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# Cost-effectiveness analysis of 10- and 13-valent pneumococcal conjugate vaccines in Peru

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ABSTRACT

*Objective:* To evaluate the cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine (PCV10) versus the 13-valent PCV (PCV13) to the National Immunization Schedule in Peru for prevention of pneumococcal disease (PD) in children <5 years of age.
*Methods:* The integrated TRIVAC vaccine cost-effectiveness model from the Pan American Health Organization's ProVac Initiative (version 2.0) was applied from the perspective of the Government of Peru. Twenty successive cohorts of children from birth to 5 years were evaluated. Clinical outcomes were pneumococcal pneumonia (PP), pneumococcal meningitis (PM), pneumococcal sepsis (PS) and acute otitis media from any causes (AOM). Measures included prevention of cases, neurological sequelae (NS), auditory sequelae (AS), deaths and disability adjusted life years (DALYs). A sensitivity analyses was also performed.
*Findings:* For the 20 cohorts, net costs with PCV10 and PCV13 were US$ 363.26 million and US$ 408.26 million, respectively. PCV10 prevented 570,273 AOM; 79,937 PP; 2217 PM; 3049 PS; 282 NS; 173 AS; and 7512 deaths. PCV13 prevented 419,815 AOM; 112,331 PN; 3116 PM; 4285 PS; 404 NS; 248 AS; and 10,386 deaths. Avoided DALYs were 226,370 with PCV10 and 313,119 with PCV13. Saved treatment costs were US$ 37.39 million with PCV10 and US$ 47.22 million with PCV13. Costs per DALY averted were US$ 1605 for PCV10, and US$ 1304 for PCV13. Sensitivity analyses showed similar results. PCV13 has an extended dominance over PCV10.
*Conclusion:* Both pneumococcal vaccines are cost effective in the Peruvian context. Although the net cost of vaccination with PCV10 is lower, PCV13 prevented more deaths, pneumococcal complications and sequelae. Costs per each prevented DALY were lower with PCV13. Thus, PCV13 would be the preferred policy; PCV10 would also be reasonable (and cost-saving relative to the status quo) if for some reason 13-valent were not feasible.



## 1. Introduction

*Streptococcus pneumoniae* (SP) is an important cause of pneumonia, meningitis and other invasive pneumococcal diseases (IPD) in children <5 years of age, especially in developing countries [1–3]. Each year, IPD is the cause of over half a million deaths in children <5 years worldwide [4], with more than 10,000 of those deaths in Latin America and the Caribbean (LAC) [5]. It is estimated to be the most common cause of vaccine-preventable deaths in children <5 years in the region of the Americas [5] and IPD treatment is responsible for a significant economic burden [6].

Although there are more than 90 serotypes of SP [7], not all cause disease. The new pneumococcal conjugate vaccines (PCV) protect against the serotypes most commonly associated with invasive disease [4,8]. In Peru, the 7-valent PCV (PCV7) was added to the

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National Immunization Schedule in 2009 by the *National Immunization Program of the Ministry of Health (MINSA)* [9]. PCV7 had been proven effective in preventing IPD [8] and providing modest protection against all-cause acute otitis media (AOM) [10].

In 2011, however, PCV7 was withdrawn from the global market and replaced by higher valence vaccines: the 10-valent (PCV10) (Synflorix®, GlaxoSmithKline) and the 13-valent (PCV13) (Prevenar 13®, Wyeth/Pfizer). PCV10 added three additional serotypes—1, 5 and 7F—plus a Non-Typeable *Haemophilus influenzae* (NTHi) protein carrier that could protect against AOM [11]. PCV13 covers an additional three—3, 6A and 19A (i.e., six more than PCV7) [12]. Evidence shows that their safety and immunogenicity profiles of these higher valences vaccines are similar to that of PCV7 and they do not interference with other vaccines in young children [11,12]. Since these two higher valence vaccines differ in serotypes covered, NTHi protein carrier, and unit price per dose, their impact as a public health intervention could differ. Economic evaluations (EE) should play an important role in decision-making regarding their adoption [13].

In this context, the *National Institute of Health* of Peru (Instituto Nacional de Salud, INS), the MINSA scientific research branch that provides evidence for public health decision-making, with support from the ProVac Initiative of the Pan American Health Organization (Washington, DC, USA; PAHO) [14,15], carried out this EE. The study objective was to evaluate the cost-effectiveness of introducing the PCV10 versus the PCV13 to the National Immunization Schedule for prevention of IPD in children <5 years of age in Peru.

## 2. Methods

### 2.1. General modeling approach and comparators

This study employed the TRIVAC cost-effectiveness model, developed by the London School of Hygiene and Tropical Medicine in collaboration with the PAHO ProVac Initiative [14,15]. The pneumococcal component of TRIVAC (version 2.0) [16] was adapted for Peru to conduct the cost-effectiveness analysis (CEA) from the perspective of the Government of Peru, including direct costs borne by its public health system—MINSA and the *EsSalud* Social Security System [17].

Since PCV7 had been withdrawn from the market, PCV10 and PCV13 were compared to having no PCV vaccination program. The incremental cost-effectiveness of the less costly vaccine was compared to that of the more costly to estimate whether the additional benefits would be worth the additional cost.

The TRIVAC model was populated with data on demographics, disease burden, local vaccine serotype distribution, vaccine efficacy, health services utilization, health service costs and vaccination program costs.

It followed 20 stacked cohorts of children from birth to death. IPD cases and deaths were only considered for the first 5 years of life, but permanent meningitis sequelae, life-years gained (LYG) and Disability Adjusted Life-Years (DALY) were calculated over the life-time of each birth cohort. The model estimated the number of cases, deaths and sequelae due to *S. pneumonia*, as well as associated costs in scenarios with and without vaccination. These outputs were then used to calculate health impact (e.g., DALYs averted), economic impact (e.g., net costs, incremental program costs and treatment costs averted), cost-effectiveness (e.g., cost-per-death averted) and cost-utility (e.g., cost-per-DALY averted). The results from each cohort were combined and used to report both the cumulative and annual health benefits and costs associated with each scenario [16].

DALYs were estimated using the disability weights defined for each disease syndrome by the World Health Organization (WHO) [18] and the life-expectancy-at-birth estimated for each cohort by the *National Institute of Statistics and Informatics* of Peru (INEI), using validated international methods [19]. A 3% discount rate for both costs and benefits was used and did not include age weighting (preference for life-years gained during productive years of life) [20,21]. A Gross Domestic Product Per Capita (GDP-PC) for the year 2011 of US$ 6009 (1 US$ = 2.80 PEN [Peruvian Nuevos Soles]) was used as the cost-effectiveness threshold.

The model calculated the number of cases of all-cause AOM, pneumococcal pneumonia, pneumococcal meningitis and pneumococcal sepsis by multiplying the incidence rate by the estimated life-years at risk between birth and 5 years of age. Life-years at risk were calculated for each birth cohort using projections for the number of births and the infant and child mortality rate. Fig. 1 shows the general model structure. In the scenario with vaccination, the total number of averted cases was estimated by multiplying the number of cases in each age group (<3 months, 3–5 months, 6–8 months, 9–11 months, 12–23 months, 24–35 months, 36–47 months, 48–59 months) by the dose- and age-specific program coverage (using DTP1/2/3 timing of vaccination as a proxy), the dose-specific vaccine efficacy and the vaccine-type coverage. Other factors were varied in "what-if" scenario analysis (e.g., waning protection, herd effects <5 years, serotype replacement, low efficacy, low program coverage). Deaths were estimated by applying the reported case-fatality ratio (CFR) to estimates of the number of cases post-vaccination. Pneumococcal meningitis sequelae were obtained by multiplying meningitis survivors (total estimated cases minus deaths) by the estimated proportion of those children that would develop neurological and auditory sequelae [16].

