utility*") OR "Cost benefit") OR "Cost effectiveness") OR (("Incremental cost effectiveness ratio") OR ICER)) OR (("life years") OR "Life year")) OR ((DALY) OR "Disability adjusted life year")) OR ((QALY) OR "Quality adjusted life year")) OR (((((economics) OR economics[MeSH Terms]) OR economic) OR "Economic* evaluation") OR "economic assessment")

Medline-PubMed search and strategies in intervention and outcome using Boolean operator "AND" (cont.)

Search number	Builder	Term
3	1 AND 2	Search ((((((((((((("Hepatitis A") OR "Hepatitis A"[MeSH Terms])) AND Vaccination) OR ((((((((((Vivaxim) OR ViCPS) OR Hepatyrix) OR Biovac A) OR Viatim) OR Twinrix) OR Vaqta) OR Havpur) OR Havrix) OR Avaxim)) OR ((immunisation) OR immunisation[MeSH Terms])) OR ((immunization[MeSH Terms]) OR immunization)) OR Vaccination) OR Vaccine) OR immunization) OR Vaccine) AND "Hepatitis A")) AND (((((((("Cost utility*") OR "Cost benefit") OR "Cost effectiveness") OR (("Incremental cost effectiveness ratio") OR ICER)) OR (("life years") OR "Life year")) OR ((DALY) OR "Disability adjusted life year")) OR ((QALY) OR "Quality adjusted life year")) OR (((((economics) OR economics[MeSH Terms]) OR economic) OR "Economic* evaluation") OR "economic assessment"))

Search terms with strategies combined for intervention and outcome domain using Boolean operator “AND” in Scopus

Query
(((((TITLE-ABS-KEY (“Hepatitis A vaccine”)) OR (TITLE-ABS-KEY (“Hepatitis A vaccination”)) OR (TITLE-ABS-KEY (“hepatitis A immunisation”)) OR (TITLE-ABS-KEY (“hepatitis A immunization”)) OR (TITLE-ABS-KEY (avaxim)) OR (TITLE-ABS-KEY (havrix)) OR (TITLE-ABS-KEY (havpur)) OR (TITLE-ABS-KEY (vaqta)) OR (TITLE-ABS-KEY (vaqta)) OR (TITLE-ABS-KEY (twinrix)) OR (TITLE-ABS-KEY (“Biovac A”)) OR (TITLE-ABS-KEY (viatim))) OR ((TITLE-ABS-KEY (hepatyrix)) OR (TITLE-ABS-KEY (vicps)) OR (TITLE-ABSKEY (vivaxim))))) AND ((TITLE-ABS-KEY (economics)) OR (((TITLE-ABS-KEY (“Cost benefit”)) OR (TITLE-ABS-KEY (“Cost effectiveness”)) OR (TITLE-ABS-KEY (“Cost utility”)) OR (TITLE-ABS-KEY (“Cost analysis”)) OR (TITLE-ABS-KEY (“Econom* evaluation”))) OR ((TITLE-ABS-KEY (icer)) OR (TITLE-ABS-KEY (“Incremental cost effectiveness ratio”))) OR (TITLE-ABS-KEY (“Incremental cost effectiveness ratio”)) OR ((TITLE-ABS-KEY (qaly)) OR (TITLE-ABS-KEY (“Quality adjusted life year”))) OR ((TITLE-ABS-KEY (daly)) OR (TITLE-ABS-KEY (“Disability adjusted life year”)))))) OR ((((“Econom* evaluation”) OR (“Cost analysis”) OR (“Cost utility”) OR (“Cost effectiveness”) OR (“Cost benefit”)) OR ((daly) OR (“Disability adjusted life year”)) OR ((icer) OR (“Incremental cost effectiveness ratio”)) OR ((qaly) OR (“Quality adjusted life year”))) AND (((vivaxim) OR (“ViCPS”) OR (hepatyrix) OR (viatim) OR (“Biovac A”)) OR ((“Hepatitis A vaccine”) OR (avaxim) OR (havrix) OR (havpur) OR (vaqta) OR (“Hepatitis A vaccination”) OR (“hepatitis A immunization”) OR (“Hepatitis A immunisation”) OR (twinrix))))

Search terms with strategies combined for intervention and outcome domain using Boolean operator AND in Scopus (cont.)

