A critical approximation to the use of cost-effectiveness evaluation for Vaccines inclusion in Immunization Programs: the case of pneumococcal vaccines in Latin America

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Dedicatory

To Sandra, Alison and Oliver. The Love in every way. An entire life together. Always felt your warm and affectionate support. I finished this thanks to you.

A mis padres, Mariela y Carlos, por quienes empredí este camino.

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Abstract

Background: Worldwide, vaccination is considered a very successful and cost-effective public health strategy to prevent a wide range of communicable diseases, especially in children. New vaccines are available but at higher costs than those originally included in the basic Expanded Program on Immunization (EPI). Latin American and the Caribbean (LAC) is a region with a great commitment with the inclusion of new vaccines, supported mainly by the Pan American Health Organization (PAHO), however, budget impact of universal immunization is still a challenge for national EPIs. The present research considered both positive and normative dimensions of decision making (DM) in health, particularly in settings with limited resources such as LAC countries, to explore the key rationalities considered to make investment decisions in public health. Pneumococcal conjugated vaccines (PCVs) were selected for the case study to approximate the way in that DM are done at national EPIs with public funds. The exploration of DM frameworks in public health, particularly in low- and middle-income countries (LMIC) settings, is very scarce in the scientific literature, but health-care system around the world are continuously choosing and financing new interventions. It is important to approach to the rationalities involved in the DM process, to evaluate the knowledge of the stakeholders about the arguments and evaluations exposed in the discussion, and to propose improvements in the DM from a democratic perspective. An advance in this sense could give to public health practitioners several tools to guarantee better decisions and more points of view to be included in the discussion, as well as identify potential pitfalls of the available methods, most of them from an utilitarian perspective, to inform the DM in public health.

Aim: To critically address how PCVs have been included in the EPIs and the role played by the economic evaluations of their introduction in low- and middle-income countries from the LAC region.

Methods: A combination of methodologies was performed to carry out the present research project: 1) A proposal of conceptual reference framework to identify the potential utility of cost-effectiveness analyses (CEAs) in a DM was discussed from our experience of its use in developing countries at the national EPIs. 2) A systematic review of literature about the PCVs' CEAs in children from LAC countries to understand how they informed the DM about their inclusion in national EPIs was carried out. We evaluated several characteristics and quality of the published CEAs as well as the recommendations of introductions generated by the authors. 3) A survey to EPI managers, participants at National Immunization Advisory Groups (NITAGs), was carried out to review the DM process for new vaccine introduction in LAC, evaluating the role and knowledge about CEAs. 4) In addition, a CEA of switch to PCV13 versus continue PCV10 in Colombian children was run as update of previous one, now including more recent evidence and new serotype distribution after the initial adoption of PCV10. 5) Finally, a cost-effectiveness re-estimation for the identified PCVs' CEAs in

LAC was performed integrating information provided in published analyses and additional data from international databases for demographic and mortality parameters, making the comparison in a competitive scenario, guaranteeing the theoretical approach, and validating the conclusions reached by the authors in the original CEA. A narrative synthesis of the findings was performed and recommendations generated according with the dialogue with the published evidence and results of diverse analyses performed.

Results: According to implemented methodologies the main findings were: 1) CEAs are valuable inputs in the negotiation process between different actors with different legitimate interests (i.e., producers of health technologies finding profits and decision makers at the health system investing public resources to reach maximize the population well-being). New vaccine introduction is a good example to approximate the use of CEA in DM, and LAC countries are the setting where the approach of inform the DM with economic evaluations is encouraged by several stakeholders: PAHO, national authorities and donors. 2) The systematic review of literature evidenced that more than a half of published PCVs' CEAs in LAC were sponsored by pharmaceutical industry with some potential bias in the results and recommendations provided. We arise concerns about quality and conflict of interest involved in the realization of CEAs to inform DM about the selection between PCV10 and PCV13, with contradictory results, for example in countries with simultaneous CEAs performed of industry and independent researchers. Nevertheless, cost-effectiveness profiles of PCVs introduction in LAC children showed that it is a good value for money investment of public funds. To inform the best economic profile for different vaccine formulation (10 vs. 13 valences) requires include unbiased parameters in the model, and discusses the normative framework such as the agreement about the willingness to pay (WTP) threshold to DM. 3) The survey to EPI managers shows that introduction of new vaccine in national EPIs from the region is a process of discussion with participation of several actors where economic rationalities had a high role in the DM, but limitations in the technical capacity was identified and many of the local key parameters to performed a CEA were reported as lacking. 4) The updated analysis of PCVs CEA in Colombian evidenced that a national immunization strategy based in Switch-to PCV13 was found to be good value for money and prevent additional burden of pneumococcal disease saving additional treatment costs, when compared with to Keep-PCV10. 5) The effort to validate the published CEAs from the original parameters and replicating the models used showed that implemented evaluations correspond in many cases to black-boxes hard to replicate and in a half of cases obtaining recommendations different to originally reported by the authors.

Conclusion: The relevance of rationalities beyond economical are highlighted in the DM ans particularly for new vaccine introduction in nationals EPIs from LAC region, but also noted the centrality that CEAs has been gained in the recent years, with different technical capacities in the countries. Interests such as pharmaceuticals should be kept away in the evaluation and discussion of PCVs CEAs, because today the industry is the main sponsor

of CEAs in the region, potentially biasing the discussion to their interests. It is necessary to strengthen the technical capacity to understand economical inputs to inform DM and advocate to include other rationalities as important in the discussion. However additional criteria to decision making must be taken into account.

Keywords: Pneumococcal Vaccines, Cost-Benefit Analysis, Decision Making, Public Policy, Resource Allocation, Latin America.

Resumen

Título en español: Aproximación crítica al uso de evaluaciones de costo-efectividad para inclusión de vacunas en los programas nacionales de inmunización: el caso de la vacunación contra neumococo en Latinoamérica.

Introducción: En todo el mundo, la vacunación se considera una estrategia de salud pública muy exitosa y rentable para prevenir una amplia gama de enfermedades transmisibles, especialmente en los niños. Las vacunas nuevas están disponibles, pero a costos más altos que aquellas incluidos originalmente en el Programa Ampliado de Inmunizaciones (PAI) básico. América Latina y el Caribe (ALC) es una región con un gran compromiso con la inclusión de nuevas vacunas, apoyada principalmente por la Organización Panamericana de la Salud (OPS), sin embargo, el impacto presupuestal de la inmunización universal sigue siendo un desafío para los PAI nacionales. La presente investigación consideró las dimensiones tanto positiva como normativa de la toma de decisiones en salud, particularmente en entornos con recursos limitados como los países de ALC, para explorar las racionalidades clave consideradas para tomar decisiones de inversión en salud pública. Las vacunas conjugadas contra neumococo (VCN) fueron seleccionadas para el estudio de caso para aproximarnos a la forma en que se realizan la toma de decisiones en los PAI nacionales financiados con fondos públicos. La exploración de los marcos de toma de decisiones en salud pública, particularmente en escenarios de países de bajos y medianos ingresos (LMIC, por sus siglas en inglés), es muy escasa en la literatura científica, pero los sistemas de atención de la salud en todo el mundo eligen y financian continuamente nuevas intervenciones. Es importante acercarse a las racionalidades involucradas en el proceso de DM, evaluar el conocimiento de los actores sobre los argumentos y valoraciones expuestos en la discusión, y proponer mejoras en la toma de decisión desde una perspectiva democrática. Un avance en este sentido podría dar a los profesionales de la salud pública varias herramientas para garantizar mejores decisiones y más puntos de vista para ser incluidos en la discusión, así como identificar posibles escollos de los métodos disponibles, la mayoría de ellos desde una perspectiva utilitaria, para informar la toma de decisiones en salud pública.

Objetivo: Abordar críticamente la forma en que se han incluido las vacunas antineumocócicas conjugadas en los PAI y el papel que han jugado las evaluaciones económicas en su introducción en países de ingresos bajos y medios de la región de ALC.

Métodos: Se realizó una combinación de metodologías para el desarrollo de la presente investigación. 1) Se discutió una propuesta de marco de referencia conceptual para identificar la utilidad potencial de los análisis de costo-efectividad (ACE) en la toma de decisiones a partir de nuestra experiencia de su uso en los PAI nacionales de países en desarrollo. 2) Se realizó una revisión sistemática de la literatura sobre los ACE de las VCN en niños de países de ALC para entender cómo informaban a la toma de decisiones sobre su inclusión en los PAI

nacionales. Evaluamos varias características y la calidad de los ACE publicados, así como las recomendaciones de introducciones generadas por los autores. 3) Se realizó una encuesta a los gerentes del PAI, participantes de los Grupos Asesores Nacionales de Inmunización (CNPI por su sigla en Colombia), para revisar el proceso de toma de decisiones para la introducción de nuevas vacunas en ALC, evaluando el rol y el conocimiento de los ACE. 4) Además, se realizó un ACE del cambio a VCN13 versus continuar con VCN10 en niños colombianos como actualización del anterior ACE, incluyendo evidencia más reciente y la nueva distribución de serotipos después de la adopción inicial de VCN10. 5) Finalmente, se realizó una reestimación de la costo-efectividad de los ACE de las VCN identificadas en ALC integrando información proporcionada en análisis publicados y datos adicionales de bases de datos internacionales para parámetros demográficos y de mortalidad, haciendo la comparación en un escenario competitivo, garantizando el enfoque teórico y validando las conclusiones alcanzadas por los autores en el ACE original. Se realizó una síntesis narrativa de los hallazgos y se generaron recomendaciones de acuerdo con el diálogo con la evidencia publicada y los resultados de los diversos análisis realizados.

Resultados: Con respecto a los enfoques metodológicos implementados se encontró que: 1) los ACE son insumos valiosos en el proceso de negociación entre diferentes actores con diferentes intereses legítimos (productores de tecnologías sanitarias que encuentran ganancias y tomadores de decisiones en el sistema de salud que invierten recursos públicos para alcanzar el máximo bienestar de la población). La introducción de nuevas vacunas es un buen ejemplo para aproximarse a comprender el uso de ACE en la toma de decisiones y los países de ALC son el escenario donde el enfoque (informar al tomador de decisiones con evaluaciones económicas) es alentado por varias partes interesadas: OPS, autoridades nacionales y donantes. 2) La revisión sistemática de la literatura evidenció que más de la mitad de los ACE de VCN publicados en ALC fueron patrocinados por la industria farmacéutica con algún sesgo potencial en los resultados y recomendaciones proporcionadas. Surgen inquietudes sobre la calidad y el conflicto de intereses involucrado en la realización de los ACE para informar la toma decisiones sobre la selección entre VCN10 y VCN13, con resultados contradictorios, por ejemplo, en países con ACE simultáneos realizados por la industria e investigadores independientes. Sin embargo, los perfiles de costo-efectividad de la introducción de VCN en niños de ALC es una inversión de fondos públicos con una buena eficiencia. Para informar el mejor perfil económico para diferentes formulaciones de vacunas (10 frente a 13 valencias) es necesario incluir parámetros imparciales en el modelo y analizar la dimensión normativa de la evaluación (valores inmersos), como la definición del umbral de disposición a pagar para la toma de decisiones. 3) La encuesta a los gerentes del PAI muestra que la introducción de nuevas vacunas en los PAI nacionales de la región es un proceso de discusión con participación de varios actores donde las racionalidades económicas jugaron un papel importante en la toma de decision, pero se identificaron limitaciones en la capacidad técnica y muchas de las autoridades informaron que faltaban parámetros clave

para realizar un ACE. 4) El análisis actualizado del ACE de las VCN en Colombia evidenció que una estrategia de inmunización nacional basada en cambiar a VCN13 resultó tener una buena relación costo-efectividad en prevenir una carga adicional de enfermedad neumocócica ahorrando costos de tratamiento adicionales, en comparación con mantener VCN10. 5) El esfuerzo por validar los ACE publicados a partir de los parámetros originales y replicando los modelos utilizados mostró que las evaluaciones implementadas corresponden en muchos casos a cajas negras difíciles de replicar y en la mitad de los casos obtienen recomendaciones diferentes a las reportadas originalmente por los autores.

Conclusión: Se destaca la relevancia de las racionalidades más allá de la económica en la toma de decisiones y particularmente para la introducción de nuevas vacunas en los EPI nacionales de la región de ALC, pero también se señala la centralidad que han ganado los CEA en los últimos años, con diferentes capacidades técnicas en los países. Intereses como los de la industria farmacéuticos deben mantenerse alejados en la evaluación y discusión de los CEA de las VCN, porque hoy en día la industria es la principal fundadora de los ACE en la región, lo que potencialmente sesga la discusión a favor de sus intereses. Es necesario fortalecer la capacidad técnica para comprender los insumos económicos para informar la toma de decisiones y abogar por incluir otras racionalidades igualmente importantes en la discusión, sin embargo, se deben tener en cuenta criterios adicionales para la toma de decisiones.

Palabras clave: Vacunas neumocócicas, Análisis de costo-efectividad, Toma de decisiones, Política Pública, Asignació de recusos, Lationamérica.

Content

Abbreviations, Acronyms and Symbols

The following acronyms are included in the present document.

Acronyms

Acronym	Meaning
AOM	Acute Otitis Media
BoD	Burden of disease
CAP	Community-acquired pneumonia
CEA	Cost-effectiveness analysis
$CHEERS$	Consolidated Health Economic Evaluation Reporting Standards
COP	Colombian Pesos (*currency*)
$DALY$	Disability Adjusted Life Year
DM	Decision Making
DSA	Deterministic Sensitivity Analysis
ED	Extended dominated
EEs	Economic Evaluations
EPI	Expanded Program on Immunization
$EUnetHTA$	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HPV	Human Papillomavirus
HTA	Health Technology Assessment
$ICER$	Incremental cost-effectiveness ratio
IPD	Invasive pneumococcal disease
LAC	Latin America and the Caribbean

Acronym	Meaning
LCU	Local currency
LMIC	Low- and Middle-Income Countries
LYG	Life Year Gained
MeSH	Medical Subheadings
MoH	Ministry of Health
NICE	National Institute for Health and Clinical Evidence
NIH	National Institute of Health
NITAG	National Immunization Technical Advisory Group
NPI	National Program on immunizations NTHi
OC	Opportunity costs
PAHO	Pan American Health Organization
PCV	Pneumococcal Conjugated Vaccine
PD	Pneumococcal disease
PPP	Purchasing power parity
PSA	Probabilistic sensitivity analysis
QALY	Quality Adjusted Life Year
Rx	X Ray
SIREVA	*Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bac*
USD	Unites States Dollars (*currency*)
WHO	World Health Organization
WTP	Willingness to pay
YLS	Years of Live Saved

Thesis details

This thesis is submitted as a requirement to obtain the Ph.D. in Public Health degree. It is structured as an article-based thesis, comprising a collection of research papers authored by the candidate as part of their doctoral research project. The following chapters present these research papers, some of which have already been published, showcasing the culmination of the candidate's academic and scientific endeavors. Below is the list of papers included in this thesis:

- Castañeda-Orjuela C., García-Molina M., De la Hoz-Restrepo F. Is There Something Else Beyond Cost-Effectiveness Analysis for Public Health Decision Making? Value Health Reg Issues. 2020 Dec;23:1-5. doi: 10.1016/j.vhri.2019.09.009. Epub 2019 Dec 24. PMID: 31881441.

  Status: Published as Journal article

- Castañeda-Orjuela C., Alvis Guzman N., De la Hoz-Restrepo F. Cost-effectiveness of Pneumococcal Conjugated Vaccines in Children in Latin America and the Caribbean: A Systematic Review.

  Status: Unpublished manuscript

- Castañeda-Orjuela C., De la Hoz-Restrepo F. Criteria for new vaccine introduction in a National Expanded Program on Immunization: A survey of Expanded Program on Immunization managers. Value Health Reg Issues. 2022; 31:142-7.

  Status: Published as Journal article

- Castañeda-Orjuela C., De la Hoz-Restrepo F. How cost effective is switching universal vaccination from PCV10 to PCV13? A case study from a developing country. Vaccine. 2018 Sep 11;36(38):5766-5773. doi: 10.1016/j.vaccine.2018.07.078. Epub 2018 Aug 4. PMID: 30087049.

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Preface: A reader's guide

Before you read this doctoral thesis 'A critical approximation to the use of cost-effectiveness evaluation for Vaccines inclusion in Immunization Programs: the case of pneumococcal vaccines in Latin America', it has been written to fulfill the graduation requirements of the Public Health doctoral program at the Universidad Nacional de Colombia, Bogotá. I was engaged in researching and writing this thesis from March 2018 to February 2023.

This doctoral thesis is a compilation of research works (published and unpublished research papers) about the critical use of cost-effectiveness analyses (CEAs) to inform decision-making (DM) in low- and middle-income countries (LMIC) from Latin America and the Caribbean (LAC) region, using the Pneumococcal Conjugated Vaccines' (PCVs) introduction in children as case study to explore different criteria considered for DM. A reflexive approximation, from the "normal science", is done to address how the use of CEAs justify the PCVs introduction funded by public resources and also shifts between available broader serotype formulations (10 and 13 valences) in LAC countries.

This research process was originated with the initial work at the Epidemiology and Public Health Evaluation Research Group from the Public Health Department at the Universidad Nacional de Colombia, where as consultants for the Colombian Ministry of Health (in partnership with the Universidad de Cartagena) we carried out several CEAs to inform the DM about the new vaccines introduction, presenting the results and participating in the discussions at the Colombian National Immunization Advisory Technical Group (NITAG). CEAs exercises were complemented with costing evaluations and budget impact analyses. All of those economic evaluations, together with some impact assessments of the introduced vaccines, received attention from the Pan American Health Organization's (PAHO) ProVac Initiative and we were identified as Center of Excellence to provide technical support to countries from the LAC region. This active participation in the discussion of the NITAGs from the region and with researchers from the top-ranked world universities and decision analysis research centers started a deep reflection about the usefulness, scope and limitations of the economic evaluations and it was the seed to plan this research project as part of my doctoral study.

I wish that this critical approximation from the normal science allows to the readers understand the way in that CEAs are involved in the DM of new vaccines introduction and particularly the case of PCVs in children form LAC and the role and knowledge about the

specific techniques by the involved actors.

Finally, I would like to thank my director, Dr. Fernando De la Hoz-Restrepo, for the excellent guidance and support during the process. I chose you as my supervisor because I knew you would provide me a lot of orientation, learning experiences and deep knowledge. I am grateful and in debt with you. I also want to thank Drs. Nelson Alvis-Guzmám from the Universidad de Cartagena and Stephen Resch from Harvard University for their contribution to this formative process.

Carlos Castañeda-Orjuela

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1. Introduction

Health systems should make decisions about the investment of scarce resources, facing innovations as likely good alternatives to the usual health care that could mean improvements in population welfare, but usually at higher costs [1]. These innovations and their social use can reinforce hierarchical and exclusionary relationships, impede the social development of certain individuals, or spread questionable social practices [2]. In the looking for the best interventions that benefit the health and well-being of populations, it is necessary to understand how decisions are made for the inclusion of new technologies to be financed by the health systems, as well as the process by which certain innovations are imposed on others [3]. Although the criteria for decision-making (DM) are not limited to the use of scientific evidence [4] and even less to carrying out cost-effectiveness analyses (CEAs), in certain scenarios, the latter are used more and more to define the interventions in Public Health covered by health systems, as has been seen with the vaccines introduction. For instance, the World Health Organization (WHO) advocates for approaches such as evidence-informed decision-making [5].

Economic evaluations (EEs) of health technologies have been incorporated in the DM process to assess their health benefits relative to the implementation net costs evaluated as the value for money of the assessed interventions [6, 7]. However, when adopting a new technology, health systems should consider also other rationalities beyond the evidence and economic criteria, such as context, public opinion, equity, feasibility of implementation, affordability, sustainability, and acceptability to stakeholders [5]. Despite this, many scenarios privilege the CEAs results as criteria for deciding whether include new technologies in benefit plans, leaving aside criteria such as financial viability or budgetary impact, in addition to other non-economic criteria, which are necessary when it comes to DM, (i.e., political decision, social agreements, cooperation interest). In addition, in most low- and middle-income countries (LMIC) there are not information regarding the value for money for commonly used interventions; besides, the economical models are initially built for high income countries with good quality information available (i.e., surveillance systems to provide parameters of the EEs). Then, how is informing the DM to identify the covered interventions in LMIC?.

New health technologies are in general more expensive and, usually but not ever, more effective that previous available ones. Their inclusion requires additional budgetary efforts by the health systems, generally funded by public resources. Prioritization about the health

problem to intervene is crucial to identify interventions to be cover. For example, in children and elderly, the burden of disease (BoD) from respiratory infections is significant, occupying the top ranks of healthy life years lost (DALYs, in the modern interpretation of burden of disease metrics) [8]. Among the causal agents of these infections is the *Streptococcus pneumoniae*, which also causes meningitis, sepsis, and acute otitis media (AOM). Despite the availability of very cost-effective population interventions for the prevention of pneumococcal disease (PD), such as adequate nutrition, breastfeeding, improved life conditions - that also reduce the burden of other relevant diseases - or adequate antibiotic treatment, in case of the occurred infection, vaccination against *S. pneumoniae* has become the most used tool for its prevention, supported by evidence about its efficacy, effectiveness, and population impact [9], with benefits that reach the unvaccinated population through the herd effects [10]. Globally, vaccination is considered a very successful public health strategy to prevent a wide range of communicable diseases, which are responsible of an important proportion of the total BoD, especially in developing world and deprived populations, affecting disproportionately to children. New vaccines are available at the market but at prices per dose or per schedule many folds higher than vaccines originally included in the basic Expanded Program on Immunization (EPI).

Latin American and the Caribbean (LAC) is a LMIC region with a great commitment with the new vaccines introduction. This has been supported by the Pan American Health Organization (PAHO) and the engagement of National Governments and funding organizations. The Revolving fund, sponsored by PAHO, is an example of better purchase strategies that guaranty the best market prices for vaccines and vaccine supplies. However, beside of better prices, budget impact of immunization in universal coverage basis is still a challenge for national EPIs. Then, initiatives like ProVac from PAHO was developed to build and strengthen capacities to use EEs to inform the DM for new vaccine introduction at national level in the LAC region [11]. It is an approach that undoubtedly includes rational elements to the DM, better than decision based on particular interest or marketing pressures, but it needs to be evaluated about the actual impact in the mastering of the theoretical foundation of the EEs by local stakeholders and it appropriation in a more robust DM framework that includes aspects additional to economical dimensions and immerse in a deliberation process to reach social agreements.

The decision to introduce the Pneumococcal Conjugated Vaccines (PCVs) into national EPIs in LAC, most of which are financed by governments and seek universal coverage, has been mainly based on results of CEAs and evidence of its population impact [12, 13]. In spite of this, we could not forget the interests involved in the vaccines' EEs, as evidenced by the best cost-effectiveness profiles reported by pharmaceutical industry funding CEAs; or the shortcomings of local information to feed the available EE models usually built in high-income settings with high quality standards in epidemiological and demographics surveillance systems. In the other hand, it is important the need of negotiation strategies by governments

to get better prices for the vaccines, for example, in a settings where there is limited evidence of interchangeability between available PCVs [14], and the availability of a local CEA could contribute in that way.

In LAC there are only few analyses about the analysis of new vaccine introduction into the EPIs, but not formal research about the DM process have been performed at the moment, according to our knowledge. For example, a review analysis about the lessons learned from PCV introduction was limited to the implementation of the vaccination, and problems associated to it, without make an exploration in how the introduction was reached in each country [15]. It was a similar approach carried out in the documentation of Rotavirus vaccine introduction process in LAC, with similar shortcoming in their findings [16]. Also was available an overview of the implementation of PAHO's ProVac Initiative and results reached, focused in the involvement of regional and international researchers and academic in the generation of capacities of evidenced-based DM, although limited to the EEs [17]. Finally, a qualitative evaluation of the process of new vaccine introduction in Bolivia, Brazil, Nicaragua, Peru, and Venezuela was performed more than ten years ago, focusing on Rotavirus vaccine and PCV. However the criteria for DM on new vaccine introduction defined by the authors to guide the analysis only included political, technical, and programmatic aspects associated with the introduction, identifying actors and some positions but not deepening in the understanding of the discussions or arguments in tension to reach the DM or evaluating the quality of available inputs [18]. In the international setting, a recent systematic review about the processes and frameworks for DM on new vaccine introduction identified how policymakers and NITAG members increasingly value the interventions based on EEs [19], but again other models of DM appear to be less relevant.

In the case of new vaccine introduction, but in general in any health technology introduction DM, both epidemiological and economical evidence could not be considered isolated from other dimension of the DM problem, and decision makers should include a diversity of criteria to decide about the financed interventions in public health plans. At the end of the day the decision of vaccine introduction is political. Then an important knowledge gap to be resolved is delimited with the research question: how have decisions been made about the inclusion of PCVs in LAC and what has been the role and limitations of cost-effectiveness studies?

It is necessary to critically address, from the normal science [20], how PCVs have been included in EPIs and the role played by the CEAs of their introduction into LMIC from the LAC region. To achieve this goal we carried-out a critical analysis of the inclusion processes of PCVs into national EPIs, proposing a reference framework for the DM where the CEA is only a particular input; reviewing the CEAs published in LAC about the PCVs to identify their scope, pitfalls and validate the published results; inquiring about the comprehension and use of CEAs by decision makers at national EPIs from LAC region; re-estimating the cost-effectiveness of the vaccine strategies in a competitive scenario with updated evidence about the differential vaccine formulations impact; and validating the original reported results and

recommendations of published PCVs' CEAs in LAC, replicating the original model and parameters implemented to calculate the incremental cost-effectiveness ratios (ICERs) in a standard way. We generated a new entire proposal to use this type of evidence when discussing the inclusion of a new technology in health benefit plans.

The present research considered both positive and normative dimensions of DM in health, particularly in settings with limited resources such as LAC countries, to explore the key rationalities considered to make investment decisions in public health. In this context, the PCVs introduction was the selected case study to approximate the way in that investment decision are done at national EPIs and the involvement of evidence (positive dimension) or the values and discussion under debate (normative dimension) in a democratic perspective.

1.1. Key Elements of the Theoretical Framework

The critical appraisal of the CEAs to inform DM for new vaccine introduction in LAC, from a perspective of the normal science [20], presented in this thesis, implemented methodologies from the Wellness Theory, Health Technology Assessment (HTA), and Classical Epidemiology. Some aspects considered to choose the methods presented in the following chapters are detailed below.

Wellness Theory and Health Technology Assessment

EEs serve as the basis for DM when budget constraints limit the implementation of all available interventions and health programs, enabling decision makers to choose the most favorable intervention among several alternatives [6]. The fundamental economic question underlying such evaluations is whether an intervention generates greater welfare than other possible uses of the available resources. It is important to note that the answer to this question may vary across different scenarios, and therefore, a single solution does not apply universally [21].

EEs refer to a set of techniques designed to assess the costs and outcomes associated with alternative resource allocations, thereby enhancing the efficiency of health service provision [21, 22]. The evaluation process encompasses both objective technical components (positive dimension) and subjective judgments (normative dimension) [23]. From the perspective of well-being theory, it is crucial to ensure optimal DM in the allocation of health resources. EE of health interventions or technologies involves comparing the resources utilized (inputs) with the products and results obtained (outcomes). This evaluation aims to equip decision makers with tools that facilitate the rationalization of resource allocation, enabling the establishment of priorities in investments [7].

The primary objective of EE is to identify, measure, value, and compare the costs and consequences associated with different alternatives [7]. This information aids decision makers

in making value-for-money judgments regarding each intervention or health program [24]. Central to this field of study are the concepts of opportunity cost and incremental change, along with the assumption of utility maximization, which posits that the value gained from an activity should compensate for the value lost. Thus, a policy is considered fair when it maximizes the sum of utilities across individuals and population groups, assuming a decreasing utility function in relation to income or consumption.

EEs are an integral part of a broader discipline known as Health Technology Assessment (HTA). According to the European Network for Health Technology Assessment (EUnetHTA), HTA is a multidisciplinary process that systematically, transparently, and robustly summarizes information on medical, social, economic, organizational, and ethical aspects related to the use of technology in healthcare. The ultimate goal of HTA is to inform the development of safe and effective health policies centered on the patient, thereby achieving the greatest impact [25]. While various definitions of HTA exist, including those emphasizing its ethical dimension [26], some authors have noted that ethics has rarely been incorporated into HTAs [27].

Critics of CEAs and the broader welfare theory have raised several concerns. One commonly discussed limitation is the reliance on assumptions in these evaluations [28]. There is a need for public policy decisions to consider the separate evaluation of costs and effectiveness components rather than solely relying on a decision rule based on their ratio, known as the Incremental Cost-Effectiveness Ratio (ICER), as this can oversimplify DM processes. Furthermore, the number of individuals who will benefit from the intervention and who will bear the costs are often not adequately taken into account [28]. However, it is important to acknowledge that EEs incorporate diverse types of information, varying in quality, and therefore require certain assumptions. Additionally, the ICER is not a single value, but rather a confidence interval can be estimated through re-sampling techniques. It is also possible to report total costs and outcomes separately, identifying the stakeholders responsible for payment [29]. Nevertheless, the use of a payment threshold lacks scientific justification, and alternative criteria are necessary to inform DM since assessments of value-for-money are inherently subjective despite the objective nature of the ICER [29].

Classical Epidemiology

The evaluation of efficacy, effectiveness, and impact of health technologies needs the application of tools from Classical Epidemiology. Classical epidemiologists are recognized for their ability to adapt methods and concepts to specific research questions [30], including the efficacy, effectiveness, and impact of different pneumococcal vaccines. Over the past 300 years, the methods and concepts of Classical Epidemiology have continuously evolved, incorporating methodological refinements, particularly in statistical techniques [30]. This approach is grounded in two fundamental epistemological pillars: population thinking and group comparison. By combining these pillars, researchers can estimate disease frequency and assess

whether its occurrence is attributable to exposure differences between groups, while controlling for confounding phenomena (mixed effects) and other biases to draw causal inferences [30]. Elements of Classical Epidemiology are central in the modeling of natural history of PD, and parameters related with direct and indirect effects of the immunization considered in the EEs of PCVs.

1.2. General objective

- To critically approach the decision-making processes for new vaccines introduction in national expanded programs on immunization, in particular the role of cost-effectiveness analyses, to propose adjustments in their estimation based on pneumococcal conjugated vaccines case study in Latin America and the Caribbean countries.