Costs were estimated based on the number of children vaccinated according to vaccine coverage per dose and adjusted for wastage, freight, handling and extra system costs, which included all other incremental costs, in addition to the vaccine and supply procurement. An average number of ambulatory visits and hospitalizations were estimated for disease type and multiplied by the weighted average cost per case. The cost per case was derived from the proportion receiving care by provider type and the associated treatment cost per provider. To estimate the life-time costs associated with meningitis sequelae, an average estimated annual cost until death was assigned [16].

### 2.2. Demographics

INEI provided data on the number of live births per year, infant mortality rate and life expectancy at birth for each of the 20 cohorts. Mortality rate in children <5 years of age was obtained from United Nations Department of Economic and Social Affairs' Population Division [22]. This demographic information was included for each of the 20 birth cohorts (2012–2031) and four previous cohorts (2008–2011). The latter was needed to calculate more accurate 'annual' events and the cost of the first 5 years of the vaccination program.

### 2.3. Disease burden

Pneumococcal pneumonia, pneumococcal meningitis, pneumococcal sepsis and all-cause acute otitis media were evaluated. AOM was included due to the etiologic role of NTHi in this disease [23,24]. Disease burden data on pneumococcal syndromes in Peru is sparse, and there are concerns about how representative the available data is and whether the full extent of disease is being detected in laboratories. Consequently, we have included a description of how disease incidence and CFRs were derived for each syndrome studied; Table 1 shows the estimates. Low and high range estimates were defined to explore the "what if" scenario analysis.

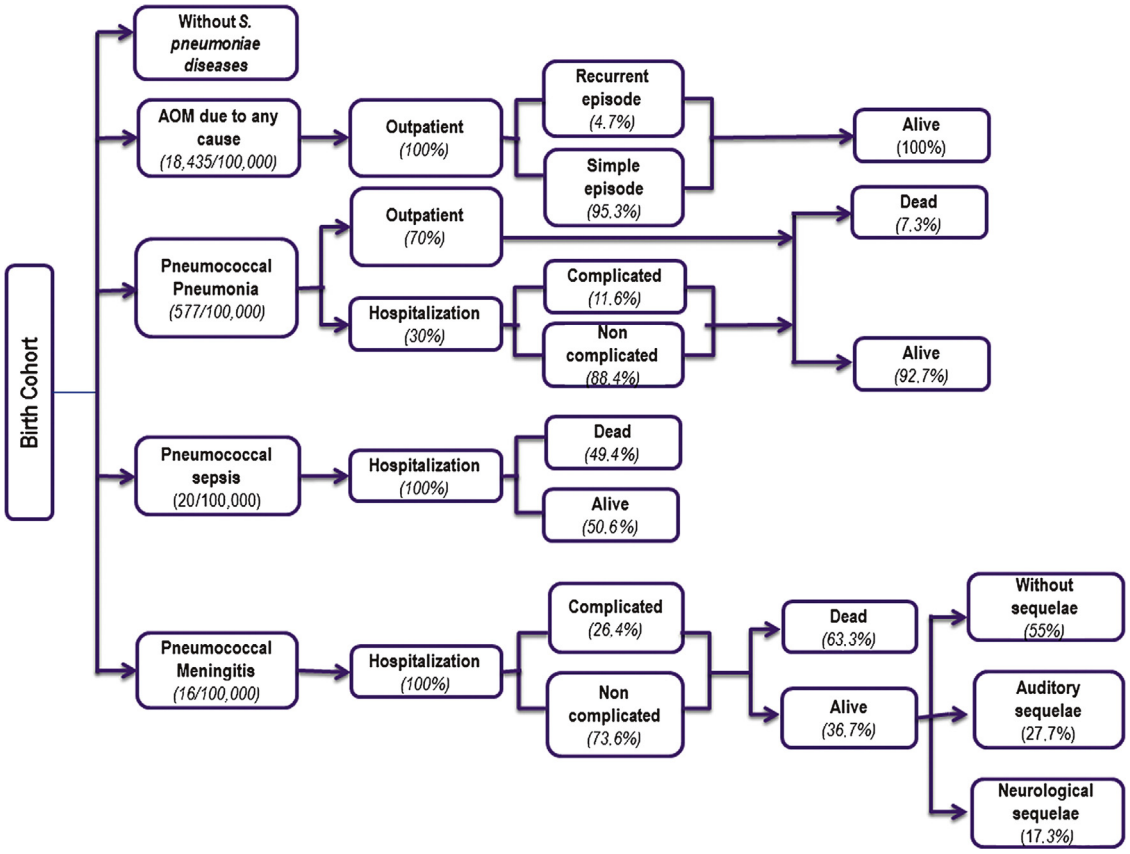



**Fig. 1.** Conceptual framework for the model and invasive pneumococcal disease burden in Peru.

*2.3.1. Pneumococcal pneumonia*

For the base case, estimates of cumulative incidence and case fatality rates for pneumococcal pneumonia in Peru were taken from a systematic review by O'Brien and colleagues [3]. For the scenario analysis, the cumulative incidence of pneumococcal pneumonia estimates were derived from primary data: cases of clinical pneumonia reported by MINSA and EsSalud, the percentage of radiologically confirmed pneumonia cases projected in a systematic review of LAC data [5], and the proportion of molecular confirmations of *S. pneumoniae* from radiological pneumonia reported in a primary study of a Peruvian population [25].

*2.3.2. Pneumococcal meningitis*

Cumulative incidence and case fatality rates for pneumococcal meningitis came from O'Brien's and colleagues estimations [3]. Also, the proportions of auditory and neurological sequelae were based on a systematic review by Baraff and colleagues [26].

*2.3.3. Non-pneumonia non-meningitis is pneumococcal diseases (NPNM): pneumococcal sepsis*

No reliable data on cumulative incidence of pneumococcal sepsis in Peru was found. Thus, estimates reported by O'Brien [3] were used: a ratio of 1.27 cases of NPNM for each case of Pneumococcal meningitis in countries with <75 deaths per 100,000 live births (Peru). Also, pneumococcal-specific sepsis case fatality was assumed to be 78% of the case fatality rate for pneumococcal meningitis, based on the same systematic review [3].

*2.3.4. Acute otitis media*

The base case cumulative incidence of AOM used came from data reported by Rudan and colleagues [27]. However, two other estimates were assessed in the "what if" scenario analysis, one based on outpatient reports from the Peruvian ambulatory care health system, and the other, on data published by Teele and colleagues [28]. The TRIVAC model assumes that there are no AOM cases severe enough to lead to hospitalization or to be a cause of death [16].