Query
((((TITLE-ABS-KEY (“Hepatitis A vaccine”)) OR (TITLE-ABS-KEY (“Hepatitis A vaccination”)) OR (TITLE-ABS-KEY (“hepatitis A immunisation”)) OR (TITLE-ABS-KEY (“hepatitis A immunization”)) OR (TITLE-ABS-KEY (avaxim)) OR (TITLE-ABS-KEY (havrix)) OR (TITLE-ABS-KEY (havpur)) OR (TITLE-ABS-KEY (vaqta)) OR (TITLE-ABS -KEY (vaqta)) OR (TITLE-ABS-KEY (twinrix)) OR (TITLE-ABS-KEY (“Biovac A”)) OR (TITLE-ABS-KEY (viatim))) OR ((TITLE-ABS-KEY (hepatyrix)) OR (TITLE-ABS-KEY (vicps)) OR (TITLE-ABS-KEY (vivaxim))))) AND ((TITLE-ABS-KEY (economics)) OR (((TITLE-ABS-KEY (“Cost benefit”)) OR (TITLE-ABS-KEY (“Cost effectiveness”)) OR (TITLE-ABS-KEY (“Cost utility”)) OR (TITLE-ABS-KEY (“Cost analysis”)) OR (TITLE-ABS-KEY (“Econom* evaluation”))) OR ((TITLE-ABS-KEY (icer)) OR (TITLE-ABS-KEY (“Incremental cost effectiveness ratio”))) OR (TITLE-ABS-KEY (“Incremental cost effectiveness ratio”)) OR ((TITLE-ABS-KEY (qaly)) OR (TITLE-ABS-KEY (“Quality adjusted life year”))) OR ((TITLE-ABS-KEY (daly)) OR (TITLE-ABS-KEY (“Disability adjusted life year”)))))

Search terms with strategies combined for intervention and outcome domain using Boolean operator”AND” in Scopus (cont.)

Query
(((“Econom* evaluation”) OR (“Cost analysis”) OR (“Cost utility”) OR (“Cost effectiveness”) OR (“Cost benefit”)) OR ((daly) OR (“Disability adjusted life year”)) OR ((icer) OR (“Incremental cost effectiveness ratio”)) OR ((qaly) OR (“Quality adjusted life year”))) AND (((vivaxim) OR (“ViCPS”) OR (hepatyrix) OR (viatim) OR (“Biovac A”)) OR ((“Hepatitis A vaccine”) OR (avaxim) OR (havrix) OR (havpur) OR (vaqta) OR (“Hepatitis A vaccination”) OR (“hepatitis A immunization”) OR (“Hepatitis A immunisation”) OR (twinrix)))

Appendix II
Data extraction form

Appendix I **DATA EXTRACTION FORM**

Form Number: ☐☐☐☐

Part I General Article Information

1. Date of data extraction ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)
2. Study ID ☐☐☐☐
3. Reviewer ☐ 1. Yogesh ☐ 2. Bhavani
4. First Author ……
5. Journal ……
6. Year of publication ☐☐☐☐

Part II General Study characteristics

7. Country ……
8. Setting ☐ 1. Country ☐ 2. Province ☐ 3. State ☐ 4.Profession ☐ 5. Risk group
9. Study perspective ☐ 1. Societal. ☐ 2. Government ☐ 3. Healthcare provider ☐ 4. Others ……
10. Type of EEs
    ☐ 1. cost-effectiveness analysis (CEA) ☐ 2. cost-utility analysis (CUA) ☐ 3. and cost-benefit analysis (CBA)
11. Analytic approach: ☐ 1. Cohort ☐ 2 Alongside trial ☐ 3. Markov Model ☐ 2. Dynamic model ☐ 3. Decision tree ☐ 4. Discrete event simulation ☐ 6. Not specified ☐ 7. Other……
12. Funding. ☐ 1. Yes, (details)…… ☐ 2. No ☐ 3. Not mentioned
13. Conflict of Interest ☐ 1. Yes (details)…… ☐ 2. No ☐ 3. Not mentioned

Part III Characteristics of studied participants

14. Type of population. ☐ 1. General
    If specific, ☐ 2.1.Students ☐ 2.2 Health worker ☐ 2.3 Food handlers ☐ 2.4 Army ☐ 2.5 Homosexuals ☐ 2.7 Diseased ☐ 2.8 Hepatits C ☐ 2.9 Liver diseases ☐ 2.10 Other……..
15. If targeted, what is target population? ☐ 1. Children (≤ 9 years) ☐ 2. Adolescents (10-19 years) ☐ 3. Adults (≥ 20 years)
16. What is population/sample/cohort size. ☐☐☐☐☐☐☐☐
17. Mean BMI ☐☐.☐☐ Kg/M^2 18. Mean age (years) ☐☐.☐☐
19. Gender male % ☐☐.☐☐
20. Hepatitis A burden given in terms of ☐ 1. Incidence ☐ 2. Prevalence
    Actual data ☐☐ Per ☐☐☐☐☐☐☐☐☐ Population