1.3. Specific objectives

- To reflect on the arguments and decision rules involved to inform the discussions about the introduction of new technologies in health benefit plans from Latin America and the Caribbean, proposing a reference framework for decision making.
- To systematically and critically review the scientific evidence about the pneumococcal conjugated vaccines' cost-effectiveness analyses in children from Latin American and the Caribbean countries to explore how they informed the decision making about their inclusion in national expanded programs on immunization.
- To critically review the decision-making processes for new vaccines introduction in Latin America's Expanded Program on Immunization and role of cost-effectiveness analyses with a survey to managers.
- To update the estimation of the cost-effectiveness of switch to PCV13 versus continue PCV10 in Colombian children after the initial introduction and including recent evidence and impacts.
- To validate the cost-effectiveness models implemented in Latin American and Caribbean countries, based on the review of parameters included, the structure of the model, results and recommendations obtained from a competitive approach.

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2. Use of cost-effectiveness for decision making in public health

Is There Something Else Beyond Cost-Effectiveness Analysis for Public Health Decision Making?

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Is There Something Else Beyond Cost-Effectiveness Analysis for Public Health Decision Making?

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ABSTRACT

Healthcare costs are a concern for the sustainability of health systems in both rich and poor countries. Achieving a balance between the aspirations of payers and the manufacturers of new technologies is a challenge for democratic societies. Evidence about the efficacy and effectiveness of a new intervention is a fundamental aspect for its inclusion, but additional information about organization, implementation, and feasibility is required. Economic evaluations, especially cost-effectiveness analyses (CEA), help inform the choice of a particular health intervention, but they are not the only input for decision making (DM). Use of CEA is relatively recent but has quickly become widespread. CEA techniques have evolved into increasingly complex and sophisticated methods intended to reflect reality closely but, at the same time, their results have become more difficult to verify and validate. In developed countries, CEA results have generated intense debates, but in developing countries, these reflections are still weak due to lack of technical capacity. Competing perspectives on CEAs exist and can heavily influence the DM process. The use of CEAs and the interpretation of their results requires critical analysis, especially when public funds are to be invested. Here, we present a perspective on the use of CEAs for DM that arises from our experience of its use in developing countries and requires the consideration of other rationalities, in addition to the economic one, for DM.

Keywords: biomedical, cost-benefit analysis, decision making, public health, technology assessment.

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Different Views of the Same Problem: How to Make Decisions

Increasing healthcare costs is a concern for health systems in both rich and poor countries. Health systems financing is in danger partly because of the availability of more expensive, but not always more effective, technologies. The need to analyze the rationality of incurring bigger expenses and to compare the costs with their potential benefits is one of the origins of health economics as a scientific discipline.[1] Although not all increases in healthcare costs can be attributed to the introduction of new technologies and larger investments in healthcare may yield significant gains in health benefits, every costly new technology should be examined carefully and critically, and cost-effectiveness analyses (CEA) provide some tools to do that.[2] Nevertheless, the question remains: do developed and developing countries handle decision making (DM) and the use of CEA in similar ways? Here we will explore how CEAs are used to inform DM in developing countries, using as an example the case of new vaccine inclusion at populational scale and based in a proposed conceptual model of DM in public health to highlight the importance of including non-economic rationalities in DM.

The increase in costs and the limited availability of resources are of equal concern for both payers and manufacturers, albeit for different reasons. Payers try to protect public money and achieve efficiency (defined by minimization of opportunity costs [OC] when achieving a result or maximizing results for a given OC, OC being the value of a resource in its most highly-valued alternative use[3]) by investing in the developments that both produce maximum health and well-being and preserve health system financial viability. On the other hand, manufacturers must cover the costs of research and development and distribute dividends to shareholders; this is only achieved when they are able to demonstrate the value for money of a new technology, and health systems managers agree to pay for it. Achieving a balance between both sides' aspirations and needs is a challenge for democratic societies where people and institutions have the desire, opportunity, and confidence to participate together, and

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is the point at which economic theories and methods support the DM.[4-6]

Often, conflicting interests are present when a CEA is used in DM. Decision makers are worried about the quality and validity of the information supporting the choice of a particular intervention, but manufacturers are more concerned about the profit to be obtained from the technology.[7] Therefore, disclosing the source of funding and potential conflicts of interest is a critical part of any CEA.[8]

Implementing a particular technology may lead to the defunding of other interventions for the same or different problem. Thus selection must ensure that all relevant options have been considered; otherwise, potentially good alternatives that are equal to or even more effective than those included (and possibly less costly) may be left out of the comparison. If this happens, it can reinforce hierarchical or exclusionary relationships, constrain the social development of certain individuals, or extend questionable social practices.[9,10]

Understanding the DM in Public Health: A Reference Conceptual Model

The analysis of DM in public health, specifically selecting new technologies among competing alternatives, is of great academic and political interest.[11] Understanding the ways in which decisions are made and why certain innovations are imposed on others[12] may help policy makers and manufacturers alike satisfy their needs. DM is not a neutral process because the legitimate interests of decision makers, manufacturers, and the users of the programs and technologies come into play. To complicate the matter further, technical criteria such as technology effectiveness and safety are not the only aspects considered in DM; values like equity, ethics, or political priorities also play an important role. These additional dimensions are more difficult to identify and assess, but they need to be included within the health technology assessment (HTA).

We are proposing Figure 1 as a synthesis of the DM framework based on the roles of involved actors. There is a central role for decision makers, but others also have leverage. Deciding how to best invest in new technologies is driven by the perceived priority of public health problems as identified by all actors; the availability of resources; and the ability of technologies to help solve those problems (as developed by manufacturers). The decision ultimately affects the general population's welfare and the resources left to intervene in other problems.

Evidence on efficacy or effectiveness plays a fundamental role when discussing the pertinence of including new technologies in a benefit plan. Nevertheless, questions about affordability (which can be understood as a synonym for budget impact and means any combination of assets below a budget constraint[3]), target population acceptability, and logistical needs during the implementation phase need to be answered during the DM. Furthermore, it should not be forgotten that generating evidence may consume resources that, otherwise, could be used for implementing the technology itself (Figure 1).[13-15] Remarkably, there is little information on how or to what extent scientific evidence is used in public health DM.[16]

The historical development of CEAs to inform DM is relatively recent but quite prolific. A search in PubMed with the terms "Cost-Benefit Analysis"[MeSH] OR "cost-effectiveness analysis" AND "Public Health"[MeSH] shows almost 47,000 studies published up until December 2018, with the first one published in 1963. The first CEA was conducted in 1973,[17] but more than 100 articles of this type have been published every year and more than 1000 since 1995. Australia was the first country to use pharmacoeconomics studies as part of its formal DM on new medicines in 1993, followed by Canada, New Zealand, Norway, Finland, Sweden, Scotland, and England.[6] In 1999, the National Institute for Health and Clinical Evidence (NICE) was created in the United Kingdom, which includes in its mandates the consideration of clinical effectiveness and cost-effectiveness in DM and is a global reference in this regard, promoting HTA.[18]

Economic Evaluations and Their Pitfalls in Public Health DM

Given the complexity of the DM, economic evaluations, and particularly CEAs, have become very important tools to provide a rationale for selecting a particular intervention when several options are available. CEAs are based on the expected utility theory, which is the basis for most evaluation techniques and measurements of utility in a scenario of uncertainty[19] and has become an innovative and vibrating field of research.[20] A CEA assesses the net cost per additional unit of health outcome; it arises from evidence-based assumptions and its results are widely accepted by health professionals, researchers, and decision makers. Several guides have helped to standardize the CEA methods, ensuring the generalization of results.[21]

Despite their acceptance, CEAs have limitations, and their widespread use has not been free of criticism; for example, some authors mention:

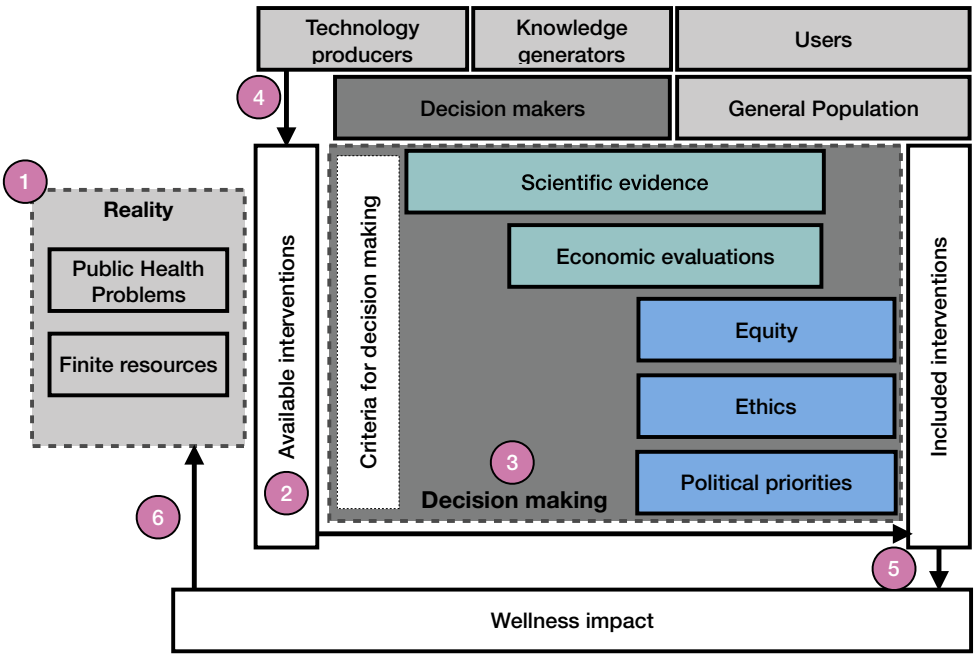
1. The low quality of available information to develop models[22];
2. The use of strong assumptions as a model's parameters[22];
3. The incremental cost-effectiveness ratio (ICER) as an oversimplified output measurement,[22] whose estimation highly depends on the costing methods used, even after good sensitivity analyses[23];
4. The comparison against a threshold, in this case willingness to pay (WTP; defined as the maximum amount that an individual is willing to pay to acquire a good/service, or the maximum amount he is willing to pay to avoid a loss[3]), which is a subjective construct with several shortcomings (ie, lack of a sound theoretical base, lack of a consensus on its value, lack of a definition strategy, and unreliability on its values, which oscillate widely in scientific literature).[24]
5. The attempt to pretend to be a normative theory for medical DM, omitting other perspectives that need to be taken into account.[25,26]

NICE has provided some solutions to these problems to minimize the waste of resources associated with adopting a very early or inadequate technology but also avoid the potential damage from restricting access to a likely beneficial technology.[27] They insist on protecting the evidence base because an early inclusion may discourage the generation of new conclusive evidence on the true effect of the particular technology. NICE recommends adoptions conditioned to generate more conclusive additional evidence to reevaluate its initial results.[27]

New Perspectives in CEAs: Implications for DM

There are technological advances in the CEA field, especially the development of increasingly complex and sophisticated methods. Models are increasingly dependent on high computing capacity because they include more variables, use

Figure 1. Reference framework for decision making in Public Health.



more complex mathematical expressions and algorithms (eg, Markov models, differential equations, discrete event simulations), and simulate synthetic populations in agent-based models. This sophistication has been introduced to help CEAs resemble reality in more detail, but it has consequences: the results are harder to understand and validate, it requires very specific technical expertise, and these tools transform in a sort of black box. Increased sophistication does not solve the most important limitations of CEAs, such as the lack of empirical evidence about WTP thresholds or what costs and results should be included.

Adding complexity to CEAs may increase the social costs of making better decisions because knowledge become less accessible to decision makers. In some cases, it may lead them to give priority to other rationalities, which are more biased than economic evaluations. These downsides are more pronounced in developing countries, where making better decisions is more pressing owing to the scarce resources, larger inequalities, and low-skilled health system's workers.

Methodologies such as Bayesian CEAs and the analysis of the value of information have been identified as potential tools to guide the adoption of new technologies and research priorities in a more coherent way.[28] Bayesian methods allow us to reach better evidence synthesis to include in DM by combining information sources, checking for consistency, and increasing transparency.[29] The expected value of perfect information (the difference between net benefits achieved if all uncertainty were resolved and the expected net benefits achieved if the decision were based on the current evidence) provides information on the additional investment needed to improve the body of evidence to make less uncertain decisions.[13]

Alternatives to CEAs for DM

There are alternatives to CEA when deciding whether a new intervention should be financed. Other economic evaluations, such as budget impact analysis, are required to assess the economic sustainability of a new technology in the middle and long term and guarantee that the new introduction will not defund other interventions.[30] Also, it is required to assess how many people will benefit, how much the total costs will be, and who will pay for it.[22]

There is also a knowledge gap in the valuation of those interventions that, although not cost-effective, represent intangible benefits to the populations in terms of strengthening community participation, empowerment, solidarity, and social cohesion. Non-economic criteria such as equity, ethics, political priorities, and vulnerable populations' needs complement the CEAs of healthcare interventions and could support the implementation of non–cost-effective alternatives, identifying as valid options certain social programs or community strengthening strategies which may provide health benefits.

The Immunization Case: Differences on How to Use CEAs for DM

The debate regarding the scope of the evidence to inform DM is not new. An interesting case is immunization, which is a highly effective public health strategy, but new vaccines are becoming more and more expensive. In developed countries, which are under pressure to include any new intervention immediately, even with scant evidence, CEA results have generated intense debates, triggering tensions between access and efficiency.[27] For example, expensive new vaccines, such as heptavalent pneumococcal conjugate (PCV7) or human papillomavirus (HPV), strain the Expanded Programs on Immunization's (EPI) budgets around the world. Less controversy has been observed in developing countries, probably as a consequence of lower technical capacity, thus showing the difference in the way evidence is considered for DM according to context.

In the developed world, PCV CEAs have not been questioned because of the efficacy of the vaccine but because there is no

agreement on how to include in economic models unexpected outcomes such as herd effect, decrease of antimicrobial resistance, and the serotype replacement.[31] For HPV, references to non-economic and normative criteria to define the vaccine inclusion were evident. In the UK the criticism focused on that, despite being the most cost-effective bivalent vaccine, the decision should have been the quadrivalent vaccine, which represented an additional effect of protection against genital warts.[32] In the United States, where the HPV vaccine is not provided by universal program, the age of vaccination of girls (11 to 12 years), and moral aspects, such as the possible consequences on the promiscuity of adolescent users, were discussed.[33]

Discussions for the same interventions in developing countries has a different focus. The center of interest is on identifying the optimal purchasing mechanisms to provide cost-effective vaccines. Another point of disagreement is about the adequacy of the WTP threshold proposed by the World Health Organization (WHO): 3 times the Gross Domestic Product (GDP) per capita per disability-adjusted life-year averted, whereas most developed countries estimate their own WTP. Relevant aspects of immunization for developing countries have been neglected in the economic discussion, such as in HPV, which has not considered that the possible negative impact on the screening programs may be based on vaginal cytology.

One of the few examples of the systematic use of CEA in DM in developing countries came from Latin America and the Caribbean. Pan American Health Organization (PAHO) ProVac initiative is aimed at strengthening the capacity of Latin American countries to conduct CEAs of new vaccines (rotavirus, PCV, and HPV) to make better decisions about the universal introduction of them in their national extended program on immunization (EPI).[34,35] The increasing use of such evaluations, although it gives technical support to DM, requires a critical analysis of how they are being used to prioritize the interventions to be financed, especially when public funds are invested.

Making Better Decisions in Public Health: Not Only CEAs

Public health requires the provision of alternatives for health promotion and disease prevention, not only the use of technologies, drugs, or devices. Furthermore, most public policies have effects on health, even those outside of the health sector.[36] Decision makers must decide on the public programs or interventions to be financed to improve the population's well-being. They need to combine fair judgment with different approaches that guarantee the best coverage decision. This process must be comprehensive and value consequences beyond the health system, including social determinants of health.[37]

Given the amount of financial resources devoted to public health programs and that interventions compete for limited resources, it is impossible to omit the economic dimension in DM. CEAs forecast the intervention's benefits for society in general, making it possible, despite its limitations, to approach the potential benefits in a more impartial way. To use CEAs more efficiently and transparently, decision makers should state, early in the process, the criteria on which the decision will be made and what the role of economic evaluation will be on it.

Decision makers should be taught what a good CEA includes: all the necessary comparisons are made, the correct models are used, all evidence included has been validated, WTP thresholds are critically evaluated, sensitivity analyzes are performed, and potential conflicts of interest are removed or, at least, declared.

Society and decision makers should also understand that decisions are not irreversible. Even evidence-based decisions can be reevaluated after their adoption. It is necessary to periodically validate the DM models and update them with the best available evidence. Updated results must be contrasted against the previously obtained results. CEA should also be used to help reassess the decisions because new technologies are constantly changing.

CEA practitioners also must know how and why to provide scientific evidence to decision makers. There are moments in the process where scientific evidence is more useful. For instance, evidence is very important when identifying the right strategies to intervene in a problem, but it is less needed when the problem is being defined and prioritized.[38] Although the problem definition should include decision makers, researchers, and the general population, it is not enough to generate evidence about the effects of certain interventions; instead all the actors should participate in the selection of the interventions to evaluate, including multiple criteria beyond the economic.

Emerging strategies should be considered. For example, for vaccines investigated at the population scale, collegiate bodies such as National Immunization Practices Committees are very valuable, acting as consultative bodies with experts that advise to decision makers, combining multiple rationalities. In certain circumstances, as happened in Colombia, they can recommend the election of non–cost-effective interventions, basing their decision on the prioritization of a particular health domain impact. This was the case with the introduction of the rotavirus vaccine, instead of other, more cost-effective alternatives, such as the hepatitis A vaccine. Ultimately, it was a political commitment, legitimately prioritizing the infant mortality reduction.

CEA is a tool for DM, but the decision is not based on economic criteria alone. It requires spaces enabled to understand the implications of technology in society, involving multiple values and belief systems, creating legitimate relationships with different entities, and considering the sociopolitical aspects of the development, diffusion, and use of technology. Other dimensions have been suggested as possibilities for improving the application of the CEA.[9] Despite the criticisms and their limitations, CEAs remain a tool that introduces a "rational" element to the assessment of available evidence. Based on a decision rule, it allows us to select an alternative to finance over its competitors. Without this economic component, DM would reflect the preference of a few stakeholders and not the potential benefit for the whole population.

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3. Review of cost-effectiveness of pneumococcal conjugate vaccines in LAC children

Cost-effectiveness of Pneumococcal Conjugated Vaccines in Children in Latin America and the Caribbean: A Systematic Review.

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Cost-effectiveness of Pneumococcal Conjugated Vaccines in Children in Latin America and the Caribbean: A Systematic Review.

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Abstract

Background: Pneumococcal Conjugated Vaccines (PCVs) are cost-effective public health interventions to prevent peneumococcal disease, however different vaccine formulations could generate heterogeneous economic profiles according to particular setting and health budgets.

Goal: To systematically and critically review the scientific evidence about the PCVs' cost-effectiveness analyses (CEAs) in children from Latin American and the Caribbean (LAC) countries to understand how they informed the decision making about their inclusion in National Programs on Immunization (NPIs).

Methods: Studies published between January 2007 and August 15th, 2022 were identified through PubMed, Scopus, LILACS, Cochrane, and NHSEED databases. Only complete economical evaluations including any PCV in LAC children population were considered. Titles and abstracts were screened, the selected articles were read in full text, and information extracted in a previous validated forms by independent reviewers. Quality of studies were scored with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to evaluate the risk of bias. Characteristics of the CEAs were evaluated and compiled. ICERs results by study were validated and re-estimated from the incremental costs (in 2020 international dollars) and incremental outcomes in a competitive setting. Result were desegregated by country, vaccine, and funding actor.

Results: A total of 25 studies were included, published between 2008 and 2021, performed a CEA evaluating a PCV alternative for LAC children. Thirteen of them (52 %) were financed by pharmaceutical industry. All studies reported PCVs as cost-effective alternative compared with not vaccination or *statu quo*. No alternatives different to PCVs were included in comparisons. Range of incremental costs varies between I$ 0 to 600, while the

incremental benefits are less than 0·05 live year gained (LYG), both values per children in birth cohort. Faults in the comparative setting were identified as well as recommendation bias when pharmaceutical industry was involved in the CEA.

Conclusion: Existing evidence shows cost-effectiveness profiles of PCVs introduction in LAC children as good value-for-money investment of public funds through the NPIs. However to inform about the best PCV between 10 or 13 valences requires to include unbiased parameters in the model, and discusses the normative framework such as the willingness to pay (WTP) threshold to decision making. Interests such as pharmaceuticals should be keep away in the evaluation and discussion, because today the industry is the main founder of CEAs in the region, potentially biasing the discussion to their interests.

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Systematic Review Registration: PROSPERO number CRD42022342730.

Keywords: Cost-Benefit Analysis, Pneumococcal Vaccines, Systematic Review, Latin America.

Research in context

Evidence before this study: We searched PubMed in December 2022 using terms 'Cost-Benefit Analysis' AND 'Pneumococcal Vaccines' AND 'Review' to identify the synthesis performed about the cost-effectiveness analyses (CEAs) of Pneumococcal Conjugated Vaccines (PCVs). We did not identify any comprehensive analysis that provided a critical approach to performed CEAs on PCVs beyond the classic systematic reviews (SRs). The individual published studies and SRs support that PCVs in children is a cost-effective strategy versus no vaccination or *statu quo*. Some mechanistic evaluations had been carried out over a set of available models highlighting the lack of transparency but not going in depth on the drivers for the final recommendations of the economic evaluations.

Added value of this study: We evaluated several characteristics and quality of published CEAs of PCVs in Latin America and the Caribbean (LAC) countries. More than a half of them were sponsored by pharmaceutical industry with some potential bias in the results and recommendations provided. We arise concerns about quality and conflict of interest involved in the realization of CEAs to inform the decision making about the selection between PCV10 and PCV13, with contradictory result for both vaccines.

Implications of all the available evidence: A democratic approach about the use of CEAs to inform decision making is highly valuable to help the society decides about how to invest public and scarce resources, especially in settings where the relative participation of

pneumococcal serotypes as 19A increases and there is availability of new serotype coverage with new PCVs. New evaluations of vaccine benefits should include as comparators wider social and less expensive interventions.

3.1. Introduction

Streptococcus pneumoniae remain as a leading cause of burden of disease worldwide, been responsible for more than 300,000 deaths in children under the age of five every year [1]. Pneumococcal Conjugated Vaccines (PCVs) have been widely documented as cost-effective interventions to prevent Pneumococcal Disease (PD), particularly in children [2]. Cost-effectiveness analyses (CEAs) are complete economical evaluations used as input to inform the decision making about the PCVs' inclusion as well as for the selection of the best vaccine formulation coverage, considering many simultaneous parameters such as local epidemiological profile, economical costs, and projected population impact including indirect herd effects in not vaccinated populations, i.e., elderly. Due to its high costs, PCV's inclusion in the National Program on Immunization (NPI) stresses the limited budgets of health systems, especially in low- and middle-income countries (LMICs) [3], and in these cases CEAs could be not enough to inform the decision making.

Available PCVs for children at the global market correspond to different formulation (10 and 13 valences) which could generate variable population and economic impacts according to the particular setting of evaluation. In these cases CEAs are valuable inputs to discuss about the pertinence to select a particular health intervention, but other rationalities are recommended to be involved in a decision process [4]. Today, the use of CEAs have been widely extended to inform the decision making, but the validity of their models, parameters, assumptions implemented, and estimations have not been subject to a critical appraisal, especially in Latin America and the Caribbean (LAC). This lack requires a systematic approximation to identify the drivers of the final course of action selection and reporting of most cost-effective alternatives, although some mechanistic evaluation had been carried out over a set of available models highlighting the lack of transparency of them [5].

In LAC many LMICs had hosted discussions to include a particular PCV informed with local CEAs, but a critical examination of this evidence is lacking to identify the reasons why there are differences on health economics profiles of available PCVs and why a PCV was included over other. The Pan American Health Organization (PAHO), for example, have been a recognized promoter to perform CEAs for new vaccine inclusion at the NPIs in countries from the region, considering PCVs in its models and providing technical support to national teams [6], but other actors both public and private had conducted their own evaluations, generating an interesting scenario with multiple and even contradictory evidence about the cost-effective of PCVs in the region. The goal of this analysis was to systematically

and critically review the scientific evidence about the PCVs CEAs obtained from different LAC countries and analyse the drivers of the differences in cost-effectiveness profiles and recommendations.

3.2. Methods

A systematic review of literature on CEAs estimation in children population from LAC countries about universal intervention based in PCVs of either 7, 10, or 13 valences, compared between them or with no vaccination, was carried out. The main identified outcome was the Incremental Cost-effectiveness Ratio (ICER) of the alternatives compared, in a competitive scenario. A subgroups analysis was performed by LAC country and other variables such as research founder. We collected the characteristics of the selected studies to assess how can they influence in CEAs results and recommendations.

Eligibility criteria

Published studies at national level with reported CEA's results of any alternative considering at least one PCV in children, in universal coverage, from LAC countries were included. Multi-country estimations were included if at least one LAC country were considered with individual results or estimation grouped to entire LAC region. Were excluded CEAs with only other pneumococcal non-conjugated vaccines (i.e., Polysaccharide Pneumococcal Vaccine - PPV23), evaluation conduced only in adults, only high-risk populations, subnational estimations or CEA for regions beyond LAC, i.e., including countries from other continents. Conference reports, unpublished studies or not peer reviewed were considered ineligibles.

Information sources

Studies were searched for the following databases such as PubMed, Scopus, LILACS, Cochrane, and the The National Health System Economic Evaluation Database (NHSEED). Research included were published between 2007 and August 15, 2022, without language restrictions. Search terms included both Medical Subheading (MeSH) and textual terms related to pneumococcal vaccines and CEAs. Control references was performed in the selected articles to identify additional references in the bibliography to be included in the present analysis.

Search strategy

The algorithms and terms included in different searches are reported in **Annex A**. Terms related to PCVs, CEAs, children, and LAC countries were included in the algorithm in different combinations.

Selection process

Two independent reviewers (CCO and FDLH) were involved to read title, abstract and, for the selected articles, the full text. Paired and independent verification of selection criteria in title and abstract, and subsequently in the full text were carried out. Disagreement in studies selection were resolved by informal consensus between both reviewers and, failing that, by a third reviewer (NAG).

Data collection process

In a previously validated Microsoft ®Excel form, data extraction were done by two independent reviewers, disagreement was solved by discussion or a third reviewer. Extracted general information of study included year of publication, countries where the CEA was performed, background and objectives, characteristics of the study population, setting and location, perspective, comparators, time horizon, discount rates, outcomes, effectiveness, costs, model, assumptions, parameters, methods to estimate ICER, and uncertainty analysis.

Data items

Information about the ICERs reported in each analysis was the main outcome identified by article and subject of analysis. Both incremental costs and health outcomes were extracted to validated the estimation of original ICERs, especially when more than two alternatives are compared to warranty a competing analysis. Valuation of pertinence of comparisons was judged in reference to the international recommendations in CEAs [7], then for multiple alternatives in the CEA, only the competitive scenario was considered (sorting the alternatives according to total net costs). For the study comparison only base cases scenarios were considered.

Study risk of bias assessment and reporting

Quality assessment was conducted for included CEAs according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist version 2013 [8]. The CHEERS checklist included 24 items. CEAs were categorized as being of good reporting quality, moderate reporting quality and low reporting quality if they reported 21 to 24 items, 15 to 20 items and less than 15 items, respectively. CHEERS checklist was applied by two independent reviewers to each included study to evaluate the quality of the economical evaluation and disagreement was solved by informal consensus between both and, failing that, by a third reviewer.

Effect measures

ICERs parameter correspond to the incremental cost per additional unit of health outcome reached in the CEAs. Benefits, according to literature included, could correspond to additional life year gained (included disability adjusted - DALY, and quality adjusted - QALY) or live saved.

For incremental costs additional adjustments were needed to reach comparability across studies. Costs reported in the original CEAs were converted to 2020 international dollars ($I) for comparison. Information about the consumer price index (CPI), exchange rates between United Stated dollars (USD) and local currency (LCU), and purchasing power parity (PPP) conversion factor were extracted from the World Bank databases [9]. Information of these parameters for Argentina and Cuba was consulted in the respective Central Banks due to lack to report to the World Bank.

Synthesis methods

Both qualitative and quantitative analyses of the selected articles exploring and summarising the structure of performed CEAs, model selection, parameters, alternatives included, ICERs estimated, and conclusion and recommendations reached were carried out to identify the reasons to select different PCVs according to the particular scenarios. Influence of founder of the analysis was also considered. A comparative analysis of ICERs in $I 2020 for countries with concurrent CEAs founded by industry and not industry was performed to identify differences in results and recommendations. Differences between groups were evaluated with Student t-test. Data was collected in Microsoft Excel, cleaning, statistical analyses and graphs were performed in R software, version 4.2.2.

3.3. Results

Study characteristics

There were 597 initial search results; following screening of titles/abstracts, 443 articles were assessed. After applying selection criteria and reading full texts and including reference control, we identified 25 documents that performed a CEA of any PCV in children population from a LAC country **(Figure 6-1)**. All included CEAs start at zero years of children cohorts modelled. The studies were published between 2008 and 2021, with no studies in 2017. Periods analyzed included 2005 to 2020 **(Table 3-1)**.

The characteristics of the included articles are detailed in **table 3-1**. The perspectives implemented by the complete economic evaluations are mainly third payer (in 16 studies, 64 %), societal (14, 56 %), government (six, 24 %), and household or private perspectives (two, 8 %). Most of the CEAs define as primary outcome, to calculate the ICER, the Disability Adjusted Life Years (DALYs) avoided (10, 40 %), following by Quality Adjusted Life Years (QALYs) gained (nine, 36 %), Life Years Gained (LYG) (five, 20 %), and only in one case avoided hospitalizations (4 %).

Figure 3-1.: PRISMA flow diagram: search results, study selection, and inclusion process.