*2.3.5. Disability weights, distribution of disease cases and deaths by age*

The disability weights due to pneumococcal cases, as well as auditory and neurological sequelae, came from the Global Burden of Disease: 2004 Update [18]. The distribution of cases and deaths by age were taken from Hortal and colleagues [29] who evaluated the incidence of pneumococcal serotypes in pediatric inpatients <5 years of age in Uruguay. This report was used because the baseline distribution of pneumococcal serotypes (pre-vaccination period) in Uruguay was similar to the distribution reported in Peru [30].

*2.4. Vaccine impact*

*2.4.1. Vaccination schedule and coverage*

The approved National Immunization Schedule for PCV7 in Peru included two primary doses at 2 and 4 months of age, plus a booster at 12–18 months (PCV2 + 1) [4,31,32]. Vaccination coverage was assumed based on coverage levels achieved with PCV7 for 2011, which were 99.2% for the first dose, 95.8% for the second and 92.5% for the booster. The model also assumed that vaccination coverage could have an annual increase of 5%, up to a possible maximum of 99%. Moreover, coverage and timing estimates were based on Diphtheria, Pertussis and Tetanus (DPT) vaccine coverage as showed in Table 2 [33]. On the other hand, the coverage reported by the Peruvian Demographic and Family Health Survey (ENDES) [34] was considered for the "what-if" scenario analysis as low coverage,

**Table 1**
Input parameters for estimating disease burden of all causes acute otitis media, pneumococcal pneumonia, pneumococcal meningitis and pneumococcal sepsis in Peru (2011).

| Parameter | Estimate | Scenarios | | Source/s |
|---|---|---|---|---|
| | | Low | High | |
| Annual incidence per 100,000 children 1–59 months of age | | | | |
| All causes acute otitis media | 18,435 | 2552 | 90,000 | Rudan I, and colleagues [27] (estimate), Teele and colleages [28]. (High), Peruvian statistics (Low) |
| Pneumococcal pneumonia | 577 | 63 | 718 | O'Brien, and colleagues [3] (estimate and high), Modified Peruvian statistics[c] (low) [5,25] |
| Pneumococcal meningitis | 16.0 | 12.0 | 19.0 | O'Brien, and colleagues [3] (estimate, high and low) |
| Pneumococcal NPNM (sepsis)[a] | 22.0 | 21.9 | 68.0 | O'Brien, and colleagues [3] (estimate, High and low) |
| % case fatality ratios in ages 1–59 m[b] | | | | |
| All causes pneumonia cases | 7.3% | 6.3% | 9.9% | O'Brien, and colleagues [3] (estimate, high and low) |
| Pneumococcal meningitis | 63.3% | 54.9% | 72.6% | O'Brien, and colleagues [3] (estimate, high and low) |
| Pneumococcal NPNM (sepsis)[a] | 49.4% | 49.4% | 49.4% | O'Brien, and colleagues [3] (estimate, high and low) |
| % sequelae in pneumococcal meningitis survivors | | | | |
| % Auditory sequelae | 27.7% | – | – | Baraff and colleagues [26] |
| % Neurological sequelae | 17.3% | – | – | Baraff and colleagues [26] |
| Disability weight for DALY calculations | | | | |
| All causes acute otitis media | 0.02 | – | – | WHO[d] Global Burden of Disease (GBD) 2004 [18] |
| Pneumococcal pneumonia cases | 0.26 | – | – | WHO GBD 2004 [18] |
| Pneumococcal meningitis | 0.62 | – | – | WHO GBD 2004 [18] |
| Pneumococcal NPNM (sepsis)[a] | 0.26 | – | – | PROVAC Model assumption |
| % Auditory sequelae | 0.12 | – | – | WHO GBD 2004 [18] |
| % Neurological sequelae | 0.38 | – | – | WHO GBD 2004 [18] |
| Mean duration of illness (in days) | | | | |
| All causes acute otitis media | 7 | – | – | Delphi whit Peruvian physicians |
| Pneumococcal pneumonia cases | 6 | – | – | Delphi whit Peruvian physicians |
| Pneumococcal meningitis | 10 | – | – | Delphi whit Peruvian physicians |
| Pneumococcal NPNM (sepsis)[a] | 6 | – | – | Delphi whit Peruvian physicians |
| Age distribution of disease cases and deaths (in months) | | | | |
| <3 m | 9.4% | – | – | Hortal and colleagues [29] |
| 3–5 m | 9.4% | – | – | Hortal and colleagues [29] |
| 6–8 m | 9.8% | – | – | Hortal and colleagues [29] |
| 9–11 m | 9.8% | – | – | Hortal and colleagues [29] |
| 12–23 m | 28.6% | – | – | Hortal and colleagues [29] |
| 24–35 m | 15.3% | – | – | Hortal and colleagues [29] |
| 36–47 m | 8.9% | – | – | Hortal and colleagues [29] |
| 48–59 m | 8.9% | – | – | Hortal and colleagues [29] |

[a] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).
[b] In the absence of vaccination, Case Fatality Ratios are assumed to decline in each successive birth cohort in line with the general trend in under-five mortality. This is done by assuming the fraction of under five deaths caused by the disease remains fixed over time.
[c] Peruvian statistics provided clinical pneumonia cases, Which was modified for obtaining pneumococcal pneumonia estimations.
[d] WHO = World Health Organization.

which assumes 69.0% for the first dose, 65.6% for the second and 62.3% for the booster.

### 2.4.2. Vaccine effectiveness estimations

Both PCV10 and PCV13 were licensed based on WHO' immunological non-inferiority criteria for correlation of protection in efficacy trials of PCV7 [4]. The efficacy of both of the newer pneumococcal vaccines was based on a meta-analysis of PCV7 clinical data that estimated 81% efficacy (PCV3 + 1 schedule) [8]. Efficacy was multiplied by the serotype coverage of each vaccine. Serotype distribution was obtained from sentinel surveillance in Peru [30].

The efficacy of PCV10 to prevent AOM was extrapolated from a study carried out in Czech Republic and Slovakia that assessed a PCV11 prototype [35] and reported a 33.6% efficacy in preventing all-cause AOM. PCV10 includes Haemophilus Influenzae Type b (Hib) surface protein D as a carrier—possibly providing additional protection against NTHi, an important cause of AOM—and is similar in composition to the PCV11 prototype [24,36]. Efficacy for PCV13 in preventing AOM cases was directly extrapolated from the meta-analysis of PCV7 clinical data [37]. However, given that the frequency distribution of etiologic agents for AOM may vary by country, the effectiveness of each vaccine was weighted according to Eq. (1), which takes into account the proportional distribution of Hib and *S. pneumoniae* in Peru, together with the country-specific pneumococcal serotype coverage. The proportion of cases of AOM caused by *S. pneumoniae* and NTHi was 32.4% and 18.3%, respectively, based on the meta-analysis published by Bardach and colleagues [36]. The proportional vaccine coverage of pneumococcal AOM (excluding cross-protection serotypes) was 58% for PCV10 and 70% for PCV13 [38]. Therefore, the weighted effectiveness to prevent AOM cases was 12.3% for PCV10 and 7% for PCV13 (Table 3).