Part III Intervention for studied participants

21. Intervention(s) details Hepatitis A vaccine ☐ 1. Attenuated. ☐ 2. Inactivated
    Details, ☐ 3. Brand name …….. ☐ 4. Dose ☐☐ .☐☐ ml
    ☐ 5. One doses ☐ 6. Two doses
    ☐ 6. If two doses, duration between doses ☐☐ years ☐☐ Months
    ☐ 7. Vaccination coverage % ☐☐.☐☐
22. Comparator(s) ☐ 1. No vaccination ☐ 2. Screening blood sample & then decide ☐ 3. Other (if combination) ……

Part IV Methods of economic evaluations

23. Time horizon ☐ 1. Lifetime ☐ 2. Others specified ☐☐☐ years
24. Discount rate. ☐ 1. Yes ☐ 2. No
25. Discount rate for costs. ☐☐.☐☐ % 26. Discount rate for effects ☐☐.☐☐ %
27. Reference year of analysis ☐☐☐☐ 28. Currency. ……
29. Country name:……..
30. Threshold used for ICER . ☐ Country specific ☐ GDP based
31. Threshold in currency/GDP. ☐☐☐☐☐☐☐☐☐ 31. Literacy rate:……

Part V: Outcome measures

32. ☐ Cost ☐ Life years ☐ Quality adjusted life years. ☐ Incremental cost effectiveness
33. Category of costs ☐ 1. DMC ☐ 2. DNMC. ☐ 3. IDC ☐ 4. Not given
34. Data source of cost ☐ 1. Elicited in the study ☐ 2. Systematic review ☐ 3. Clinical database. ☐ 4. Medical record ☐ 5. Published literature. ☐ 6. Not clear ☐ 7. Others …….
35. Data source of utility ☐ 1. Elicited in the study ☐ 2. Systematic review ☐ 3. Other study ☐ 4. Not done
36. Data source of effectiveness (LYG) ☐ 1. Elicited in the study ☐ 2. Model based
37. Analysis of uncertainty ☐ 1. One way sensitivity analysis ☐ 2. Probabilistic

Sr No	Intervention	Comparator	Findings (Dominant/Cost effective/Not cost effective)
1			
2			
3			

I Base case	Intervention	Comparator	Remark
Costs			
Life years			
QALY			
DALY			
Incremental Cost			
Incremental life year			
Incremental QALY			
Incremental DALY			
ICER			
Other			
Probabilistic simulation analysis (PSA)details (No. of iteration/population)			
PSA	Intervention Mean ± SD (95%CI)	Comparator Mean ± SD (95%CI)	Remark
Costs			
Life year			
QALY			
DALY			
Incremental Cost			
Incremental life year			
Incremental QALY			
Incremental DALY			
ICER			
Other			

Appendix III. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist

Section/topic	#	PRISMA Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes, 1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes, 1
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes, 4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes, 6
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes, 5,6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes, 8,9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes, 6 and all appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes, 6 & appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes, 6,7 Figure
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes, 6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes, 6,7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes, 9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes 6, 7 appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes, 9,10 and Figure
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes, 6-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes, Appendix

Contd...

Section/topic	#	PRISMA Checklist item	Reported on page #
		RESULTS	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes, 8-11 Figure , Table II, Table III, Table IV
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes, Appendix IV
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes, 8-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes, 13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes, 14
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes, 15

Adopted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6 (7): e1000097. doi: 10.1371/journal.pmed1000097

