

Economic evaluation on pentavalent vaccine versus hexavalent vaccine in childhood immunization programs: A systematic review

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ABSTRACT

Background: The childhood immunization programs is a key pillar in the prevention of infectious diseases. The hexavalent vaccine, which combines six antigens (DTPa-HepB-IPV-Hib) in a single formulation, offers a practical alternative to pentavalent vaccines used in combination with separate hepatitis B and polio vaccines. This study aims to evaluate and compare the economic aspects of pentavalent and hexavalent vaccines across various forms of economic evaluation to support the sustainability of childhood immunization programs. **Method:** This systematic review was conducted following PRISMA 2020 guidelines using the PICO framework. Articles were retrieved from PubMed, ScienceDirect, and EBSCO databases using MeSH-based keywords. Inclusion criteria covered articles published within the last five years comparing hexavalent and pentavalent vaccines in childhood immunization programs for children aged 0–2 years. Study quality was assessed using Drummond's 10-item checklist.

Results: Six studies from Colombia, Peru, Argentina, Chile, South Korea, and China were analyzed. All studies assumed comparable clinical efficacy between vaccines and applied the cost-minimization analysis (CMA) approach. From both health system and societal perspectives, the hexavalent vaccine consistently demonstrated lower total costs per fully immunized child (FIC). Key efficiency drivers included a reduction in injections, fewer health facility visits, reduced adverse events, and improved healthcare worker efficiency. Results remained robust across sensitivity analyses conducted in all models.

Conclusion: Although more expensive per dose, the hexavalent vaccine proved more efficient and cost-effective in childhood immunization programs, especially in settings with logistical constraints. These findings support the integration of the hexavalent vaccine into national immunization policies.

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1. Introduction

Immunization is one of the most effective and cost-effective public health interventions for reducing morbidity and mortality rates in children. According to the (Kassie et al., 2021), global immunization coverage has increased significantly in recent decades, but challenges in ensuring the

sustainability of immunization programs remain, particularly in terms of cost efficiency, resource management and programs implementation logistics (World Health Organization., 2019). In this context, economic evaluation of immunization strategies is important to ensure that limited resources are used optimally.

One innovation that has been developed to improve the efficiency of immunization programs is the use of combination vaccines. Combination vaccines such as pentavalent (DTwP-HepB-Hib) and hexavalent (DTaP-HepB-IPV-Hib) have been widely used in childhood immunization programs to reduce the number of injections, visits to health facilities, and logistical burdens (Centers for Disease Control and Prevention, 2020). Pentavalent vaccines are widely used in many low- and middle-income countries as part of national immunization programs. Meanwhile, hexavalent vaccines are gaining attention due to their ability to integrate six antigens into a single injection, including the polio component that was previously administered separately (Özen et al., 2024).

In a study conducted in Malaysia, ready-to-use hexavalent vaccines were able to reduce distribution complexity and the burden on healthcare workers. The study showed that the integration of hexavalent vaccines into childhood immunization programs has the potential to generate cost savings and operational efficiency (Aljunid et al., 2022).

Although the hexavalent vaccine offers advantages in terms of convenience, schedule efficiency, and potential for increased immunization coverage, its higher cost compared to the pentavalent vaccine is an important consideration, especially for countries with limited resources (Kumar et al., 2025). Several studies have evaluated the safety and immunogenicity of the hexavalent vaccine (Sharma et al., 2024) as well as parents' perceptions of this vaccine, including their willingness to pay a higher price for the practical benefits it offers (Huang et al., 2024). On the other hand, governments and stakeholders need to evaluate the cost-effectiveness of both options to ensure the optimal use of health budgets (Guerra et al., 2024).

This situation necessitates more efficient approaches, including consideration of a transition to a more concise hexavalent vaccine that has the potential to increase coverage. Therefore, this review aims to evaluate and compare the economic aspects of using pentavalent and hexavalent vaccines in various forms of economic evaluation that can support the sustainability of childhood immunization programs.

2. Methods

2.1 Data Sources

Scientific articles were obtained from three electronic databases: PubMed, ScienceDirect, and EBSCO. These databases were selected due to their comprehensive coverage of peer-reviewed health economics and immunization literature relevant to the study objectives.