Estimation of PCV efficacy against AOM:

$$\text{Efficacy} = \%\text{Spc} \times \text{ESpc} + \%\text{Spnc} \times \text{ESpnc} + \%\text{NTHi} \times \text{ENTHi} \quad (1)$$

where:

*%Spc*: Proportion of AOM cases due to *S. pneumoniae* serotypes included in PCV.
*%ESpc:* Efficacy against serotypes *S. pneumoniae* serotypes included in PCV.
*%Spnc:* Proportion of AOM cases due to *S. pneumoniae* serotypes not included in PCV.
*%Espnc:* Efficacy against serotypes *S. pneumoniae* serotypes not included in PCV.
*%NTHi:* Proportion of AOM cases due to NTHi.
*ENTHi:* Efficacy against NTHi (relative negative effect for PCV13 and positive effect for PCV10).

The estimated efficacy of 2 + 1 schedule against vaccine-type IPD was assumed to be similar to the 3 + 1 efficacy per the WHO Strategic Advisory Group of Experts (SAGE) on Immunization [4]. For a two-doses and one dose were estimated based on the report by

**Table 2**
Input parameters for estimating coverage and timing of pneumococcal conjugate vaccine (PCV) in Peru, 2012–2031[a]

| Parameter | Estimate | Scenarios | | Source/s |
|---|---|---|---|---|
| | | Low | High | |
| Coverage of DTP1 by age in year 2012 (proxy for PCV doses given with DTP1) | | | | |
| 3 m | 85.9% | 59.8% | 86.6% | |
| 6 m | 95.9% | 66.7% | 96.7% | Clark and |
| 9 m | 96.7% | 67.3% | 97.5% | Sanderson |
| 12 m | 98.0% | 68.2% | 98.8% | [33] |
| 24 m | 98.3% | 68.4% | 99.1% | |
| Coverage of DTP2 by age in year 2012 (proxy for PCV doses given with DTP2) | | | | |
| 3 m | 16.8% | 11.5% | 17.6% | |
| 6 m | 89.0% | 60.9% | 92.9% | Clark and |
| 9 m | 92.7% | 63.5% | 96.8% | Sanderson |
| 12 m | 94.0% | 64.4% | 98.1% | [33] |
| 24 m | 95.5% | 65.4% | 99.7% | |
| Coverage of DTP3 by age in year 2012 (proxy for PCV doses given with DTP3) | | | | |
| 3 m | 0.0% | 0.0% | 0.0% | |
| 6 m | 75.6% | 50.9% | 81.8% | Clark and |
| 9 m | 84.2% | 56.7% | 91.0% | Sanderson |
| 12 m | 86.9% | 58.5% | 94.0% | [33] |
| 24 m | 91.5% | 61.6% | 98.9% | |
| Coverage of Measles dose 1 by age in year 2012 (proxy for PCV booster doses given with Measles dose 1) | | | | |
| 3 m | 0.5% | 0.5% | 0.5% | |
| 6 m | 0.6% | 0.6% | 0.6% | Clark and |
| 9 m | 1.0% | 1.0% | 1.0% | Sanderson |
| 12 m | 13.4% | 13.6% | 13.6% | [33] |
| 24 m | 89.4% | 90.8% | 90.8% | |

[a] Coverage projections over the period 2012–2031 were estimated by assuming PCV will achieve the same coverage and timeliness as DTP, and by assuming a 0% annual decrease in the gap between final coverage in the cohort (coverage by age 24 m) and a ceiling of 100% (DTP1), 99% (DTP2) and 99% (DTP3) and 100% (Measles dose 1).

Mahon and colleagues [39] and Urueña and colleagues, respectively [40].

### 2.4.3. Vaccine serotype coverage

Based on sentinel surveillance reports of bacterial pneumonia and meningitis among children <5 years in Peru for the period 2000–2008 (before introduction of PCV7) [30], we estimated a 70.8% coverage from serotypes included in PCV10 and 81.3% for those in PCV13. The estimated distributions were concordant to the findings of a report from several hospitals in Lima [41]. Table 3 shows the estimated impact of each of the vaccination alternatives by clinical syndrome, relative efficacy and serotype coverage for the base case.

### 2.4.4. Relative coverage of deaths

This parameter adjusts vaccine coverage to account for the effective coverage of children who would have contracted IPD or, more importantly, would have died if the population had not been vaccinated, as a percent of overall national coverage. A 90% relative coverage of deaths was assumed [16].

### 2.4.5. Indirect effects of vaccination

Serotype replacement is a phenomenon characterized by an increase in IPD cases caused by serotypes not included in the vaccines, such as previously reported for serotype 19A [42]. Because 19A is not included in PCV10, we estimated an overall 1.3% reduction in disease protection with each successive vaccinated cohort; whereas for PCV13, the reduction assumed was 1.25%. The base case scenario did not consider herd effect; however, the "what if" scenario analysis did consider it for unvaccinated children <5 years of age, for both vaccines, with an assumed 10% effect [43].

**Table 3**
Input parameters for estimating PCV10 and PCV13 impact in Peru, 2012–2031.

| Parameter | PCV10 | | | PCV13 | | | Source/s |
|---|---|---|---|---|---|---|---|
| | Estimate | Scenarios | | Estimate | Scenarios | | |
| | | Low | High | | Low | High | |
| Vaccine efficacy versus all-cause acute otitis media | | | | | | | |
| Dose 1 | 6.5% | 6.5% | 25.8% | 3.9% | 3.0% | 6.9% | Urueña and colleagues [40] |
| Dose 2 | 11.8% | 11.8% | 33.6% | 7.1% | 5.5% | 9.0% | Mahon and colleagues [39] |
| Dose 3 | 12.8% | 12.8% | 33.6% | 7.7% | 6.0% | 9.0% | Prymula and colleagues(PCV10) [35], Pavia and colleagues(PCV13) [37] |
| Vaccine efficacy versus vaccine type pneumococcal pneumonia/pneumococcal meningitis/pneumococcal NPNM (sepsis)[e] | | | | | | | |
| Dose 1 | 41.0% | 31.9% | 74.8% | 41.0% | 31.9% | 74.8% | Urueña and colleagues [40] |
| Dose 2 | 74.5% | 58.0% | 97.4% | 74.5% | 58.0% | 97.4% | Mahon and colleagues [39] |
| Dose 3 | 81.0% | 63.0% | 97.4% | 81.0% | 63.0% | 97.4% | Lucero and colleagues [8] |
| % vaccine serotype coverage | | | | | | | |
| Pneumococcal pneumonia cases | 70.8% | 70.8% | 70.8% | 81.3% | 81.3% | 81.3% | SIREVA-Peruvian Surveillance [30] |
| Pneumococcal meningitis | 70.8% | 70.8% | 70.8% | 81.3% | 81.3% | 81.3% | SIREVA-Peruvian Surveillance [30] |
| Pneumococcal NPNM (sepsis)[a] | 70.8% | 70.8% | 70.8% | 81.3% | 81.3% | 81.3% | SIREVA-Peruvian Surveillance [30] |
| Other vaccination impact assumptions | | | | | | | |
| % relative coverage[b] | 90% | 90% | 100% | 90% | 90% | 100% | TRIVAC assumption [16] |
| % decrease in dose efficacy per year[c] | 1.3% | 0.0% | 5.0% | 1.3% | 0.0% | 5.0% | TRIVAC assumption [16] |
| Decline in vaccine type coverage/year [d,e] | 2.5% | 0.0% | 5.0% | 0.0% | 0.0% | 5.0% | TRIVAC assumption [16] |

[a] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).

