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Review

Systematic review of economic evaluations of vaccination programs in mainland China: Are they sufficient to inform decision making?

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ABSTRACT

The purpose of the study was to systematically review economic evaluations of vaccine programs conducted in mainland China. We searched for economic evaluations of vaccination in China published prior to August 3, 2015 in eight English-language and three Chinese-language databases. Each article was appraised against the 19-item Consensus on Health Economic Criteria list (CHEC-list). We found 23 papers evaluating vaccines against hepatitis B (8 articles), *Streptococcus pneumoniae* (5 articles), human papillomavirus (3 articles), Japanese encephalitis (2 articles), rotavirus (2 articles), hepatitis A (1 article), Enterovirus 71 (1 article) and influenza (1 article). Studies conformed to a mean of 12 (range: 6–18) items in the CHEC-list criteria. Five of six Chinese-language articles conformed to fewer than half of the 19 criteria items. The main criteria that studies failed to conform to included: inappropriate measurement (20 articles) and valuation (18 articles) of treatment and/or vaccination costs, no discussion about distributional implications (18 articles), missing major health outcomes (14 articles), no discussion about generalizability to other contexts (14 articles), and inadequate sensitivity analysis (13 articles). In addition, ten studies did not include major cost components of vaccination programs, and nine did not report outcomes in terms of life years even in cases where QALYs or DALYs were calculated. Only 13 studies adopted a societal perspective for analysis. All studies concluded that the appraised vaccination programs were cost-effective except for one evaluation of universal 7-valent pneumococcal conjugate vaccine (PCV-7) in children. However, three of the five studies on PCV-7 showed poor overall quality, and the number of studies on vaccines other than hepatitis B vaccine and PCV-7 was limited. In conclusion, major methodological flaws and reporting problems exist in current economic evaluations of vaccination programs in China. Local guidelines for good practice and reporting, institutional mechanisms and education may help to improve the overall quality of these evaluations.

1. Introduction

Infectious diseases are one of the leading causes of morbidity and mortality in China [1,2]. Vaccination has been essential in the control and prevention of infectious diseases in China in the past three decades [3]. In 2015, the national Expanded Program on Immunization (EPI) offered 11 vaccines for free to children as either a normal dose or an independent booster dose protecting against 12 diseases: tuberculosis, polio, diphtheria, tetanus, pertussis, measles, mumps, rubella, Japanese encephalitis, meningococcal meningitis, and hepatitis A and B. It is estimated that the EPI has prevented 300 million cases of tuberculosis, polio, measles, pertussis, diphtheria, and tetanus, and 4 million deaths from these diseases since its inception in 1978 [4]. Polio has been eliminated due to high coverage of oral polio vaccine. The seroprevalence of hepatitis B surface antigen reduced from 9.7% to 1.0% in children under 5 years, and from 10.7% to 2.3% in those aged 5–14 years between 1992 and 2006 [5].

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Despite major progress, China still faces challenges from vaccine-preventable infectious diseases [3,6]. Only the above 11 vaccines are currently provided without charge by the central government, although some other vaccines are offered without charge by regional governments in more developed areas, such as Beijing and Shanghai. World Health Organization (WHO) recommendations to vaccinate children against rotavirus, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib) and human papillomavirus (HPV) have yet to be implemented [3]. While Hib and pneumococcal conjugate vaccines (PCVs) for children and influenza vaccine for high-risk groups can be accessed in the private market, the HPV vaccine, widely available in other countries, has yet to be licensed in China pending completion of local trials [7,8]. National surveys have found that the uptake of non-EPI vaccines, such as PCV and Hib vaccines, is much lower than for the EPI vaccines, especially in the less developed central and western regions [9,10]. Unvaccinated children are often those already at the highest risk of infectious diseases [11].

The decision process for adding a vaccine to the national EPI schedule is complicated in China and lacks a transparent system for evidence-based policy making [12]. Decision-making reportedly considers evidence of high burden of disease and cost-effectiveness of vaccination as well as the production capacity of domestic suppliers [3,12]. Only Chinese-produced vaccines are regarded as a reliable supply for the national immunization program and vaccines allocated through the EPI are presently all supplied by domestic manufacturers. With universal health coverage, China has to make difficult decisions on which health programs and interventions to fund [13,14]. Since national vaccination programs require substantial public funding, evidence on the value of this investment would seem essential to the decision making process. Furthermore, WHO recommends that an economic evaluation be conducted before adding a vaccine to a national immunization program [15].