Appendix IV. Results of risk of bias assessment

Bias	Ramsey *et al*[26], 2019	Luyten *et al*[24], 2012	Chapko *et al*[50], 2010	Armstrong *et al*[49], 2007	Hankin-Wei *et al*[60], 2016	Wilson *et al*[59], 2020	Dhankhar *et al*[61], 2015	Ghildayal *et al*[25], 2019
1.Narrow perspective bias	P	Y	P	Y	U	P	Y	Y
2.Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y
3.Cost measurement omission bias	P	Y	P	Y	Y	P	Y	Y
4.Intermittent data collection bias	Y	Y	Y	Y	U	U	Y	Y
5.Invalid valuation bias	Y	Y	Y	Y	U	N	Y	Y
6.Ordinal ICER bias	Y	Y	Y	U	Y	Y	Y	Y
7.Double-counting bias	Y	N	P	U	N	U	U	N
8. Inappropriate discounting bias	Y	Y	Y	Y	Y	U	Y	Y
9.Limited sensitivity analysis bias	P	P	P	N	Y	P	P	P
10.Sponsor bias	Y	Y	Y	N	Y	N	N	N
11.Reporting and dissemination bias	X	X	X	X	X	X	X	X
12.Structural assumptions bias	Y	Y	Y	Y	U	U	Y	Y
13.No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y
14. Wrong model bias	Y	Y	Y	U	Y	U	Y	Y
15. Limited time horizon bias	Y	Y	U	N	Y	N	U	N
16.Bias related to data identification	Y	Y	Y	Y	P	N	Y	Y
17.Bias related to baseline data	Y	Y	Y	Y	U	N	Y	Y
18.Bias related to treatment effects	Y	Y	Y	Y	U	U	Y	Y
19.Bias related to quality-of-life weights (utilities)	P	P	U	P	U	X	P	U
20.Non-transparent data incorporation bias	Y	Y	Y	Y	P	U	Y	Y
21.Limited scope bias	P	P	P	N	P	P	P	P
22.Bias related to internal consistency	U	U	U	U	U	U	U	U

Contd...

Bias	Rein *et al*[57], 2007	Postma *et al*[42], 2004	Jacobs *et al*[42], 2003	Arguedas *et al*[48], 2002	Chodick *et al*[38], 2002	Jacobs *et al*[54], 2000	Jacobs *et al*[52], 2002	Chodick *et al*[37], 2001	Diel *et al*[34], 2001
1.Narrow perspective bias	Y	Y	Y	Y	P	Y	Y	Y	Y
2.Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.Cost measurement omission bias	Y	P	Y	Y	P	Y	P	Y	Y
4.Intermittent data collection bias	Y	Y	Y	Y	Y	Y	P	U	Y
5.Invalid valuation bias	Y	Y	Y	Y	Y	Y	U	Y	Y
6.Ordinal ICER bias	Y	Y	Y	Y	P	P	P	P	Y
7.Double-counting bias	Y	U	N	Y	Y	N	U	U	P
8. Inappropriate discounting bias	Y	U	Y	Y	Y	Y	Y	Y	Y
9.Limited sensitivity analysis bias	P	N	P	P	P	P	P	P	P
10.Sponsor bias	N	N	P	N	Y	P	P	Y	N
11.Reporting and dissemination bias	X	X	X	X	X	X	X	X	X
12.Structural assumptions bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
13.No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
14. Wrong model bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
15. Limited time horizon bias	Y	U	Y	Y	Y	U	U	N	N
16.Bias related to data identification	Y	Y	Y	Y	Y	Y	Y	Y	Y
17.Bias related to baseline data	Y	Y	Y	Y	Y	Y	P	P	Y
18.Bias related to treatment effects	Y	Y	Y	Y	Y	Y	P	P	Y
19.Bias related to quality-of-life weights (utilities)	P	X	P	P	P	X	X	P	X
20.Non-transparent data incorporation bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
21.Limited scope bias	P	N	P	P	P	P	P	P	P
22.Bias related to internal consistency	U	U	U	U	U	U	U	U	U

Contd...

Bias	Ginsberg *et al*[36], 2001	Jacobs *et al*[51], 2000	Jacobs *et al*[53], 1999	O'Conner *et al*[56], 1999	Buma *et al*[43], 1998	Arnal *et al*[44], 1997	Smith *et al*[58], 1997	Severo *et al*[53], 1995	Van-Doorslaer *et al*[23], 1994
1.Narrow perspective bias	Y	Y	Y	Y	U	U	Y	Y	U
2.Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.Cost measurement omission bias	Y	Y	Y	Y	P	P	P	Y	P
4.Intermittent data collection bias	Y	Y	Y	Y	Y	Y	Y	U	Y
5.Invalid valuation bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
6.Ordinal ICER bias	Y	Y	Y	Y	Y	P	Y	Y	Y
7.Double-counting bias	U	Y	P	Y	U	P	Y	Y	P
8. Inappropriate discounting bias	Y	Y	Y	Y	U	Y	Y	Y	Y
9.Limited sensitivity analysis bias	P	P	P	P	N	P	P	P	P
10.Sponsor bias	N	P	P	N	N	Y	N	N	N
11.Reporting and dissemination bias	X	X	X	X	X	X	X	X	X
12.Structural assumptions bias	Y	Y	Y	Y	Y	P	Y	Y	Y
13.No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
14. Wrong model bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
15. Limited time horizon bias	N	U	Y	Y	U	U	Y	N	N
16.Bias related to data identification	Y	Y	Y	Y	Y	P	Y	Y	Y
17.Bias related to baseline data	Y	Y	Y	Y	Y	P	Y	Y	Y
18.Bias related to treatment effects	Y	Y	Y	Y	P	P	Y	Y	Y
19.Bias related to quality-of-life weights (utilities)	X	X	X	X	P	X	P	X	X
20.Non-transparent data incorporation bias	Y	Y	Y	Y	Y	P	Y	Y	Y
21.Limited scope bias	P	P	P	P	N	P	P	P	P
22.Bias related to internal consistency	U	U	U	U	U	U	U	U	U

Contd...