[b] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

[c] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 months, 4–5 m, 6–8 m, 9–11 m, 12–23 m, 24–35 m, 36–47 m, 48–59 m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

[d] We did not include a herd effect multiplier according to Peruvian physicians' expert opinion (Delphi) for case base. However, we use herd effect multiplier in scenario analyses.

[e] Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T^*(1-R)N]$ where, $T$ = % of disease caused by vaccine types in the year of vaccine introduction, $R$ = % reduction in vaccine type coverage per year following vaccine introduction, $N$ = number in the sequence of vaccinated birth cohorts.

**Table 4**
Input parameters for estimating health service utilization and costs (in 2012 US$) in Peru.

| Parameter | Estimate | Scenarios | | Source/s |
|---|---|---|---|---|
| | | Low | High | |
| *Outpatient visits* | | | | |
| Outpatient visits per disease episode | | | | |
| All causes acute otitis media | 0.79 | 0.79 | 0.79 | Delphi whit Peruvian physicians |
| Pneumococcal pneumonia cases | 0.68 | 0.68 | 0.68 | Delphi whit Peruvian physicians |
| Government cost per outpatient visit | | | | |
| All causes acute otitis media[a] | $18 | $18 | $134 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| Pneumococcal pneumonia cases[b] | $41 | $41 | $171 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| *Inpatient admissions* | | | | |
| Inpatient admissions per disease episode | | | | |
| Pneumococcal pneumonia cases | 0.30 | 0.30 | 0.30 | DGE-Ministry of Health |
| Pneumococcal meningitis | 0.75 | 0.75 | 0.75 | Delphi whit Peruvian physicians |
| Pneumococcal NPNM (sepsis) | 1.00 | 1.00 | 1.00 | Delphi whit Peruvian physicians |
| Government cost per inpatient admission | | | | |
| Pneumococcal pneumonia cases[c] | $643 | $643 | $1585 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| Pneumococcal meningitis[d] | $1148 | $1148 | $3225 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| Pneumococcal NPNM (sepsis)[e] | $2806 | $2806 | $5241 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| *Meningitis sequelae* | | | | |
| Government cost of meningitis sequelae per year[f] | | | | |
| Auditory sequelae | $80 | $50 | $150 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |
| Neurological sequelae | $113 | $50 | $150 | Average Peruvian cost (estimate and low), Peruvian private sector cost (High) |

[a] Government costs per outpatient visit (all cause acute otitis media) include Ministry of Health and Social Security. Outpatients visits are distributed as follows: 88.8% Ministry of Health, 11.1% Social security. The cost presented is the weighted average of the provider-specific costs.
[b] Government costs per outpatient visit (pneumococcal pneumonia) include Ministry of Health and Social Security. Outpatients visits are distributed as follows: 78.4% Ministry of Health, 21.6% Social security. The cost presented is the weighted average of the provider-specific costs.
[c] Government costs per inpatient admission (pneumococcal pneumoniae) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 77% Ministry of Health, 23% Social security. The cost presented is the weighted average of the provider-specific costs.
[d] Government costs per inpatient admission (pneumococcal meningitis) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 97.2% Ministry of Health, 2.8% Social security. The cost presented is the weighted average of the provider-specific costs.
[e] Government costs per inpatient admission (pneumococcal sepsis) include Ministry of Health and Social Security [the cost per bed day multiplied by the expected length of stay and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 83.1% Ministry of Health, 16.9% Social security. The cost presented is the weighted average of the provider-specific costs. All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).
[f] Sequelae costs borne by the Government include Ministry of Health and Social Security and are applied annually from the age of meningitis onset until full life expectancy. These costs are included and discounted over time in the base case (best estimate) scenario.

### 2.4.6. Health services utilization and costs

The ENDES estimations show that 51.9% and 22.6% of children <5 years are covered by the SIS (Seguro Integral de Salud) of MINSA and EsSalud as public insurance modalities [34]. Treatment for childhood pneumococcal disease in the Police and Armed Forces Health Service Sector or by the Private Sector was excluded from this analysis. Data on health services utilization was provided by MINSA and EsSalud.

To define routine treatment protocols for each of the clinical syndromes analyzed, a cross-sectional survey of pediatricians was conducted. These were chosen by a stratified random sample with proportional distribution to the number of physicians in each region of the country. Of the 100 pediatricians invited to participate nationwide, 76 accepted. Participants completed an AOM questionnaire developed with the support of the Peruvian Society of Pediatrics and ad hoc questionnaires developed by PAHO for invasive disease, pneumonia, and meningitis [16]. Disease management of auditory and neurological sequelae was obtained directly from experienced physicians from the National Rehabilitation Institute. The proportion of pneumonia cases requiring inpatient treatment was provided by the MINSA and EsSalud.

Cost savings to the health system due to the prevention of pneumococcal clinical syndromes were estimated according to the type of health provider, complexity of care level and the type of management (outpatient or inpatient).

Unit costs for health care services were based on the cost of public sector care, using official documents delineating standard pricing methodology used by MINSA [44]. Medication costs were based on the Peruvian Observatory of Pharmaceutical Products, mandatory for MINSA and EsSalud [45].

A survey on health care utilization was completed by the 76 Peruvian physicians to estimate the number of medical procedures and medication quantities prescribed for each condition. Table 4 summarizes the input parameters for estimating health care services utilization and costs from the perspective of the Government of Peru.

### 2.4.7. Vaccination program costs

Vaccine unit prices were obtained from the PAHO Revolving Fund. In the year of analysis (2012), the price per dose of PCV10 was US$ 14.24 and of PCV13 was US$ 16.34. These prices were adjusted for capitalization of the PAHO Revolving Fund (3.5% of dose price), delivery, freight and insurance (15% of dose price).

All additional costs incurred by the health system were estimated at US$ 1.40 per dose, which included expansion of cold chain, transportation, materials, training, supervision and monitoring. An annual decrease rate of 2% over the vaccine price was assumed. The price of the safety box was valued at US$ 0.64 per unit, with each box holding a maximum of 150 syringes. In addition, safety boxes were subject to a delivery expense of 7.5% over price, plus an estimated 20% wastage; no extra cost was assumed for capitalization. Also additional was the cost per syringe: US$ 0.16, plus an 8% adjustment factor for freight/handling and 1% for wastage. This information was provided by the MINSA National Department of Supplies and Strategic Resources in Health (DARES). Table 5 shows the input parameters for PCV10 and PCV13 program costs, including estimations for all predicted birth cohorts.