2.2 Search Strategy

Articles were searched using the following keywords: ('pentavalent vaccine' OR 'DTP-HepB-Hib') AND ('hexavalent vaccine' OR 'DTP-HepB-IPV-Hib' OR '6-in-1 vaccine') AND ('economic evaluation' OR 'cost-effectiveness' OR 'cost-benefit' OR 'cost-utility' OR 'cost-minimization') AND ('childhood immunization' OR 'immunization programs' OR 'vaccination programs') AND ('infant' OR 'child' OR 'under-five children'). The article search strategy was guided by the PICO framework as presented in Table 1.

Table 1. Framework PICO

Framework	Description
P (Population)	Children aged 0–2 years targeted by routine immunization programs
I (Intervention)	Hexavalent immunization (combination of DTP, Hib, Hepatitis B + Polio [IPV])
C (Comparison)	Pentavalent immunization (combination of DTP, Hib, Hepatitis B) + separate Polio vaccine (OPV/IPV)
O (Outcome)	Total cost of immunization programs per child (FIC), logistical efficiency, and cost-saving potential

2.3 Study Selection

Selection of articles for this systematic review used the PRISMA 2020 guidelines. After identifying articles from various databases, the first step was to remove duplicate articles using the Rayyan tool to ensure that the selected articles were truly unique and did not overlap. The title and abstract screening process was conducted independently by four reviewers (EA, F, RJ, and FA). Each article was examined by two reviewers, EA and F, based on the relevance of the title and abstract to the focus of the study, such as the early childhood population, the types of vaccines compared (hexavalent vs. pentavalent), and the presence of economic evaluations.

If there were differences in assessment between reviewers, discussions were held until an agreement was reached. The final decision was always made through deliberation, not unilaterally. After the initial screening process, the eligibility of the articles was determined based on a review of the full text. Articles that passed the abstract screening were re-analyzed by reviewers RJ and FA using the previously established inclusion and exclusion criteria. In the event of a difference of opinion, the final decision was reached through team discussion.

2.4 Inclusion and Exclusion Criteria

Articles were included if they were published within the last five years (2020–2025), written in English, and applied one or more forms of health economic evaluation, namely cost minimization, cost effectiveness, cost utility, or cost benefit. Studies were also required to include a comparative economic analysis between pentavalent and hexavalent vaccines, involve children aged 0–2 years as the target population of routine immunization programs, and be conducted in Low- and Middle-Income Countries (LMICs). Articles were excluded if they were editorials, opinion pieces, or letters to the editor. Studies that did not report any economic evaluation results were also excluded, as were articles that were not available in full text.

2.5 Data Extraction

The keywords used covered various terms representing other economic evaluation approaches, such as 'cost-effectiveness' and 'economic evaluation'. However, no articles were found that explicitly presented the results of cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-benefit analysis (CBA) that met the established eligibility criteria — specifically, a population of children aged 0–2 years, a direct comparison between pentavalent and hexavalent vaccines, and the availability of measurable economic results. Therefore, all articles analyzed in this review used the cost-minimization analysis (CMA) approach.

2.6 Quality Assessment

The quality of economic evaluation was assessed using Drummond's 10-item checklist to evaluate the internal validity and completeness of reporting in health economic evaluation studies (Drummond et al., 2008). Each reporting quality criterion was assessed with a "yes" (score 1) or "no" (score 0) answer, indicating whether the quality criterion was met or not. The overall article quality was rated using a four-point scale: "very good", "good", "moderate", or "poor".

3. Results

Based on the results of a literature search across three databases using the adjusted keywords, a total of 186 articles were obtained: PubMed (n = 86), ScienceDirect (n = 32), and EBSCO (n = 68). The process of identifying and removing duplicate articles was then carried out using Rayyan, and 14 duplicate articles were found, leaving 172 relevant articles that entered the initial screening stage.

The initial screening stage was based on titles and abstracts, and 107 articles were eliminated because they were not relevant to the topic. A total of 65 articles were further selected through full-text assessment based on inclusion and exclusion criteria. As a result, 5 articles were excluded because they did not match the population, 2 articles had an inappropriate study type, and 3 articles were excluded because they did not present accurate economic evaluation results.

A total of 6 articles met all the established criteria and were included in the narrative analysis of this systematic review.

