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Cost-Effectiveness of Diphtheria Pertussis Tetanus Combo Vaccination

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Cost-Effectiveness Analysis, DPT-IPV-Hib-Hb Vaccine

Abstract
Backgrounds: To explain and systematically review the modelling and reporting of cost effectiveness analysis of vaccination DPT combo. Methods : We conducted a comprehensive and systematic review of cost-effectiveness studies related to vaccination DPT Combo and government immunisation programmes in the world published from 2000 to 2021, through database search of PubMed and Science Direct. We assessed the methodological quality of the selected studies using a specific approach Consolidated Health Economic Evaluation Reporting Standards checklist (CHEERS). Results : Eight eligible studies reporting comparative cost-effectiveness comparisons of vaccination DPT combination were identified. Every year the DPT combo vaccine always develops into more combinations, from single to combination with a composition of 6 types. The increasing development of the DPT combination vaccine means the costs incurred will be higher, but it will have better effectiveness and fewer repeat doses. Conclusion : The DPT Combination vaccine is a more complete combination for higher costs but with better effectiveness and lower side effects.

INTRODUCTION

The World Health Organisation combination vaccines are instrumental in maintaining the coverage of protection against infectious diseases (Sánchez-Gómez et al., 2022). Immunization has changed medicine by lowering mortality and morbidity and drastically altering the epidemiology of infectious illnesses (Kempe et al., 2020). The Expanded Program on Immunization (EPI) for the Indonesia was created in 1991 at present consists of BCG, DPT, Polio, and Measles. The standard procedure to immunize infant against DPT is to go three times and 1 booster (Peraturan Menteri Kesehatan, 2017). However, in 2015, According to estimates from the World Health Organization (WHO), only 86% of children worldwide have got the three doses of the diphtheria-tetanus-pertussis (DTP3) vaccination, whereas 19.4 million infants are thought to have not (World Health Organization, 2017). Given WHO's concerns about differences between national estimates, administrative data reported, and WHO-UNICEF coverage estimates, the coverage mentioned above may not be entirely accurate (World Health Organization, 2015).

The increasing expenses of healthcare systems pose a significant challenge for health administrators, professionals, and policymaker (Çiftçi et al., 2024; Narin et al., 2024). Until recently, the integration of new technologies was guided primarily by assessments focusing on effectiveness and safety (Kamiya et al., 2016; Sartori et al., 2016). However, as the production of new, more costly technologies rises and formal regulatory processes are established, studies on cost-effectiveness, and budget impact analysis have become essential for informed decision-making by health care system authorities (Loze et al., 2017). Despite this need, there remains a gap in consolidated evidence specifically evaluating the economic value of increasingly complex DPT-based combination vaccines across different settings (Kim et al., 2023: Liu et al., 2023: Ma et al., 2024).

Previous economic evaluations have often focused on single vaccines or older combinations, lacking a systematic synthesis of evidence for modern multi-antigen DPT combos. Therefore, this study addresses an urgent need by providing a systematic review of cost-effectiveness models for DPT combination vaccines. The novelty of this research lies in its exclusive focus on combo formulations, its application of the standardized CHEERS checklist for quality appraisal, and its synthesis of evidence across diverse geographical and economic contexts. The primary objective is to compile and critically appraise existing cost-effectiveness evidence on DPT combination vaccinations. The findings are expected to benefit policymakers and health program managers by clarifying the economic value of these vaccines, thereby informing more efficient and effective immunization program design and resource allocation.

METHODS

Systematic literature search

1. Selection criteria

The criteria for eligibility of the studies included was to evaluate the cost effectiveness of vaccination DPT actions opposing the current state (i.e. clinical practice and existing vaccination policy) as the comparator. Articles lacking accessible full text or complete report were omitted. In cases of duplicated articles or reports, the most comprehensive work produced by the authors was chosen. After the initial check for duplicated articles, the authors screened the abstracts of the remaining articles to eliminate, letters, editorials, study protocols, commentaries, pure literature reviews, case reports, and conference proceedings, past and current clinical guidelines, meta-analyses, and recommendations.