The objective of the study was to systematically review economic evaluations of vaccine programs conducted in mainland China, in order to assess the suitability of existing work to inform evidence-based changes to the EPI schedule. We explore strengths and weaknesses in the economic evaluation work, evaluate the evidence base for the cost-effectiveness of vaccine programs and their relevance to policy making, and make recommendations on improvements to conduct economic evaluations of vaccination programs.

2. Methods

2.1. Search strategy

A systematic review was conducted according to the literature search procedure recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. Eight English-language and three Chinese-language databases were searched for published articles on economic evaluations of vaccination programs in mainland China. The English-language databases were PubMed/MEDLINE, Embase, SCOPUS, ISI Web of Knowledge, EconLit, NHS Economic Evaluation Database, Health Economic Evaluation Database, and HTA Database of the Center for Reviews and Dissemination. Chinese-language databases were China National Knowledge Infrastructure, Wanfang, and Chongqing VIP.

Chinese- and English-language search algorithms combining free text and MeSH headings were created for searches in Chinese-language and English-language databases, respectively. Three groups of MeSH terms, key words and free texts were used, including "vaccine", "economic evaluation", and geographical area limitations to China (see Appendix A for terms used in the PubMed/Medline search). References cited in included articles were reviewed to identify any additional papers that may have been missed. The search ended on 3 August 2015 (31 July 2015 for EconLit) with no lower time limit. Prior to searching for original articles, a search for systematic reviews on the topic using the above mentioned terms in the MEDLINE and the Campbell Systematic Reviews databases confirmed that there were no relevant existing reviews.

2.2. Selection criteria

All economic evaluations of vaccination programs (i.e. addressing both incremental costs and health outcomes of introducing a vaccine compared with an alternative) conducted in mainland China were included. Our review only focused on full economic evaluations such as cost-effectiveness analyses, cost–utility analyses, and cost–benefit analyses [17]. In case of duplicate publications, only the most recently published article was included.

2.3. Quality appraisal

The first author and a research assistant independently screened the articles and discrepancies were resolved based on consensus after discussion. After the final list of articles was identified, the first author extracted general information from all included articles, such as author names, year of publication, and type of vaccine analyzed. In addition, technical features for appraisal were extracted, including the target population, comparator(s), perspective, time horizon, use of modeling, source of effectiveness data, unit of effectiveness, source of utility data, source of cost data, and sensitivity analysis. Articles were then appraised according to the Consensus on Health Economic Criteria list (CHEC-list) [18]. The CHEC-list consists of 19 yes-or-no questions to assess the methodological quality of economic evaluations. We assigned each article a quality score according to the number of CHEC-list items satisfied.

2.4. Cost-effectiveness thresholds

There are no official benchmarks for determining the cost-effectiveness of health care programs in China. However, many studies evaluated cost-effectiveness according to the WHO vaccine introduction guidelines [15,19], which state that an intervention is highly cost-effective if the incremental cost-effectiveness ratio (ICER) is less than the gross domestic product (GDP) per capita of that nation, and cost-effective if it is less than three time the GDP per capita. To facilitate comparison, ICERs extracted from included articles were converted to 2014 values based on the consumer price index and exchange rates for appropriate years [20]. Chinese GDP per capita was US$7598 in 2014.

3. Results

3.1. Screened articles

Our searches identified 2709 records, of which 1887 remained after deduplication (Fig. 1). After screening the abstracts, 148 full text articles were retrieved. Of these, 125 (all published in Chinese-language journals) were not found to be full economic evaluations. In particular, 114 of these were labelled as cost–benefit analyses but failed to monetize health outcomes, and 11 were labelled as cost-effectiveness or cost–utility analyses but failed to consider both disease costs and health outcomes in vaccinated individuals. After exclusions, only 17 English-language [21–37] and six Chinese-language [38–43] articles met our criteria, one of which was an MSc thesis [38].