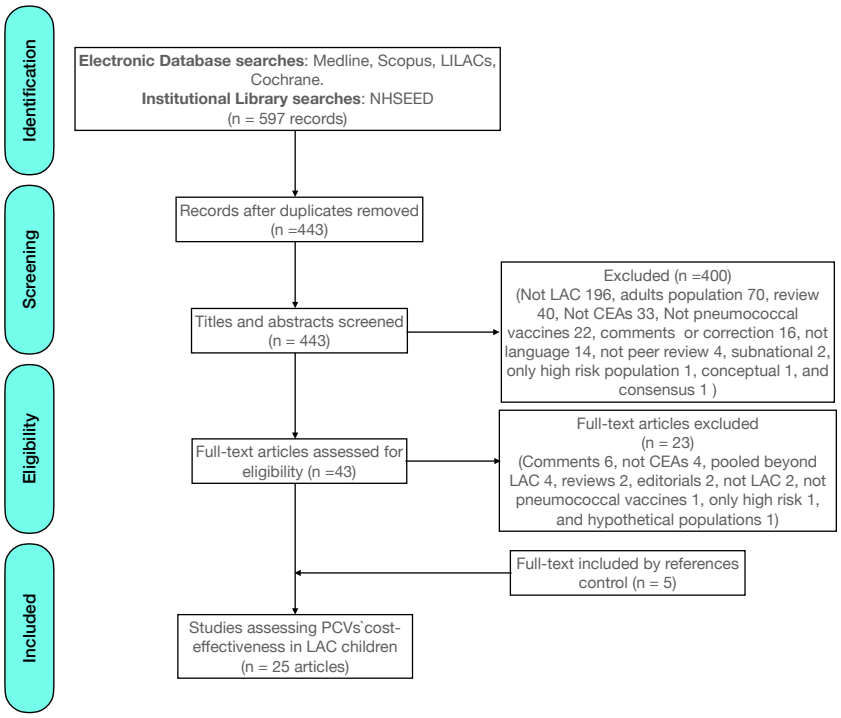


Table 3-1.: Study characteristics of selected articles and quality assessment.

Article information				Alternatives included							Perspective				Outcomes, funding, quality, and recommendation				
	Author	Ref Country	Year analysis	Number	No vax	PCV7	PCV10	PCV13	PCV7TT	High risk	3rd Pay	Societal	Gov	Other	Outcomes	CHEERS	Financing	Industry	Recommend
1	Sinha, 2008	[10] LAC	2005	2	✓	✓	✘	✘	✘	✘	✓	✓	✘	✘	DALY avoided	21·5	Sabin VI		PCV7
2	Constenla, 2008	[11] Multicountry	2005	2	✓	✓	✘	✘	✘	✘	✘	✓	✘	✘	DALY avoided	22·0	BMGF and PAHO		PCV7
3	Vespa, 2009	[12] Brazil	2006	2	✓	✓	✘	✘	✘	✘	✓	✓	✘	✘	DALY avoided	21·0	Industry	Wyeth	PCV7
4	de Souza, 2009	[13] Brazil	2008	2	✓	✓	✘	✘	✘	✘	✓	✘	✘	✘	LYG	17·5	Industry	Wyeth	PCV7
5	de Souza, 2009 (1)	[14] Brazil	2009	2	✓	✘	✘	✓	✘	✘	✓	✘	✘	✘	LYG	19·0	Industry	Wyeth	PCV13
6	Giglio, 2010	[15] Argentina	2006	2	✓	✓	✘	✘	✘	✘	✓	✓	✘	✓	LYG	22·0	Industry	Wyeth	PCV7
7	Talbird, 2010	[16] Mexico	2008	3	✓	✓	✓	✘	✘	✘	✓	✘	✘	✘	QALY gained	18·0	Industry	GSK	PCV10
8	Giachetto Larraz, 2010	[17] Uruguay	2007	2	✓	✓	✘	✘	✘	✘	✓	✓	✘	✘	QALY gained	19·5	Not stated		PCV7
9	Urueña, 2011	[18] Argentina	2010	3	✓	✘	✓	✓	✘	✘	✓	✓	✘	✘	DALY avoided	21·5	MoH and PAHO		None
10	Muciño-Ortega, 2011	[19] Mexico	2010	4	✓	✓	✓	✓	✘	✘	✓	✘	✘	✘	QALY gained	21·5	Industry	Pfizer	PCV13
11	Sartori, 2012	[20] Brazil	2004	2	✘	✘	✓	✘	✘	✓	✓	✓	✘	✘	DALY avoided	20·0	MoH		PCV10
12	Castañeda-Orjuela, 2012	[21] Colombia	2009	4	✓	✓	✓	✓	✘	✘	✘	✓	✘	✘	LYG	21·0	MoH		PCV10
13	Garcia-Marti, 2013	[22] Multicountry	2006-8	2	✓	✘	✓	✘	✘	✘	✓	✓	✘	✘	QALY gained	22·0	Industry	GSK	PCV10
14	Gomez, 2013	[23] Peru	2007	4	✓	✓	✓	✓	✘	✘	✓	✓	✘	✘	QALY gained	21·0	Industry	GSK	PCV10
15	Mezones-Holguín, 2014	[24] Peru	2011	4	✓	✓	✓	✓	✘	✘	✘	✘	✓	✘	Hx. avoided	20·0	NIH		PCV13
16	Ordoñez, 2015	[25] Colombia	2012	3	✓	✘	✓	✓	✘	✘	✓	✘	✘	✘	LYG	21·0	Industry	Pfizer	PCV13
17	Constenla, 2015	[26] Multicountry	2013	3	✓	✘	✓	✓	✘	✘	✘	✓	✘	✘	DALY avoided	22·0	PneumoADIP		None
18	Kieninger, 2015	[27] Paraguay	2010	3	✓	✘	✓	✓	✘	✘	✘	✓	✓	✓	DALY avoided	20·0	MoH and PAHO		None
19	Mezones-Holguín, 2015	[28] Peru	2012	3	✓	✘	✓	✓	✘	✘	✘	✘	✓	✘	DALY avoided	22·0	NIH		PCV13
20	Gomez, 2016	[29] Mexico	2012	3	✓	✘	✓	✓	✘	✘	✓	✓	✘	✘	QALY gained	22·5	Industry	GSK	PCV10
21	Castañeda-Orjuela, 2018	[30] Colombia	2014	3	✓	✘	✓	✓	✘	✘	✓	✘	✘	✘	DALY avoided	22·5	Academic and MoH		PCV13
22	Wasserman, 2019	[31] Mexico	2014	3	✓	✘	✓	✓	✘	✘	✘	✓	✓	✘	QALY gained	18·0	Industry	Pfizer	PCV13
23	Pugh, 2020	[32] Colombia	2016	3	✓	✘	✓	✓	✘	✘	✓	✘	✘	✘	QALY gained	20·5	Industry	Pfizer	PCV13
24	García Fariñas, 2020	[33] Cuba	2020	2	✓	✘	✘	✘	✓	✘	✘	✘	✓	✘	DALY avoided	21·0	PAHO and MoSc		PCV7-TT
25	Perdrizet, 2021	[34] Brazil	2018	3	✓	✘	✓	✓	✘	✘	✘	✘	✓	✘	QALY gained	20·0	Industry	Pfizer	PCV13

Gov: Government; Hx: Hospitalizations; Other perspective: Household or private; LYG: Life Year gained; DALY: Disability Life Adjusted Year; QALY: Quality Adjusted Life Year.

With respect to the alternatives compared in the selected CEAs, ten articles compared only two alternatives, six of them correspond to PCV7 vs. do nothing (or traditional management) [10–13, 15, 17], one compare PVC7-TT vs. do nothing [33], one PCV10 vs. do nothing [22], one PCV13 vs. do nothing [14], and one PCV10 vs. high risk population [20]. In 11 studies were included three alternatives in the CEA, ten compared do nothing, PCV10, and PCV13 [18, 25–32, 34], and one paper compared do nothing, PCV7, and PCV10 [16]). Finally, only four CEAs compared the four available alternatives (do nothing, PCV7, PCV10, and PCV13) [19, 21, 23, 24] **(Table 3-1)**.

Risk of bias in studies

Financing plays a key role in the results of the CEAs. In 13 studies (52 %) the funding were provided by the pharmaceutical industry producer of the PCVs [12–16, 19, 22, 23, 25, 29, 31, 32, 34], while the Ministry of Health (MoH) funded five of them (20 %) [18, 20, 21, 27, 30], PAHO four (16 %)[11, 18, 27, 33], and National Institute of Health (NIH) two (8 %) [24, 28]. In one case the funding statement was no provided in the manuscript [17]. Most industry CEAs included the third payer perspective (only excluded in two studies [31, 34]), and six included the societal perspective [12, 15, 22, 23, 29, 31] **(Table 3-1)**.

Results of individual studies

In **table 3-2** compiled information could be identified by key categories. Most articles included as model's states the pneumococcal meningitis, acute otitis media (AOM), or invasive disease non pneumonia non meningitis (NPNM) (more than 84 % of the studies). The inclusion of herd effect in their analysis was reported in 68 %, but most of them not included it in the base case scenario. The most common vaccine schedule in their base case scenario was 2+1 (primary doses at 2 and 4 months of age, with a booster at a year) in 60 % studies. For the final recommendation of the CEA more than half studies included thresholds recommended by WHO [35], and 68 % reported comparison in a competitive analysis.

Most studies recommended the inclusion of PCVs. The most common recommendation was the inclusion of PCV13 (nine studies, 36 %): three for Colombia [25, 30, 32], and two for Brazil [14, 34], Mexico [19, 31], and Peru [24, 28], respectively. For PCV10 and PCV7 six studies each (24 %) recommended their inclusion. In the case of PCV10 the studies are two for Mexico [16, 29], and one each for Brazil [20], Colombia [21], Peru [23], and multicountry [22], while for PCV7 there are two for Brazil [12, 13], one each for LAC pooled [10], Argentina [15], Uruguay [17], and multicountry [11]. PCV7 was only recommended in studies performed before 2010, while the Cuban PCV7-TT was recommended in one (4 %) CEA [33]. No recommendation was identified in three CEAs, despite PCV was reported as cost-effective (12 %), one each from Argentina [18], Paraguay [27], and a multicountry [26] **(Table 3-1)**.

Table 3-2.: **Synthesis of additional characteristics in the selected CEAs.**

Variable	n studies (N = 25)	Proportion
Included events		
Pneumococcal meningitis	23	92 %
AOM	23	92 %
NPNM	21	84 %
All-cause pneumonia	10	40 %
Inpatient pneumonia	9	36 %
Outpatient pneumonia	8	32 %
X-ray pneumonia	6	24 %
Pneumococcal pneumonia	3	12 %
Herd effect		
Inckuded in the model	17	68 %
Schedule dose		
2+1	15	60 %
3+1	6	24 %
3+0	4	16 %
Currency reporting		
USD	15	60 %
LCU	10	40 %
WTP threshold and competitive comparison		
Three GDP per capita	10	40 %
One GDP per capita	5	20 %
Half GDP per capita	1	4 %
Competitive CEA	17	68 %

AOM: Acute Otitis Media; NPNM: Invasive pneumococcal disease non pneumonia non meningitis; USD: United State Dollars; LCU: Local Currency; WTP: Willingness to Pay; GDP: Gross Domestic Product.

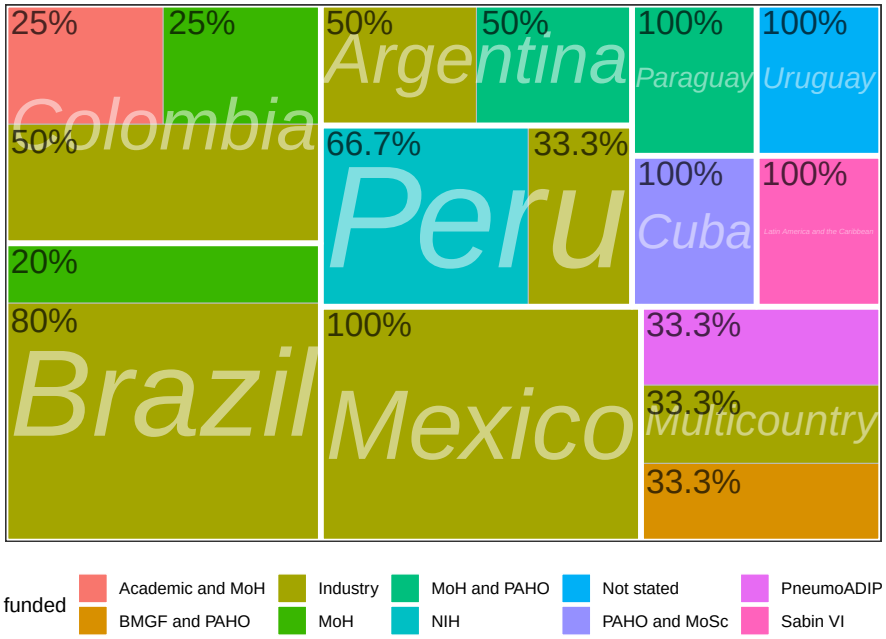
Most articles funded by the industry were from Brazil, Mexico, Colombia and Peru **(Figure 3-2)**. According with the involvement of industry funds, of 13 papers with reported industry funds the recommendations derived were six for PCV13 in 46·2 % [14, 19, 25, 31, 32, 34], four for PCV10 in 30·8 % [16, 22, 23, 29], and three for PCV7 in 23·2 % [12, 13, 15]. When studies funded by the industry were excluded the figure change to no recommendation, PCV13 or PCV7 in 25 % (four of 12), respectively, PCV10 in 16·7 % (two of 12), and PCV7-TT in one case (8·3 %) **(Table 3-1)**.

Results of syntheses

On the incremental analyses to estimate the ICERs for the comparison across PCVs and countries the most common outcome evaluated was LYG **(Figure 3-3)**. Some articles also reported as secondary health outcome the incremental cost per additional live saved **(Figure S1)** in **Annex A**. In each setting, differences in the order of alternatives is observed due to changes in position for net costs then the comparisons vary across studies. In some cases (LAC pooled, Mexico and Colombia) the PCV13 is the dominant alternative over either do nothing, PCV10, or PCV7 **(Figure 3-3)**. However most of comparisons for LYG correspond to PVC7 vs. do nothing, PCV13 vs. do nothing and PCV10 vs. do nothing. In the cases of analysis with lives saved, most of the studies correspond to comparison of PCV7 vs. do nothing **(Figure S1)**.

In general, the range of incremental costs varies between I$0 and 600 per children in

Figure 3-2.: Funding by country and number of studies.



the birth cohort. The incremental benefit estimated in most of the CEAs is less than 0·05 LYG per children in the birth cohort, independent of the vaccine coverage, but for all CEAs it is of 85 % or more **(Figure 3-3 and Table 3-3)**. Some outliers can be identified in the incremental costs estimated from a study in Mexico [19], with I$1221 incremental cost comparing do noting vs. PCV13 (in this case PCV13 is a dominant alternative). For the effectiveness, the outlier is from Brazil [11] study, with 0·25 additional LYG per children in the birth cohort in the comparisons of PCV13 vs. do noting **(Figure 3-3)**.

Figure 3-3.: Average per birth cohort population incremental and competitive analyses per life year gained in children's PCV CEAs from LAC.

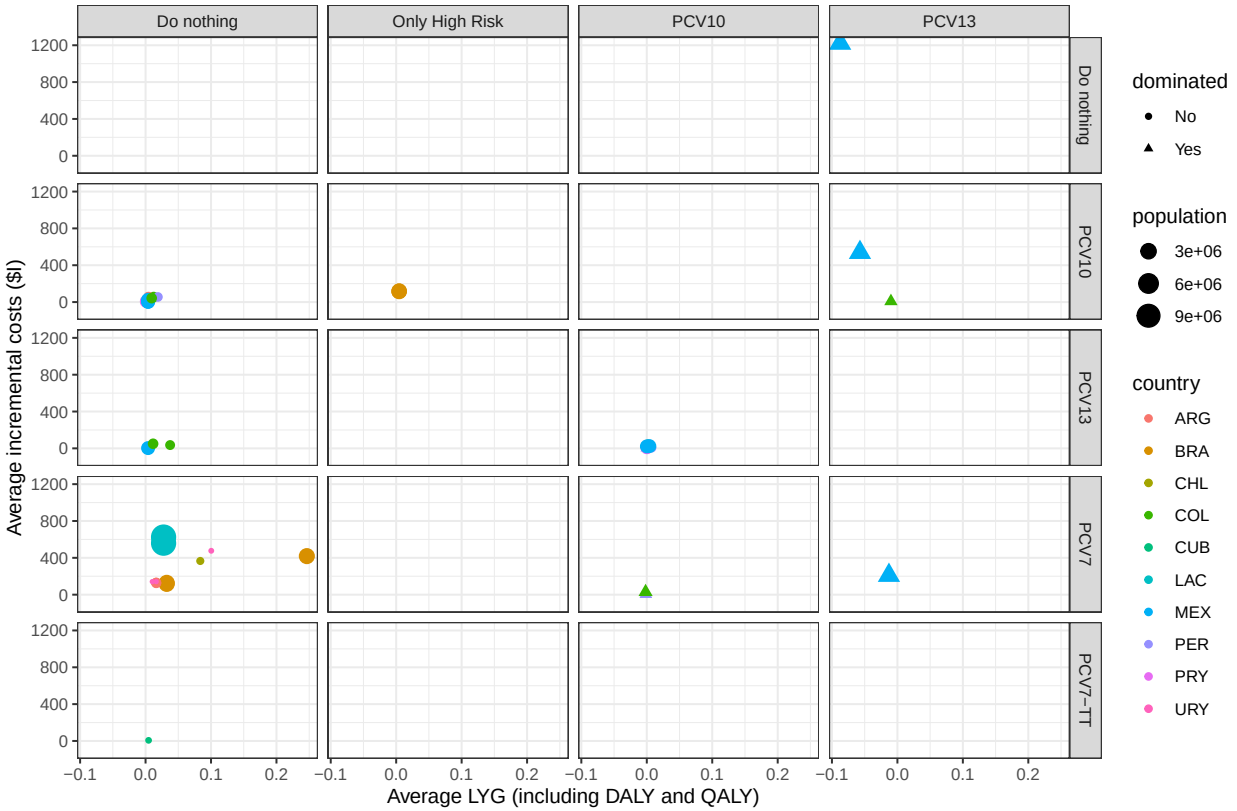


Table 3-3.: ICERs reported and re-estimated for additional year of life (including DALYs and QALYs).

	Ref	Outcome	Country	Year of analysis	Intervention	Comparator	Perspective	Currency	ICER reported	Re-estimated ICER	Population	N. co-horts	Costing year	Dominated	AI Cost (2020 I$)	AI Benefit
1	[20]	DALY	BRA	2004	PCV10	Only High Risk	Societal	LCU	22 066	26 140·07	3189 616	25	2004	No	115·88	0·00
2	[20]	DALY	BRA	2004	PCV10	Only High Risk	Third payer	LCU	24 930	26 722·12	3189 616	25	2004	No	118·46	0·00
3	[10]	DALY	LAC	2005	PCV7	Do nothing	Third payer	USD	5735	5735	11 700 500	1	2005	No	625·49	0·03
4	[10]	DALY	LAC	2005	PCV7	Do nothing	Societal	USD	5252	5124·22	11 700 500	1	2005	No	558·88	0·03
5	[11]	DALY	BRA	2005	PCV7	Do nothing	Societal	USD	664	592·44	3 471 000	1	2004	No	418·50	0·25
6	[11]	DALY	CHL	2005	PCV7	Do nothing	Societal	USD	2019	1792·44	286 000	1	2004	No	365·84	0·08
7	[11]	DALY	URY	2005	PCV7	Do nothing	Societal	USD	1546	1426·32	57 000	1	2004	No	476·57	0·10
8	[12]	DALY	BRA	2006	PCV7	Do nothing	Third payer	LCU	4516	4516	3469 937	1	2006	No	128·52	0·03
9	[12]	DALY	BRA	2006	PCV7	Do nothing	Societal	LCU	3946	4111·99	3469 937	1	2006	No	117·02	0·03
10	[15]	LYG	ARG	2006	PCV7	Do nothing	Societal	USD	5599·42	5599·42	696 451	1	2007	No	125·32	0·02
11	[15]	LYG	ARG	2006	PCV7	Do nothing	Third payer	USD	5827·76	5827·75	696 451	1	2007	No	130·43	0·02
12	[15]	LYG	ARG	2006	PCV7	Do nothing	Private	USD	5777·68	5777·68	696 451	1	2007	No	129·31	0·02
13	[23]	QALY	PER	2007	PCV10	Do nothing	Third payer	LCU	4500	4499·61	500 700	1	2009	No	29·98	0·01
14	[23]	QALY	PER	2007	PCV7	PCV10	Third payer	LCU	NA	Dominated	500 700	1	2009	Yes	3·15	−0·00
15	[23]	QALY	PER	2007	PCV13	PCV10	Third payer	LCU	NA	Dominated	500 700	1	2009	Yes	5·11	−0·00
16	[23]	LYG	PER	2007	PCV10	Do nothing	Third payer	LCU	170 391	4292·66	500 700	1	2009	No	29·98	0·01
17	[23]	LYG	PER	2007	PCV7	PCV10	Third payer	LCU	NA	Dominated	500 700	1	2009	Yes	3·15	−0·00
18	[23]	LYG	PER	2007	PCV13	PCV10	Third payer	LCU	NA	170 391·20	500 700	1	2009	No	5·11	0·00
19	[17]	LYG	URY	2007	PCV7	Do nothing	Societal	USD	7334·61	7334·61	48 000	1	2008	No	141·43	0·01
20	[17]	QALY	URY	2007	PCV7	Do nothing	Societal	USD	4665·82	4655·82	48 000	1	2008	No	141·43	0·02
21	[13]	LYG	BRA	2008	PCV7	Do nothing	Third payer	LCU	3673		3035 096	1	2008	No	−122·26	
22	[21]	LYG	COL	2009	PCV10	Do nothing	Societal	USD	1837	1837·40	858 137	1	2009	No	54·74	0·01
23	[21]	LYG	COL	2009	PCV7	PCV10	Societal	USD	Dominated	Dominated	858 137	1	2009	Yes	29·70	−0·00
24	[21]	LYG	COL	2009	PCV13	PCV10	Societal	USD	9516	9516·07	858 137	1	2009	No	38·66	0·00
25	[27]	DALY	PRY	2010	PCV10	Do nothing	Government	USD	3851	3850·91	1513 510	10	2009	No	9·25	0·00
26	[27]	DALY	PRY	2010	PCV13	PCV10	Government	USD	12 181	12 177·83	1513 510	10	2009	No	4·22	0·00
27	[27]	DALY	PRY	2010	PCV10	Do nothing	Societal	USD	1920	1920·48	1513 510	10	2009	No	4·61	0·00
28	[27]	DALY	PRY	2010	PCV13	PCV10	Societal	USD	15 696	15 692·84	1513 510	10	2009	No	5·43	0·00
29	[19]	QALY	MEX	2010	PCV7	PCV13	Third payer	USD	NA	Dominated	3793 867	1	2010	Yes	208·99	−0·01
30	[19]	QALY	MEX	2010	PCV10	PCV13	Third payer	USD	NA	Dominated	3793 867	1	2010	Yes	537·97	−0·06
31	[19]	QALY	MEX	2010	Do nothing	PCV13	Third payer	USD	NA	Dominated	3793867	1	2010	Yes	1221·03	−0·09
32	[18]	QALY	ARG	2010	PCV10	Do nothing	Third payer	USD	8973	8973·40	721 786	20	2009	No	57·04	0·00
33	[18]	QALY	ARG	2010	PCV13	PCV10	Third payer	USD	28 147	28 146·66	721 786	20	2009	No	20·54	0·00
34	[18]	QALY	ARG	2010	PCV10	Do nothing	Societal	USD	8546	8546·83	721 786	20	2009	No	54·33	0·00
35	[18]	QALY	ARG	2010	PCV13	PCV10	Societal	USD	27 614	27 613·69	721 786	20	2009	No	20·15	0·00
36	[28]	DALY	PER	2012	PCV10	Do nothing	Government	USD	1605	1604·76	599 408	20	2012	No	55·24	0·02
37	[28]	DALY	PER	2012	PCV13	PCV10	Government	USD	519	518·69	599 408	20	2012	No	6·84	0·01
38	[25]	LYG	COL	2012	PCV13	Do nothing	Third payer	USD	NA	489·25	676 835	1	2014	No	35·92	0·04
39	[25]	LYG	COL	2012	PCV10	PCV13	Third payer	USD	NA	Dominated	676 835	1	2014	Yes	8·07	−0·01
40	[29]	QALY	MEX	2012	PCV10	Do nothing	Third payer	LCU	5616	5616·53	2240 979	1	2013	No	2·93	0·00
41	[29]	QALY	MEX	2012	PCV13	PCV10	Third payer	LCU	NA	47 214·36	2240 979	1	2013	No	24·59	0·00

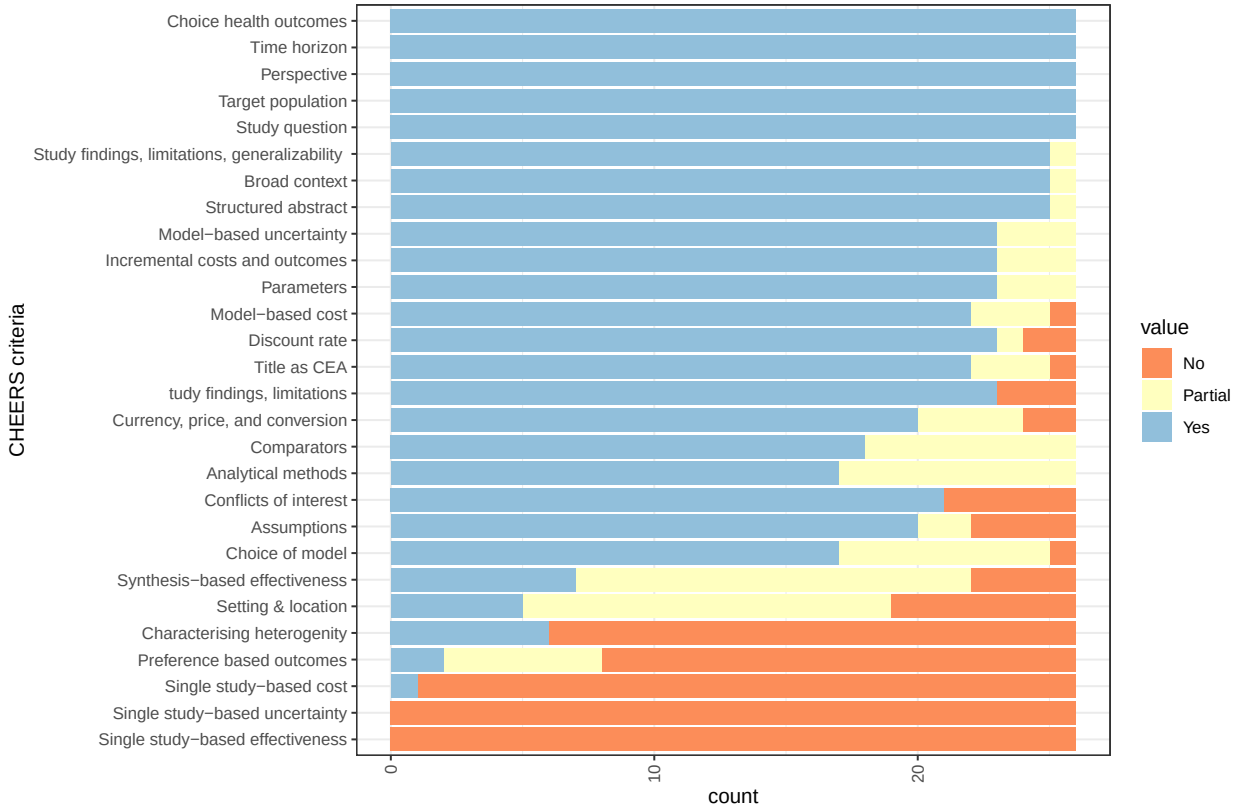
42	[29]	LYG	MEX	2012	PCV10	Do nothing	Third payer	LCU	5556	5555·63	2240 979	1	2013	No	2·93	0·00
43	[29]	LYG	MEX	2012	PCV13	PCV10	Third payer	LCU	887 156	887 992·37	2240 979	1	2013	No	21·66	0·00
44	[30]	LYG	COL	2014	PCV10	Do nothing	Third payer	USD	Extd dominated	2318·99	870 130	1	2014	No	42·54	0·01
45	[30]	LYG	COL	2014	PCV13	Do nothing	Third payer	USD	2217	2217·33	870 130	1	2014	No	49·93	0·01
46	[33]	DALY	CUB	2020	PCV7-TT	Do nothing	Government	LCU	374	374·15	107 459	10	2016	No	6·82	0·00

DALY: Disability adjusted life year; LYG: Life year gained; QALY: Quality adjusted life year; AI Average incremental (for cost and results); NA: Not available/Not reported; Extd: Extended. Do nothing could correspond, most of the cases, to traditional management or business as usual

Reporting biases and certainty of evidence

Of 24 points as maximum possible score in 2013 CHEERS checklist, the average in the included CEAs was 20·7 (SD. 1·4) **(Table 3-1)**, but nine reported 20 or less items of the checklist [13, 14, 16, 17, 27, 31, 34]. Differences not statistically significant, with Student's t-test, were found according with the source of funding (CHEERS score in industry funds 20·3 SD 1·7, while for not industry were 21·1, SD 1·0; p value = 0·17). The CHEERS' items reported by all included studies were the study question, target population, perspective, time horizon, and choice of health outcomes. While none study reported single study measurement effectiveness or single study characterizing uncertainty. Other less reported criteria in LAC PCVs' CEAs were single study cost estimation, preference based outcomes, heterogeneity characterization, setting and location, and synthesis-based effectiveness **(Figure 3-4)**. The rest of items are correctly reported in between 80-98 % of the studies. Only three studies report confidence intervals for ICER estimated [21, 30, 33].