2. Search engines and strategies

A comprehensive literature search was performed in PubMed and Web of Science to identify studies that examined the economic assessment in public clinical environments to be acknowledged in both Europe and Asia. Combined with were ‘‘cost-effectiveness” “Vaccine” “Vaccine DPT-HB-Hib” “Vaccine DPT-HB-Hib-IPV”. Research was restricted to the English language and publications dated from 2000 and 2021. The year 2000 was selected as the earliest because the DPT combo vaccine concept emerged in the early 2000s. Searching methods were taken from an earlier literature review.

3. Quality assessment

The quality of the studies included was carefully checked to ensure that all the methods were clearly recorded and explained to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist Husereau et al., (2022), which was accepted as the standard for evaluating health economics analysis reporting. The CHEERS checklist include 20 criteria that evaluate various dimensions of quality and reporting standards in economic assessment. For each study included, the quality standards were checked one by one. Each standard was marked as "yes" with a score of 1 if it was met, or "no" with a score of 0 if it wasn't. This showed whether each standard was followed. The overall quality of each study was than rated on a four-point scale, from "excellent" to "low". The ratings depended on how many of the standards were met: "excellent"for 100 %, "good" for more tha 75%, "moderate" for between 50% and 75%, and "low" for the less than 50%. Studies that were rated "low" and lacked clear information were excluded from further analysis. This way of grouping studies has been used in previous reviews of health economics studies (Geng et al., 2015; Hamberg-van Reenen et al., 2012).

A standardized form was utilized while extracting the data presented in the studies included. The main data obtained from each article included: last name of the first author, year of publication, design or type of economic evaluation, targeted disease (DPT single vaccine and DPT combo vaccine), targeted population included infants under 1 year old children between 1 and 17 years old, senior aged 65 or older, girls aged 10 to 17, and the general population, the comparator different option study perspective, year cost, price of vaccine, clinical data source, modelling approaches, sensitivity analysis performed, and cost effectiveness outcomes. The models used could be Markov models, decision trees, discrete event simulations, dynamic model or no models at all, time horizons, the discount rate, how preference were valued, and sensitivity analysis were all considered. Each health economic study compared a vaccination strategy to an alternative and was treated as a single cost effectiveness analysis. For each comparison, the ICER value was calculated in the base case, showing the cost per event prevented, cost per life year gained, cost per quality adjusted life year gained, or cost per diability adjusted life year avoided. The conclusions were based on these ICER values from the base case. All expenses and ICER results were not adjusted for the year they were valued.

RESULTS AND DISCUSSION

The process of finding literature, checking abstract screening for eligibility, and selection of original studies during the literature and hand search presented in a Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) flow diagram (Figure 1). Systematic database search identified 134 potentially relevant studies (112 PubMed and 22 Science Direct) that met the search criteria in four research databases. After the removal of duplicated (n=7) and non-original research articles (n = 91) by abstract screening, the full-text of 36 studies were assessed for eligibility. Among them, 28 were not vaccine and did not focus cost effectiveness DPT combo vaccine9. Based on bibliographic database search, eight cost-effectiveness analyses related to the DPT combo vaccination were included (Romero et al., 2021). The earliest study was published in year 2001.