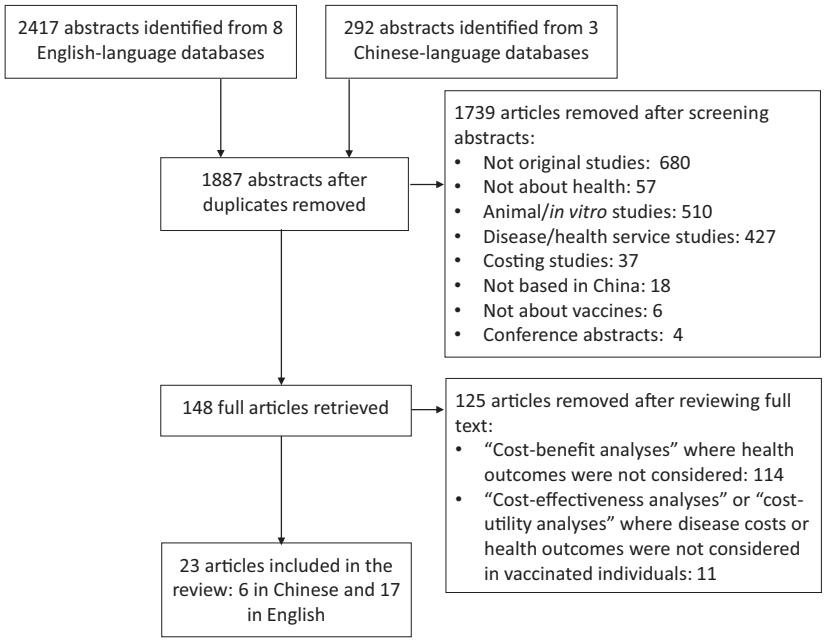

Fig. 1. PRISMA flowchart showing the study selection process.

3.2. Study characteristics

The 23 included studies are summarized in Table 1. Seventeen studies were published in six English language general medical or health journals, including nine in *Vaccine*. Seventeen first authors were affiliated to a Chinese institution. The earliest study was published in 2003, but 19 were published between 2010 and 2015 (Table 2 and Appendix B). An increasing trend was noted in the number of publications. Fourteen studies were funded by a non-profit organization. In total, the studies evaluated eight vaccines, with the most often studied being hepatitis B vaccine (in 8 studies) and 7-valent pneumococcal conjugate vaccine (PCV-7) (in 5 studies).

All studies were model-based, with 10 using decision trees, and only one (on HPV vaccination) using a dynamic transmission model [27] (Table 3). Five studies utilizing a Markov model [31,33,35,41,42] and one utilizing a dynamic transmission model [27] incorporated estimates of herd immunity. Thirteen adopted a societal perspective (with three of them additionally using a healthcare or patient perspective), but two [39,40] did not state the perspective or give enough detail about costing methodology to allow this to be determined. Fifteen studies had a lifetime time horizon. One study for influenza vaccine [29] and two studies for rotavirus vaccine [24,32] considered very short (one-year and five-years) time horizons. Four articles (three Chinese-language [39,41,43] and one English-language [33]) did not report the time horizon.

3.3. Quality appraisal

Studies conformed to a mean of 12 (range: 6–18) items in the CHEC-list criteria. Five of the six Chinese-language articles met fewer than half of the 19 criteria; in contrast all the English-language articles conformed to more than half (Table 4). One study met all but one of the criteria [28].

Ideally, vaccine efficacy parameters in evaluations should be derived from major clinical trials or systematic reviews of clinical trials. However, only seven studies obtained efficacy data from such sources [22,24,27,32,33,35,40]; one study (on hepatitis A vaccine) used estimates from an expert consultation despite being for a licensed vaccine [23], and four (on Enterovirus 71 vaccine [26], hepatitis B vaccine [34,43], and HPV vaccine [36]) did not explicitly report the source of efficacy data. (For the Enterovirus 71 vaccine study, this was because the vaccine candidates were still in development.)

Methodological choices, such as the perspective and discount rate, were not given due attention in many economic evaluations. Both WHO guidelines [19] and Chinese guidelines for pharmacoeconomic evaluation [44] recommend a societal perspective, but only 13 studies adopted this perspective. Three studies did not mention the discount rate [26,36,41], and one did not discount health outcomes or costs because it adopted a one-year time horizon [29] (Table 3). A failure to discount appropriately may overestimate health benefits and economic costs.

Ten studies did not include major cost components of vaccination programs (such as the cost of program organization, vaccine administration or treatment of adverse effects), and 20 and 18 studies, respectively, measured and valued treatment and/or vaccination costs inappropriately. Costs of non-EPI vaccines were derived from private market prices in six studies without any adjustment for bulk purchase tenders [24,31,33,35,41,42]. In other studies of non-EPI vaccines, costs were estimated from the contract price offered to the Chinese government [23,29] or international organizations [36], from unpublished data [21,28] or from assumptions [26,27,32,36]. Only three studies presented the costs of treatment in a disaggregated form from which component costs could be discerned [21,25,28]. This limits the transparency of the analysis and assessments about the transferability of results across jurisdictions.