**Table 5**
Input parameters for estimating PCV10 and PCV13 program costs in Peru, 2012–2031.

| Parameter | PCV10 | | | PCV13 | | | Source/s |
|---|---|---|---|---|---|---|---|
| | Estimate | Scenarios(US$) | | Estimate | Scenarios(US$) | | |
| | (US$) | Low | High | (US$) | Low | High | |
| Vaccine dose price projection | | | | | | | |
| 2012 | $14.24 | $14.24 | $14.24 | $16.34 | $16.34 | $16.34 | PAHO Revolving Fund |
| 2013 | $13.96 | $12.82 | $14.24 | $16.01 | $14.71 | $16.34 | National Team estimations |
| 2014 | $13.68 | $11.53 | $14.24 | $15.69 | $13.24 | $16.34 | National Team estimations |
| 2015 | $13.40 | $10.38 | $14.24 | $15.38 | $11.91 | $16.34 | National Team estimations |
| 2016 | $13.13 | $9.34 | $14.24 | $15.07 | $10.72 | $16.34 | National Team estimations |
| 2017 | $12.87 | $8.41 | $14.24 | $14.77 | $9.65 | $16.34 | National Team estimations |
| 2018 | $12.61 | $7.57 | $14.24 | $14.47 | $8.68 | $16.34 | National Team estimations |
| 2019 | $12.36 | $6.81 | $14.24 | $14.19 | $7.82 | $16.34 | National Team estimations |
| 2020 | $12.11 | $6.13 | $14.24 | $13.90 | $7.03 | $16.34 | National Team estimations |
| 2021 | $11.87 | $5.52 | $14.24 | $13.62 | $6.33 | $16.34 | National Team estimations |
| 2022 | $11.64 | $4.97 | $14.24 | $13.35 | $5.70 | $16.34 | National Team estimations |
| 2023 | $11.40 | $4.47 | $14.24 | $13.08 | $5.13 | $16.34 | National Team estimations |
| 2024 | $11.17 | $4.02 | $14.24 | $12.82 | $4.61 | $16.34 | National Team estimations |
| 2025 | $10.95 | $3.62 | $14.24 | $12.57 | $4.15 | $16.34 | National Team estimations |
| 2026 | $10.73 | $3.26 | $14.24 | $12.31 | $3.74 | $16.34 | National Team estimations |
| 2027 | $10.52 | $2.93 | $14.24 | $12.07 | $3.36 | $16.34 | National Team estimations |
| 2028 | $10.31 | $2.64 | $14.24 | $11.83 | $3.03 | $16.34 | National Team estimations |
| 2029 | $10.10 | $2.37 | $14.24 | $11.59 | $2.73 | $16.34 | National Team estimations |
| 2030 | $9.90 | $2.14 | $14.24 | $11.36 | $2.45 | $16.34 | National Team estimations |
| 2031 | $9.70 | $1.92 | $14.24 | $11.13 | $2.21 | $16.34 | National Team estimations |
| Other vaccine dose costs | | | | | | | |
| International handling (% of vaccine price) | 3.50% | 1.22% | 1.22% | 3.50% | 1.22% | 1.22% | PAHO Revolving Fund |
| International delivery (% of vaccine price) | 22.00% | 1.22% | 1.22% | 22.00% | 1.22% | 1.22% | PAHO Revolving Fund |
| Wastage (% of doses discarded etc.)[a] | 1.00% | 0.00% | 0.00% | 1.00% | 0.00% | 0.00% | Ministry of Health-Ministry of Health |
| Safety box cost (150 syringes per box) | | | | | | | |
| Price of each safety box | 0.64 | – | – | 0.64 | – | – | DARES-Ministry of Health |
| International handling (% of vaccine price) | 0.00% | – | – | 0.00% | – | – | DARES-Ministry of Health |
| International delivery (% of vaccine price) | 7.52% | – | – | 7.52% | – | – | DARES-Ministry of Health |
| Wastage (% of doses discarded etc.)[a] | 20.00% | – | – | 20.00% | – | – | PROVAC estimations |
| Incremental system costs of introduction | | | | | | | |
| Incremental system cost per dose | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | National Estrategy of Inmunizations-Ministry of Health |

[a] The % wastage is converted into a factor [1/(1 − % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.

### 2.5. Sensitivity analysis and "what if" scenarios

A one-way sensitivity analysis was conducted, varying each input systematically by ±10% and recording the % change in the discounted US$ per DALY averted. Since an important aspect of an EE is analysis of results under different assumptions [20,46], this study modified the base case assumptions and parameters to create and analyze different scenarios.

We generated a scenario of low pneumococcal disease incidence based on statistics that were lower than the expected incidence projected for Peru by the WHO pneumococcal burden report [18]; meningitis and invasive NPNM disease were below the lower limit of the 95% CI of the incidence for each disease reported in the systematic review [3]. Additionally, a scenario of high AOM incidence was estimated based on data from the study by Teele and colleagues [28]. Moreover, we created a scenario of low and high case fatality rates based on the lower and upper confidence interval limits from the meta-analysis by O'Brien and colleagues [3].

We assumed a scenario of low efficacy of PCV13 in preventing AOM cases taking the point estimate of 6% from the meta-analysis of Pavia and colleagues and one high efficacy of 9% from the same study [37]. The high efficacy scenario for the effect of PCV10 on AOM cases was 33.6% based on Prymula and colleagues [35]. For other syndromes, we considered a high efficacy of 97.4% against vaccine serotypes for both PCVs based on the study of Black and colleagues [47] and a low efficacy of 85% against vaccine serotypes from the meta-analysis by Lucero and colleagues [8]. Additionally, we proposed a scenario without reduced efficacy over time and another that incorporated a herd effect of 10% for both PCVs.

We also incorporated a scenario with low immunization coverage based on data from the ENDES survey. Its coverage proportions were lower than those provide by the NIS and used in the base case analysis. Additionally, a scenario with a reduction (80%) and another with an increase (100%) of the relative coverage of deaths for both PCVs were included.

We used estimated costs of private sector health care services to build a scenario of higher ambulatory and inward costs in the public sector. We proposed a scenario with a discount rate of 5% [20,21] and one analyzing only 10 birth cohorts. Regarding the price of the vaccine, we evaluated the effect of a fixed price versus an annual decrease of 10%.

We generated a scenario favorable to vaccination that included a high incidence and high case fatality ratio, high efficacy, a decrease of 10% in the price of annual vaccination, a herd effect (direct effect × 110%), no adjustment for relative coverage, higher outpatient and hospital costs and lower serotype replacement (i.e., 1% per PCV10). We also ran a scenario that was unfavorable to the vaccine, with lower incidence, mortality efficacy, coverage, in/outpatient costs, and a relative coverage adjustment of 80%, with no change in the vaccine price over time.

## 3. Results

### 3.1. Vaccine impact

All results reported are discounted by 3%. Among the 20 cohorts of children evaluated from 2012 to 2031, the scenario without vaccination would result in 7,327,014 AOM cases; 229,238

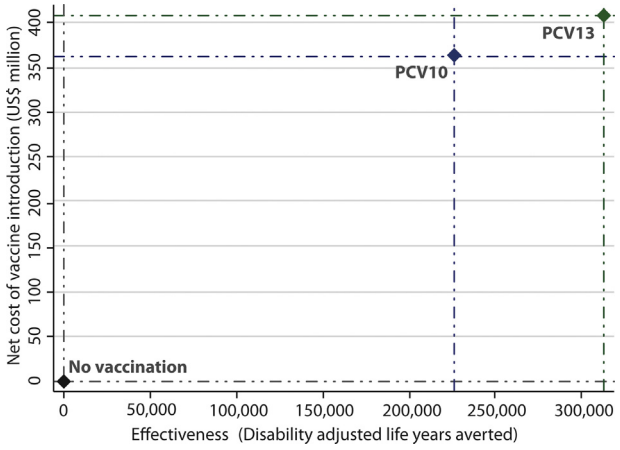



**Fig. 2.** Incremental cost effectiveness analysis between 10- and 13- valent pneumococcal conjugate vaccines in Peru, 2012.

pneumococcal pneumonia (PP); 6359 pneumococcal meningitis (PM); 8744 pneumococcal sepsis (PS); 1323 neurologic and auditory sequelae (NAS); and 21,194 deaths. With PCV13 or PCV10 vaccination, the number of cases of PP, PM and PS and associated deaths would be reduced by 49% and 35%, respectively. Also, PVC13 would reduce neurological and auditory sequelae by 49%; PCV10, by 34%. The total number of DALYs averted and LYG would be 38.3% higher with PCV13 than with PCV10.