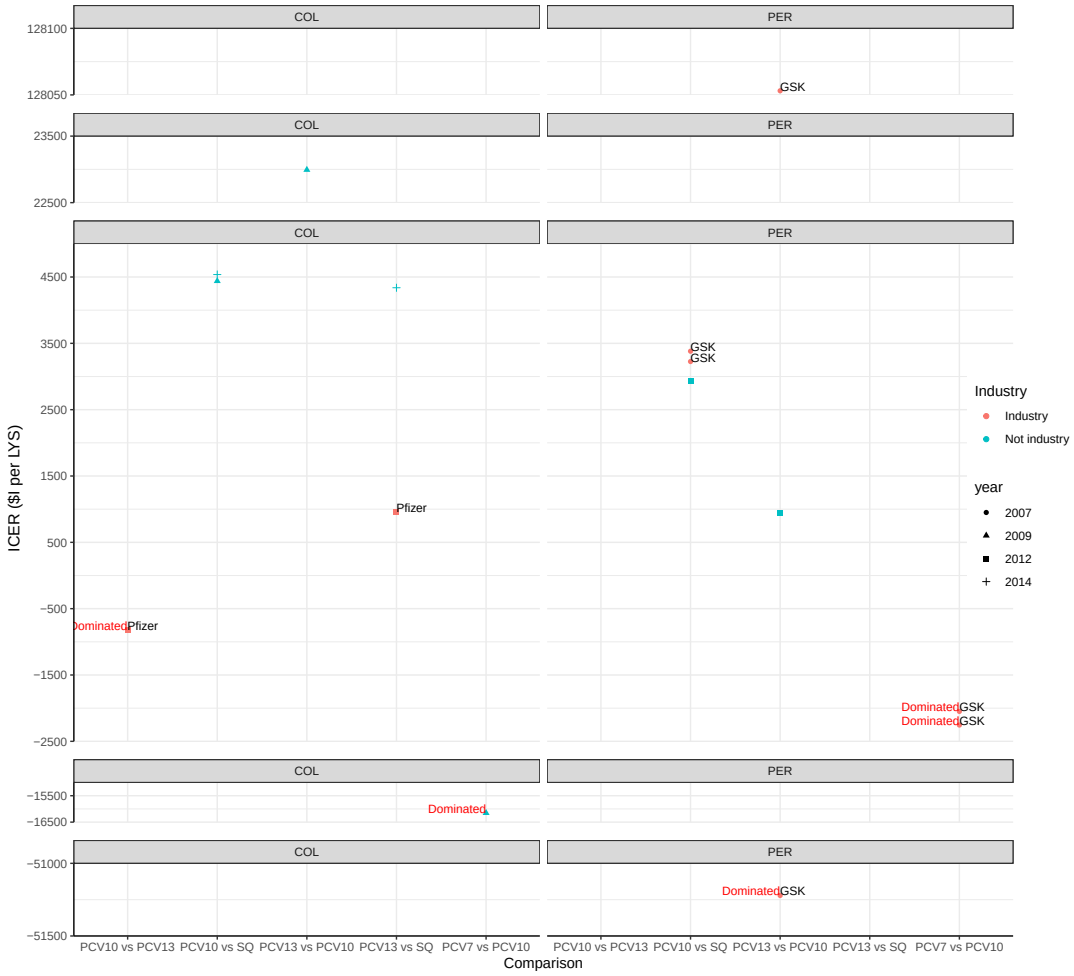
Figure 3-4.: Number and distribution of studies meeting individual items of CHEERS checklist.



Colombia and Peru were the countries with simultaneous CEAs from industry and independent founders. Cost-effectiveness results were highly depend of founder's interests **(Figure 3-5)**, while the perspective was not determinant in the ICERs estimated according

to incremental costs and health outcomes in LYS, DALYs, or QALYs, i.e., societal perspective are traduced in lower ICER or better cost-effectiveness profile.

Figure 3-5.: ICERs (in I$ 2020 per LYS, DALY or QALY) for comparison across CEAs from Pharmaceutical industry and other founders in Colombia and Peru.



In Colombia, when not pharmaceutical industry was involved the ICER per YLS was around $I 4500 for PCV10 [21, 30] or PCV13 [30] vs. do nothing. The only comparison for PCV13 vs. PCV10 reported an ICER of $I 23 000 [21]. For the study funded by PCV13 industry in Colombia, the PCV10 were reported as dominated, while PCV13 vs. do nothing reported a low ICER as $I 1000 per LYS in the same study [25]. In Peru, independent CEAs reported an ICER around $I 3000 for PCV10 vs. do nothing [28], similar to a study of PCV10 producer [23]. For the PCV13 vs. PCV10 comparison, the ICER was around $I 1000 for independent CEA [28], but PCV10 producer reported PCV13 as dominated or very high

ICER, more than $I 128 000 per LYG [23] **(Figure 3-5)**. In both countries the PCV7 was dominated against PCV10 independently of the founder [21, 23].

3.4. Discussion

This review evaluates several characteristics and quality of published cost-effectiveness analyses (CEAs) of Pneumococcal Conjugated Vaccines (PCVs) in LAC countries. A group of studies that potentially provided evidence base for decision makers at the National Programs on Immunization (NPIs) of the region. Our analysis evidences a prolific production of CEAs on PCVs in children from LAC countries, with more than a half of them financed by pharmaceutical industry with some potential bias in the relative advantage between vaccines. All published studies concluded that PCV inclusion at universal coverage in children is a cost-effective strategy versus no vaccination or *statu quo*, despite the significant budget impact on the NPIs. However, there are concerns about CEAs quality and conflict of interest involved in the generation of this kind of positive evidence to inform the decision making about the selection between PCV10 and PCV13.

A wide heterogeneity in the PCVs' effectiveness input data were identify in the selected CEAs, possibly associated with the uncertainty about the relative advantage of PCV10 or PCV13 in each study. When the industry sponsored a CEA is more likely to generate a recommendation for PCV10 or PCV13 inclusion. In general, CEAs that included effectiveness against non-typeable *Haemophilus influenzae* for PCV10 (particularly in AOM) or some cross protection of this vaccine against 19A serotype produce a better cost-effective profile for PCV10. While more costs or benefits estimated for avoided pneumonia case or consider only limited effectiveness of vaccine to serotype included in the vaccines favor PCV13. To overcome the discussion about the actual effectiveness of different PCV, some authors advocate for use of real world data about vaccines effectiveness [36], however these information have not been generated yet for LAC countries.

Evaluating the quality criteria of PCV economic evaluations through specific checklist such as CHEERS, made evident the need to improve the transparency and assurance of basic requirements of CEAs in LAC, but also in other contexts. For example, the reporting of setting and location of the evaluation had very low adherence by the authors, then it is difficult to judge the context in witch the decision is evaluated, beyond the estimated ICER. Also information about the synthesis-based effectiveness is not well identified in the papers, and most of the parameters for both PCV10 and PCV13 effectiveness did use adjustments from PCV7 specific stereotype efficacy combined with available data of serotype distribution from SIREVA lab surveillance system [37]. Because, CHEERS checklist only evaluates formal aspects reported in the CEAs, more detailed approach need to review the model structure, source of parameters, rationality of alternatives included, assumptions, and comparisons

made (not only verifying the report of them, as CHEERS propose), and replicate the ICERs considering incremental costs, and outcomes. The new 2022 version of the CHEERS checklist, recently published [38], do not solve this limitation.

The models implemented in the identified CEAs are not transparent enough to evaluate the intrinsic uncertainty of the economic evaluation. Some input data are not accessible through the publications. For example, demographic structure of the populations are usually not provided in the manuscript or supplementary material. It is needed additional analysis to replicate the CEAs in order to identify the key drivers of the results, as well as to validate the intermediate results to produce the incremental costs and outcomes and re-calculate the ICERs in a competitive scenario, where the knowledge to inform the decision making about the selection between different valences vaccines could be more valuable.

Uncertainty in the evaluated CEAs corresponds more to a mechanistic evaluation of some parameters variability, in most cases only with deterministic sensitivity and scenario analyses. It is not a regular practice to report estimates of ICERs as ranges, but a simple central value is often communicated, given the incorrect impression, for the decision makers, that estimation in the base case scenario are close to the truth. In addition, there are not available explicit willingness to pay (WTP) thresholds in LAC countries, then the normative dimension of CEAs are in debt to be approached, limiting the capacity of a real practical use of the CEAs in the decision making. For example, to have bargaining power in the discussion about the price of the intervention to be paid with public funds to private producers. Even more when some times the vaccine production is also funded with public resources, such as the COVID-19 vaccines [39]. In the other hand, Some CEAs keep reporting ICERs with life saved or hospitalization avoided despite to the difficulty to have a normative value to reference for the decision making.

Decision to choose between PCV10 or PCV13, since the economical point of view, needs to consider many issues simultaneously. The role of relative increase of 19A serotype in IPD is also be carefully evaluated [37]. In addition new PCVs of higher valences are available in the near future for children, due to need of a broader serotypes coverage across all ages to further reduce PD [40]. Recently a new PCV15 [41] and PCV20 [42] vaccines had been approved by the US Food and Drug Administration (FDA) to population's use, however its production costs and prices for the NPIs will be higher than another PCVs and keeping the serotype-dependent effectiveness, highlighting the need to develop other non-capsular based vaccines [43]. In this scenario, our results highlight that when industry founded the CEA is more likely that competitive alternative be judged with worst cost-effectiveness profile, i.e., higher ICER or valued as a dominated alternative, different to independent analyses performed by the Academic or Ministers of Health.

There are other reviews about PCVs economic evaluations in contexts beyond LAC

and all of them coincide in the cost-effectiveness of PCVs and the significant public health impact of PCV implementation, but call attention to the role of sponsorship in the CEAs. For example, a global review funded by the industry, identified significant differences in assumptions about vaccine efficacy against AOM, herd effects, and cross protection, highlighting the highly variable results [44], and another recommend to include emergent evidence, particularly these in favor of PCV13 [36]. A review in 2015, including global studies, reported that pivotal assumptions and results of these analyses depended on which manufacturer sponsored the study and recommended that decision makers using these analyses should not just rely on an analysis from a single manufacturer [45]. Other review in 2016, focused in LMICs, reported that results were sensitive to vaccine efficacy, price, burden of disease, and sponsorship. Decision makers should consider economic evaluation findings and affordability before adoption of PCV, but sponsored analysis were influenced by several parameters used in the model [46]. A recent review and meta-analysis of CEAs, funded by the industry, was focused in the incremental cost-effectiveness of PCV13 vs. PCV10 reporting a better meta-analyzed profile for PCV13 in LMICs [47].

Finally, none CEA for PCVs in LAC included alternatives different to vaccination in the economic evaluation, i.e., breastfeeding, improve nutrition, access to antibiotics to treat the pneumococcal infection. There is evidence of significant impact of these intervention [48], and their inclusion in the CEAs likely decrease the cost-effectiveness of the PCVs. In addition "do nothing.[a]lternative reported by most of CEAs included actually corresponds to *statu quo*, traditional management or business as usual. The present analysis provided additional tools to public health practitioners and decisions makers for rethink and approach critically about the use of economical evaluation results for decision making discussion about the new interventions considered to be founded by public budgets. Estimations of cost-effectiveness could be not neutral positive evidence and discuss about their shortcomings and interests involved could be also important together with other normative and positive arguments in the discussion.

This review has some limitations. First, only studies that were published in peer-review journals were included, which has restricted our findings since some economic evaluation, i.e., carried out by governments, could be communicated as internal reports and grey literature. A wider dissemination of performed CEAs is needed to increase use and visibility. Second, the included CEAs were carried out during the evolution of the market availability of PCVs, then in some cases only evaluated available options at the moment of the analysis, but time after these options could be outdated because the new vaccine was available of a withdrawal of the market of other alternative. Third, EMBASE database was not included in the systematic review, however additional results retrieved in that database only included gray literature and conference abstracts, excluded in the selection criterion of the review. Fourth, we can not identified which CEAs were explicitly considered in the national discussions about the PCV inclusion then the national discussions about the NPI inclusion of new PCVs could be

informed or not by the selected CEAs in this review.

3.5. Conclusion

Our review supports the cost-effectiveness of PCVs in LAC setting, however the decision about to include either 10 or 13 valences looks inconclusive and results of CEAs could be highly influence by producers' interests, biasing the models and parameters implemented in the published complete economic evaluations. There is a need to strengthen the surveillance on *S. pneumoniae* serotypes after any of PCV is included to make changes, if required, in a timely manner. We highlight the need of better instruments to evaluate CEAS's quality in more detail. A democratic approach about the use of CEAs to inform decision making is highly valuable to help the society decides about how to invest public and scarce resources, especially in settings where the relative participation of serotypes such as 19A increases and there is availability of new serotype coverage with new PCVs (15 and 20 valences) at increasing costs. New evaluations of vaccine benefits should include as comparators wider social and less expensive interventions.

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Authors' contributions

Carlos Castañeda-Orjuela provided conceptualization, development, and implementation of the study, and wrote the first draft of the manuscript. Fernando De la Hoz-Restrepo provided leadership and oversight in protocol development, data collection, data analysis, and manuscript development. All authors contributed to the final writing of the paper and read and approved the submitted version.

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Competing interests

All the authors declare that they have no competing interests.

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Registration of protocol

The protocol of this study was made in PROSPERO with number CRD42022342730.

Availability of data, code and other materials

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4. Decision makers' perceptions about new vaccines introduction

Criteria for new vaccine introduction in a National Expanded Program on Immunization: A survey of Expanded Program on Immunization managers

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Healthy Policy Analysis

Criteria for New Vaccine Introduction in a National Expanded Program on Immunization: A Survey of Expanded Program on Immunization Managers

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ABSTRACT

Objectives: This study aimed to critically review the decision-making (DM) processes for new vaccines introduction in Latin America's Expanded Program on Immunization (EPIs) and role of cost-effectiveness analyses (CEAs).

Methods: An online survey was conducted between August and December 2019 to Latin America and the Caribbean (LAC) EPI managers, participants of the National Immunization Technical Advisory Group (NITAG). Information about criteria to introduce the most recent vaccine was asked. CEA role in that decision and technical knowledge of informants were investigated. Frequencies of categorical data were calculated. Bar plots and stacked bar plots were used to visualize the data.

Results: A total of 26 EPI managers and stakeholders participated in the survey from 14 LAC countries. Respondents worked at the Ministry of Health and the Pan American Health Organization. Most recent vaccines included were human papillomavirus (42.3%), injectable polio (26.9%), and varicella (15.4%). High burden of disease and cost-effectiveness/cost-utility were identified as the main a priori criteria used to new vaccine introduction, but not all inputs are available or good quality. Discussion about vaccine introduction was conducted at NITAG meetings, reported as independent by most countries. Nevertheless, NITAG members did not master the essential CEAs concepts.

Conclusions: DM of vaccine introduction in LAC is reported by EPI managers as a process of discussion with participation of several actors where economic rationalities had a high role in the decision. It is necessary to strengthen the technical capacity to understand economical inputs to inform DM and advocate to include other rationalities as important in the discussion.

Keywords: decision making, immunization programs, Latin America, surveys and questionnaires, vaccination.

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Introduction

The National Expanded Program on Immunization (EPI) was launched in 1974, and since its introduction, millions of cases, disability, and deaths due to vaccine preventable communicable diseases have been avoided worldwide,[1] making vaccination a cost-effective public health strategy.[2,3] A new vaccine could be understood as either a vaccine not previously available in a particular context, one with new technology, or new combination of previous ones. In any case, including new vaccines in the EPI is not an easy task and traduce in increasing costs. For example, in low- and middle-income countries (LMICs), the public sector investment priorities, healthcare and immunization financing, are all shaped with limited resources, and then discussion about the new vaccine introduction could be delayed. In fact, LMICs usually start it when high-income countries have already introduced it,[4] although in certain cases this wait could imply lessons in the introduction process.

Criteria to decide on vaccine introduction may vary significantly across societies and include society specific values and rationalities beyond economic or monetary inputs.[5] Using a previously discussed reference framework for decision making (DM) in public health, we could identify additional inputs such as scientific evidence, equity, ethics, and political priorities. All of them extended the use of cost-effectiveness analysis (CEA) results in a democratic setting where discussion involves different stakeholders and political actors.[5] To identify how the decision makers value those different inputs and rationalities is an important research area to fill knowledge gaps about how DM works and could be improved.

Including new vaccines in national EPIs will deliver health benefits but also additional costs that need to be financed by already financially strained health systems. New vaccines are produced using new technologies and tend to be more expensive than traditional vaccines; nevertheless, when these new vaccines use existing delivery platforms or are implemented in combination with already introduced vaccines, the impact on the EPI and the additional administrative costs are less significant.[6] Vaccine introduction may provide opportunities for strengthening a country's immunization program and overall health system

Table 1. Study participant characteristics.

Variable	Frequency (%)
Institution where they work in relation to the EPI	
Ministry of Health	12 (46.2)
PAHO	5 (19.2)
NITAG	3 (11.5)
Scientific society	3 (11.5)
States Secretary of Health	2 (7.7)
Laboratory of Public Health	1 (3.8)
Position at the EPI	
Medium-level manager (EPI director, etc)	11 (42.3)
Other NITAG advisor PAHO advisor Scientific advisor Laboratory advisor	10 (38.5) 5 (19.2) 2 (7.7) 2 (7.7) 1 (3.8)
Low-level manager (coordinator, etc)	4 (15.4)
High-level manager (minister, vice minister, NIH director, etc)	1 (3.8)
Age of participant	
50-59 years	15 (57.7)
60+ years	6 (23.1)
40-49 years	4 (15.4)
30-39 years	1 (3.8)
Academic level	
MSc	14 (53.8)
Sp	12 (46.2)

EPI indicates Expanded Program on Immunization; MSc, master's degree; NIH, National Institutes of Health; NITAG, National Immunization Technical Advisory Group; PAHO, Pan American Health Organization; Sp, specialization.

governance.[4] An up-to-date EPI scheme could consider the delivery up to 15 to 20 antigens,[7,8] which implies a significant increase in resources devoted to this area of national health systems; therefore, a variety of rationalities are invoked when decision should be made about introducing a new one.

Latin America and the Caribbean (LAC) is a region at the forefront of new vaccines introduction. Some strategies have been developed in the region to strengthen the capacities to inform the DM of vaccine introduction.[9] This study tries to identify the set of criteria implemented to make decision about new vaccines introduction in the national EPIs of the region. The objective of this article was to critically review the DM processes undertake by the EPIs in Latin America for new vaccines introduction, in particular the role of CEAs.

Methods

Study Design

A cross-sectional survey was conducted among people of extensive experience and leadership at the EPIs in LAC countries in August to December 2019. Potential respondents were identified because of their involvement in the national EPIs of the region or their work at immunization area of the Pan American Health Organization (PAHO) and participation at the National Immunization Technical Advisory Group (NITAG). They were contacted through direct email, obtained from institutional web pages. The survey seeks to explore the DM process for new vaccines introduction in the studied countries. An online survey in Spanish and English was designed with 40 questions in kobotoolbox.org platform. The answers were recorded in an electronic database.

Study Instruments

Questionnaire included information about demographics of the interviewees, country, and position at the EPI. In addition, a group of questions asked regarding to a priori broad criteria considered as necessary to take into account on the discussion about a new vaccine introduction in the national EPI and their relative importance, as a ranking. Other sections inquired about the most recent vaccine included in their country, participation of the interviewees at that discussion, actors involved, and perception about quality and availability of information related with the criteria implemented in the decision. Finally, knowledge and personal experience in CEAs were also reported. The full survey can be accessed at https://ee.kobotoolbox.org/x/LcGQpXoG.

Statistical Analysis

The frequencies of all categorical data were calculated. Bar plots and stacked bar plots were used to visualize the data. Answers from multiple respondents from the same country were grouped to show the distribution of responses by country for some questions. All statistical analyses were conducted using R software version 4.0.3.

Ethical Aspects

This project was approved for the Ethical Committee of the Universidad Nacional de Colombia (approbation number 018-268-17). All the data in this survey were collected anonymously, with no personal information (apart from their name and publicly available contact details).

Results

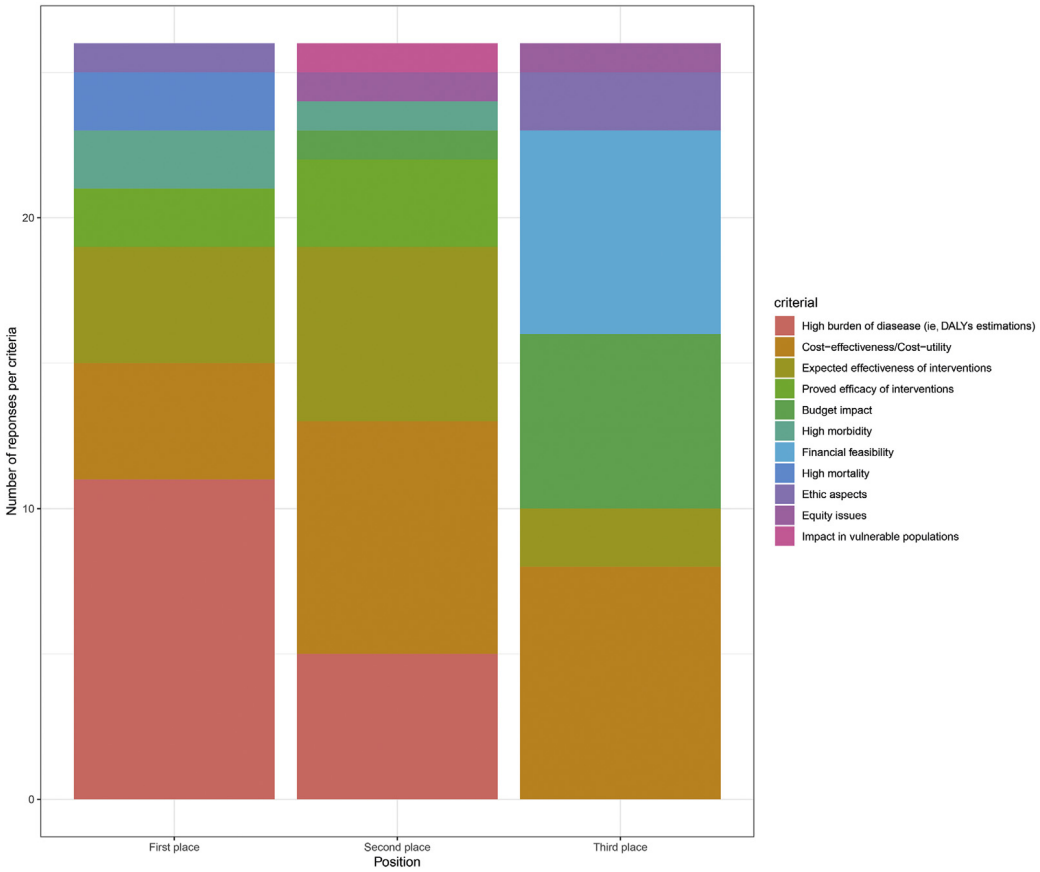
Participant Demographics

A total of 26 EPI managers and stakeholders participated in the survey with responses from 14 countries (Argentina, Bahamas, Barbados, Belize, Brazil, Curaçao, Dominican Republic, Guatemala, Honduras, Jamaica, Mexico, Paraguay, Peru, and Trinidad and Tobago). Argentina was the country with most responses (11 surveys). Most of the respondents worked at the Ministry of Health (MoH) and PAHO, with a master's degree. Ages >50 years were preponderant. Medium-level manager (as EPI directors) was a more frequent position (Table 1).

A Priori Criteria Used to Include New Vaccine

Respondents reported as main a priori criteria used to include new vaccines in LAC region countries the "High burden of disease" and "cost-effectiveness/cost-utility" (Fig. 1). In second place, the most cited terms were "cost-effectiveness/cost-utility" and "expected effectiveness of interventions" whereas at third "cost-effectiveness/cost-utility" and "financial feasibility" were next in frequency (Fig. 1). "Impact in vulnerable populations" and "equity issues" were the less common selected criteria, and aspects such as "budgetary constraints," "political interests," and "technological pressures" were not selected by any respondent.

Figure 1. A priori criteria to new vaccine introduction in national EPIs of LAC region.



DALY indicates daily-adjusted life-year; EPI, Expanded Program on Immunization; LAC, Latin America and the Caribbean.

Recent Vaccines Included and Perceptions About This DM

When EPI managers were asked about the most recent vaccine introduced in their EPIs, these were human papillomavirus (42.3%), injectable polio (26.9%), and varicella (15.4%). Most of the respondents did not participate directly in the decision (65.4%) (Table 2), but they reported that in 92.3% of cases (24 of 26) there was a discussion to reach the DM. In the 24 cases with discussion, the managers reported the participation of EPI director (95.8%), scientific society (79.2%), and MoH (75.0%), whereas most of them reported the absence of pharmaceutical industry, patient representatives, and academics (Table 2). The NITAG is where the discussion took place and were reported as an independent instance in most countries; nevertheless, both Colombian and Curaçao reported a not independent NITAG, whereas Dominican Republic reported it does not have NITAG.

With respect to the valuation of inputs available to make this decision, the best evaluated were "expected vaccine effectiveness," "efficacy of interventions," "budget impact," and "cost-effectiveness analysis" (Fig. 2). The most not available or not good quality inputs were "explicit political interests," "burden of disease," and "differential health impact." When surveyed, asking about the main reason to include the vaccines, the responses can be classified as high burden of disease (BoD) (46.2%) and vaccine's effectiveness and safety (11.5%) (Appendix Fig. S1a in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001). By country, in Argentina most people attribute the decision to BoD, whereas in Honduras BoD and CEA and political interest were reported (Appendix Fig. S1a in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001). BoD was the most common response independent of the direct participation in the discussion, position at the EPI, institution, or most recent vaccine included (Appendix Fig. S1c-e in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001). People who did not directly participate in the discussion reported a wider kind of motives for vaccine introduction (Appendix Fig. S1b in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001), such as representatives of MoH and PAHO (Appendix Fig. S1d in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001), or human papillomavirus vaccine introduction (Appendix Fig. S1e in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001).

Knowledge About the Economic Evaluations

In general, interviewees thought that CEA influenced just fairly or less than desirable the DM about the introduction of new technologies, including vaccines (Fig. 3). Nevertheless, most people did not have taken economic evaluation course (84.6%), and 61.5% did not know the willingness to pay (WTP) threshold of their countries, whereas 23.1% reported no threshold, and 7.7% reported 1 and 3 gross domestic products, respectively (Appendix Fig. S2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001). There is a similar picture when only data of Argentina are considered (Appendix Fig. S2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.05.001).

Table 2. Discussion information in new vaccine introduction at the EPI.

Variable	Frequency (%)
Most recent vaccine included	
HPV	11 (42.3)
IPV	7 (26.9)
Varicella	4 (15.4)
Rotavirus	2 (7.7)
HiB	1 (3.8)
PCV13	1 (3.8)
Participation in the decision making	
Yes	9 (34.6)
No	17 (65.4)
Discussion for the decision making	
Yes	24 (92.3)
No	2 (7.7)
Participants of the discussion*	
EPI director	23 (95.8)
Scientific society	19 (79.2)
MoH	18 (75.0)
Academic	11 (45.8)
Other	9 (37.5)
Patients' representatives	2 (8.3)
Pharmaceutical industry	1 (4.2)
Independent NITAG	
Yes	23 (88.5)
No	3 (11.5)
Took economic evaluation course	
Yes	4 (15.4)
No	22 (84.6)

EPI indicates Expanded Program on Immunization; HiB, *Haemophilus influenzae* type B; HPV, human papillomavirus; IPV, injected polio vaccine; MoH, Minister of Health; NITAG, National Immunization Technical Advisory Group; PCV13, 13-valence pneumococcal conjugated vaccine.
*Percentages estimated over the discussion report.

Discussion

An approximation of the DM about the new vaccine introduction is valuable to understand the process and to reach better national immunization programs and high vaccine coverages, maximizing the population wellbeing through the investment of limited resources. DM of vaccine introduction in LAC countries is reported, by EPI managers and stakeholders, as a discussion process with participation of different actors and many rationalities involved, including health economic evaluations, although respondents do not report deep technical knowledge in this regard. Most of the inputs considered as more relevant are related with the high BoD, the cost-effectiveness, and safety of the intervention. Nevertheless, aspects such as differential impact, explicit political interest, and, particularly, the BoD data are reported usually as not available or of poor quality for the decision of the most recent vaccine. In addition, it was reported that most of participants, although members of NITAG, did not participate directly in the discussion and neither have expertise in methods of formal health economic evaluations, despite high responsibility putted into these inputs for the decision of new vaccine introduction.

Most of the reported criteria to include new vaccines are related with the CEA itself, that is, BoD and vaccine effectiveness/efficacy, but diverse aspects such as ethical considerations, equity, differential impact in vulnerable population, political interests, and technological pressures are reported as less important or not considered during the discussion. Despite this, the respondents do not consider that CEA has a cardinal influence in the decision. That is striking, because other rationalities beyond the economic evaluations appear to be lesser considered in the explicit discussion in LAC countries. DM should include many rationalities from a democratic perspective, where economic evaluation is only one input of all possible.[5] It is necessary to strengthen the process of discussion and not only include a new vaccine in the EPI because it is cost-effective. Initiatives to integrate economic studies into the DM process for the introduction of new and underutilized vaccines as ProVac[10] should not displace other criteria at the time of new vaccine introduction discussion.

It is contradictory in our findings that although BoD and cost-effectiveness information is reported as the main criteria to introduce a new vaccine (a priori and during the discussion of the most recent vaccine), the BoD is reported as generally lacking or poor-quality input in LAC countries. It could be reflecting that CEAs would be implemented with BoD data from other settings, that is, similar countries with more available data. A limitation of this approach is that any CEA exercise requires a formal validation of inputs implemented, for example, the BoD. In addition to data inputs validation, ISPOR recommendations for vaccines economic evaluations also suggest including current epidemiologic data for the disease and competing causes of death in the population of interest.[11] BoD in the base case scenario in the absence of vaccine intervention is crucial to estimate the value for money of the vaccine introduction, including estimation of intervention`s impact through the relative risks or odds ratios from international literature reviews.