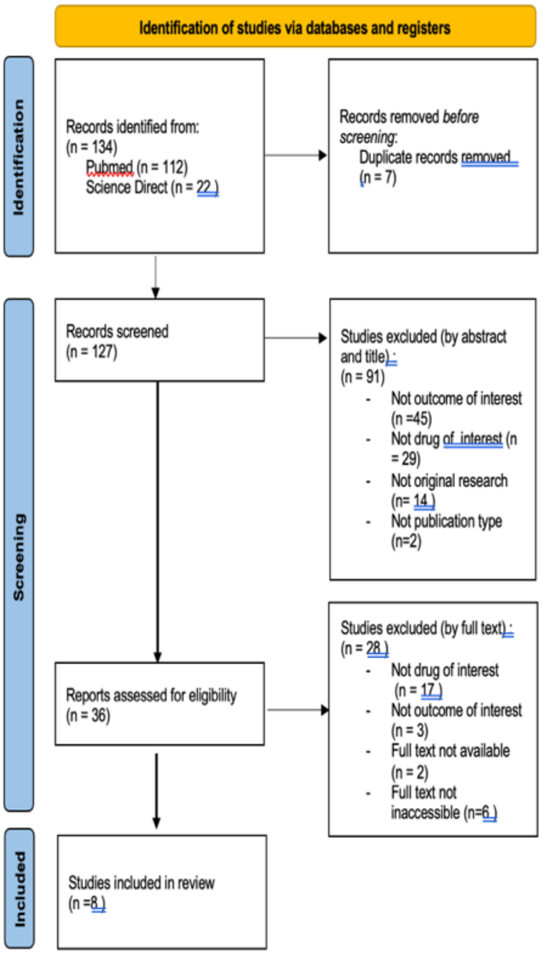

Fig 1. PRISMA Flow Diagram of the literature search and selection process

Table 1 summarizes the description and modelling characteristics of included studies. Eight eligible studies reporting twelve combination of cost-effectiveness between of Diphtheria-Pertussis-Tetanus (DPT) (combo vaccination including Diphtheria-Pertussis-Tetanus, Hepatitis B, Haemophilus influenzae, Polio (DPT-Hb-Hib-polio) (1), Diphtheria-Tetanus-Pertussis, Hepatitis B (DTP-Hb) (1), Diphtheria-Pertussis-Tetanus Haemophilus influenzae (DPT-HIB) (1), Diphtheria-Pertussis-Tetanus, Hepatitis B, Haemophilus influenzae (DPT-Hb-Hib) (1), Diphtheria-Pertussis-Tetanus (DPT) (1), Diphtheria-Tetanus (DT) and Diphtheria-Tetanus-Pertussis DTaP(1), Haemophilus influenzae, Hepatitis B (Hib-Hep B) (1), Tetanus (Tdap) (1), Diphtheria-Tetanus-Pertussis, Hepatitis B DTP-Hb(1) were identified., Six studies did not disclose the funding source and 2 studies were funded government .

Most studies established a Markov model (50%), evaluated from the societal perspective (50 %), reported an ICER of LY (50%), applied an annual discount rate of 5.0% (37,5%), performed probabilistic sensitivity analysis (62,5%), and adopted list price or acquisition price of vaccine (62,5%). Time horizon applied in modelling varied between studies.

Vaccination, comparators, target disease population and key study results are outlined in table 2. Vaccinations assessed consist of DPT-Hb-Hib-polio, DTP-Hb, DPT-HIB, DPT-Hb-Hib, DPT, DT and DTaP, Hib-Hep B, Tdap, and DTP-Hb. Hexaxime vaccine indicated safe application in infant and preterm. Romero et al., (2021) or benefit cost ratio due to the evaluation design focused on cost minimization.Vaccines were deemed either cost saving or highly cost-effective based on the findings of those included. The cost-effective or advised vaccinations can be explained as varying due to different doses and combination of the DPT Combo Vaccine, excluding the DPT single Vaccine (Griffiths et al., 2011).

Table 3 shows the reporting quality for each study, as reflected by the scores from the CHEERS checklist. According to the CHEERS checklist, six studies were of high quality 9,11-15, two were moderate quality (Romero et al., 2021; Griffiths et al., 2011; Powell-Jackson et al., 2018; Itatani et al., 2013; McGarry et al., 2013), and none were deemed low quality. In particular, two studies met the quality criteria of identifying heterogeneity, and elucidated variations in costs, outcomes or cost- effectiveness among subgroups. Four out of the eight studies, specifically numbers Griffiths et al. (2011), Powell-Jackson et al. (2018), Harris et al. (2001), did not indicate the time frame for evaluating costs and outcomes.. Three studies McGarry et al., 2013 did not disclose any potential conflicts of interest among those involved in the research. Two studies (Harris et al., 2001; McGarry et al., 2013) recognized the backing from industry funding. Three studies10,12,16 failed to detail the parameters including ranges, values, references, and probability distributions for each parameter (Chunsuttiwat et al., 2002; Powell-Jackson et al., 2018).