Twelve studies did not report outcomes in terms of life years even in cases where QALYs or DALYs were calculated, including three studies without any other health outcomes [26,39,43]. All 13 studies reporting QALYs used utility data from other populations (six studies reporting DALYs used disability weights from the global burden of disease studies), and only three additionally used utilities generated in a Chinese population [30,34,37]. The use of utilities derived from non-Chinese populations may not reflect health preferences in the Chinese population. Fourteen studies were not

Table 1
Summary of results from economic evaluation of vaccines in China.

Publication	Perspective	Target population	Vaccine options	Conclusion*	Reference year
Ding et al. [21]	Healthcare	Children <10 years in Shanghai	Inactivated and live attenuated Japanese encephalitis vaccines vs. no vaccine	Both vaccines cost saving; live vaccine saves more costs and prevents more DALYs	1997
Goldie et al. [22]	Societal	Girls aged 9–12 years	HPV-16/18 vaccine vs. no vaccine	US$626 per DALY averted at a cost of US$12 per vaccinated girls	2005
Zhuang et al. [23]	Societal and healthcare	Children 12–18 months	Universal hepatitis A vaccine vs. no vaccine	Cost-saving or cost-effective depending on region	2005
Wang et al. [24]	Societal and patient	Children 0–6 months in rural Zhengding County	Rotavirus vaccine compared with no vaccine	Cost saving	2004
Hutton et al. [25]	Societal	Children 1–19 years	Catch-up hepatitis B vaccine vs. current program	Cost saving	2008
Lee et al. [26]	Healthcare	Children 6 months—5 years	Enterovirus 71 vaccine vs. no vaccine	Cost-effective at a price of US$27 per vaccine dose and efficacy ≥70% or US$11 per dose and efficacy ≥50%. In areas with higher infection risk, cost-effective at a price of US$54–82 per dose and efficacy ≥50%	2010
Chen [38]	Healthcare	10,000 children aged 15 years	Booster dose in children negative for hepatitis B vaccine induced antibody vs. no booster.	Cost saving at 50–100% coverage	2010
Canfell et al. [27]	Societal	Girls 15 years in rural China	HPV vaccine plus screening vs. screening alone	Cost-effective at a cost of <US$59 per vaccinated girl	2008
Si and Jiang [39]	Not stated	Children <15 years	Hepatitis B vaccine catch-up campaign vs. current program	Cost-saving (based on the stated conclusion in the original article)	2009
Liu et al. [32]	Societal	Children 3–4 months	Two-dose rotavirus vaccine vs. no vaccine	Cost-effective at a price of US$12–24 per dose	2007
Yin et al. [28]	Societal	Children aged 8–23 months in Guizhou province	Universal Japanese encephalitis vaccine vs. no vaccine	US$109 per DALY averted	2009
Lu et al. [30]	Societal and healthcare	Children 0–6 months	Hepatitis B vaccine vs. no vaccine	Cost saving	2002
Lv et al. [40]	Not stated	Children 0–6 months in Shenzhen	S1: Screening pregnant women for HBsAg and vaccinating newborn infants of positive mothers with HBIG and hepatitis B vaccine S2: Screening for HBsAg and HBeAg and vaccinating newborn children of both-positive mothers with HBIG and hepatitis B vaccine Comparator is vaccinating newborns with hepatitis B vaccine without screening pregnant mothers	Both S1 and S2 cost saving; S1 most cost-effective	2010
Fu et al. [42]	Societal	Children 0–2 years	3 + 1 PCV-7 vaccine vs. no vaccine	Cost saving	2010
Zhu et al. [41]	Healthcare	Children 0–2 years in Shenzhen	3 + 1 PCV-7 vaccine vs. no vaccine	US$18,888 per QALY gained	2010
Che et al. [31]	Societal	Children 4–12 months	PCV-7 vaccine vs. no vaccine	US$539,894 per QALY gained and US$97,034 in case of herd immunity	2011

Table 1 (*Continued*)