EPI managers in LAC region are confident about the use and influence of CEAs in DM of vaccines introduction, but the knowledge of the specific techniques could be limited. For example, they do not recognize the WTP threshold, a critical aspect being the decision rule in a CEA. In fact, any decision rule from CEA must include valuation of opportunity costs, and then the use of 1 to 3 gross domestic products per capita as WTP, reported by some EPI managers, has been recently evaluated. Some estimations for WTP thresholds from LMIC are available as opportunity cost based in public data.[12] Our findings highlight the need to strength the national capacities of the NITAG members about the use and limitations of the CEAs as methodology to obtain evidence-based inputs to discuss the potential impact of a new vaccine, as well as the knowledge on other inputs and methodologies involved in the discussion. For example, compressive approximation from a health technology assessment approach conducted from the European Network for Health Technology Assessment in different models could improve the general process of the DM to form complex new technologies.[13]

The independence of the NITAGs is critical in accordance with their goals and necessary legitimacy. A NITAG is both a technical resource and a deliberative body to empower the national authorities and policy makers to make evidence-based decisions.[14] The report found here about the lack independence of some NITAGs could be biased about the composition of this instance and their role in the DM. Additional analysis could be done about the role of these bodies in LAC in the introduction or not of new vaccines.

This analysis has limitations. First, not only considered stakeholders in the survey are involved in the DM about the new vaccine introduction at national EPIs; nevertheless, we focused the analysis in the NITAG members to identify the criteria used to inform DM from an evidence-based perspective in a setting where the discussion occurs with political actors. Second, the educational profile of interviewees could be related to the weight assigned to different inputs at the DM; although we were also looking for generalizable results of the NITAG participants in relation to CEAs' perceptions, there are complexity in the vaccine introduction process as shown

Figure 2. Valuation of inputs' quality in decision making.

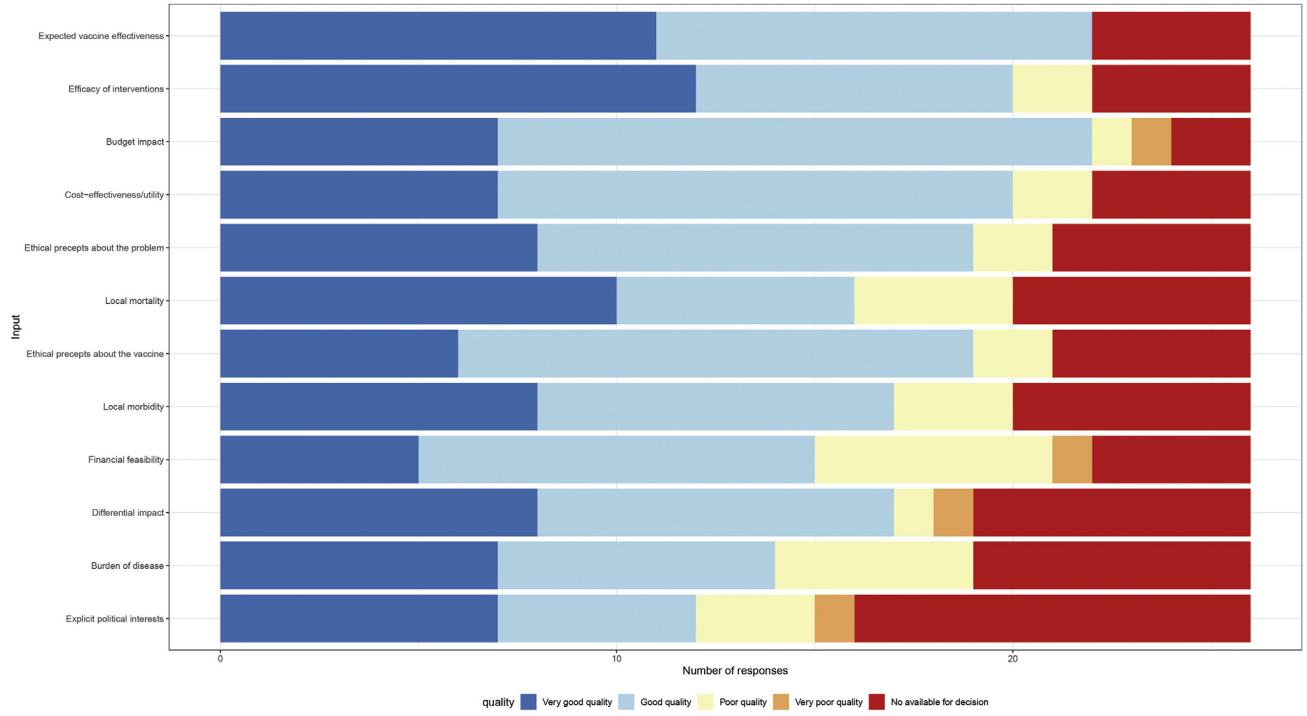
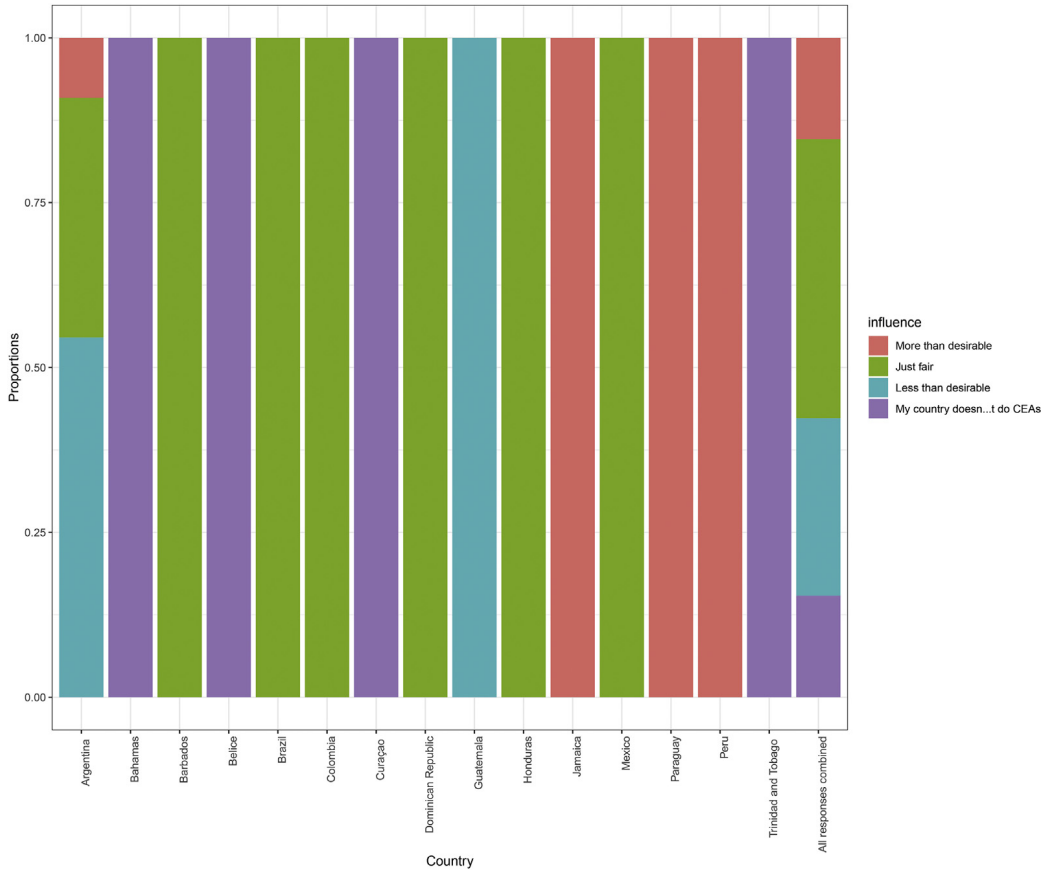


Figure 3. Valuation of influence of cost-effectiveness analysis on decision making.



CEA indicates cost-effectiveness analysis.

by heterogeneity in the responses. Third, perceptions could be distant of the actual reason to introduce a new vaccine in a country, but in the NITAGs' deliberative spaces, the reported information can reasonably approach to these reasons in the LAC setting.

New vaccine introduction funded by public health system should be a process to create local capacities and where the democratic discussion arises. Investing scarce resources in health should be into the framework of the social contract where a population must identify their priorities and reach an agreement about the goals of their health system and the technologies to be covered by public money. Not only initiatives to strengthen the use of evidence synthesis and health economic techniques are necessary in LMIC (positive dimension of DM), but also capacity in priority settings and criteria beyond utilitarianism economic perspective are needed in our countries to reach real wellbeing objectives for or population goals (normative dimension of DM).

Supplemental Materials

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5. Re-estimation of PCV's cost-effectiveness after initial introduction in Colombia

How cost effective is switching universal vaccination from PCV10 to PCV13? A case study from a developing country

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How cost effective is switching universal vaccination from PCV10 to PCV13? A case study from a developing country

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ABSTRACT

Background: Children immunization with pneumococcal conjugate vaccine (PCV) had profound public health effects across the globe. Colombian adopted PCV10 universal vaccination, but PCV incremental impact need to be revalued. The objective of this analysis was to estimate the cost-effectiveness of switch to PCV13 versus continue PCV10 in Colombian children.

Methods: A complete economic analysis was carried-out assessing potential epidemiological and economic impact of switching from PCV10 to PCV13. Epidemiological information on PCV10 impact was obtained from lab-based epidemiological surveillance on pneumococcal isolates at the Colombian National Institute of Health. Economic inputs were extracted from the literature. Incremental PCV13 effectiveness was based in additional serotypes included. Comparisons among alternatives were evaluated with the Incremental Cost-Effectiveness Ratio (ICER) at a willingness to pay of one GDP per capita (USD$ 6631) per Year of Live Saved (YLS). All costs were reported in 2014USD. Deterministic and probabilistic sensitivity analyses were performed, and 95% confidence interval reported.

Results: After four years using PCV10 for universal vaccination on children the Colombian health surveillance system showed a relative increment on non PCV10 isolates. To change from PCV10 to PCV13 would avoid 587 (CI95% −49–1008) ambulatory Rx community-acquired pneumoniae (CAP), 1622 (CI95% 591–2343) Inpatient RxCAP, 10 (CI 95% 6–11) pneumococcal meningitis, and 79 (CI95% 76–98) deaths. ICER per YLS was USD$ 2319 (CI95% Dominated – USD$ 4225) for Keep-PCV10 and USD$ 1771 (CI95% USD$ 1285–9884) for Switch-to PCV13. In spite of its cost-effectiveness Keep-PCV10 is an extended dominated alternative and Switch-to PCV13 would be preferred. Results are robust to parameters changes in the sensitivity analyses.

Conclusion: A national immunization strategy based in Switch-to PCV13 was found to be good value for money and prevent additional burden of pneumococcal disease saving additional treatment costs, when compared with to Keep-PCV10 in Colombia, however additional criteria to decision making must be taken into account.

1. Introduction

Infections due to *Streptococcus pneumoniae* are major causes of morbidity, hospitalization, and mortality in children and adults. *S. pneumoniae* causes invasive pneumococcal disease (IPD) such as meningitis and bacteremia as well as non-invasive disease, including community-acquired pneumonia (CAP) and acute otitis media (AOM) [1,2]. O'Brien et al estimated in 2000 there were about 14.5 million cases of serious pneumococcal disease around the world with 826 thousand deaths in children less than 5 years old [3]. In Latin America and the Caribbean (LAC), during 2009 were estimated between 12,000 and 28,000 deaths due to pneumococcus, 182 thousand hospitalization and 1.4 million outpatient consults [4,5].

Colombia already evaluated the cost-effectiveness of the Pneumococcal Conjugate Vaccines (PCV) and implemented in 2011 the universal vaccination at free of charge with ten-valent PCV (PCV10) in a 2 + 1 schedule (2, 4 and 12 months) for children less than one year old, through the public health system [6]. The PCV10 implementation, the cost-effective alternative at that moment, produced a switch on the pneumococcal serotypes reported to the SIREVA II initiative after six years [7–9]. Especially a relative increase in 19A serotype had been observed, similarly to other countries those included PCV10 [10]. Compared with the initial Colombian

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0264-410X/

cost-effectiveness analysis (CEA), new evidence had emerged about disease occurrence, vaccine effectiveness and costs of pneumococcal disease. For the Colombian Ministry of Health (MoH) is needed to evaluate the up-to-date cost-effectiveness of the available PCVs in the Colombian children population, to reconsider the initial decision about the PCV to be finance through the Expanded Program on Immunization (EPI).

In spite of the initial PCV10 inclusion in the Colombia EPI was informed and discussed with a CEA, the effectiveness of this intervention should be monitored in the population and the inclusion of other alternatives considered for the decision-makers considering the new available evidence, seeking the bigger population welfare. To update the cost-effective profile of available PCVs is useful for EPI's manager to wisely invest the scarce public resources. The objective of this analysis was to estimate the cost-effectiveness to switch the immunization to PCV13 versus to continue PCV10 vaccination in the Colombian children.

2. Methods

2.1. Model and target population

We adapted a previous built simulation model [6] for the present CEA. Due to pneumococcal disease incidence and mortality vary across ages, we implemented an age-dependent Markov model, including a cohort of children younger than one year old (870,130 children according with the *Departamento Nacional de Estadística – DANE*), followed up to the life expectancy (76 years). This population corresponds to the total target vaccination groups for PCV in Colombia in a 2 + 1 doses schedule applied at 2, 4 and 12 months of age. Five states were included: Healthy, AOM, Radiological confirmed CAP, Pneumococcal Meningitis, and death (Fig. 1). The model runs in MS Excel with annual cycles and implemented half cycle corrections. Transitions between states were based in annual probabilities. The occurrence of related pneumococcal disease was considered only during the first five years of life.

2.2. Setting and location

Colombian is a middle-income tropical country located in northwestern South America. The health system is funded entirely by public resources and delivered by both public and private providers. Immunization is delivered in Colombia through this public health system free of any charge for the target population, mainly under one-year children. Vaccines and immunization supplies are bought directly by the MoH and distributed to public and private health facilities, most of them of primary care, that deliver the immunization shots in a continuous way during all the year. The MoH defines the vaccines included in the EPI, through discussion in a National Immunization Technical Advisory Group (NITAG).

2.3. Comparators

In the present CEA three alternatives were evaluated: (1) No vaccination (leave the PCV vaccination), (2) Continue the PCV10 vaccination, and (3) Switch to PCV13 vaccination. To model the current Colombian pneumococcal related burden an additional scenario was simulated (Initial PCV10 vaccination), however it was not included in the comparison to evaluate the cost-effectiveness ratios (Fig. 1). PCV10 covers serotypes 1, 4, 5, 6B,

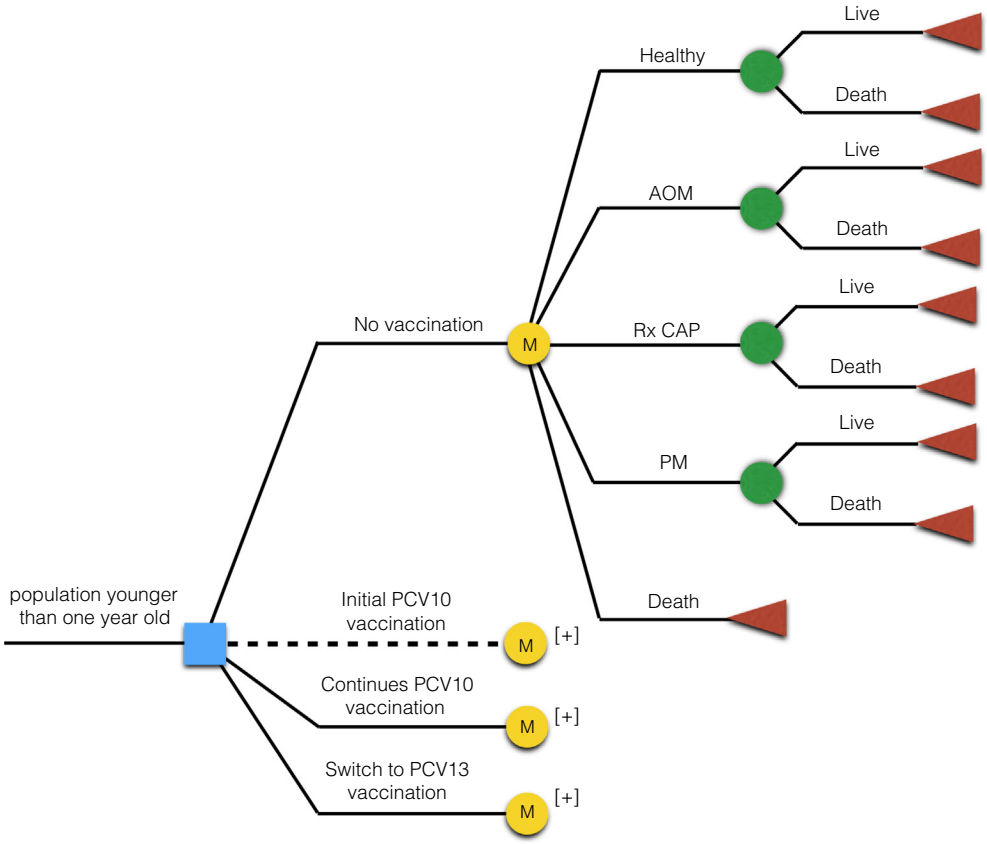

Fig. 1. Decision tree model for the PCVs costs-effectiveness analysis. Colombia, 2014. AOM: Acute Otitis Media; Rx CAP: Radiological confirmed community-acquired pneumonia; PM: Pneumococcal Meningitis. The mark [+] in the 'M' node means inclusion of the showed Markov model. Dashed line represents a base line scenario to model the impact of the considered alternatives.

7F, 9V, 14, 18C, 19F and 23F, conjugated to Non-typeable *Haemophilus influenzae* (NTHi) protein D. PCV13 covers in addition serotypes 3, 6A and 19A, and use as carrier the diphtheria-derived protein CRM(197).

2.4. Demographic and epidemiological parameters

Based on parameters included in previous model [6], a literature review was performed to identify recent publications about the demographic and epidemiological parameters to update the estimation of the pneumococcal related burden of disease in Colombian children (Table 1) [5,11–14]. We included the new serotype distribution (after the PCV10 introduction) reported by SIREVA II for invasive isolates during 2011 to 2014 period, at the Colombian National Health Institute.

Burden of pneumococcal related disease was estimated with the included parameters in each of the model arms that included immunization. The burden of disease in the vaccination arms were estimated based in the serotype coverage vaccine effectiveness. The impact of keeping PCV10 or switching to PCV13, were modeled on the initial estimation for PCV10 vaccination strategy (Table 1).

2.5. Vaccine effectiveness

The vaccine effectiveness against all-cause CAP and pneumococcal meningitis were estimated based in data reported for PCV7 [15,16] adjusted by coverage of pneumococcal serotypes. For all-cause AOM, the PCV10 effectiveness was extracted from the recent COMPAS study [17], while for the PCV13 estimation was based in the PCV7 effectiveness against AOM [16] adjusted by serotypes coverage. Effect against pneumococcal related disease was assumed constant during the first five years of life in vaccinated children. No herd effect was taken into account for any vaccine strategy.

2.6. Costs

Cost of the health states (CAP, AOM, and PM) were obtained from a Latin American's estimation, with measurements for the

Table 1
Parameters and distributions used in the model for the CEA of PCV10 and PCV13 in Colombian Children, 2014.

Parameter	Mean value	Inferior limit	Superior limit	Distribution	Reference
Evaluation year	2014				
Vaccination cohort	870,130			Fixed	*DANE*
Discount rate	3%				
Pneumococcal-related disease occurrence					
Before PCV10 introduction					
Pneumococcal meningitis probability	0.00004	0.00002	0.00006	Beta (3, 3)	[11,12]
Ambulatory all-cause Rx CAP probability	0.0036	0.0033	0.0038	Beta (4, 5, 3)	[11–13]
Inpatient all-cause Rx CAP probability	0.0063	0.0060	0.0068	Beta (2, 3)	[11–13]
All-cause AOM probability	0.3020	0.25	0.35	Beta (3, 25, 3)	[12,14]
Case Fatality ratio pneumococcal meningitis*	37%	33%	54%	Beta (0, 7, 3)	[5,12]
Case Fatality ratio all-cause pneumonia*	3%	2%	6%	Beta (1, 3)	[5,12]
After PCV10 introduction					
Pneumococcal meningitis probability	0.00001	0.00001	0.00002		Adjusted from the model
Ambulatory all-cause Rx CAP probability	0.0028	0.0023	0.0033		
Inpatient all-cause Rx CAP probability	0.0050	0.0042	0.0059		
All-cause AOM probability	0.2054	0.1661	0.2501		
Vaccine effectiveness					
PCV10 before its introduction					
All-cause AOM	16%	−1%	30%	Log-normal	[17]
All-cause Rx CAP	20%	4%	35%		[15] *adjusted by coverage in SIREVA 2007–2008*
Pneumococcal meningitis	71%	48%	82%		[16] *adjusted by coverage in SIREVA 2007–2008*
PCV10 after its introduction					
All-cause AOM	16%	−1%	30%	Log-normal	[17]
All-cause Rx CAP	8%	2%	14%		[15] *adjusted by coverage in SIREVA 2011–2014*
Pneumococcal meningitis	50%	35%	59%		[16] *adjusted by coverage in SIREVA 2011–2014*
PCV13 after PCV10 introduction					
All-cause AOM	13%	9%	19%		[16] *adjusted by coverage in SIREVA 2011–2014*
All-cause Rx CAP	17%	4%	28%		[15] *adjusted by coverage in SIREVA 2011–2014*
Pneumococcal meningitis	69%	48%	79%		[16] *adjusted by coverage in SIREVA 2011–2014*
Costs (USD)					
Care cost per case					
Inpatient CAP	$1163	$930	$1395	Beta (3, 3)	[18] *for low income countries*
Ambulatory CAP	$104	$84	$125	Beta (3, 3)	
Pneumococcal meningitis	$1421	$1137	$1705	Beta (3, 3)	
AOM	$122	$97	$146	Beta (3, 3)	
Immunization costs					
PCV-10 dose	$14.12			Fixed	MoH communication
PCV-13 dose	$15.68			Fixed	
Administration cost per dose	$1	$0.5	$2	Beta (1, 5, 3)	Assumption
Wastage rate	10%	5%	15%	Beta (3, 3)	
Doses per complete schedule	3			Fixed	
Immunization coverage	90%			Fixed	

Rx CAP: Radiological confirmed community acquired pneumonia; AOM: Acute Otitis Media.
* Keep constant after PCV-10 introduction.

Colombian children population [18]. Those costs estimations were obtained from either physicians' interviews and WHO—choosing Interventions that are Cost Effective (WHO-CHOICE) project [19]. Coverage of the vaccination was assumed in 90% for each vaccination alternatives. An administrative cost of USD $ 1 per dose, and a wastage rate of 10% were assumed. Costs per dose of PCV were reported by the Colombian MoH and correspond to prices of the Pan American Health Organization (PAHO) revolving fund. All costs were adjusted to 2014 American dollars (exchange rate of COP$ 2392.46 per USD$ 1)

2.7. Cost-effectiveness analysis

A CEA was made to calculate the Incremental Cost-Effectiveness Ratio (ICER) for each alternative y terms of costs per Year of Life Saved (YLS) including all causes of death during the time horizon of the life expectancy to evaluate the impact of competing causes of death. Pneumococcal disease and its associated costs were only considered during the first five years of life. The ICER calculation was made considering in numerator the net costs of each alternative and in denominator their incremental effectiveness (additional YLS). Costs and results were discounted to the recommended discount rate of 3%. The evaluation was carried out from the third payer perspective (Colombian Health System) and in a competitive scenario, because all the evaluated alternatives are mutually exclusive.

2.8. Sensitivity analyses

Deterministic and probabilistic sensitivity analyses (DSA and PSA) were made for epidemiological parameters, vaccines' effectiveness, and costs included in the model. All parameters were included with their probability distributions to include their uncertainty, according with the uncertainty reported in the original information source. In general, probabilities use Beta, costs use Gamma, and relative risks use log-normal distributions. For the PSA, a Monte Carlo simulation with ten thousand iterations was performed, in order to evaluate each expected value of the ICER in the distribution of costs, diseases likelihood, and effectiveness for each strategy, reporting mean and 95% confidence intervals of the results. An acceptability curve was constructed with the Expected Net Benefits and a willingness to pay (WTP) threshold equal to 1 GDP per capita (USD$ 6631) per YLS. The 95% confidence intervals (CI 95%) are reported for all estimations.

3. Results

Table 2 shows the estimations of burden of pneumococcal-related disease, including cases, deaths, discounted YLS, and net costs for each evaluated alternative in the cohort during first five years of life. Estimations of the avoided cases for each alternative are presented in Table 3. In general, switching to PCV13 would avoid additional cases of pneumococcal-related diseases, except for AOM, where keep PCV10 avoids more cases than PCV13.

Costs of treatment of pneumococcal-related disease in absence of PCV vaccination rise to USD$ 111.8 million (CI95% USD$ 98.3–125.3 million), including all-cause AOM and all-cause Rx CAP. The annual costs of PCV immunization program were estimated in USD$ 38.8 million (CI95% USD$ 37.1–40.8 million) for PCV10 and USD$ 42.9 million (CI95% USD$ 41.0–44.9) for PCV13.

3.1. Cost-effectiveness analysis

Table 4 shows health outcomes, costs, and the ICERs in a competitive setting, excluding initial PCV10 introduction. Fig. 2 shows

Table 2
Burden of pneumococcal-related disease in a Colombian children cohort until 5 years of life by vaccine alternative, 2014.

	AOM	Ambulatory Rx CAP	Inpatient Rx CAP	Pneumococcal meningitis	Deaths due to ambulatory Rx CAP	Deaths due to inpatient Rx CAP	Deaths due to TOTAL pneumococcal meningitis	Immunization cost	Discounted Lived Years of Life	Discounted net Costs (Immunization + care costs)
No Vaccination	719,246 (679,970–753,117)	15,210 (14,492–15,840)	26,626 (25,573–27,878)	171 (111–232)	455 (308–740)	796 (539–1288)	63 (40–92)	1314 (911–2096)	US$ 0 (US$ 0–0)	22,033,197 (22,032,920–22,033,727)	US$ 111,788,343 (US$ 98,341,713–125,300,458)
PCV10 introduction	665,955 (594,540–732,076)	12,109 (10,246–14,104)	21,781 (18,427–25,430)	61 (35–100)	372 (238–617)	651 (417–1077)	23 (13–38)	1046 (680–1719)	US$ 38,839,273 (US$ 37,113,972–40,778,044)	22,039,502 (22,035,408–22,045,532)	US$ 138,790,310 (US$ 124,194,609–153,882,673)
Keep PCV10	609,660 (492,255–724,000)	11,049 (9065–13,249)	20,441 (16,774–24,593)	45 (26–73)	339 (215–561)	611 (383–1018)	17 (9–28)	967 (617–1595)	US$ 38,839,273 (US$ 37,113,972–40,778,044)	22,041,356 (22,036,464–22,048,668)	US$ 130,708,962 (US$ 113,316,439–149,265,872)
Switch to PCV13	619,187 (549,462–686,831)	10,463 (8057–13,298)	18,820 (14,430–24,002)	35 (20–62)	312 (189–527)	563 (338–957)	13 (7–23)	888 (541–1497)	US$ 42,871,020 (US$ 41,046,954–44,881,760)	22,043,212 (22,037,108–22,052,047)	US$ 133,994,945 (US$ 119,684,712–148,832,830)

Rx CAP: Radiological confirmed community acquired pneumonia; AOM: Acute Otitis Media. Confidence interval 95% in parenthesis.

Table 3
Avoided Burden of pneumococcal-related disease for PCV10 introduction, keep PCV10 and switch to PCV13 strategies in Colombian children (less than 5 years old), 2014.

	OMA	Ambulatory Rx CAP	Inpatient Rx CAP	Pneumococcal meningitis	Deaths due to ambulatory Rx CAP	Deaths due to inpatient Rx CAP	Deaths due to pneumococcal meningitis	TOTAL deaths
PCV10 introduction (actual impact)	53,291 (21,041–85,430)	3101 (1736–4246)	4845 (2447–7146)	111 (76–132)	83 (70–123)	145 (121–212)	41 (27–54)	268 (232–377)
Keep PCV10	56,294 (8076–102,285)	1060 (855–1181)	1339 (837–1653)	16 (9–27)	33 (23–56)	40 (34–58)	6 (4–10)	79 (63–123)
Switch to PCV13*	-9527 (-57207 – 37,169)	587 (-49–1008)	1622 (591–2343)	10 (6–11)	27 (26–34)	48 (46–61)	4 (2–5)	79 (76–98)

Rx CAP: Radiological confirmed community acquired pneumonia; AOM: Acute Otitis. Mean values reported and Confidence interval 95% into parenthesis.
* Avoidable events estimated with respect to Keep PCV10.

Table 4
ICER for the modeled vaccination alternatives in Colombian children (less than 5 years old), 2014.

Alternative	Deaths due to pneumococcal related disease	Years of Life Lived	Total costs	Avoided deaths*	Years of Life Saved (YLS)*	Additional costs*	ICER (USD per YLS)
No Vaccination	1314 (911–2096)	22,033,197 (22,032,920–22,033,727)	USD$ 111,788,343 (USD$ 98,341,713–125,300,458)				
Keep PCV10	967 (617–1595)	22,041,356 (22,036,464–22,048,668)	USD$ 130,708,962 (USD$ 113,316,439–149,265,872)	Extended Dominated			
Switch to PCV13	888 (541–1497)	22,043,212 (22,037,108–22,052,047)	USD$ 133,994,945 (USD$ 119,684,712–148,832,830)	426 (370–599)	10,015 (4188–18,320)	USD$ 22,206,602 (USD$ 21,342,999–23,532,372)	USD$ 2217 (USD$1285–5096)

* Estimated compared to relevant alternative. ICER: Incremental cost effectiveness ratio. Confidence interval 95% in parenthesis.

the cost-effectiveness plane of the present comparisons. The more expensive alternative is Switch to PCV13, but it is the more effective alternative with 1856 (CI95% 644–3379) additional YLS with respect to Keep PCV10. It becomes the cost-effective alternative with an ICER of USD$ 2217 (CI95% USD$ 1285–5096) per additional YLS. Keep PCV10 is an extended dominated (ED) alternative. Its ICER compared with No Vaccination would be USD$ 2319 (USD$ 1604–4225) but comparing Switch to PCV13 with Keep PCV10 would estimate an ICER of US$ 1770 (US$ −128–9889). If a decision-maker were willing to pay enough for Keep PCV10 seem worthwhile then they will also be willing to pay the additional costs to move to PCV13 because the ICER is lower [20].