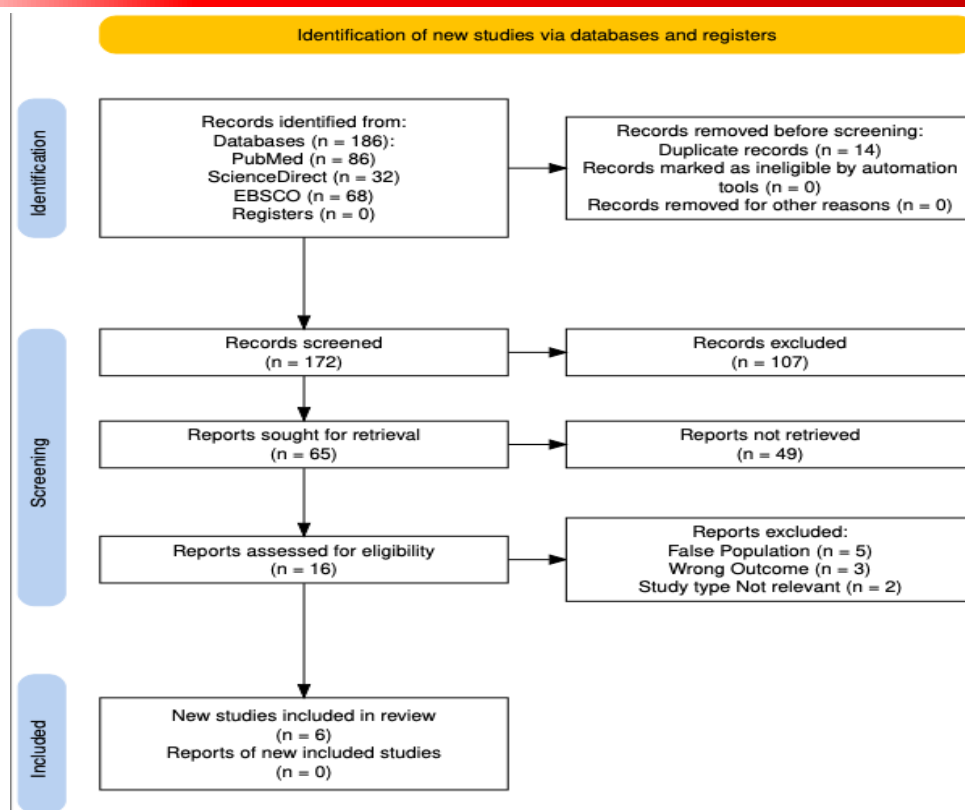


Fig. 1. PRISMA SyRFlow Diagram

3.1. Study Characteristics

All articles originate from various geographical regions, covering developing countries with diverse immunization system characteristics. Four articles were conducted in Latin America, namely Colombia (Romero et al., 2021), Peru (Seinfeld et al., 2024), Argentina (Olivera et al., 2023), and Chile (Olivera et al., 2020). The other two studies originated from East Asia, namely South Korea (Min et al., 2023) and China (Liu et al., 2023). This diversity of locations reflects the significant global attention given to the cost-effectiveness of the hexavalent vaccine and its potential for integration into national immunization policies.

The study perspective greatly determines the scope of costs analyzed. Two articles adopted a health system perspective, calculating costs from the service provider side (Romero et al., 2021; Seinfeld et al., 2024). Four other articles used a social perspective, covering direct and indirect costs that impact individuals and families. The use of a social perspective allows for a more comprehensive assessment of the economic impact of vaccination (Liu et al., 2023; Min et al., 2023; Olivera et al., 2020, 2023).

All articles compared the hexavalent vaccine with the conventional immunization regimen consisting of separate vaccine combinations. Four articles used a combination of Pentavalent + Hepatitis B (HBV) + Inactivated Poliovirus Vaccine (IPV) as a comparator. The study by Min et al. (2023) used the combination of Pentavalent + HBV, (Olivera et al., 2020) used Pentavalent alone, and (Liu et al., 2023) used Pentavalent + IPV. The variation in comparators reflects differences in basic vaccination policies in each country.

The analysis time frame was generally one year. Four studies set a one-year analytical horizon, namely (Min et al., 2023; Olivera et al., 2020, 2023; Romero et al., 2021), in line with the basic immunization schedule for infants. The study by Liu et al. (2023) used a two-year horizon to evaluate the entire immunization series. (Seinfeld et al., 2024) did not specify the time horizon used. The selection of a short horizon generally aims to describe the cost burden and benefits in the short term.