Publication	Perspective	Target population	Vaccine options	Conclusion*	Reference year
Zhou et al. [29]	Healthcare	Children 6 months—14 years	Influenza vaccination promotion (telephone reminder or comprehensive package) vs. current self-payment policy	Cost of US$0 (6–59 month olds) or US$40 (60 month–14 year olds) per medically attended case averted	2010
Hu et al. [33]	Healthcare	Children 0–1 year in Shanghai	3 + 1 PCV-7 vaccine vs. no vaccine	US$6550 per QALY gained	2011
Jia et al. [34]	Societal	Children 8–15 years in Shandong	Hepatitis B vaccine catch-up vs. current program	Cost saving	2013
Caldwell et al. [35]	Healthcare	Children 0–2 years	3 + 1 PCV-7 vaccine vs. no vaccine in typical and pandemic influenza seasons	US$2163 per QALY gained during a normal influenza season; cost saving during an influenza pandemic	2011
Levin et al. [36]	Healthcare	Girls aged 0–12	HPV vaccine plus screening vs. screening alone	Cost-effective at a cost of <US$57 per vaccinated girl. Poorer women received higher benefits	2009
Yin et al. [37]	Societal	Children aged 0–6 months	3-dose 10 μg series of hepatitis B vaccine vs. 3-dose 5 μg series	Cost saving	2013
Xiao et al. [43]	Societal	Health professionals and adults with close household contact with hepatitis B carriers in Beijing	3-dose 20 μg series of hepatitis B vaccine vs. no vaccine	Cost saving	2010

* All currencies were transformed to the current value in 2014 based on exchange rates and consumer price indexes in reference years and 2014.

explicit about how generalizable the results were to other contexts, while eighteen did not discuss the distributional implications of the vaccination program.

Although all but one conducted sensitivity analysis, only nine studies performed probabilistic sensitivity analysis (Table 3). Probabilistic sensitivity analysis is required to fully capture the joint effect of uncertainties around multiple parameters [19]. In addition, many economic evaluations were based on regional data limiting

Table 2
Bibliometric information for economic evaluations of vaccines in China.

Characteristic	Number
Country of primary author affiliation	
China	17
USA	5
Australia	1
Year of publication	
2003–2009	4
2010–2015	19
Type of external funding	
Not for profit	14
For profit	3
No funding	1
Not explicitly stated	5
Geographic location covered	
National	11
Subnational	12
Type of study	
Cost-effectiveness	6
Cost–utility	17
Type of vaccine	
Japanese encephalitis vaccine	2
HPV vaccine	3
Hepatitis A vaccine	1
Rotavirus vaccine	2
Hepatitis B vaccine	8
Enterovirus 71 vaccine	1
PCV-7 vaccine	5
Influenza vaccine	1

Table 3
Technical characteristics of economic evaluations of vaccines in China.

Characteristic	Number
Use of model	
Decision tree	10
Markov model	8
Dynamic transmission model	1
Monte Carlo simulation model	1
Decision tree & Markov model	2
Markov model & Monte Carlo simulation model	1
Perspective	
Societal	10
Healthcare	8
Societal and healthcare	2
Societal and patient	1
Not explicitly stated	2
Time horizon	
Lifetime	15
0–30 years	1
0–5 years	2
0–1 year	1
Not explicitly stated	4
Discount rate	
0%	1
3%	16
5%	3
Not explicitly stated	3
Unit of health outcomes	
Cases	2
Deaths	1
QALY/DALY	3
Deaths & QALY/DALY	1
Cases & deaths & life years	1
Cases & deaths & QALY/DALY	8
Cases & deaths & life years & QALY/DALY	7
Sensitivity analysis	
One-way	11
One- & multiple-way	2
One-way & probabilistic	6
One- & multiple-way & probabilistic	3
None	1

Table 4
Quality appraisal of economic evaluations of vaccines in China.

CHEC-list	Ding et al. [21]	Goldie et al. [22]	Zhuang et al. [23]	Wang et al. [24]	Hutton et al. [25]	Lee et al. [26]	Chen [38]	Canfell et al. [27]
1. Study population clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Competing alternative clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Well defined question in answerable form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Economic study designed appropriately[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Time horizon appropriate	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Perspective appropriate[b]	No	Yes	Yes	Yes	Yes	No	No	Yes
7. All relevant cost items included[c]	No	Yes	Yes	Yes	No	No	No	No
8. All costs measured appropriately in physical units	No	No	No	No	No	No	No	Yes
9. Costs valued properly	Yes	No	No	No	Yes	No	No	Yes
10. All relevant outcomes identified	No	Yes	Yes	No	No	No	No	Yes
11. Outcomes measured appropriately	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Outcomes valued appropriately	Yes	Yes	No	Yes	No	Yes	No	Yes
13. Incremental analysis of costs and outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Cost and outcomes discounted	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
15. Sensitivity analysis appropriately done	Yes	No	No	Yes	Yes	Yes	No	Yes
16. Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Discussion about generalizability	Yes	Yes	No	Yes	No	No	No	No
18. Disclosure of potential conflict of interests	Yes	Yes	No	Yes	Yes	Yes	No	No
19. Ethical and distributional issues discussed[d]	No	Yes	No	No	No	Yes	No	No
No. of conforming items	13	16	12	15	13	12	9	15