Table 6 details the results for each of the three strategies analyzed: no vaccination, PCV10 vaccination and PCV13 vaccination. In summary, we found that PCV10 prevents more AOM cases and PCV13 avoids more cases of PP PM, PS, NAS and deaths.

### 3.2. Costs

The study results demonstrated that, in Peru, a vaccination program that uses PCV13 is more costly than one using PCV10, with cumulative net costs amounting to US$ 54.8 million more for PCV13 over the 20 cohorts studied. However, discounted cost savings to health system are greater for PCV13, which saves US$ 9.8 million more than PCV10. Therefore, the net cost difference of PCV13 minus PCV10 for the 20 cohorts is US$ 44.9 million. Table 7 conveys the discounted economic benefits in the three case-base scenarios, and Table 8 presents the discounted net cost for the two vaccination options.

### 3.3. Cost-effectiveness and incremental cost-effectiveness ratio

The intervention was considered cost-effective if the cost per DALY averted was $\leq 3\times$ the GNI-PC, and highly cost-effective if $<1\times$ the GNI-PC [48]. The discounted cost per avoided DALY was US$ 1605 with PCV10 and US$ 1304 with PCV13; both ratios fall below the 2011 GDP-PC of Peru (US$ 6009). The more costly ratio was PCV13—when its base case results were compared directly to those of PCV10, its additional benefits would be worth the additional investment (incremental cost-effectiveness ratio [ICER] = US$ 519 per DALY averted). Moreover, the cost per LYG, avoided hospitalization and avoided death were lower with PCV13 than with PCV10. These results show that PCV13 has extended dominance over PCV10 in the Peruvian context (Fig. 2).

### 3.4. Sensitivity analyses

The scenario analyses for PCV10 and PCV13 are shown in Figs. 3 and 4, respectively. In nearly all scenarios, both PCV vaccines were highly cost-effective, and even, cost-saving when compared to no vaccination. A scenario with several unfavorable scenarios was still cost-effective, suggesting the recommendation to introduce PCV is robust. In all scenarios, PCV13 was slightly more cost-effective than PCV10. This was driven by the assumption that PCV13 would cover a larger number of pneumococcal-related diseases, and therefore, would prevent a greater number of deaths. PCV10 was shown to prevent a greater number of AOM cases, but the reduction in AOM treatment costs did not shift enough to make PCV10 a more favorable option. PCV10 was assumed to have an effectiveness reduction for each successive cohort (simulating a scenario of serotype replacement). However, even when this assumption was removed, PCV13 was still the more cost-effective option.

## 4. Discussion

Our findings indicate that introducing PCV10 or PCV13 to the National Immunization Schedule in Peru is a cost-effective measure when compared to no vaccination. PCV10 introduction would have lower program costs than PCV13. PCV13 would reduce more cases of PP, PM, PS, sequelae and deaths than PCV10. However, PCV10 would prevent more AOM cases. Also, the cost per prevented hospitalization, death and DALY would be lower with PCV13. These results are a clear example of extended dominance in economic evaluation areas. Despite the fact that the PCV13 program is more costly than the PCV10, the cost-per-unit effectiveness is lower for PCV13 [49,50]. Observed differences between the two currently available PCV options are driven by the greater assumed serotype protection of PCV13, which implies a greater impact on IPD prevention; and the NTHi coverage by PCV10 and its effect on AOM. Therefore, IPD prevention with PCV13—and its subsequent impact on deaths, hospitalizations and disabilities—makes this vaccine an intervention with a higher value at the public health level, particularly for effect on LYG and avoided DALYs. Even though the cost of introducing PCV10 is lower, PCV13 is projected to provide a greater overall health benefit; it may therefore, be useful to perform a budget impact analysis to determine the fiscal impact of introducing one vaccine rather than the other [51]. Thus, these findings that PCV13 would be the most favorable option for the Government of Peru as it endeavors to meet its commitment to bring health to all Peruvians [52,53], in a fiscally responsible manner.

EEs concur [54,55]. In Argentina [56], Uruguay [57], and Brazil [58,59] PCV was shown to be more cost-effective than the non-vaccination scenario.

In a report from Sweden and Denmark [60], a study from Greece, Germany and the Netherlands [61], and another from Gambia [62], PCV13 prevented more cases of IPD and deaths and gained more quality adjusted Life Years (QALYs) than PCV10. The same results were observed in Canada, which had a 2 + 1 PCV schedule like that of Peru [63]. A study in Mexico showed PCV13 to have better health outcomes and cost savings than PCV7 and PCV10 [64]. Also, a CEA in Colombia found that PCV13 prevents more disease and deaths with a higher LYG than PCV10, although PCV10 has more cost savings [42]. In Argentina, Urueña and colleagues, using the TRIVAC model, showed that PCV13 prevented more cases of pneumonia, IPD, sequelae with a higher number of LYG and averted more DALYs than PCV10 [40].

Nevertheless, there are some EEs whose findings differ. In Turkey [65] and Norway [66], PCV10 was found to be more cost-effective than PCV13. These differing conclusions underscore that EEs are context-dependent (country or region) and may be affected by the assumptions and models used [13,67].

In Peru, a prior EE showed PCV13 to be more cost-effective, and it prevented more pneumonia cases than PCV10 and PCV7

**Table 6**
Discounted health benefits (20 cohorts vaccinated over the period 2012–2031)[a]

| | No vaccine | PCV10 | | PCV13 | |
|---|---|---|---|---|---|
| | (status quo) | With vaccine | Averted | With vaccine | Averted |
| Total cases <5 years | 7,571,354 | 6,915,878 | 655,477 | 7,031,807 | 539,547 |
| All causes acute otitis media | 7,327,014 | 6,756,741 | 570,273 | 6,907,199 | 419,815 |
| Pneumococcal pneumonia cases | 229,238 | 149,300 | 79,937 | 116,906 | 112,331 |
| Pneumococcal meningitis | 6359 | 4142 | 2217 | 3243 | 3116 |
| Pneumococcal NPNM (sepsis)[b] | 8744 | 5695 | 3049 | 4459 | 4285 |
| Total outpatient visits | 5,924,759 | 5,421,711 | 503,047 | 5,518,331 | 406,428 |
| All causes acute otitis media | 5,770,023 | 5,320,934 | 449,090 | 5,439,419 | 330,604 |
| Pneumococcal pneumonia cases | 154,735 | 100,778 | 53,958 | 78,912 | 75,824 |
| Total inpatient admissions | 82,284 | 53,591 | 28,693 | 41,963 | 40,321 |
| Pneumococcal pneumonia cases | 68,771 | 44,790 | 23,981 | 35,072 | 33,699 |
| Pneumococcal meningitis | 4769 | 3106 | 1663 | 2432 | 2337 |
| Pneumococcal NPNM (sepsis) | 8744 | 5695 | 3049 | 4459 | 4285 |
| Total deaths <5 years | 21,194 | 13,682 | 7512 | 10,808 | 10,386 |
| Pneumococcal pneumonia cases | 14,148 | 9134 | 5015 | 7215 | 6933 |
| Pneumococcal meningitis | 3399 | 2194 | 1205 | 1733 | 1666 |
| Pneumococcal NPNM (sepsis) | 3647 | 2354 | 1292 | 1860 | 1787 |
| Total children with permanent disability | 1323 | 868 | 455 | 672 | 651 |
| Auditory sequelae | 820 | 538 | 282 | 416 | 404 |
| Neurological sequelae | 503 | 330 | 173 | 256 | 248 |
| Disability Adjusted Life Years (DALYs) | 642,147 | 415,778 | 226,370 | 329,028 | 313,119 |
| DALYS due to morbidity | 13,173 | 9500 | 3673 | 8098 | 5075 |
| DALYs due to mortality | 628,974 | 406,278 | 222,696 | 320,931 | 308,044 |