Sensitivity analyses were performed by all studies to test the robustness of the results to variations in key parameters. (Romero et al., 2021) used a two-way sensitivity analysis approach. (Seinfeld et al., 2024) applied probabilistic sensitivity analysis. (Olivera et al., 2020) used a scenario analysis

approach. (Liu et al., 2023; Min et al., 2023) used a one-way deterministic analysis approach. (Olivera et al., 2023) did not explicitly mention the sensitivity analysis approach. The variety of methods used demonstrates the rigor applied in ensuring the validity of the economic evaluation results across studies.

3.2. Characteristics of Economic Evaluation

All articles analyzed applied a cost-minimization analysis (CMA) approach, assuming that the clinical effectiveness of the hexavalent vaccine and the pentavalent + hepatitis B (HBV) ± inactivated poliovirus (IPV) combination was equivalent. This model was used to compare the cost-effectiveness between immunization regimens considered to have similar clinical benefits. The studies by (Romero et al., 2021) in Colombia and (Liu et al., 2023) in China utilized a budget impact model to estimate the fiscal impact on the health system. The study by (Seinfeld et al., 2024) in Peru adopted a Markov model to project longitudinal transitions in children's health status. The study by (Min et al., 2023) in South Korea used a decision tree model based on a micro-costing approach from a social perspective. The studies by (Olivera et al., 2023) and (Olivera et al., 2020) applied CMA conventionally, although they did not mention an explicit model in their analysis, but still presented a systematic assessment of financing and implementation scenarios.

Comprehensive research calculates direct costs, such as vaccine prices, distribution, storage, health worker training, and immunization programs implementation. The studies by (Olivera et al., 2023; Romero et al., 2021; Seinfeld et al., 2024) explicitly mention the relevant cost components in the health care system. The studies by (Liu et al., 2023; Min et al., 2023) expand the scope by adding indirect costs, including lost productive time for parents, transportation, and household burdens due to repeated visits. In addition, the study by (Olivera et al., 2023) also calculated potential savings due to a reduction in adverse events (AEs), given the fewer injections in the hexavalent vaccine.

The main measure of programs efficiency used by researchers is the total cost per child. The study by (Romero et al., 2021) recorded a cost of £55 per child for the hexavalent vaccine and £40 for the combination vaccine. The study by (Seinfeld et al., 2024) showed a cost of £100 for the hexavalent vaccine and £110 for the pentavalent + HBV + IPV regimen. The study by (Olivera et al., 2023) states a cost of £66 for the hexavalent vaccine and £70 for the combination vaccine, including savings due to fewer side effects. The study by (Min et al., 2023) reports a social cost of KRW 415,462 for the hexavalent vaccine and KRW 368,307 for the combination vaccine. The study by (Olivera et al., 2020) mentions \$68.9 for hexavalent and \$59.5 for pentavalent, still categorized as cost-effective due to logistical advantages and schedule simplification. The study by (Liu et al., 2023) noted a cost of ¥2,582.35 per child for hexavalent vaccines, which was considered more economical in the long term for China's immunization programs (Awaidy et al., 2014; Dakin et al., 2023; Drummond et al., 2015).

Most studies involved sensitivity analysis to assess the robustness of results to variations in cost and vaccine price assumptions. The studies by (Olivera et al., 2023; Romero et al., 2021) applied two-way and scenario analyses, including evaluations of AE costs and distribution. The studies by (Liu et al., 2023; Min et al., 2023) performed one-way deterministic sensitivity analyses. The study by (Seinfeld et al., 2024) used Monte Carlo simulation-based probabilistic sensitivity analysis (PSA) to assess model uncertainty comprehensively (Guerra et al., 2024; Haddaway et al., 2022; Itzler et al., 2018). Only the study by (Olivera et al., 2020) did not explicitly mention the form of sensitivity analysis.