3.2. Sensitivity analyses

Fig. 3 shows the acceptability curve of the CEA based in the Monte Carlo simulations and the probabilistic distribution of all included parameter (according with Table 1). Above a WTP of USD$ 2000 per YLS 'switch to PCV13' alternative begin to be likely the most cost-effective alternative. To WTP values around USD$ 6000 per YLS (near to the Colombian GDP per capita), there is a 90% of likelihood of 'Switch to PCV13' to be the most cost-effective alternative.

4. Discussion

Our results indicate that to continue PCV10 vaccination in Colombian children would had additional health outcomes to good value for money ratio, however, including recent evidence about the effectiveness of available PCVs and new pneumococcal serotypes distribution patterns, switching from PCV10 to PCV13 would be the cost-effective alternative in the Colombian setting as showed in the competitive analysis. The PCV13 inclusion would reduce more cases of Rx CAP, PM, deaths and YLLs than to keep PCV10. However, PCV10 would prevent more AOM cases then PCV13.

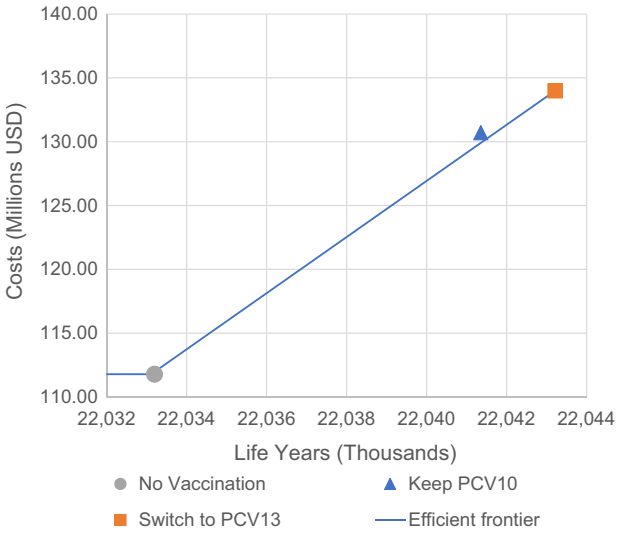

Fig. 2. Cost-effectiveness plane and efficient frontier CEA of Keep PCV10 vs PCV13 in Colombian children (less than 5 years old), 2014. Keep PCV10 is an extended dominated (ED) alternative in spite of been cost-effective in the comparison with no vaccination.

Currently there is no published CEA assessing the economic and epidemiological impact of switching from one PCV to another. Many LAC countries have currently introduced PCV10 and some of them have assessed its effectiveness. In most cases it has demonstrated a moderate effectiveness against Rx confirmed CAP and all cause pneumonia [21], but incremental PCV13 benefits are under discussion. The value for money of this change should be evaluate from the decision maker perspective and this research is a contribution in that sense.

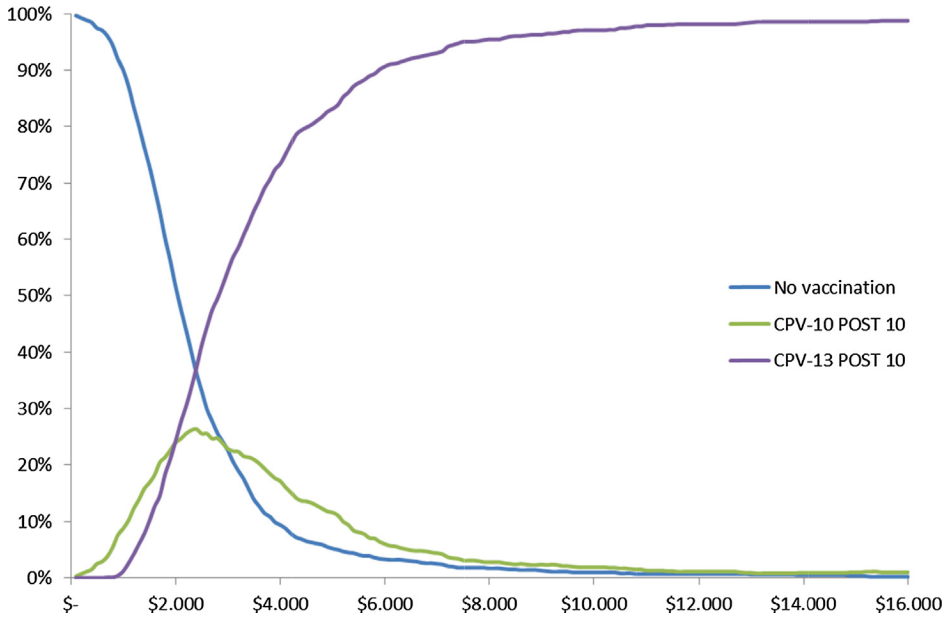

Fig. 3. Acceptability curve of the CEA of Keep PCV10 and PCV13 in Colombian children (less than 5 years old), 2014.

Our main challenge to assess the potential impact of switching between PCV vaccines is the lack of good evidence on the incremental efficacy of PCV13 to prevent invasive and non-invasive pneumococcal disease. There is no experimental field trial comparing efficacy of both vaccines head to head. The best evidence available to date is reports on effectiveness from geographies where different PCV vaccines have been implemented sequentially (PCV7, PCV10 and PCV13) [22]. This precludes us to fully guaranteed that benefits of switching from one to another would produce all the forecasted benefits. However, mechanistic evidence suggests that PCV13 may act effectively against a surge in 19A serotype. England and Wales estimated the vaccine efficacy using the 'indirect cohort' method in which non-vaccine types IPD cases are selected as controls. The PCV13 effectiveness ($\geq$1 dose) against PCV13 serotypes (including 6C) was 69% after switching from PCV7 to PCV13 [23].

Other evidence reports no differences in effectiveness between PCV10 and PCV13 vaccines. Oliveira et al. assessed the evidence on clinical effectiveness of both vaccines in LAC countries using a systematic review [21]. They did not find any study comparing directly both vaccines and they concluded that there was no evidence of any given vaccine being superior to the other one. Furthermore, most studies did not include a control group and a large proportion of them were based on analysis of secondary data from different countries with different surveillance systems which make differences in country results barely comparable. No LAC study evaluates the impact of switching between vaccines [21].

The main reason to obtain a worst cost-effectiveness profile for PCV10 with respect to our previous analysis [6] was that the most recent and high quality available evidence about all cause OMA PCV10 effectiveness [17] is most conservative than the previous reported by Prymula [24], however it still considers effects more than only on pneumococcal included serotypes. With the new effectiveness data, the costs savings of the additional OMA cases avoided related to Non-typeable *Haemophilus influenzae* (NTHi) do not exceed the benefits of the additional pneumococcal serotypes included in PCV13, according with the parameters included in the present model.

Cost-effectiveness results can be change along the time and require continuously evaluation because variation in the model key driver inputs and new available alternatives could adjust the decision. Emergent evidence can change the initial cost-effectiveness estimation, and decision makers could adjust their decisions. Initial impact of the intervention can change the setting where the technology was modelled, as occurred in Colombia with the PCVs. These highlight the importance of use models in the economic evaluation of intervention, especially in absence of complete and perfect information.

Other studies in Colombia have reproduced PCV's CEA in a similar context, but some shortcomings in their designs can be argued. Díaz et al. [25], also showed a better PCV13 cost-effectiveness profile versus PCV10. However, they implemented a deterministic model before the initial PCV10 introduction, with the corresponding serotype distribution and with PCV10's AOM effectiveness only adjusted by pneumococcal serotype distribution and therefore less than PCV13's AOM effectiveness. In addition, that study was funded by the industry. Ordoñez et al. [26] also carried out a CEA of PCV10 versus PCV13 in Colombian children reporting that PCV13 is a cost-saving strategy compared with PCV10. That study also did not consider impact on AOM different to pneumococcal and include average attention costs attention that look pretty inflated. For example, they reported a care cost of US$ 11,595 for meningitis and US$ 1854 for pneumonia while we used more conservative estimates: US$ 1421 for meningitis, US$1163 for inpatient Rx CAP, and US$ 104 for ambulatory Rx CAP. In addition these authors underestimated AOM costs (US$ 40) [26]. All of these adjustments play against the PCV10 cost-effectiveness profile.

A central issue of discussion in the PCVs competitive analysis is the serotype replacement and cross effectiveness, especially if sequential PCV implementation is carried out. We modeled the setting of the initial PCV10 implementation and compared it with the actual serotype distribution. Colombia is one of the LAC countries within the SIREVA initiative which enables us to monitor changes in serotype distribution after vaccine introduction. Raw data comparing 2007–2009 and 2011–2014 period showed that serotypes 19A, 3 and other not PCV included have increased (4% to 13%, 3% to 8% and 12% to 30%, respectively). It was pretty similar with the figure predicted after the initial PCV10 introduction (Supplementary Table 1), except for serotype 6A, which was expected a 17% but now we have 11% and 6% for Pneumonia and meningitis, respectively (Supplementary Table 1). According with these forecasting 19A serotype is no raising more than predicted. It is as an

apparent effect over the proportion of the total serotypes but by the decrease in the other PCV10 included serotypes.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.078.

The cost-effectiveness analysis is a piece of evidence to consider the value for money of a health intervention. One important reason to conduct the present analysis was to inform to Colombian national health authorities to make a decision on whether there was added value in shifting from PCV10 to PCV13. National authorities in Colombia have been compelled to analyze that issue since the surveillance system have informed on a remarkable increase on 19A and 3 serotypes after PCV10 introduction [27]. The impact of this analysis in public health in Colombia and other developing countries is to highlight the cost-effectiveness of the PCV13 in a competitive scenario against PCV10 and as long as the additional serotype coverage translate to a higher effectiveness, however programmatic adjustments of the switching should be considered in each particular setting. Other criteria, beside the CEA, should be evaluated for the decision makers to change to PCV13 or introduce it in the EPI. Although the decision making should be evidence informed, and CEA help in it, other legitimate rationalities participate in the process.

This analysis has limitations. First, as we already mentioned, we are assuming an incremental PCV13 effectiveness without head to head clinical or population analysis. In the case of similar effectiveness profile, additional cost of PCV13 with no additional health benefits will make PCV10 the best option. We rely on the usual assumptions implemented in PCVs' CEAs, however additional evidence about the real world PCVs effectiveness is needed. Second, we did not evaluate the burden of pneumococcal disease beyond the premature mortality, however is important to mention that pneumococcal related disease, different to OMA, is still responsible of many infant deaths in developing countries. Include morbidity dimension in the denominator of the ICER as avoided disability, because we consider their care cost only in the numerator, could adjust the cost-effectiveness of the interventions in favor of the one that prevent more non-lethal cases. Third, we did not include herd effect in the analysis. It goes beyond the unvaccinated children and include adult population. In this sense, our results are from a conservative scenario and if we include the herd effect the effectiveness profile will be a little better in a proportional way for all vaccination strategies. In essence, this inclusion will affect the total burden of pneumococcal disease estimate, but not the reported ICER. Fourth, we did not include sequels' attention costs, then the avoided costs due to the occurrence of less cases are underestimated. It is also proportional to each compared alternative and it would not have a significative impact in the estimated ICER between vaccines. Fifth, we did not evaluate the programmatic adjustments needed to do the effective switching to PCV13, for example the adjustment in the schedule of children with one of two doses of PCV10. It should be evaluated for the decision makers and would affect the cost-effectiveness of the program during the transition period. However, here is reported the ICER of the total adjustment of the immunization strategy. The ICER during the transition will be a value between the ICERs reported by us for switch to PCV13 and keep PCV10.

5. Conclusion

In Colombian context after the initial inclusion of PCV10 in children younger than one year of age, switch to PCV13 could show better health outcomes, but PCV10 would have lower immunization costs, and still be a cost-effective alternative compared with no vaccination. From the cost-effectiveness point of view, with these results, to switch to PCV13 would be the preferred policy in the competitive analysis. Colombian MoH must consider the Government priorities when deciding on the best option. This study is an effort to provide the best available evidence to inform a vaccine decision-making in Colombia, with result with potential impact in the health of population, especially the youngest and more vulnerable people with action that are fiscally responsible.

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Conflict of interest statement

The authors declare that they have not conflict of interest.

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6. A final validation analysis and a closing discussion for new proposals

In this section a final analysis is presented and an integration of the findings obtained in the different chapters contrasted in way of a closing discussion. The additional analysis performed corresponds to a validation of the cost-effectiveness analyses (CEAs) published for Pneumococcal Conjugated Vaccines (PCVs) introduction in children population from Latin America and the Caribbean (LAC).

6.1. A validation of published PCVs' CEAs in LAC

An additional analysis with the identified CEAs for PCVs in LAC from the systematic review presented in **Chapter 3** was the validation of the cost-effectiveness results (i.e., with the recalculation of incremental cost-effectiveness ratios -ICERs- beyond the incremental results reported by authors, running the entire models with the original set of parameters). To perform this validation, a standard model of pneumococcal disease (PD) natural history allowing to run the specific health states considered in each included study was built in Excel with the information reported by the authors in the manuscripts and supplemental materials.

The model was adapted to all states and outcomes considered in each CEA, represented as an age- and state-dependent Markov simulation national birth-cohort. From each article were identified epidemiological parameters, costs, and disability weights or dis-utilities. Demographic information was obtained from the manuscripts, but if not reported, population estimations by country were consulted from UN Population Prospects, while life tables and currency exchange rates were obtained from World Bank Data.

Table 6-1 shown the ICERs reported by 25 included CEAs, performing 33 national CEAs and one for all LAC countries combined. Analysis included Brazil (seven studies for 2004-8 period), Colombia (five for 2008-16), Mexico (five for 2008-14), Peru (four for 2007-12), Argentina (three for 2006-10), Chile (two for 2006-8), Paraguay (two for 2010-13), Uruguay (two for 2007), Cuba (one for 2020), Ecuador (one for 2013), Honduras (one for

2013), and LAC (one for 2005).

In 23 reported CEAs, from 16 individual papers, it was possible to run a new entire cost-effectiveness model and to provide a recommendation according to the re-estimated ICER. Comparison between the initial reported and the re-estimated ICERs yield concordant results in 11 CEAs (nine studies) from Brazil, Mexico, Colombia, Peru, Chile, Uruguay, and Cuba [1–9]. Of these coincident CEAs, PCV13 was recommended in four: Mexico 2010 [3], Colombia 2012 [5] and 2014 [6], and Peru 2012 [8]; PCV7 in four: Brazil 2005 [1] and 2006 [2], Chile 2006 [1], and Uruguay 2007 [1]; PCV10 in two: Colombia 2009 [4] and Peru 2007 [7]; and PCV7-TT in one from Cuba 2020 [9] **(Table 6-1)**.

Divergent recommendations were found in 12 CEAs, from seven individual studies, from Brazil, Argentina, Mexico, Colombia, Peru, Chile, Uruguay, and Paraguay [10–16]. Six CEAs from the same study originally recommended PCV10 (Brazil 2008, Argentina 2006, Mexico 2008, Colombia 2008, Peru, 2007, and Chile 2008) but PCV13 was not included in the comparison, then not recommendation could be generated in a competitive evaluation [11]. A case similar to one Brazilian CEA [10]. Four studies re-estimated an ICER above the willingness to pay (WTP) threshold reported, then those should recommend not vaccination, however originally in two of them the authors did not generated recommendation: Argentina 2010 [13] and Paraguay 2010 [16]; while another two studies recommended PCV7: Argentina 2006 [12] and Uruguay 2007 [15]. In addition, one study recommended PCV10 but after run the entire model we estimated an ICER in favor of PCV13 [14] **(Table 6-1)**.

In addition, other four CEAs (each in one study) could not generated recommendations: the LAC compiled study did not provided WTP threshold and assessing it was not possible in spite to replicate the CEA with very similar results to reported by the authors [17]. Lack of WTP also was evident in two Brazilian studies (both funded by Wyeth), by with higher difference in the re-estimated ICER [18, 19], while in Peru a CEA evaluated the outcome of hospitalization avoided [20] and no decision rule is available for that. In seven CEAs, corresponding to five studies, the replication of the economic evaluation was not possible due to lack of original model details or critical parameters to validate the initial estimation, such as PD occurrence, costs, or vaccines' effectiveness [21–25]. One of them was a CEA performed in Paraguay, Ecuador and Honduras without epidemiological data reported [25] **(Table 6-1)**.

Table 6-1.: Reported ICERs for PCVs in LAC and estimated with the standard model.

Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Sinha, 2008 [17]	LAC, 2005	PCV7 vs. Do nothing	Third payer	USD	DALY averted	Yes		$5,735		$5,735	$7,032	22.6 %		PCV7	No WTP		
Sinha, 2008 [17]	LAC, 2005	PCV7 vs. Do nothing	Societal	USD	DALY averted	Yes		$5,252		$5,252	$6,886	31.1 %					
Constenla, 2008 [1]	Brazil, 2005	PCV7 vs. Do nothing	Societal	USD	DALY averted	Yes		$664		$664	$602	-9.3 %	$14,371	PCV7	PCV7	Coincident	
Vespa, 2009 [2]	Brazil, 2006	PCV7 vs. Do nothing	Third payer	LCU	DALY averted	Yes		$4,516	$1.94	$2,328	$2,977	27.9 %	$19,233	PCV7	PCV7	Coincident	
Vespa, 2009 [2]	Brazil, 2006	PCV7 vs. Do nothing	Societal	LCU	DALY averted	Yes		$3,946	$1.94	$2,034	$2,953	45.2 %					
de Souza, 2009 [18]	Brazil, 2008	PCV7 vs. Do nothing	Third payer	LCU	LYG	Yes		$3,673	$1.40	$2,624	$5,206	98.4 %		PCV7	No WTP		
de Souza, 2009 (1) [19]	Brazil, 2009	PCV13 vs. Do nothing	Third payer	LCU	LYG	No	Alt. omit.	$2,188	$1.40	$1,563	$4,209	169.3 %		PCV13	No WTP		
de Souza, 2009 (1) [19]	Brazil, 2009	PCV13 vs. Do nothing	Societal	LCU	LYG	No	Alt. omit.	$2,002	$1.40	$1,430	Not replicable						No parameters
Sartori, 2012 [10]	Brazil, 2004	PCV10 vs. Only high risk	Societal	LCU	DALY averted	No	Alt. omit.	$22,066	$2.65	$8,327	$18,635	123.8 %	$12,104	PCV10	No reco.	Divergent	Do nothing omit.
Sartori, 2012 [10]	Brazil, 2004	PCV10 vs. Only high risk	Third payer	LCU	DALY averted	No	Alt. omit.	$24,930	$2.65	$9,408	$18,648	98.2 %					Do nothing omit.
Garcia-Marti, 2013 [11]	Brazil, 2008	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	$7,089		$7,089	$3,862	-45.5 %	$24,881	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Brazil, 2008	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	$4,811		$4,811	Not replicable						No parameters
Perdrizet, 2021 [21]	Brazil, 2018	PCV10 vs. Do nothing	Government	LCU	QALY saved	Yes		Cost-saving	$3.95		Not estimated			PCV13	No eval.		Model not reported. Nos effectiveness data
Perdrizet, 2021 [21]	Brazil, 2018	PCV13 vs. PCV10	Government	LCU	QALY saved	Yes		Cost-saving	$3.95		Not estimated						Model not reported. No effectiveness data

Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Giglio, 2010 [12]	Argentina, 2006	PCV7 vs. Do nothing	Societal	USD	LYG	Yes		$5,599		$5,599	$15,695	180.3 %	$11,670	PCV7	No vax	Divergent	
Giglio, 2010 [12]	Argentina, 2006	PCV7 vs. Do nothing	Third payer	USD	LYG	Yes		$5,828		$5,828	$17,801	205.4 %					
Giglio, 2010 [12]	Argentina, 2006	PCV7 vs. Do nothing	Private	USD	LYG	Yes		$5,778		$5,778	$17,700	206.3 %					
Urueña, 2011 [13] [13]	Argentina, 2010	PCV10 vs. Do nothing	Third payer	USD	QALY saved	Yes		$8,973		$8,973	$63,383	606.4 %	$22,098	No reco.	No vax	Divergent	
Urueña, 2011 [13]	Argentina, 2010	PCV13 vs. PCV10	Third payer	USD	QALY saved	Yes		$28,147		$28,147	Dominated						
Urueña, 2011 [13]	Argentina, 2010	PCV10 vs. Do nothing	Societal	USD	QALY saved	Yes		$8,546		$8,546							No parameters
Urueña, 2011 [13]	Argentina, 2010	PCV13 vs. PCV10	Societal	USD	QALY saved	Yes		$27,614		$27,614							No parameters
Garcia-Marti, 2013 [11]	Argentina, 2006	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	$3,348		$3,348	$4,665	39.3 %	$22,332	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Argentina, 2006	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	$1,510		$1,510	Not replicable						No parameters
Talbird, 2010 [22]	Mexico, 2008	PCV10 vs. PCV7	Third payer	USD	QALY saved	No	Alt. omit.	$3,232		$3,232	Not estimated		$17,420	PCV10	No eval.		Not effectiveness data
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV7 vs. PCV13	Third payer	USD	QALY saved	Yes		Not Reported			Dominated					t	
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV10 vs. PCV13	Third payer	USD	QALY saved	Yes		Not Reported			Dominated			PCV13	PCV13	Coinciden	
Muciño-Ortega, 2011 [3] [3]	Mexico, 2010	Do nothing vs. PCV13	Third payer	USD	QALY saved	Yes		Not Reported			Dominated						
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV7 vs. Do nothing	Third payer	USD	QALY saved	No	No comp.	Cost-saving			Not estimated						
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	No comp.	Cost-saving			Not estimated						
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV13 vs. Do nothing	Third payer	USD	QALY saved	No	No comp.	Cost-saving			Not estimated						

Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Muciño-Ortega, 2011 [3]	Mexico, 2010	PCV13 vs. PCV10	Third payer	USD	QALY saved	Yes		Not Reported			Cost-saving						
Garcia-Marti, 2013 [11]	Mexico, 2008	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	$4,594		$4,594	$3,106	- 32.4 %	$30,607	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Mexico, 2009	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	$3,243		$3,243	Not replicable						No parameters
Gomez, 2016 [14]	Mexico, 2012	PCV10 vs. Do nothing	Third payer	LCU	QALY saved	No	Not according the new model	$5,616	$13.10	$429	Not estimated		$11,224				
														PCV10	PCV13	Divergent	
Gomez, 2016 [14]	Mexico, 2012	PCV13 vs. PCV10	Third payer	LCU	QALY saved	No	Not according the new model	Not reported	$13.10		Not estimated						
Gomez, 2016 [14]	Mexico, 2012	PCV13 vs. Do nothing	Third payer	LCU	QALY saved	Yes		Not reported			$755						
Gomez, 2016 [14]	Mexico, 2012	PCV10 vs. PCV13	Third payer	LCU	QALY saved	Yes		Not reported			Dominated						
Gomez, 2016 [14]	Mexico, 2012	PCV10 vs. Do nothing	Societal	LCU	QALY saved	Yes		Dominant	$13.10	Dominant							No parameters
Gomez, 2016 [14]	Mexico, 2012	PCV10 vs. Do nothing	Third payer	LCU	LYG	Yes		$5,556	$13.10	$424	Not estimated						Model only estimates QALYs
Gomez, 2016 [14]	Mexico, 2012	PCV13 vs. PCV10	Third payer	LCU	LYG	Yes		$887,156	$13.10	$67,722	Not estimated						Model only estimates QALYs
Wasserman, 2013 [23]	Mexico, 2014	PCV13 vs. PCV10	Third payer	LCU	QALY saved	No	Alt. omit.	Cost-saving	$19.70		Not estimated			PCV13	No eval.		Model not reported. Not effectiveness data
Castañeda-Orjuela, 2012 [4]	Colombia, 2009	PCV10 vs. Do nothing	Societal	USD	LYG	Yes		$1,837		$1,837	$2,401	30.7 %	$5,474	PCV10	PCV10	Coincident	
Castañeda-Orjuela, 2012 [4]	Colombia, 2009	PCV7 vs. PCV10	Societal	USD	LYG	Yes		Dominated		Dominated	Dominated						
Castañeda-Orjuela, 2012 [4]	Colombia, 2009	PCV13 vs. PCV10	Societal	USD	LYG	Yes		$9,516		$9,516	$10,658	12.0 %					

Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Garcia-Marti, 2013 [11]	Colombia, 2008	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	$4,021		$4,021	$3,518	-12.5 %	$14,970	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Colombia, 2008	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	$2,433		$2,433	Not replicable						No parameters
Ordoñez, 2015 [5]	Colombia, 2012	PCV13 vs. Do nothing	Third payer	USD	LYG	Yes		Not Reported			$1,047		$24,075	PCV13	PCV13	Coincident	
Ordoñez, 2015 [5]	Colombia, 2012	PCV10 vs. PCV13	Third payer	USD	LYG	Yes		Not Reported			Dominated						
Ordoñez, 2015 [5]	Colombia, 2012	PCV10 vs. Do nothing	Third payer	USD	LYG	No	No comp.	$813			Not estimated						
Ordoñez, 2015 [5]	Colombia, 2012	PCV13 vs. PCV10	Third payer	USD	LYG	No	No comp.	Cost-saving			Not estimated						
Castañeda-Orjuela, 2018 [6]	Colombia, 2014	PCV10 vs. Do nothing	Third payer	USD	LYG	Yes		Exted. Dominated		Exted. Dominated	Exted. Dominated		$6,631	PCV13	PCV13	Coincident	
Castañeda-Orjuela, 2018 [6]	Colombia, 2014	PCV13 vs. Do nothing	Third payer	USD	LYG	Yes		$2,217		$2,217	$1,820	-17.9 %					
Pugh, 2020 [24]	Colombia, 2016	PCV13 vs. PCV10	Third payer	USD	QALY saved	No	Alt. omit.	Cost-saving						PCV13	No eval.		Model not reported. Not costs data
Garcia-Marti, 2013 [11]	Peru, 2007	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	$2,975		$2,975	$3,224	8.4 %	$13,150	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Peru, 2007	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	$1,536		$1,536	Not replicable						No parameters
Gomez, 2013 [7]	Peru, 2007	PCV10 vs. Do nothing	Third payer	LCU	QALY saved	Yes		$4,500	$2.78	$1,619	$468	-71.1 %	$13,068				
Gomez, 2013 [7]	Peru, 2007	PCV7 vs. PCV10	Third payer	LCU	QALY saved	Yes		Not Reported			Dominated						
Gomez, 2013 [7]	Peru, 2007	PCV13 vs. PCV10	Third payer	LCU	QALY saved	Yes		Not Reported			Dominated			PCV10	PCV10	Coincident	
Gomez, 2013 [7]	Peru, 2007	PCV10 vs. Do nothing	Third payer	LCU	LYG	Yes		$170,391	$2.78	$61,292	Not estimated						Model only estimates QALYs
Gomez, 2013 [7]	Peru, 2007	PCV7 vs. PCV10	Third payer	LCU	LYG	Yes		Not Reported			Not estimated						Model only estimates QALYs

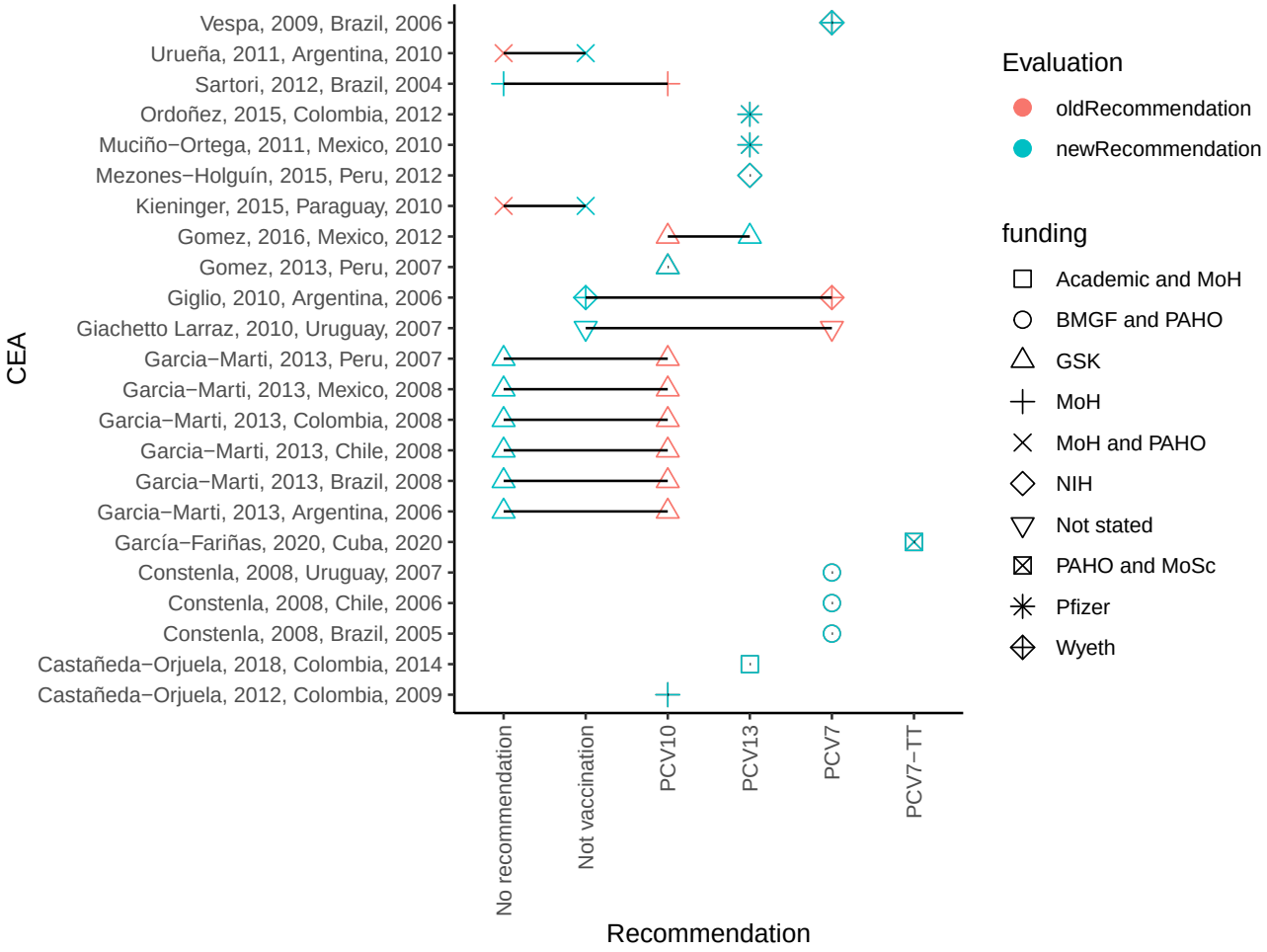
Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Gomez, 2013 [7]	Peru, 2007	PCV13 vs. PCV10	Third payer	LCU	LYG	Yes		Not Reported			Not estimated						Model only estimates QALYs
Gomez, 2013 [7]	Peru, 2007	PCV7 vs. Do nothing	Third payer	LCU	QALY saved	No	No comp.	$6,014	$2.78	$2,163	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV13 vs. Do nothing	Third payer	LCU	QALY saved	No	No comp.	$5,327	$2.78	$1,916	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV13 vs. PCV7	Third payer	LCU	QALY saved	No	No comp.	Dominated		Dominated	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV10 vs. PCV7	Third payer	LCU	QALY saved	No	No comp.	Cost-saving			Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV7 vs. Do nothing	Third payer	LCU	LYG	No	No comp.	$5,582	$2.78	$2,008	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV10 vs. Do nothing	Third payer	LCU	LYG	No	No comp.	$4,293	$2.78	$1,544	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV13 vs. Do nothing	Third payer	LCU	LYG	No	No comp.	$5,004	$2.78	$1,800	Not estimated						
Gomez, 2013 [7]	Peru, 2007	PCV10 vs. PCV7	Third payer	LCU	LYG	No	No comp.	Cost-saving			Not estimated						
Mezones-Holguín, 2014 [20]	Peru, 2011				Hosp avoided	No					Not estimated		$11,280	PCV13	No eval.	Divergent	Not allowed for hospitalization
Mezones-Holguín, 2015 [8]	Peru, 2012	PCV10 vs. Do nothing	Government	USD	DALY averted			$1,605		$1,605	Exted. Dominated		$6,009	PCV13	PCV13	Coincident	
Mezones-Holguín, 2015 [8]	Peru, 2012	PCV13 vs. PCV10	Government	USD	DALY averted			$519		$519	$1,092	110.4 %					
Constenla, 2008 [1]	Chile, 2006	PCV7 vs. Do nothing	Societal	USD	DALY averted	Yes		$2,019		$2,019	$1,775	- 12.1 %	$22,675	PCV7	PCV7	Coincident	
Garcia-Marti, 2013 [11]	Chile, 2008	PCV10 vs. Do nothing	Third payer	USD	QALY saved	No	Alt. omit.	Cost-saving			$3,178		$42,262	PCV10	No reco.	Divergent	
Garcia-Marti, 2013 [11]	Chile, 2008	PCV10 vs. Do nothing	Societal	USD	QALY saved	No	Alt. omit.	Cost-saving			Not replicable						No parameters
Constenla, 2008 [1]	Uruguay, 2007	PCV7 vs. Do nothing	Societal	USD	DALY averted	Yes		$1,546		$1,546	$1,390	- 10.1 %	$15,681	PCV7	PCV7	Coincident	