Table 1 Description and modelling characteristics of eight included studies

	n	(%)		n	(%)
Year of Publication			**Reporting of ICER**		
2000-2010	3	37,5	LY only	4	50
2011-2020	4	50	QALY only	1	12,5
2021-2023	1	12,5	Other or not reported	3	37,5
Funding Source			**Model Type**		
non-disclosed	6	75	Markov model	4	50
Non-industry (commissioned by government)	2	25	activity-based costing	1	12,5
Types of economic evaluation			randomised controlled trial	1	12,5
Cost-utility	1	12,5	Not Reported	2	25
Cost-Effectiveness	4	50	**Time horizon**		
Cost-Minimization	1	12,5	< 2 years	2	25
Not Reported	2	25	10 years	1	12,5
Target Population			40 years	1	12,5
Infant	3	37,5	Not Reported	4	50
Infant & Premature	1	12,5	**Years Cost**		
Children 0-36 Mo	1	12,5	2020	1	87,5
Teenagers > 10 yr.	1	12,5	Not Reported	7	12,5
Elderly > 65 yr.	1	12,5	**Annual Discount Rate**		
Not Reported	1	12,5	3%	1	12,5
Study Perspective			5%	3	37,5
Healthcare provider	1	12,5	Not Reported	4	50
Healthcare provider & societal	1	12,5	**Sensitive analysis**		
Societal	4	50	Probalistik	5	62,5
Societal & Payer	1	12,5	Deterministic	0	0

	n	(%)		n	(%)
Not Reported	1	12,5	Not Reported	3	37,5
Price Of Vaccine					
List Price	5	62,5			
Not Reported	3	37,5			

Note : a. ICER (Incremental cost-effectiveness ratios;)LY (life-year) QALY(quality-adjusted life-ye.

Table 2. Evaluated vaccinations ,the diseases they target, comparators, and the group of people in eight studies

Author	Years	Country	Vaccine	Schedule	Funding Source	Design/ Type evaluation	Comparator of intervention	Target Population	Study Perspective	Type of Model	Source of Clinical Data
Romero[9]	2021	Colombia	Hexaxim (DPT-HB-HIB-Polio)	2 /4 /6 months	Non-disclosed	Cost-Minimization	Interval Vaccine	Infant & premature	Healthcare provider & societal	activity-based costing	Local cohort data and overseas literature
Chunsuttiwat[10]	2002	Thailand	DTP-HB	2/6 months	Non-disclosed	NR	Vaccine DTP-HB Not combination	infant	Healthcare provider	NR	Local cohort data and overseas literature
Griffiths[11]	2011	Belarus	DPT-HIB	3 /4 /5/13 months	Non-industry (commissioned by government)	Cost-Utility Analysis	Cost effectiveness vaccine DPT-Hib in Belarus	infant	Societal	Markov Model	Local cohort data and overseas literature
		Uzbekistan	DPT-Hb-HIB	2/3/4 months	Non-industry (commissioned by government)	Cost-Utility Analysis	Cost effectiveness vaccine DPT-Hb-Hib in Uzbekistan	infant	Societal		Local cohort data and overseas literature
Powell-Jackson[12]	2018	India	DPT	6 /10/14 Weeks	Non -disclosed	Cost-Effectiveness Analysis	Tetanus cost	Children (0-36 Mo)	Societal	randomised controlled trial	Local cohort data and overseas literature
Itatani[13]	2013	Japan	DT dan DTaP	10 years	non-disclosed	Cost-Effectiveness Analysis	Booster Dtap	Teen ager > 10 yr.	Societal	Markov Model	Local cohort data and overseas literature
Harris[14]	2001	Australia	Hib-Hep B	1/2/4/6/12 months	non-disclosed	Cost-Effectiveness Analysis	Vaccine DTPa -Hep B	infant	Societal	Markov Model	Local cohort data and overseas literature
McGarry[15]	2013	Amerika	Tdap	> 65 years	Non-industry (commissioned by government)	Cost-Effectiveness Analysis	Vaccine TD	Elderly > 65 yo.	Societal & Payer	Markov Model	Local cohort data and overseas literature
Punjabi[16]	2006	Indonesia	DTP-HIB	NR	non-disclosed	NR	NR	NR	NR	NR	Local cohort data and overseas literature