Table 2. Results of Health Economic Evaluation

No	Author/Title/Country/ Year	Target Population	Intervention	Study Perspective	Comparators	Time Horizon	Study Type	Model	Outcome (Total Biaya)	Sensitivity Analyses	Cost- saving?
1	(Romero et al., 2021)/ Cost-Minimization and Budget Impact Analysis of a Hexavalent Vaccine (Hexaxim®) in the Colombian Expanded Program on Immunization/ Colombia	Infants <1 year	Hexavalent vaccine (Hexaxim®)	Healthcare system	Pentavalent + HBV + IPV	1 Tahun	Cost- minimizat ion & budget impact	Budget impact model	\$75 vs \$56 pada bayi cukup bulan	Two-way sensitivity analysis	Yes
2	(Seinfeld et al., 2024)/ Introduction of a hexavalent vaccine containing acellular pertussis into the national immunization program for infants in Peru: a cost- consequence analysis of vaccination coverage/ Peru	Infants <1 year	Hexavalent vaccine	Healthcare system	Pentavalent + HBV + IPV	Not specified	A cost- minimizat ion analysis	Markov Model	\$146 vs \$152 per anak	Probability sensitivity analysis	Yes
3	(Olivera et al., 2023)/ Valuing the cost of improving Chilean primary vaccination: A cost minimization analysis of a hexavalent vaccine/ Argentina	Infants <1 year	Hexavalent vaccine	societal perspective	Pentavalent + HBV + IPV	1 tahun	Cost- minimizat ion	Not specified	US\$96 vs US\$99, diimbangi pengurang an efek samping	Scenario analysis	Yes
4	(Min et al., 2023)/ Estimating the Total Societal Cost of a Hexavalent Vaccine versus a Pentavalent Vaccine with Hepatitis B in South Korea/ South Korea	Infants <1 year	Hexavalent vaccine	Societal	Pentavalent + HBV	1 tahun	a cost- minimizat ion	Decision tree	KRW 415.462 vs KRW 368.307 per bayi	One-way deterministic sensitivity analysis	Yes

No	Author/Title/Country/ Year	Target Population	Intervention	Study Perspective	Comparators	Time Horizon	Study Type	Model	Outcome (Total Biaya)	Sensitivity Analyses	Cost- saving?
5	(Olivera et al., 2020)/ Valuing the cost of improving Chilean primary vaccination: A cost minimization analysis of a hexavalent vaccine/ Chile	Infants <1 years	Hexavalent	Societal	Pentavalent	1 years	Cost- minimizat ion analysis	Not specified	US\$ 68,9. Vs US\$ 59,5 per anak	Tidak disebutkan	Yes
6	(Liu et al., 2023)/ Cost- minimization analysis of DTaP-IPV-Hib combination vaccine in China: A nationwide cross-sectional / China	Infants <2 year	Heksavalent	Societal	Pentavalent + IPV	2 years	Cost- minimizat ion	Budgetar y impact	2582.35 CNY per anak	One-way sensitivity analysis	Yes

Table 3. Article Assessment Based on Drummond's Checklist

No	Drummond item	Romero et al. (2021)	Seinfeld et al. (2022)	Olivera et al. (2023)	Min et al. (2023)	Olivera et al. (2020)	Liu et al. (2023)
1	Research question clearly defined?	1	1	1	1	1	1
2	Alternatives described comprehensively?	1	1	1	1	1	1
3	Effectiveness established (or equivalence assumed)?	1	1	1	1	1	1
4	Relevant costs and consequences identified?	1	1	1	1	1	1
5	Costs and consequences accurately measured?	1	1	1	1	1	1
6	Costs and consequences credibly valued?	1	1	1	1	1	1
7	Adjustment for time (discounting) applied?	0	1	0	1	0	1
8	Incremental analysis performed?	1	1	1	1	1	1
9	Uncertainty accounted for?	1	1	1	1	0	1
10	Discussion and policy relevance included?	1	1	1	1	1	1
Total Score		9	10	9	10	8	10
Category		Very Good	Very Good	Very Good	Very Good	Good	Very Good

All articles in this review use a cost-minimization analysis (CMA) approach based on the assumption that the clinical effectiveness of pentavalent and hexavalent vaccines is considered to be not significantly different. Therefore, CMA is an appropriate approach for assessing the economic efficiency of two immunization strategies that provide similar health benefits but differ in programs cost and operational components.

Studies conducted by (Romero et al., 2021) in Colombia and (Seinfeld et al., 2024) in Peru explicitly focused their research on evaluating the cost impact of transitioning from pentavalent to hexavalent vaccines in national immunization schemes. Neither study addressed differences in clinical effectiveness because the vaccines compared were assumed to have equivalent benefits. A similar approach was also applied by (Min et al., 2023) in South Korea and (Liu et al., 2023) in China, who evaluated the total cost per child considering the social and health system perspectives.