Bias	Jefferson *et al*[47], 1994	Tormans *et al*[22], 1992	Hayajneh *et al*[39], 2018	Curran *et al*[40], 2016	Carlos *et al*[41], 2016	Pan *et al*[32], 2012	Quezada *et al*[28], 2008	Ellis *et al*[21], 2007	Lopez *et al*[20], 2007
1.Narrow perspective bias	U	U	Y	P	Y	Y	Y	Y	Y
2.Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.Cost measurement omission bias	P	P	Y	P	Y	Y	Y	Y	Y
4.Intermittent data collection bias	Y	Y	Y	Y	Y	P	Y	Y	Y
5.Invalid valuation bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
6.Ordinal ICER bias	P	Y	Y	P	Y	P	P	P	Y
7.Double-counting bias	P	Y	Y	Y	N	U	Y	Y	Y
8. Inappropriate discounting bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
9.Limited sensitivity analysis bias	N	P	P	P	Y	P	P	P	P
10.Sponsor bias	N	P	P	P	N	Y	N	P	N
11.Reporting and dissemination bias	X	X	X	X	X	X	X	X	X
12.Structural assumptions bias	P	Y	Y	Y	Y	Y	Y	P	Y
13.No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
14. Wrong model bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
15. Limited time horizon bias	N	N	N	N	N	U	Y	P	Y
16.Bias related to data identification	P	Y	Y	Y	P	Y	Y	Y	Y
17.Bias related to baseline data	P	Y	Y	Y	U	Y	Y	Y	Y
18.Bias related to treatment effects	P	Y	Y	Y	U	Y	Y	N	Y
19.Bias related to quality-of-life weights (utilities)	X	X	P	U	P	P	X	P	X
20.Non-transparent data incorporation bias	P	Y	Y	Y	P	Y	Y	Y	Y
21.Limited scope bias	N	P	P	P	U	P	P	P	P
22.Bias related to internal consistency	U	U	U	U	U	U	U	U	U

Contd...

Bias	Valenzuela *et al*[27], 2005	Das *et al*[62], 1999	Suwantika *et al*[35], 2014	Zhuang *et al*[31], 2008	Soogarun *et al*[45], 2002	Teppakdee *et al*[46], 2002	Chen *et al*[30], 1999	Li *et al*[29], 1998
1.Narrow perspective bias	Y	Y	Y	Y	U	U	U	Y
2.Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y
3.Cost measurement omission bias	Y	Y	Y	P	U	U	U	Y
4.Intermittent data collection bias	Y	Y	Y	P	Y	Y	U	U
5.Invalid valuation bias	Y	P	Y	P	P	P	U	P
6.Ordinal ICER bias	N	P	Y	Y	U	U	P	P
7.Double-counting bias	N	U	Y	Y	Y	Y	U	U
8. Inappropriate discounting bias	Y	Y	Y	Y	U	U	U	U
9.Limited sensitivity analysis bias	P	P	P	P	N	N	N	N
10.Sponsor bias	P	N	N	N	N	N	N	Y
11.Reporting and dissemination bias	X	X	X	X	X	X	X	X
12.Structural assumptions bias	Y	Y	Y	Y	P	P	U	Y
13.No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y
14. Wrong model bias	Y	Y	Y	Y	P	P	U	U
15. Limited time horizon bias	P	Y	P	U	U	U	N	U
16.Bias related to data identification	Y	Y	Y	Y	Y	Y	P	P
17.Bias related to baseline data	Y	Y	Y	Y	U	U	U	P
18.Bias related to treatment effects	Y	U	Y	Y	U	U	U	P
19.Bias related to quality-of-life weights (utilities)	P	P	P	P	X	X	X	P
20.Non-transparent data incorporation bias	Y	Y	Y	Y	Y	Y	P	Y
21.Limited scope bias	P	P	P	P	N	N	N	N
22.Bias related to internal consistency	U	U	U	U	U	U	U	U

Note: Bias addressed (P: Partly; N: Not addressed; U: Unclear; X: Not applicable; Y: Yes)