Note : DPT = diphtheria, pertussis and tetanus; HB = hepatitis B; HiB = Haemophilus influenza type b; DT= diphtheria-tetanus; DTap = diphtheria, tetanus and pertussis; Hep B= Hepatitis B, Tdap = Tetanus, diphtheria, and pertussis; NR = No Reported

Table 3. Main result and conclusion of eigthh studies

Author	Years	Reporting of Cost-Effectiveness Outcomes				Conclusions	Type of Model	Time Horizon	Year Cost	Thre shold	Price of Vaccine	Discount Rate	Sensitivity Analysis
		ICER	LY	QALY	Other								
Romero[9]	2021	NR	NR	NR	NR	Hexavalent vaccine is cheaper than the vaccines currently used	activity-based costing	1-1,5 Years	2020	NR	List Price	5%	Probalistik
Chunsut tiwat[10]	2002	NR	NR	NR	NR	Combination DTP-Hb vaccine is better than a single vaccine	NR	2 Years	NR	NR	List Price	NR	NR
Griffiths[11]	2011	yes	yes	yes	Recurrence and death rates	Cost Effectiveness Vaccine DPT-HIB in Uzbekistan is more economical than Belarus	Markov Model	NR	NR	NR	List Price	3%	Probalistik
		yes	yes	yes				NR	NR	NR	List Price	3%	Probalistik
Powell-Jackson[12]	2018	NR	NR	yes	NR	The complete 3 dose DPT vaccine is more cost effective than the cost of getting sick with tetanus	randomised controlled trial	NR	NR	US$793	NR	NR	NR
Itatani[13]	2013	yes	yes	yes	NR	A DTaP vaccine booster at the age of 10 years can prevent intergenerational infections	Markov Model	40 years	NR	5-6 Juta JYP	NR	3%	Probalistik
Harris[14]	2001	NR	NR	NR	NR	cost effectiveness Hib-Heb vaccine is not accepted but is still considered useful	Markov Model	NR	NR	NR	List Price	NR	Probalistik
McG arry[15]	2013	yes	yes	yes	NR	Tdap vaccine is more cost-effective than the Td vaccine	Markov Model	10 years	NR	NR	List Price	3%	Probalistik
Punjabi[16]	2006	yes	yes	yes	NR	NR	NR	NR	NR	NR	NR	NR	NR

Note : ICER = incremental cost-effectiveness ratio; LY = life-years; QALY = quality-adjusted life years; DALY = disability-adjusted life-years

Table 4. Standards for reporting in eight included studies on health economic evaluation

First author Publication year	Rom ero[9] 2021	Chunsut tiwat[10] 2002	Griffi ths[11] 2011	Powell-Jackson[12] 2018	Itata ni[13] 2013	Har ris[14] 2001	McGa rry[15] 2013	Punj abi[16] 2006	Total % of Yes
1 Title	1	1	1	1	1	1	1	1	100%
2 Abstract	1	1	1	1	1	1	1	1	100%
3 Background and objectives	1	1	1	1	1	1	1	1	100%
4 Target population and subgroups	1	1	1	1	1	1	1	1	100%
5 Setting and location	1	1	1	1	1	1	1	1	100%
6 Study perspective	1	1	1	1	1	1	1	1	100%
7 Comparators	1	1	1	1	1	1	1	0	87,5%
8 Time horizon	1	1	0	0	1	0	1	0	50%
9 Discount rate	1	0	1	0	1	0	1	0	50%
10 Choice of health outcomes	0	0	1	1	1	0	1	1	62,5%
11 Measurement of effectiveness	0	0	0	1	1	1	1	0	50%
12 Measurement and valuation of preference based outcomes	0	0	0	1	1	1	1	0	50%
13 Estimating resources and costs	1	1	1	1	1	1	1	0	87,5%