CHEC-list	Si and Jiang [39]	Liu et al. [32]	Yin et al. [28]	Lu et al. [30]	Lv et al. [40]	Fu et al. [42]	Zhu et al. [41]	Che et al. [31]
1. Study population clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Competing alternative clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Well defined question in answerable form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Economic study designed appropriately[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Time horizon appropriate	No	Yes	Yes	Yes	Yes	Yes	No	Yes
6. Perspective appropriate[b]	No	Yes	Yes	Yes	No	Yes	No	Yes
7. All relevant cost items included[c]	No	Yes	Yes	Yes	No	No	No	Yes
8. All costs measured appropriately in physical units	No	No	Yes	No	No	No	No	No
9. Costs valued properly	No	No	Yes	No	No	No	No	No
10. All relevant outcomes identified	No	No	No	Yes	No	No	Yes	No
11. Outcomes measured appropriately	No	Yes	Yes	Yes	No	No	Yes	No
12. Outcomes valued appropriately	No	Yes	Yes	Yes	No	No	No	No
13. Incremental analysis of costs and outcomes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Cost and outcomes discounted	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
15. Sensitivity analysis appropriately done	No	No	Yes	Yes	Yes	No	No	Yes
16. Conclusions follow from the data reported	No	Yes	Yes	Yes	No	Yes	Yes	Yes
17. Discussion about generalizability	Yes	No	Yes	Yes	No	No	No	No
18. Disclosure of potential conflict of interests	No	Yes	Yes	No	No	No	No	Yes
19. Ethical and distributional issues discussed[d]	No	No	Yes	No	No	No	No	Yes
No. of conforming items	6	13	18	15	8	9	8	13

CHEC-list	Zhou et al. [29]	Hu et al. [33]	Jia et al. [34]	Caldwell et al. [35]	Levin et al. [36]	Yin et al. [37]	Xiao et al. [43]
1. Study population clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Competing alternative clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Well defined question in answerable form	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Economic study designed appropriately[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Time horizon appropriate	Yes	No	Yes	Yes	Yes	Yes	No
6. Perspective appropriate[b]	No	No	Yes	No	No	Yes	Yes
7. All relevant cost items included[c]	No	Yes	Yes	Yes	Yes	Yes	Yes
8. All costs measured appropriately in physical units	No	No	No	No	No	Yes	No
9. Costs valued properly	No	No	No	No	No	Yes	No
10. All relevant outcomes identified	Yes	Yes	No	Yes	No	Yes	No
11. Outcomes measured appropriately	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Outcomes valued appropriately	Yes	No	Yes	Yes	Yes	Yes	Yes
13. Incremental analysis of costs and outcomes	Yes	Yes	Yes	Yes	No	No	No
14. Cost and outcomes discounted	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15. Sensitivity analysis appropriately done	No	No	Yes	No	No	No	No
16. Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	No
17. Discussion about generalizability	No	No	Yes	Yes	Yes	No	No
18. Disclosure of potential conflict of interests	No	Yes	Yes	Yes	Yes	Yes	Yes
19. Ethical and distributional issues discussed[d]	No	No	No	No	Yes	No	No
No. of conforming items	11	11	15	14	13	15	10

[a] An appropriate economic study design is a full economic evaluation (comparison of costs and effects of interventions).
[b] Societal perspective is regarded as appropriate.
[c] Includes major components of treatment and vaccination costs.
[d] Notes ethical aspects and elaborates on the characteristics of the population experiencing the diseases or the intervention (young, old, poor, wealthy) and how this may have distributional implications.

the transferability of findings to other contexts, but such limitations were not discussed. Only five discussed the distributional implications of the immunization program as a whole. The distribution of costs and/or benefits, as well as the overall budget impact, is likely to influence priority setting for health services [45].

3.4. Key findings

Hepatitis B: Several hepatitis B vaccination strategies were found to be cost–saving (Table 1). These included universal vaccination comprising of a timely birth dose in a three-dose scheme [30], catch-up campaigns in individuals aged 1–19 years [25] or 8–15 years [34], booster dose programs in adolescents aged 15 years who were negative for hepatitis B vaccine-induced antibody [38], screening all pregnant women for hepatitis B surface antigen (HBsAg) followed by vaccinating newborn infants of positive mothers with both hepatitis B immune globulin (HBIG) and hepatitis B vaccine [40], 3-dose 10 μg series in children aged 0–6 months [37], and 3-dose 20 μg series in high-risk individuals including health professionals and adults with close household contact with hepatitis B carriers [43]. One study of catch-up campaigns in individuals below 15 years may contain errors because it reported loss of QALYs when a catch-up campaign was added to routine vaccination [39].