Study	Country, year	Comparison	Perspective	Currency	Outcome	Correct comparison	Why incorrect?	Reported ICER	Ex. rate	Reported ICER (USD)	Re-estimated ICER	Diff.	WTP	Authors recommendation	New recommendation	Result	Observation
Giachetto-Larraz, 2010 [15]	Uruguay, 2007	PCV7 vs. Do nothing	Societal	USD	LYG	Yes		$7,335		$7,335	Not estimated		$6,910	PCV7	No vax	Divergent	Model only estimates QALYs
Giachetto-Larraz, 2010 [15]	Uruguay, 2007	PCV7 vs. Do nothing	Societal	USD	QALY saved	Yes		$4,666		$4,666	$9,325	99.8 %					
Giachetto-Larraz, 2010 [15]	Uruguay, 2007	PCV7 vs. Do nothing	Third payer	USD	QALY saved	Yes		Not Reported			$9,416						
Constenla, 2015 [25]	Paraguay, 2013	PCV10 vs. Do nothing	Societal	USD	DALY averted			$2,416		$2,416	Not replicable			No reco.	No eval.		Occur. not available
Constenla, 2015 [25]	Paraguay, 2013	PCV13 vs. PCV10	Societal	USD	DALY averted			$3,525		$3,525	Not replicable						Occur. not available
Kieninger, 2015 [16]	Paraguay, 2010	PCV10 vs. Do nothing	Government	USD	DALY averted			$3,851		$3,851	$14,336	272.3 %	$2,516	No reco.	No vax	Divergent	
Kieninger, 2015 [16]	Paraguay, 2010	PCV13 vs. PCV10	Government	USD	DALY averted			$12,181		$12,181	Dominated						
Kieninger, 2015 [16]	Paraguay, 2010	PCV10 vs. Do nothing	Societal	USD	DALY averted			$1,920		$1,920	$13,805	619.0 %					
Kieninger, 2015 [16]	Paraguay, 2010	PCV13 vs. PCV10	Societal	USD	DALY averted			$15,696		$15,696	Dominated						
Constenla, 2015 [25]	Ecuador, 2013	PCV10 vs. Do nothing	Societal	USD	DALY averted			$2,716		$2,716	Not replicable			No reco.	No eval.		Occur. not available
Constenla, 2015 [25]	Ecuador, 2013	PCV13 vs. PCV10	Societal	USD	DALY averted			$4,289		$4,289	Not replicable						Occur. not available
Constenla, 2015 [25]	Honduras, 2013	PCV10 vs. Do nothing	Societal	USD	DALY averted			$1,588		$1,588	Not replicable			No reco.	No eval.		Occur. not available
Constenla, 2015 [25]	Honduras, 2013	PCV13 vs. PCV10	Societal	USD	DALY averted			$3,067		$3,067	Not replicable						Occur. not available
García-Fariñas, 2020 [9]	Cuba, 2020	PCV7-TT vs. Do nothing	Government	LCU	DALY averted			$374	$1.00	$374	$915	144.7 %	$4,411	PCV7-TT	PCV7-TT	Coincident	

ICER: Incremental Cost-effectiveness ratio; LYG: Life Year gained; DALY: Disability Life Adjusted Year; QALY: Quality Adjusted Life Year; Occur.: Occurrence; Alt.: Alternatives; WTP: willingness to pay; reco.: recommendation; eval.: evaluated; omit.; omitted; comp.: competitive.

When the correspondence of the original and recalculated recommendations was evaluated by CEA, according to the founder and vaccine composition **(Figure 6-1)**, it was noted that CEAs before 2007 studies recommended only PCV7 (the only available vaccine at that moment), in four of the CEAs [1] (one of Wyeth [2]) the recommendation was validated with the new model, while two of them [15] changed to no vaccination (one of Wyeth [12]). While all four studies that originally recommended PCV13 [6, 8], two of them financed by Pfizer [3, 5], can replicated the findings with the same recommendation. But for PCV10 only two [4], one of GSK [7], out of ten confirmed the original recommendation.

Figure 6-1.: Correspondence between reported recommendations in original CEAs and re-estimation model for PCVs in LAC by evaluation and founder.



6.2. A reflection about the main findings of the research

The present PhD thesis approached in a comprehensive way to the decision-making (DM) process in public health from a normal science perspective, focusing in new vaccines introduction in national Expanded Programs on Immunization (EPIs) and the role of cost-effectiveness analyses (CEAs), using Pneumococcal Conjugated Vaccines (PCVs) in Latin America and the Caribbean (LAC) as case study. We proposed an updated reference framework for DM in public health after reflect on the arguments and decision rules involved to inform the discussions about the introduction of new technologies in healthcare systems from LAC; explicitly we included normative inputs to be considered into DM framework going beyond of the published referents. Also we systematically reviewed the published CEAs on PCVs in children from LAC countries to explore how they informed the DM about their introduction in national EPIs. It is the first independent review who evaluates the potential differences between PCV10 and PCV13, as well as the role of sponsor in the recommendation raised from the CEAs. With a survey to EPI managers, participants at National Immunization Advisory Groups (NITAGs), we critically reviewed the DM for new vaccines introduction in LAC's EPIs and the role of CEAs, these results show for the first time in LAC what are the explicit criteria on which DM for vaccines is based. As well we updated the CEAs of PCVs in Colombian children, comparing switch to PCV13 versus continue PCV10 including recent evidence and impacts. It was the first study in the region that informed the need to re-evaluate the original recommendation to the Colombian NITAG. Finally, we validated the cost-effectiveness models implemented in LAC countries, reviewing parameters, models structure, results and recommendations in a competitive approach. Our analyzes performed for the first time the re-estimation of the results of the CEAs of PCVs, something that is not common in the economic literature. We also proposed adjustments and recommendation in the cost-effectiveness estimation to inform DM in our context.

This journey began with a proposal of conceptual reference framework to identify the potential utility of CEAs with their pitfalls in the DM process in public health, from our experience of its use in developing countries at the national EPIs in LAC. CEAs are an input in the negotiation process between different stakeholders with different legitimate interests, i.e., producers of health technologies finding profits, and decision makers at the healthcare system investing public resources to reach maximize the population well-being.

The relevance of rationalities beyond economical is highlighted in this research work, but also noted the centrality that CEAs has been gained in the recent years, with different technical capacities in the countries, according with the developmental level, as well as the diversity of discussions at the time to use CEAs in the DM. New vaccine introduction is a good example to approximate the use of CEA in DM, and LAC countries are the setting where the approach of inform the DM with economical evaluations (EEs) is encouraged by several stakeholders: Pan American Health Organization (PAHO), national authorities, and

donors. Other public health DM frameworks are available but focused in step by step of the discussion to generate a recommendation from the evidence-based with a very limited positive rationalities and equating the public health with healthcare system decisions [26]. In addition, for the new vaccine introduction the increased global interest to generate reference models and strengthen evidence-based policy-making is driven by the availability of more expensive vaccines with an central role of the EEs [27]. In this sense, thinking about the other not economical and positive rationalities, as we presented, is a novelty knowledge field that would help to better DM and more democratic discussion about the usage of limited resources.

It was performed a systematic review of literature about the PCVs' CEAs in children from LAC countries to understand how they informed the DM about PCVs inclusion in national EPIs from LAC. We evaluated several characteristics and quality of the published CEAs. More than a half of them were sponsored by pharmaceutical industry with some potential bias in the results and recommendations provided. We arise concerns about quality and conflict of interest involved in the realization of CEAs to inform DM about the selection between PCV10 and PCV13, with contradictory results for both vaccines formulations, for example in countries with simultaneous CEAs of pharmaceutical industry and independent researchers. Other sponsorship bias in CEAs, in oncology area, have been recently reported [28].

The evidence showed that cost-effectiveness profiles of PCVs introduction in LAC children is a good value for money investment of public funds. However to inform the best economic profile for different vaccine formulation (10 vs. 13 valences) requires to include unbiased parameters in the model, and discusses the normative framework such as the willingness to pay (WTP) threshold to the DM. Interests such as pharmaceuticals should be keep away in the evaluation and discussion, because today the industry is the main sponsor of CEAs in the region, potentially biasing the discussion to their interests. Other published systematic reviews about PCVs CEAs do not address in deep the difference between PCVs cost-effectiveness profiles or specific recommendation about the selection between available formulations. For example, a recent systematic and meta-analysis, financed by the PCV13 producer industry, found difference in favors of PCV13 only when herd effects were considered [29], while previous systematic reviews, also in LMICs, highlights the potential bias of sponsorship involvement, but avoid addressing the discussion of relative advantages of different vaccine formulations, concluding that both are cost-effective [30]. The later study was the base evidence for the more recent World Health Organization (WHO) position paper about PCVs in children, that neither reported a predilection between vaccine formulations [31].

A survey to EPI managers, participants at NITAGs, was carried out to review the DM processes for new vaccines introduction in LAC and evaluate the role of CEAs. The process

was reported by EPI managers as a space of discussion with participation of several actors where economic rationalities had a high role in the decision but the technical capacity was identified as limited and many of the local key information to performed a CEA reported as lacking. It is necessary to strengthen the technical capacity to understand economical inputs to inform DM and advocate to include other rationalities as important in the discussion. Good quality CEAs should be available to negotiate prices of vaccines, not only to justify the need to include the vaccine on the EPIs, then stakeholders have to understand the economical rationality beyond the results. Despite of the efforts to include economical inputs in the discussion to new vaccine introduction and to generate local capacities [32], knowledge gaps were identified in the field of EEs methodology in the EPI managers, as well as in the local availability of the necessary parameters to carry out this type of evaluation.

A CEA of switch to PCV13 versus continue PCV10 in Colombian children was run to update a previous CEA but now including more recent evidence. A national immunization strategy in Colombia based in Switch-to PCV13 was found to be good value for money and prevent additional burden of pneumococcal disease saving additional treatment costs, when compared with to Keep-PCV10 in Colombia, however additional criteria to DM must be taken into account. This exercise highlight the relevance of update the CEAs about a particular problem, given the dynamic nature of the situation and the continuous emergence of new evidence about the impact of a technology. Decision are no definitive course of actions. The decision makers should be open to re-evaluate and potentially switch the original decision if the evidence and discussion support the change. This evidence about the need of vaccine update, according with the CEAs result, is congruent with some additional findings about the switch in the pneumococcal serotypes reporting through lab-based surveillance from the region (SIREVA) [33].

Finally, a re-estimation of cost-effectiveness was performed by LAC countries from published CEAs, integrating information provided in published papers, standardizing an unique model, and making the comparison in a competitive scenario between the included alternatives. Interestingly many published CEAs are not possible to replicate, while significant proportion of replicable models resulted in a divergent recommendation compared with the original evaluation. It is a striking result that highlight the nature of black-boxes of these economic models and the challenge to reach a reproducibility of a CEA, a view shared by other authors that advocate for open access to model code [34]. When only PCV7 was evaluated in the CEAs from LAC, the models usually reproduced a very credible scenario, but with additional serotype formulation vaccines it is becoming more common that disagree arise between CEAs, inclusive in the same country with multiple evaluations from different sponsors. In addition, none study includes not vaccination or *status quo* alternatives in the EE. It was reported the consequences of do not include all the relevant comparators in vaccine CEAs from LAC originating sub-optimal decisions [35]. Lack of WTP definition it is also a problem for CEAs from LAC and other LMICs also mentioned in the literature, with

estimation very low in comparison with WHO's three gross domestic product (GDP) per capita [35, 36].

Improvements in the DM process are required in LAC setting, with potential extrapolation to other LMICs contexts. The case study of new vaccine introduction, with increasingly expensive vaccines such as PCVs, evidences how DM actually take in to account very few criteria to inform the DM, mainly based in CEAs' results (or their inputs) whose validity could be under discussion when many of the sponsors been at the same time producers of the technologies under evaluation. In addition the technical quality of the available CEAs is limited and the reproducibility, in many cases, is not guarantee with the available information provided by the authors of the original evaluation or the required comparison are not performed. The decision makers and participants of the NITAGs have shortcomings in the knowledge about the economic methods and the support provided by PAHO with its ProVac initiative did not fill these gaps of the local capacities required. There is no doubt that ProVac facilitated the carried out of CEAs for new vaccines in LAC, providing a rational element to NITAGs of the region, but in the case of PCVs their models are avoided systematically the discussion about the selection between different serotype formulations available, while the manufacturers are generating debate respect the introduction or not of each PCV in a particular EPI, raising unnecessary doubts in the general audience about the transparency of DM. Criteria different to positive EEs' results should be highlighted and incorporated explicitly in the process and DM should recover its relevance as democratic dimension of a deliberative process to reach social agreements.

The analyses presented here have certain limitations, which have been discussed in detail within the respective sections of each chapter/article. However, I will summarize these limitations below for clarity. Firstly, the literature review was confined to indexed articles, as peer-reviewed studies generally ensure the highest scientific integrity. Nonetheless, it should be acknowledged that there are other sources of information available in each country. National authorities and research centers involved in informing DM processes should be encouraged to publish their CEAs in indexed journals. Secondly, conducting a meta-analysis of the cost-effectiveness results was not feasible. This limitation arises from the nature of CEAs, which aim to estimate the value for money of an intervention within a specific context. This local estimation naturally varies between countries and over time. While it is possible to meta-analyze the parameters used in the model, this aspect was beyond the scope of this thesis. Thirdly, the PCV market has influenced the availability of vaccines and the corresponding CEAs at different points in time. Therefore, it is crucial to avoid making comparisons between CEAs that are not appropriately contextualized. Even within a single country, not all PCVs were available throughout the considered period, and the distribution of serotypes has also varied. This variability extends to the cost-effectiveness profiles. Fourthly, it is challenging to definitively identify which CEAs have directly informed DM processes. Hence, the studies obtained through the literature review may not necessarily correspond to those

directly influencing decisions. However, they do provide a valuable approximation of the ongoing analyses conducted and published in the countries included in the analysis. Fifthly, due to limitations in accessing all decision-makers involved, the survey respondents provide insights into the DM process but may not reflect all the arguments considered during that process. Sixth, similarly the backgrounds and expertise of interviewees may influence the weighting assigned to decision inputs, potentially not fully capturing the depth of the discussion. Seventh, head-to-head comparisons between PCVs are generally lacking in the scientific literature. Consequently, differential effectiveness between PCV10 and PCV13 is typically assumed, and the differential impacts remain a topic of ongoing discussion. Eighth, the health outcomes associated with pneumococcal disease encompass more than just premature mortality, including morbidity, loss of functionality, sequels, and treatment costs. Unfortunately, many CEAs do not incorporate these aspects comprehensively. Ninth, the herd effect, an important consideration in evaluating the impact of vaccination on a population, is often underrepresented in the analyses. Lastly, programmatic costs and the cost of implementing the immunization program itself are not consistently addressed in most analyses. The later three limitations, along with the aforementioned ones, can influence the cost-effectiveness profiles and have an impact on the calculated ICERs. Despite these limitations, the dissertation provides valuable insights into the field of CEAs of PCVs and serves as a significant contribution to the existing literature.

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7. Conclusions and recommendations

Some conclusions and recommendation are outlined here after the finding presented in the above chapters.

7.1. Conclusions

- Given the amount of financial resources devoted to public health programs and that interventions compete for limited resources, it is impossible to omit the economic dimension in decision-making (DM). Cost-effectiveness analyses (CEAs) still are rational and positive elements to inform the DM for new technologies introduction that evaluate simultaneously costs and outcomes of competing alternatives, but in spite of their usefulness, improve in their methods, and wide use, the DM is not only based on economic criteria.

- New vaccine introduction funded by public resources should be a process to create local capacities and where the democratic discussion arises. Emerging strategies to guarantee the wider participation should be considered. For example, for vaccines collegiate bodies such as National Immunization Technical Advisory Groups (NITAGs) are very valuable, acting as consultative bodies with experts that advise to decision makers, combining multiple rationalities beyond economics or epidemiological. Our proposed DM framework in public health retake these cardinal elements and explicitly included normative inputs to be considered, going beyond of the published referents. Elements from context, politics, equity, and ethical need to be considered simultaneously.

- Society and decision makers should have in mind that decisions are not irreversible. Even evidence-based decisions can be reevaluated after their initial adoption. CEAs' results can be change along the time and require continuously evaluation because variation in the model key drivers and new available alternatives could adjust the original decision. Updates of CEAs are a good practice and we presented a particular exercise in Colombia where the evidence and decision about the PCV were updated.

- Our analysis evidences a prolific production of CEAs on Pneumococcal Conjugated Vaccines (PCVs) in children from Latin America and the Caribbean (LAC) countries,

with more than a half of them financed by pharmaceutical industry with some potential bias in the relative advantage between available vaccine formulations. For first time an independent review evaluated the potential differences between PCV10 and PCV13 as well as the role of sponsor in the recommendation raised.

- There are concerns about CEAs' quality and conflict of interests involved in the generation of this kind of positive evidence to inform the DM about the selection between PCV10 and PCV13. A wide heterogeneity in the PCVs' effectiveness input data were identify in the published CEAs, possibly associated with the uncertainty about the relative advantage between vaccines, an aspect yet under discussion in the literature.

- When industry sponsored a PCVs' CEA in LAC is more likely that competitive alternative be judged with worst cost-effectiveness profile, i.e., higher incremental cost effectiveness ratio (ICER) or valued as a dominated alternative. It is different to independent analyses performed by the Academic or Ministers of Health. Sponsored bias in PCVs' CEAs is a potential risk to inform a discussion about the new vaccine introduction.

- The models implemented in the LAC CEAs are not transparent enough to evaluate the intrinsic uncertainty of the economic evaluation (EE). The required checklist for EEs (i.e., CHEERS) only evaluates formal aspects reported in the CEAs but not the actual quality and validity of the CEA. Although CHEERS is the most extensive used tool to standardized the published CEAs, actually that checklist do no perform a quality assessment. A more detailed approach need to review the model structure, source of parameters, rationality of alternatives included, assumptions, and comparisons made, not only verifying the report of them, as CHEERS propose. For the fist time these elements were simultaneously evaluated and re-estimation of CEAs' results performed for PCVs in LAC.

- There are not available explicit willingness to pay (WTP) thresholds in LAC countries, then the normative dimension of CEAs are in debt to be approached, limiting the capacity of an actual practical use of the CEAs in the DM. A high quality and unbiased CEA is useless if not WTP are defined by the society or used one that does not capture the actual opportunity cost of the population. The three times GDP *per capita* looks an over-estimation of the actual WTP of the population in LAC, especially in places where high economical inequalities exist.

- No CEA for PCVs in LAC included alternatives different to vaccination in the economic evaluation, i.e., breastfeeding, improve nutrition, access to antibiotics to treat the pneumococcal infection. Sub-optimal selection and over estimation of cost-effectiveness profiles for PCVs could be occur due to this omission.

- DM of new vaccine introduction in LAC countries is reported, by EPI managers and stakeholders, as a discussion process with participation of different actors and many rationalities involved, including health economic evaluations, although same EPI managers do not report deep technical knowledge in this regard or limitations in available local information. This is the first documented exercise that identifies the criteria used for new vaccine introduction in LAC EPIs.

- Most of the reported criteria to include new vaccines are related with the CEA itself, that is, Burden of Disease (BoD) and vaccine effectiveness/efficacy, but diverse aspects such as ethical considerations, equity, differential impact in vulnerable population, political interests, and technological pressures are reported as less important or not considered during the discussion. Despite this, the respondents do not consider that CEA has a cardinal influence in the DM. In LAC, DM about new vaccine introduction is supported in excess on CEAs and most of them are subject to potential sponsor biases in the recommendation or poor quality.

- Although BoD and cost-effectiveness information is reported as the main criteria to new vaccine introduction, the BoD is reported as generally lacking or poor-quality input in LAC countries. Then, published models could be correspond to parameters from other settings, usually high-income countries, and not necessary are reflecting the population situation.

- EPI managers in LAC region are confident about the use and influence of CEAs in DM of vaccines introduction, but the knowledge of the specific techniques could be limited.

- To continue PCV10 vaccination in Colombian children would had additional health outcomes to good value for money ratio, however, including recent evidence about the effectiveness of available PCVs and new pneumococcal serotypes distribution patterns, switching to PCV13 would be the cost-effective alternative in the Colombian setting as showed in the competitive analysis. The value for money of this change should be evaluated from the decision maker perspective and this research is a contribution in that sense, been the novel approximation to update a CEA and discuss the need of change the initial decision at the NITAG.

- There is no experimental field trials comparing efficacy of PCV10 and PCV13 head to head. The best evidence available to date is reports on effectiveness from geographies where different PCV vaccines have been implemented sequentially. There is space for the controversy about the specific advantages of one vaccine over another.

- Many published CEAs in LAC about PCVs are not reproducible or generate divergent recommendations. It is more evident when pharmaceutical sponsorship are involved in the study. Transparency in the model and possibility of detailed validation tests are

required to guaranty reproducibility and replicability of the CEA. For the first time was evaluated the validity of these analyses and recommendations validated from the CEAs published in LAC about PCVs.

7.2. Recommendations

- To use CEAs more efficiently and transparently, decision makers should state, early in the process, the criteria on which the decision will be made and what the role of EEs will be on it.
- Decision makers should be taught what a good CEA includes: all the necessary comparisons are made, the correct models are used, all evidence included has been validated, WTP thresholds are critically evaluated, sensitivity analyzes are performed, and potential conflicts of interest are removed or, at least, declared. CEA practitioners also must know how and why to provide scientific evidence to decision makers. These components have to be reviewed by the decision makers and initiatives for strengthen capabilities improve the reach in NITAGs and other audiences.
- It is needed to improve the transparency and assurance of basic requirements of CEAs in LAC, but also in other contexts. for example better instruments to evaluate CEA's quality in more detail could be generated overcome the shortcomings of populated CHEERS checklist. A space for research in quality assessment of CEAs was identified.
- To implement collegiate bodies as NITAG, not only for immunization, with wider profiles in participants, not limited to thematic experts, and assuring their independence and conditions of deliberation to recommend the technologies to be covered by the public resources.
- To strength the national capacities of the NITAG members about the use and limitations of the CEAs as methodology to obtain evidence-based inputs to discuss the potential impact of a new vaccine, as well as the knowledge on other inputs and rationalities involved in the DM. Local technical knowledge is required to counteract the potential undue technological pressure from vaccine producers.
- Public health practitioners and decisions makers should rethink and approach critically to the use of EEs' results for DM on interventions considered to be founded by public budgets. Other rationalities should be explicitly involved in the process, and deliberative approach with wider audience guaranteed.
- Not only initiatives to strengthen the use of evidence synthesis and health economic techniques are necessary in LMIC (positive dimension of DM), but also capacity in

priority settings and criteria beyond utilitarian economic perspective are needed in our countries to reach actual population well-being objectives (normative dimension of DM).

- A democratic approach about the use of CEAs to inform DM is highly valuable to help the society decides about how to invest public and scarce resources, especially in settings where the relative participation of serotypes such as 19A increases and there is availability of new PCVs with wider serotype coverage (15 and 20 valences), as expected at increasing prices and bigger impact to healthcare systems' budgets.

- To validate periodically the DM models and update them with the best available evidence. Updated results must be contrasted against the previously obtained results and decisions can change. Recognize this possibility and communicate it to the population is valuable for understanding DM as a dynamic and legitimate process.

- It is needed to generate and use real world data about vaccines effectiveness. There are no LAC study evaluating the actual impact of switching between vaccines or head to head comparisons in experimental or population trials. Approaches as the value of information (compatible with CEAs) could be a valid alternative to fill the knowledge gaps and advance in the DM.

- To strengthen the lab-based surveillance on *S. pneumoniae* serotypes after any of PCV is included in a EPI to allow make changes, if required, in a timely manner and reach the maximum impact in the population.

- EEs of vaccine benefits should include as comparators wider social and less expensive interventions. We have to strengthen the process of discussion and not only include a new vaccine in the EPI because it is cost-effective. In this way sub-optimal decision could be avoided and actual cost-effectiveness estimated.

- In Colombian context after the initial inclusion of PCV10 in children younger than one year of age, switch to PCV13 show better health outcomes, but PCV10 would have lower immunization costs, and still be a cost-effective alternative compared with no vaccination. Potential changes in other countries have to be locally evaluated and discussed, ideally with updated CEAs of available alternatives.

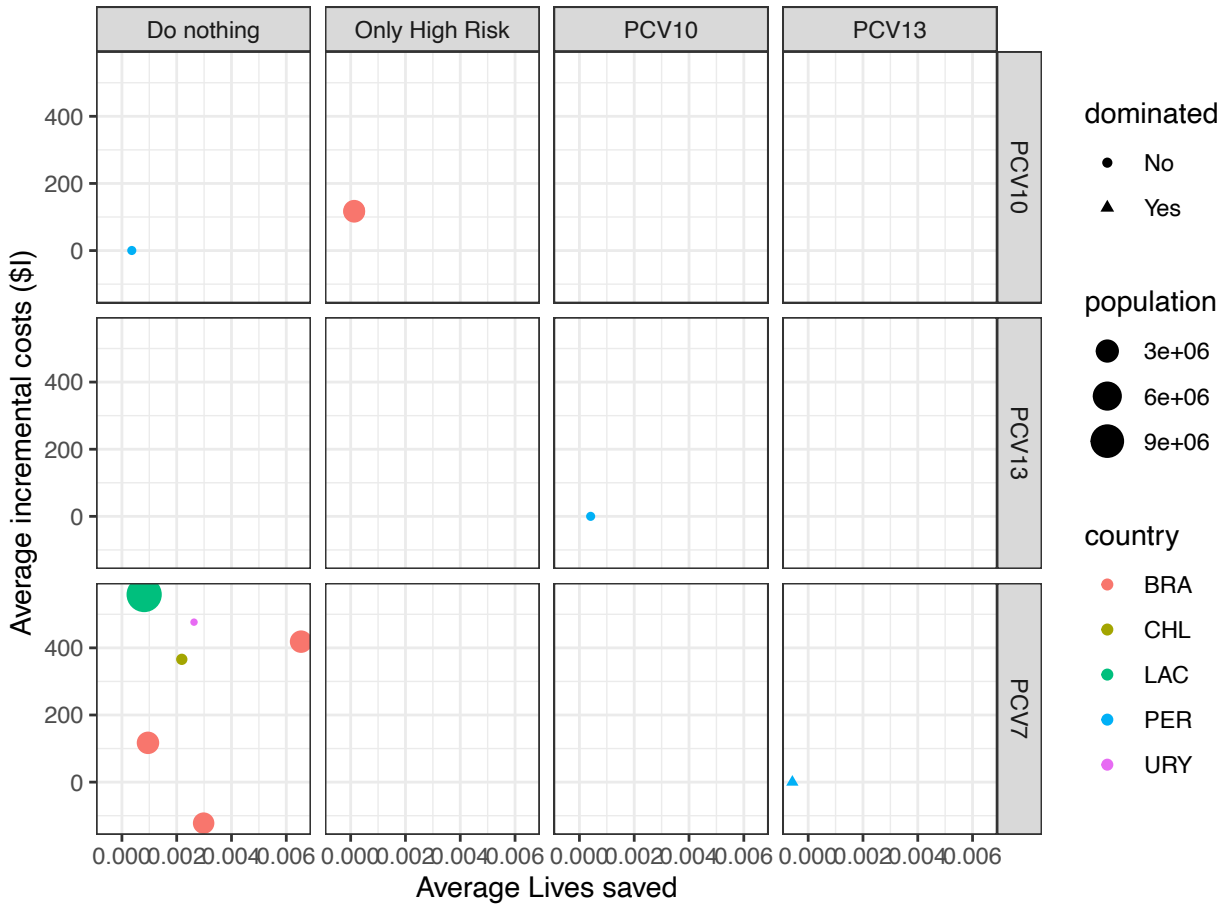
- To facilitate open access to CEAs models to allows detailed validation by audiences, verification of parameters and assumptions, and replicate the EEs in a particular context or reproduce it in other setting. Have a good quality and unbiased cost-effectiveness results put to governments in a better bargaining position to decide or not the introduction of new technology and obtain a fair price.