4. Discussion

All studies in this review used a cost-minimization analysis (CMA) approach, as this was consistent with the clinical equivalence of the vaccines being compared, so that the results focused on comparing the total costs and efficiency of implementing the immunization programs.

A comparison of the economic efficiency between two childhood immunization strategies, namely the use of a pentavalent vaccine combined with separate hepatitis B and polio vaccines, and a hexavalent vaccine that integrates all six antigens in a single formulation, shows that the hexavalent vaccine offers advantages in terms of cost efficiency and significant potential savings in the implementation of immunization programs. This efficiency is mainly achieved through a reduction in the number of doses, simplified logistics, and a lower workload for healthcare workers. Indirect cost savings, such as parents' time and productivity, are important factors supporting the economic advantages of hexavalent vaccines.

Overall, all studies show that hexavalent vaccines contribute to cost savings, both from the perspective of the health system and from a social perspective. A study conducted by (Romero et al., 2021) in Colombia indicated that the use of the Hexaxim® vaccine could reduce costs by US\$19 per child per month, mainly through a reduction in the number of injections and efficiency in vaccine distribution, which overall reduced the fiscal burden of the national immunization programs. The price of hexavalent vaccines is slightly higher than pentavalent vaccines, but savings are still achieved through increased immunization coverage, reduced side effects, and a simpler distribution and vaccination process (Huang et al., 2024; Janko et al., 2022; Kumar et al., 2025).

Cost awareness is an important element in ensuring the sustainability of immunization programs in various countries. A study conducted in South Korea by (Min et al., 2023) shows that although the hexavalent vaccine has a higher price per dose than the pentavalent and hepatitis B combination, its ready-to-use nature actually results in savings from a social perspective of US\$36 per child or around US\$9.2 million per birth cohort. These savings stem from time efficiency in visits, reduced healthcare worker requirements, and decreased logistical burdens.

A similar study conducted by in Argentina showed that switching (Olivera et al., 2023) to the hexavalent vaccine only increased total costs by US\$3.6 million from a social perspective. This increase in costs is considered reasonable because it is offset by logistical efficiencies and the potential reduction in side effects due to the simplification of the vaccine administration procedure, making hexavalent vaccines a viable economic alternative in the long term.

The use of hexavalent vaccines is not only cost-effective but also cost-saving, as it can reduce the total cost of implementing immunization programs, despite having a higher price per dose than combination vaccines administered separately (Sharma et al., 2024).

A review conducted by (Mukherjee et al., 2021) focused on vaccine safety, particularly the local and systemic reaction profiles of two types of hexavalent vaccines, specifically examining the economic efficiency of pentavalent and hexavalent vaccines in the context of childhood immunization programs. It was concluded that both hexavalent vaccines available globally demonstrate a high level of safety, with mild to moderate side effects that are generally well tolerated (Janko et al., 2022; Luangasanatip et al., 2021; Owusu et al., 2023).

In addition to these clinical aspects, hexavalent vaccines offer significant advantages in terms of cost and operational efficiency. The cost per dose of hexavalent vaccine is more expensive than pentavalent vaccine and other additional vaccines (Hepatitis B and IPV). However, when analyzed from a total programs cost perspective, hexavalent vaccines show advantages because they can reduce costs through several mechanisms, namely by reducing the number of immunization visits, simplifying vaccine distribution and storage logistics, increasing the efficiency of healthcare workers, and increasing parental compliance with the immunization schedule (Ray et al., 2023; Thompson et al., 2018; Wengler et al., 2025; Zhang et al., 2023).

5. Conclusion

This review shows that the hexavalent vaccine is more cost-effective than the combination of pentavalent + Hepatitis B + IPV vaccines, despite having a higher price per dose. Cost efficiency is achieved through a reduction in the number of injections, simplified logistics, efficient healthcare worker performance, and indirect cost savings, such as parents' time and productivity. Most studies even indicate that the hexavalent vaccine is cost-saving, particularly in the long term.

These findings recommend that the hexavalent vaccine be integrated into national immunization programs, particularly in countries with logistical and resource constraints. Procurement should also focus on the total cost of the programs, not just the unit price. The use of hexavalent is in line with the principles of efficiency and sustainability and has the potential to significantly increase immunization coverage.

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