S. pneumoniae: Results on the cost-effectiveness of PCV-7 introduction were mixed. A 2 + 1 dose schedule at 4, 6, and 12 months was found to be not cost-effective, with an ICER of US$539,894 per QALY gained or US$97,034 if indirect protection was assumed [31]. The main reason for the high ICER was the high (market) vaccine price of US$127 per dose used. Yet at the same vaccine price, other studies found that a 3 + 1 schedule with routine doses at 3–5 months plus a booster dose between 12 and 15 months was cost–saving in four cities [42], and cost-effective with an ICER of US$18,888 and $6550 per QALY gained in Shenzhen [41] and Shanghai [33], respectively. Moreover, PCV-7 vaccine for children aged 0–2 years was found cost-effective and cost saving during influenza season and pandemic, respectively [35]. All four favorable studies included indirect protection from PCV-7 for the unvaccinated [33,35,41,42]. However, two favorable studies only conformed to 8 or 9 items on the CHEC-list [41,42], compared to 13 for the unfavorable study [31].

Japanese encephalitis: Studies on Japanese encephalitis vaccine indicated that vaccination was cost saving in two regions of China. Routine vaccination using the inactivated vaccine (administered as a five-dose schedule) and attenuated vaccine (administered as a two-dose schedule) in Shanghai, respectively, was reported to avert 6456 and 6556 DALYs in addition to savings of US$466,518 and US$686,498 per 100,000 neonates, with the attenuated vaccine dominating the inactivated vaccine [21]. In a separate study, the attenuated vaccine administered in a two-dose schedule was found to cost US$109 per DALY averted in Guizhou [28].

Rotavirus: Rotavirus vaccination was found to be cost-effective. The two-dose schedule was highly cost-effective at a vaccine price of US$3 to US$6 per dose, and cost-effective at US$12–24 per dose [32]. A separate study in rural settings suggested that a universal program would be cost–saving from both societal and patient perspectives [24].

HPV: HPV vaccination was found to be cost-effective in several studies. Vaccination at 15 years plus cervical cancer screening was cost-effective for rural girls compared with screening only if cost per vaccinated girl was lower than US$59 [27]. Similarly, the vaccine was cost-effective in girls aged 0–12 years assuming a cost below US$57 per vaccinated girl [36]. A multi-country comparison of HPV vaccination compared to no vaccination found a cost per DALY averted of US$626 in China when assuming a cost per vaccinated girl of US$12 [22]. However, the study assumed that no cervical cancer screening takes place in China. In fact, 5-yearly screening in rural areas has about 70% coverage [8] and once-a-lifetime screening in urban areas reaches 20% of the relevant population [46].

Other antigens: Studies suggested that childhood hepatitis A vaccination, influenza vaccination and Enterovirus 71 vaccination were cost-effective. Universal childhood hepatitis A vaccination was found to be cost-saving or cost-effective across a range of settings with different hepatitis A risk [23]. Seasonal influenza vaccination was more cost-effective in children aged 6 to 59 months compared to those aged 60 months to 14 years because it was more effective at reducing medically attended cases in the younger age group [29]. Routine Enterovirus 71 vaccination was shown to be cost-effective for children aged 6 months to 5 years old at a vaccine price of US$11 per dose (if efficacy was over 50%) or US$27 per dose (if efficacy was over 70%) [26].

4. Discussion

The number of economic evaluations of vaccination in China has increased sharply since 2010. However, there are still only a few studies for vaccines which are not in the current national immunization program but are being considered for inclusion (such as Hib vaccine [12]), or are recommended by WHO (HPV, Hib, hepatitis A, rotavirus and influenza vaccines [47–51]). Many relevant vaccine implementation scenarios have never been assessed. For example, there are no studies assessing the cost-effectiveness of HPV vaccination in urban areas, in males, or as catch-up campaigns in China [26,27].

Furthermore, we found methodological shortcomings with many of the studies. Similar findings have been reported in a review of economic evaluations in health care in China [52]. In particular, studies published in Chinese-language journals were found to be of lower quality, based on the number of criteria on the CHEC-list they conformed to. Since most health care policy makers in China do not routinely read English articles, many better quality studies may fail to reach this audience [52].