A. Annex: Supplementary material of Systematic Review

Following is the supporting additional material for Cost-effectiveness of Pneumococcal Conjugated Vaccines in Children in Latin America and the Caribbean: A Systematic Review.

Supplementary Material

Figure S1: Average per birth cohort population incremental and competitive analyses per lives saved in children's PCV CEAs from LAC.



Search strategies

Pubmed Search

Search conducted on the 14h August 2022

Search String

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("Cost-Benefit Analysis"[Mesh] OR “Analyses, Cost-Benefit” OR “Analysis, Cost-Benefit” OR “Cost-Benefit Analyses” OR “Cost Benefit Analysis” OR “Analyses, Cost Benefit” OR “Analysis, Cost Benefit” OR “Cost Benefit Analyses” OR “Cost Effectiveness” OR “Effectiveness, Cost” OR “Cost-Benefit Data” OR “Cost Benefit Data” OR “Data, Cost-Benefit” OR “Cost-Utility Analysis” OR “Analyses, Cost-Utility” OR “Analysis, Cost-Utility” OR “Cost Utility Analysis” OR “Cost-Utility Analyses” OR “Cost Benefit” OR “Costs and Benefits” OR “Benefits and Costs” OR “Cost-Effectiveness Analysis” OR “Analysis, Cost-Effectiveness” OR “Cost Effectiveness Analysis”) AND

(("Americas"[Mesh] NOT "North America"[Mesh]) OR "Mexico"[Mesh])

Results: 40

LILACS Search

Search conducted on the 15h August 2022

Search String

(cost-effectiveness OR mh:("analyses, COST-BENEFIT")) AND mh:("pneumococcal vaccines")

(cost-effectiveness OR mh:("analyses, COST-BENEFIT")) AND (“Pneumococcal vaccine” OR mh:("pneumococcal vaccines"))

(cost-effectiveness) or "analyses, COST-BENEFIT" [Subject descriptor] and (Pneumococcal vaccine) or "pneumococcal vaccines" [Subject descriptor]

Results: 394

Cochrane search

Search conducted on the 14h August 2022

Search String

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#3 MeSH descriptor: [Cost-Benefit Analysis] explode all trees (7762)

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#6 MeSH descriptor: [North America] explode all trees (24910)

#7 MeSH descriptor: [Mexico] explode all trees (683)

#8 #1 OR #2 (1600)

#9 #3 OR #4 (30436)

#10 (#5 NOT #6) OR # 7 (510921)

#8 AND #9 AND #10 (26)

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Scopus search

Search conducted on the 14th August 2022

Search String

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Results: 29

NHSEED search

Search conducted on the 15th August 2022

Search String

“Pneumococcal vaccine" AND Cost-Benefit Analysis

Results: 108

Google scholar search

"cost-effectiveness" AND "Pneumococcal vaccine" AND ("Aruba" OR "Argentina" OR "Antigua and Barbuda" OR "Bahamas" OR "Belize" OR "Bolivia" OR "Brazil" OR "Barbados" OR "Chile" OR "Colombia" OR "Costa Rica" OR "Cuba" OR "Curacao" OR "Cayman Islands" OR "Dominica" OR "Dominican Republic" OR "Ecuador" OR "Grenada" OR "Guatemala" OR "Guyana" OR "Honduras" OR "Haiti" OR "Jamaica" OR "St. Kitts and Nevis" OR "St. Lucia" OR "St. Martin" OR "Mexico" OR "Nicaragua" OR "Panama" OR "Peru" OR "Puerto Rico" OR "Paraguay" OR "El Salvador" OR "Suriname" OR "Turks and Caicos Islands" OR "Trinidad and Tobago" OR "Uruguay" OR "St. Vincent and the Grenadines" OR "Venezuela" OR "British Virgin Islands")

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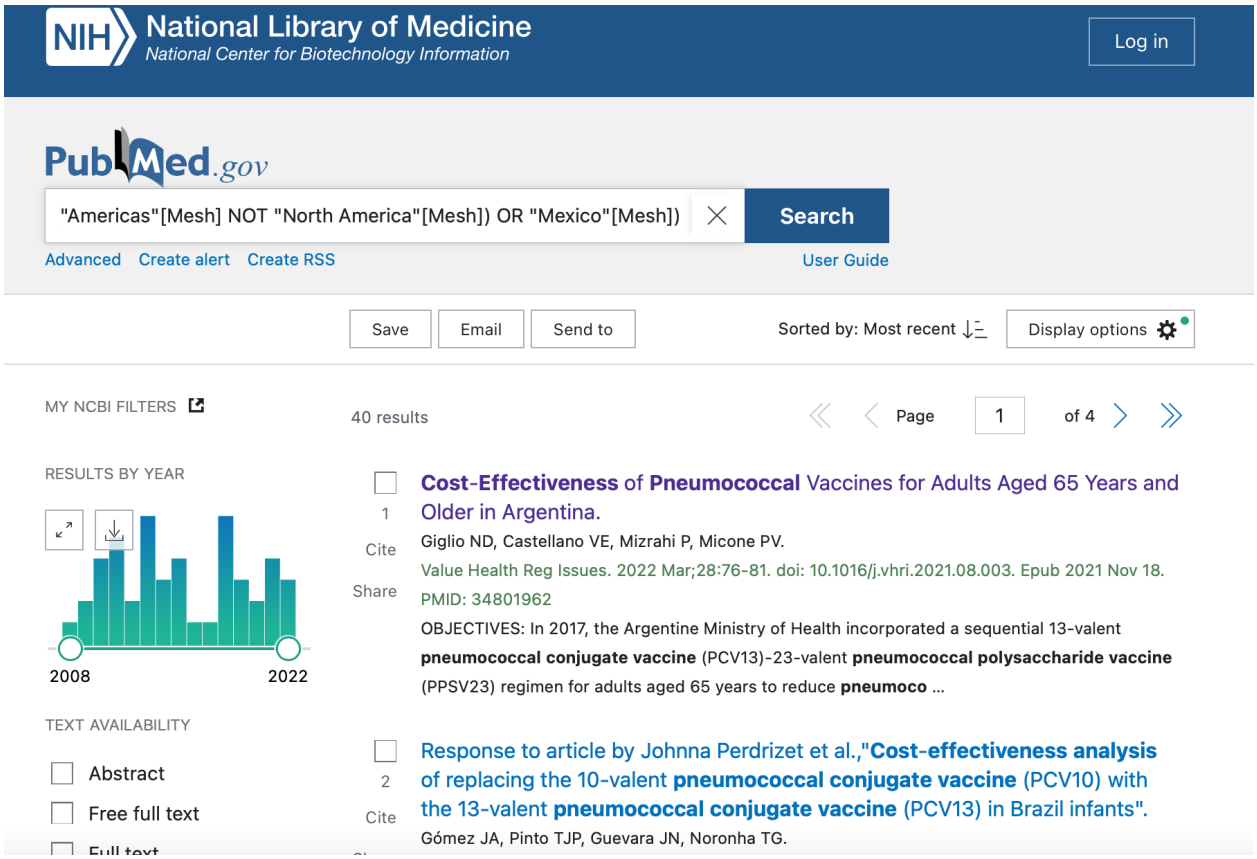
Database Screenshots

Pubmed



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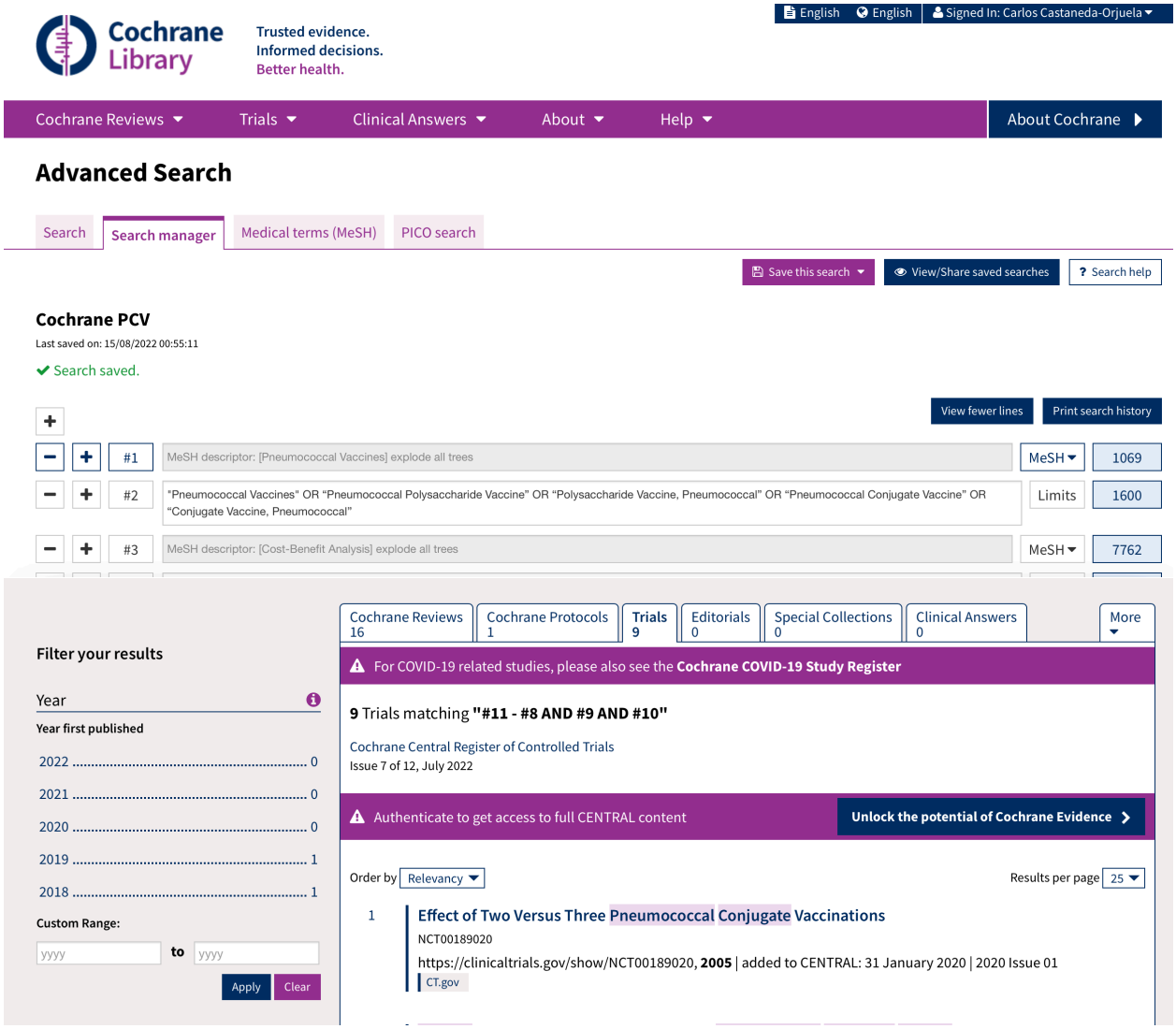
Cochrane Library
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Save this search View/Share saved searches Search help
Cochrane PCV
Last saved on: 15/08/2022 00:55:11
Search saved.
View fewer lines Print search history
#1 MeSH descriptor: [Pneumococcal Vaccines] explode all trees MeSH 1069
#2 "Pneumococcal Vaccines" OR "Pneumococcal Polysaccharide Vaccine" OR "Polysaccharide Vaccine, Pneumococcal" OR "Pneumococcal Conjugate Vaccine" OR "Conjugate Vaccine, Pneumococcal" Limits 1600
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Filter your results
Year
Year first published
2022 0
2021 0
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2019 1
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Cochrane Reviews 16
Cochrane Protocols 1
Trials 9
Editorials 0
Special Collections 0
Clinical Answers 0
More
For COVID-19 related studies, please also see the Cochrane COVID-19 Study Register
9 Trials matching "#11 - #8 AND #9 AND #10"
Cochrane Central Register of Controlled Trials
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1 Effect of Two Versus Three Pneumococcal Conjugate Vaccinations
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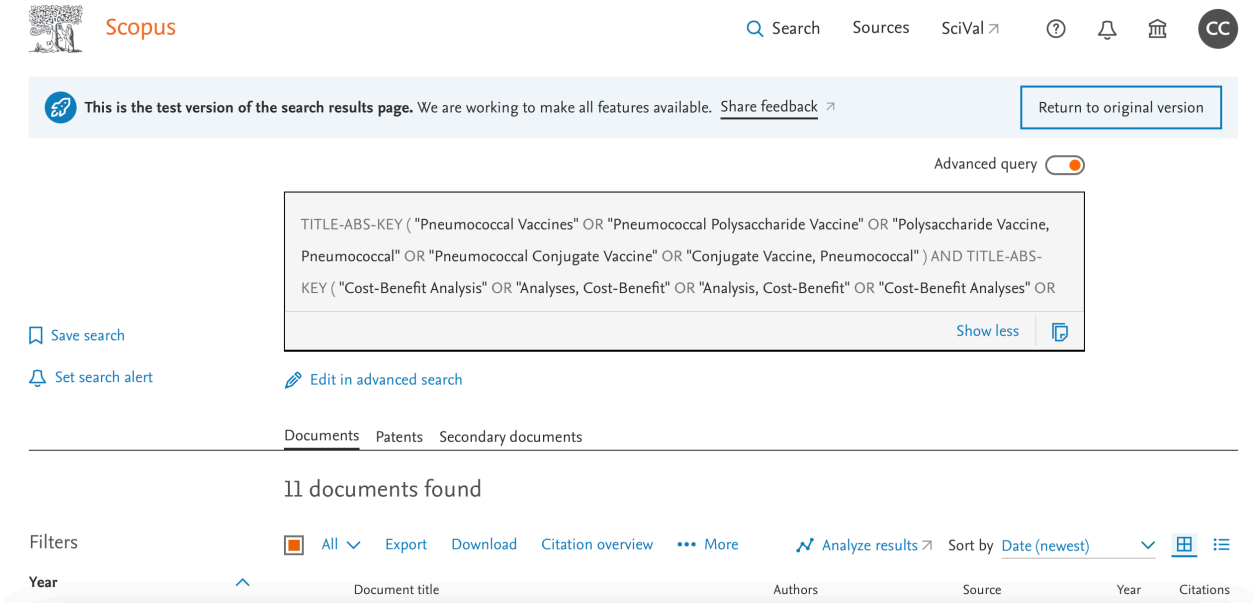

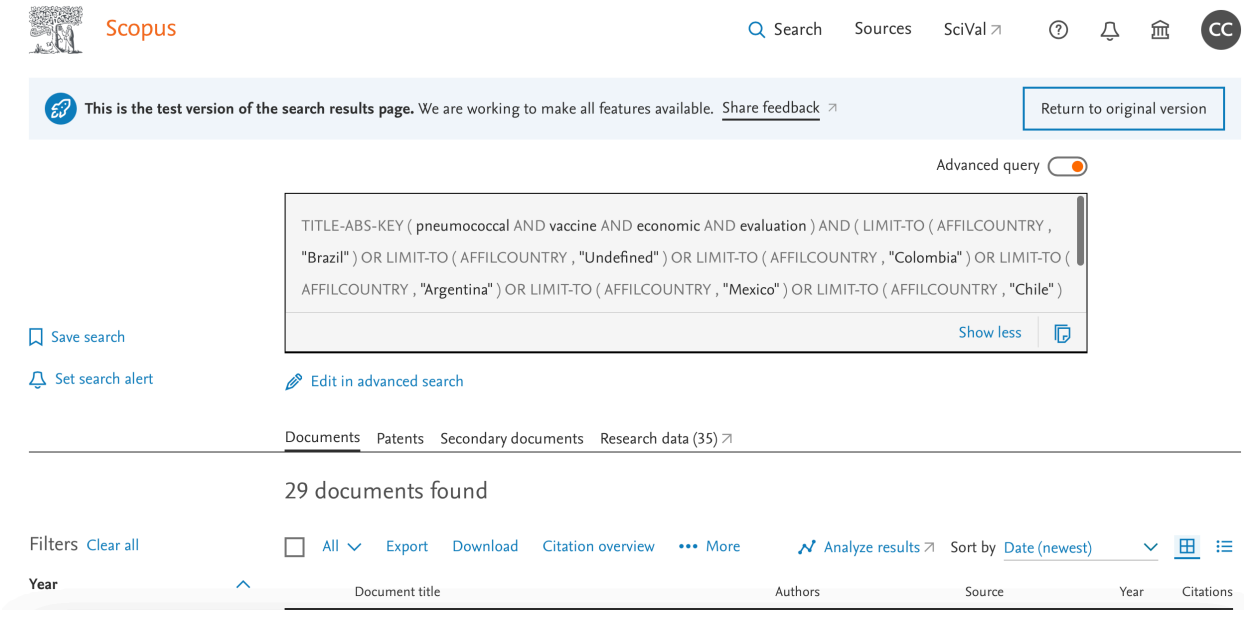
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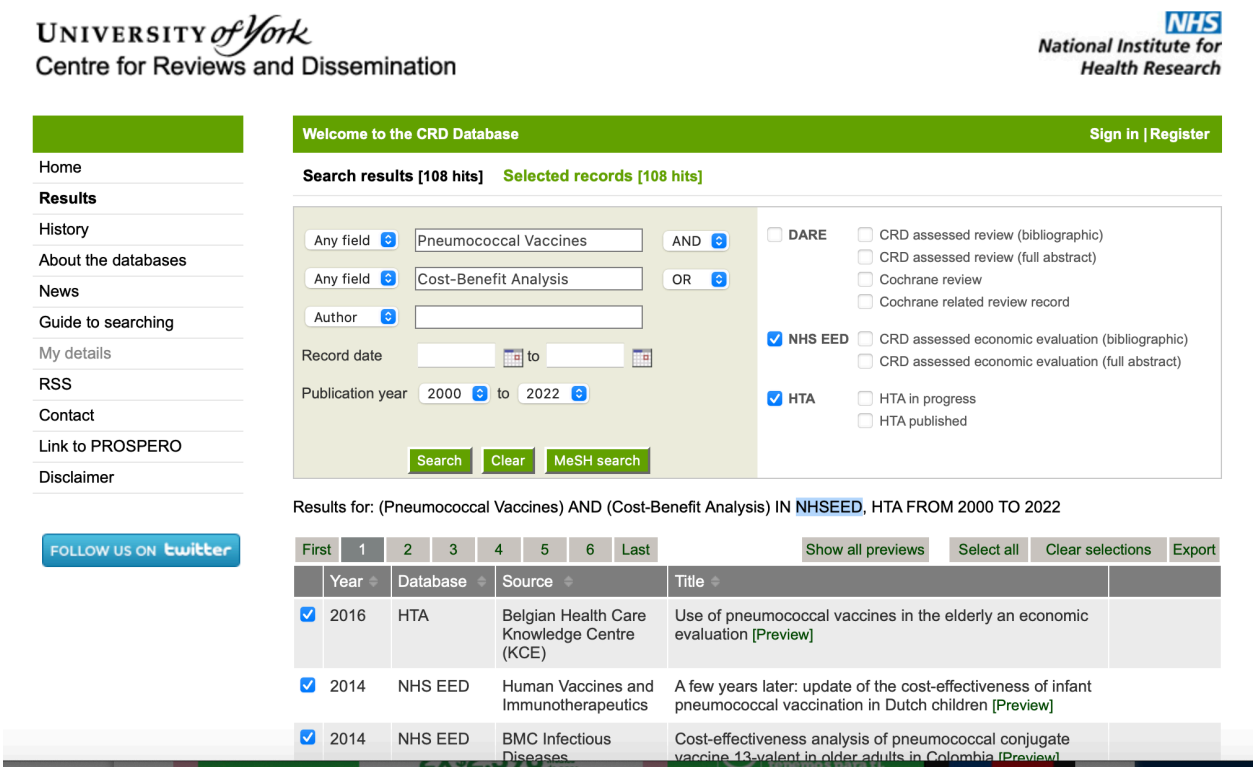
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Clear
MeSH search
DARE
CRD assessed review (bibliographic)
CRD assessed review (full abstract)
Cochrane review
Cochrane related review record
NHS EED
CRD assessed economic evaluation (bibliographic)
CRD assessed economic evaluation (full abstract)
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HTA in progress
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2016
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Belgian Health Care Knowledge Centre (KCE)
Use of pneumococcal vaccines in the elderly an economic evaluation [Preview]
2014
NHS EED
Human Vaccines and Immunotherapeutics
A few years later: update of the cost-effectiveness of infant pneumococcal vaccination in Dutch children [Preview]
2014
NHS EED
BMC Infectious Diseases
Cost-effectiveness analysis of pneumococcal conjugate vaccine 13-valent in older adults in Colombia [Preview]

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Excluded full text articles

Count	PMID or identificatory	Reference	Database	Reason to exclusion
1	17276779	Sinha A, Levine O, Knoll MD, Muhib F, Lieu TA. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis. Lancet. 2007 Feb 3;369(9559):389-96. doi: 10.1016/S0140-6736(07)60195-0. PMID: 17276779.	NHSEED	Pooled beyond LAC
2	Alvis2010	Alvis-Guzman and De la Hoz, Cost effectiveness of heptavalent pneumococcal conjugate vaccine in populations of high risk in Colombia. Colombia Médica 2010:41(4);315-22	NHSEED	Only High risk
3	24038500	Nakamura MM, Tasslimi A, Lieu TA, Levine O, Knoll MD, Russell LB, Sinha A. Cost effectiveness of child pneumococcal conjugate vaccination in middle-income countries. Int Health. 2011 Dec;3(4):270-81. doi: 10.1016/j.inhe.2011.08.004. PMID: 24038500.	NHSEED	Pooled beyond LAC
4	24038499	Tasslimi A, Nakamura MM, Levine O, Knoll MD, Russell LB, Sinha A. Cost effectiveness of child pneumococcal conjugate vaccination in GAVI-eligible countries. Int Health. 2011 Dec;3(4):259-69. doi: 10.1016/j.inhe.2011.08.003. PMID: 24038499.	NHSEED	Pooled beyond LAC
5	30554762	Chen C, Cervero Liceras F, Flasche S, Sidharta S, Yoong J, Sundaram N, Jit M. Effect and cost-effectiveness of pneumococcal conjugate vaccination: a global modelling analysis. Lancet Glob Health. 2019 Jan;7(1):e58-e67. doi: 10.1016/S2214-109X(18)30422-4. PMID: 30554762; PMCID: PMC6293964.	LILACS	Pooled beyond LAC
6	28922054	Ceyhan M, Ozsurekci Y, Aykac K, Hacibedel B, Ozbilgili E. Economic burden of pneumococcal infections in children under 5 years of age. Hum Vaccin Immunother. 2018 Jan 2;14(1):106-110. doi: 10.1080/21645515.2017.1371378. Epub 2017 Nov 7. Erratum in: Hum Vaccin Immunother. 2021 Jul 3;17(7):2350. PMID: 28922054; PMCID: PMC5791583.	LILACS	Not LAC
7	28161238	Bhatt AS, DeVore AD, Hernandez AF, Mentz RJ. Can Vaccinations Improve Heart Failure Outcomes?: Contemporary Data and Future Directions. JACC Heart Fail. 2017 Mar;5(3):194-203. doi: 10.1016/j.jchf.2016.12.007. Epub 2017 Feb 1. PMID: 28161238; PMCID: PMC5336530.	LILACS	Not pneumococcal

8	30556985	Patchay A. The economic benefits of vaccination. Nurs N Z. 2017 Mar;23(2):17-19. PMID: 30556985.	LILACS	Review
9	29295048	Cohen A, Kulikowski CA, Elbert T, Clark S, Constenla D, Sinha A. Decision-Tree Model for Support of Health Policy Choices Based on Pneumococcal Conjugate Vaccine (PCV) Program Outcomes. Stud Health Technol Inform. 2017;245:40-44. PMID: 29295048.	LILACS	Not CEA
10	26135209	Kohli MA, Farkouh RA, Maschio MJ, McGarry LJ, Strutton DR, Weinstein MC. Despite High Cost, Improved Pneumococcal Vaccine Expected To Return 10-Year Net Savings Of $12 Billion. Health Aff (Millwood). 2015 Jul;34(7):1234-40. doi: 10.1377/hlthaff.2014.1274. PMID: 26135209.	LILACS	Not CEA
11	23002969	Gladstone RA, Jefferies JM, Faust SN, Clarke SC. Pneumococcal 13-valent conjugate vaccine for the prevention of invasive pneumococcal disease in children and adults. Expert Rev Vaccines. 2012 Aug;11(8):889-902. doi: 10.1586/erv.12.68. PMID: 23002969.	LILACS	Review
12	21569402	Chaiyakunapruk N, Somkrua R, Hutubessy R, Henao AM, Hombach J, Melegaro A, Edmunds JW, Beutels P. Cost effectiveness of pediatric pneumococcal conjugate vaccines: a comparative assessment of decision-making tools. BMC Med. 2011 May 12;9:53. doi: 10.1186/1741-7015-9-53. PMID: 21569402; PMCID: PMC3117724.	LILACS	Hypotetical pops
13	21501444	Webster J, Theodoratou E, Nair H, Seong AC, Zgaga L, Huda T, Johnson HL, Madhi S, Rubens C, Zhang JS, El Arifeen S, Krause R, Jacobs TA, Brooks AW, Campbell H, Rudan I. An evaluation of emerging vaccines for childhood pneumococcal pneumonia. BMC Public Health. 2011 Apr 13;11 Suppl 3(Suppl 3):S26. doi: 10.1186/1471-2458-11-S3-S26. PMID: 21501444; PMCID: PMC3231900.	LILACS	Not CEA
14	20171397	Light DW. GAVI's Advance Market Commitment. Lancet. 2010 Feb 20;375(9715):638. doi: 10.1016/S0140-6736(10)60267-X. PMID: 20171397.	LILACS	Comment
15	18419359	Davis MM. Challenges in cost-effectiveness analyses of hospital interventions to improve quality. Infect Control Hosp Epidemiol. 2008 May;29(5):395-7. doi: 10.1086/587966. PMID: 18419359.	LILACS	Comment
16	14505970	Boomers, not just babies, need to get their shots. Harv Health Lett. 2003 Sep;28(11):7. PMID: 14505970.	LILACS	Comment
17	12229878	Grabenstein JD. Vaccines: worth paying for the value returned. Ann Pharmacother. 2002 Sep;36(9):1471-2. doi: 10.1345/aph.1A125. PMID: 12229878.	LILACS	Comment

18	11923145	Spoulou V, Gilks CF, Ioannidis JP. Protein conjugate pneumococcal vaccines. BMJ. 2002 Mar 30;324(7340):750-1. doi: 10.1136/bmj.324.7340.750. Erratum in: BMJ 2002 Apr 27;324(7344):1002. PMID: 11923145; PMCID: PMC1122694.	LILACS	Comment
19	11700581	Ament A, Fedson DS, Christie P. Pneumococcal vaccination and pneumonia: even a low level of clinical effectiveness is highly cost-effective. Clin Infect Dis. 2001 Dec 15;33(12):2078-9. doi: 10.1086/324356. Epub 2001 Nov 7. PMID: 11700581.	LILACS	Comment
20	11388708	Zimmerman RK, Jackson RE. Vaccine policy decisions: tension between science, cost-effectiveness and consensus? Am Fam Physician. 2001 May 15;63(10):1919, 1923. PMID: 11388708.	LILACS	Editorial
21	10706207	Hueston WJ, Mainous AG 3rd, Brauer N. Predicting cost-benefits before programs are started: looking at conjugate vaccine for invasive pneumococcal infections. J Community Health. 2000 Feb;25(1):23-33. doi: 10.1023/a:1005136817158. PMID: 10706207.	LILACS	Not LAC
22	9805173	Thomas R. Preventing pneumococcal disease. Can Fam Physician. 1998 Oct;44:2180-1, 2184-5. PMID: 9805173; PMCID: PMC2277924.	LILACS	Not CEA
23	3079635	LaForce FM, Eickhoff TC. Pneumococcal vaccine: the evidence mounts. Ann Intern Med. 1986 Jan;104(1):110-2. doi: 10.7326/0003-4819-104-1-110. PMID: 3079635.	LILACS	Editorial

Consolidated CHEERS score by included article

PMID	title	abstract	context	question	target	setting	perspective	comparators	horizon	discount	outcomes	singleEffect	synthesisEffect
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22266291	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0	Partially
24171921	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
25500653	Yes	Partially	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
25919156	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
25919155	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0	Partially
25878563	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
20107706	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	0	Yes
20064478	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	0	Yes
19141172	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Yes
26837524	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
21839902	Partially	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Partially
21621575	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0	Partially
20963275	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Yes
21075266	Partially	Yes	Partially	Yes	Yes	No	Yes	Partially	Yes	No	Yes	0	No
24038500	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	0	Partially
30087049	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0	Partially
souza2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Partially	Yes	0	Yes
souza12009	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Partially	Yes	Yes	Yes	0	Partially
27986203	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Yes
24004943	Yes	Yes	Yes	Yes	Yes	No	Yes	Partially	Yes	Yes	Yes	0	Partially
19062601	Partially	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Yes	0	Yes
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32966176	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Partially	Yes	Yes	Yes	0	No
30156978	No	Yes	Yes	Yes	Yes	Partially	Yes	Partially	Yes	No	Yes	0	No
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Continuation of table

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Continuation of table

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souza2009	0	Yes	Yes	No
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24004943	Yes	Yes	Yes	Yes
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32474199	0	Yes	Yes	Yes
32966176	0	Yes	Yes	Yes
30156978	0	Yes	Yes	Yes
32096144	Yes	Yes	Yes	Yes