First author Publication year	Romero[9] 2021	Chunsutiwat[10] 2002	Griffiths[11] 2011	Powell-Jackson[12] 2018	Itatani[13] 2013	Harris[14] 2001	McGarry[15] 2013	Punjabi[16] 2006	Total % of Yes
14 Currency, price date, and conversion	1	1	1	1	1	1	1	0	87,5%
15 Choice of model	1	1	1	1	1	1	1	0	87,5%
16 Assumptions	1	1	1	1	1	1	1	1	100%
17 Analytical methods	1	0	1	0	1	1	1	0	62,5%
18 Study parameters	1	1	1	1	1	1	1	0	87,5%
19 Incremental costs and outcomes	0	0	1	1	1	1	1	1	75%
20 Conflicts of interest	1	0	1	1	1	1	0	0	62,5%
% of yes	80%	65%	85%	85%	100%	85%	95%	45%	80%
Overall quality	Good	Moderate	Good	Good	Good	Good	Good	Moderate	

Note : A "1" means it meets the quality standards and a "0" means it doesn't fully meet the quality standards.

CHEERS- Consolidated Health Economic Evaluation Reporting Standards This systematic review compiled the cost-effective evidence and appraised the reporting quality of cost effectiveness analysis related to of DPT vaccination combination. The main results from available evidence indicated that the assessed vaccinations and immunizations, including DPT, tDaP, Hib, DPT-Hb, DPT-Hib, and DPT-Hb-Hib-Ipv, were deemed cost-saving according to health economic data presented in earlier reviews. This review's evidence did conclude on whether the ICER values were linked to government decision-making regarding the recommendation and implementation of the vaccination and immunisation programme, such as Hexavalent in Colombia's expanded immunisation program.9 As a result, along with budget-friendly evidence, other practical factors like disease prevalence, vaccine effectiveness, financial limitations, and public acceptance were also considered when the government made recommendations and funding choices (Wong et al., 2017).

Employing the CHEERS checklist enables uniform and equitable assessments of quality reporting among various studies. The overall quality of reporting was satisfactory when evaluating the quality assessment criteria defined in the CHEERS checklist, with one study being rated as excellent in overall quality. The quality of study reporting steadily progressed from 'moderate' to 'good' or 'excellent' over the years. To attain the 'excellent' quality standard, future health economic evaluations should include subgroup analysis that reflects variability among subgroups (Husereau et al., 2022).

The majority of studies used local real-world cohort data and international literature as their source of clinical data, but the clinical data source for the other eight studies (Romero et al., 2021; Griffiths et al., 2011; Powell-Jackson et al., 2018; Itatani et al., 2013; McGarry et al., 2013) was mainly founded on assumption and regional data alone. This occurred partly due to a lack of randomized controlled trial data to measure the ineffectiveness and adverse effects of vaccines, along with epidemiological cohort data to assess the natural progression and impact of disease. The World Health Organization has created an extensive online platform that provides data on the average vaccine cost for countries of varying income levels to address the demand for transparency in vaccine pricing.

Health economic outcomes were primarily modelled using static modelling techniques, such as decision trees and Markov models, in terms of methodology and modelling. In theory, the model type should be selected appropriately based on the disease population that is being targeted (World Health Organization, 2016). Systematic assessments of immunizations in low- and middle-income nations brought to light the variations in the ICER threshold applied to various studies within the same nation (Fesenfeld et al., 2013).

CONCLUSION

Few cost-effectiveness models assessing immunization were available. Based on results from included studies, all analysed DPT combo vaccines and immunization regimens were deemed to be either very cost-effective or cost-saving when compared. Subgroup analysis, dynamic modelling for simulation, and improved reporting quality, particularly in the list of study parameters, are important areas for future research assessing the cost-effectiveness of DPT combo vaccinations.

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