Our initial search revealed that many studies labelled cost–benefit analyses did not value the health benefits of vaccination. This may reflect a general misunderstanding that the benefits in cost–benefit analyses are cost savings rather than monetized health outcomes, a finding reported in a similar review in Korea [53]. Failure to value health benefits may result in misleading conclusions that a vaccine is not of good value if costs related to the immunization program are not outweighed by costs of disease prevented. However, the overall conclusion may still be correct if the cost–benefit analysis reports a favorable benefit–cost ratio, since inclusion of additional benefits will only make the result even more favorable.

All but one of the reviewed studies were based on static models, while only one used a dynamic transmission model. Five studies incorporated indirect (herd) protection through assuming reduced disease incidence in the unvaccinated population [31,33,35,41,42]. Both transmission dynamic models and post-vaccination surveillance have shown that vaccines such as rotavirus [54], HPV [55] and influenza [56] vaccines can result in substantial decreases in disease in unvaccinated individuals. Hence, static models are likely to underestimate the economic benefits of vaccination, and should not be used to conclude that vaccination is not cost-effective without being validated using dynamic models [57]. Although approximate methods may be used in static models to capture herd immunity, such methods tend to be relatively unreliable compared to estimates from dynamic models unless informed by robust post-vaccination observations in similar populations [57]. In addition,

some vaccines, such as PCV, may also result in detrimental indirect effects such as serotype replacement, which are difficult to capture using static models [58].

To address the aforementioned quality issues, standard guidelines may be necessary for good practice and reporting of economic evaluation of vaccines in China. Whilst guidelines for economic evaluation have been criticized by some health economists as too prescriptive [59], they would improve comparability of evaluations and might be useful in the Chinese context where the research base for health economic evaluation is still being established. Chinese guidelines for pharmacoeconomic evaluations were published in 2011 [44], but were not referred to in any of our reviewed articles. These guidelines could be adapted for economic evaluations of vaccines, with consideration of the WHO guidelines in this area [19].

In addition, some studies may have been well performed but presented poorly. Hence good reporting guidelines, such as the Consolidated Health Economic Evaluation Reporting Standards statement, might be helpful [60]. Current Chinese guidelines do not provide much detail about appropriate presentation of economic evaluations [44].

Our review demonstrates the limitations in the economic evidence on vaccines for policy makers in China. The hepatitis B vaccine was the most studied, possibly because of a high HBsAg carrier rate (9.75%) during the 1990s [61], and ample evidence showing it was cost saving. There were several studies on PCV-7. However, we found that the studies indicating that vaccination was cost-effective [33,41,42] were of poorer quality than the one suggesting vaccination was not cost-effective [31]. This suggests potential publication bias, with studies showing cost-effectiveness perhaps more likely to be published. Hence decision makers should be careful not to take the number of studies reaching the same conclusion as an indicator of strength of evidence, without examining the quality of those studies. Other vaccines were only evaluated in one or two studies, with many of the studies suffering from quality issues. Since HPV, rotavirus, Enterovirus 71 and influenza vaccines are not included in the EPI, there is a need for high quality economic evaluations to aid vaccine introduction decisions. For hepatitis (A and B), HPV and Japanese encephalitis vaccines, attention needs to be directed to the evaluation of the booster dose, catch-up campaigns and other scenarios. The China Experts Advisory Committee on Immunization Program, which advises the central government on the EPI and other immunization issues, may in future place a greater role in the use of economic evaluations as part of an evidence-based process for decision making on vaccination programs.

Our review has several limitations. Although multiple databases were searched, it is possible that some economic evaluations for vaccines were missed because they were not published in journals (e.g. government reports and conference proceedings), were published in journals that were not indexed in any of the databases we searched, or were unpublished (such as academic theses, or those with negative findings). Also, this is not intended to be a technical review. We do not address technical issues such as appropriateness of model structure and calibration methods in the reviewed studies. Despite these limitations, we have been able to provide a broad overview of the main conclusions and limitations of economic evaluations for vaccines in China.

In conclusion, there are insufficient high-quality economic evaluations of vaccination in China to inform many key vaccine introduction decisions. Local guidelines for good practice and reporting are vital in addition to institutional mechanisms and education to improve the overall quality of economic evaluations of immunization programs in China, and to facilitate evidence-based decisions about introduction of new vaccines into the national immunization schedule.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.09.081.

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