[a] Health benefits are discounted at 3% per year.
[b] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).

[31]. Also contrasting our findings, GlaxoSmithKline® (GSK) performed a cost-utility analysis on PCV introduction in Peru whose results suggested that PCV10 was more cost-effective than PCV13 [68]. Because the GSK analysis assumed a higher effectiveness of PCV10 on 6A and 19A serotypes, and our analysis was driven by an assumption of cross-protection, the findings differed. These serotypes have an important impact on invasive disease; these assumptions could foster better results for the PCV1. Serotype 19A is a key factor in the CEA on PCV [69]; its increasing frequency and its direct effects, producing more IPD cases, deaths and sequelae in LAC, have been previously recognized [42]. However, official reports suggest a minimal participation of NTHi etiologic agent in pneumonia [30]. Our study included an explicit, direct adjustment for serotype replacement over time, focused mainly on 19A [16,67].

Overall, in response to a request by MINSA, our study provides a comprehensive assessment of the cost-effectiveness introducing a new PCV to the National Immunization Schedule in Peru. The strengths of our study are several. First, we used the TRIVAC model, which has been previously used in several countries in LAC: Argentina, Bolivia, Ecuador, El Salvador, Guatemala, Nicaragua and Paraguay [15,16,40] and validated by an external expert panel [16,67]. Second, the development of this study was transparent, with various independent, public and private institutions participating; all participants were required to declare any potential conflicts of interest and none were reported; data was registered and based on official communications by organizations. Third, the scenario analyses considered variations based on other data sources and differences were found between the two PCVs that were consistent across the circumstances. Fourth, TRIVAC is a deterministic, static cohort model that follows more than one live cohort over time. It is better able to evaluate trends in key parameters, e.g., vaccine price, type replacement, mortality in the absence of vaccination, among others. This approach also provided had the added benefit of being useful for carrying out a Budget Impact Analysis [16,67]. Finally, costs were calculated based on official reports, and this included weighting by distribution of cases per health care level, region and specific syndrome management.

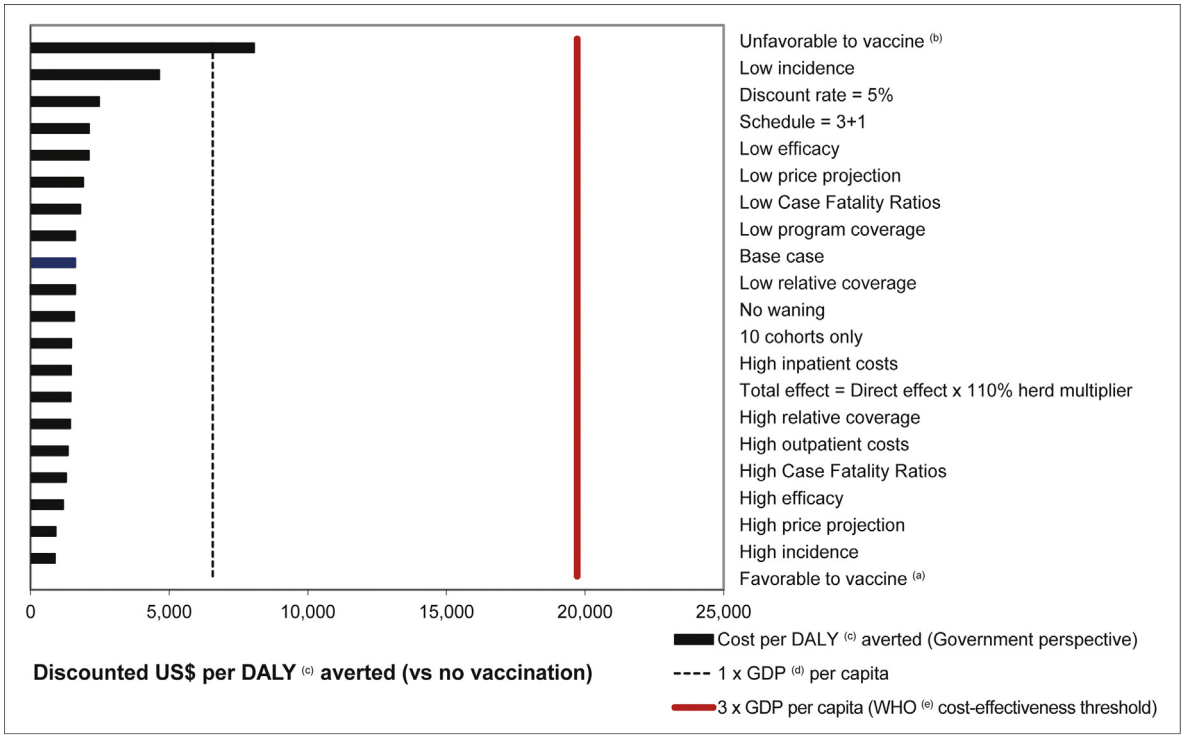
### 4.1. Limitations

This EE has some limitations as well. The TRIVAC model has been found to be consistent with the PneumoADIP cohort model and the

**Table 7**
Discounted economic benefits of pneumococcal conjugate vaccine-10 (PCV10) versus PCV13 in Peru (20 cohorts vaccinated over the period 2012–2031).

| | No vaccine | PCV10 | | PCV13 | |
|---|---|---|---|---|---|
| | (status quo) | With vaccine | Averted | With vaccine | Averted |
| Total government health service costs[a] | $187,084,198 | $149,699,031 | $37,385,167 | $139,864,039 | $47,220,160 |
| Total outpatient visit costs | $109,119,066 | $98,901,345 | $10,217,721 | $100,111,508 | $9,007,558 |
| All causes acute otitis media | $102,751,561 | $94,754,250 | $7,997,311 | $96,864,221 | $5,887,340 |
| Pneumococcal pneumonia cases | $6,367,505 | $4,147,095 | $2,220,410 | $3,247,288 | $3,120,217 |
| Total inpatient admission costs | $74,222,749 | $48,340,565 | $25,882,184 | $37,851,971 | $36,370,778 |
| All causes pneumonia cases | $44,215,372 | $28,797,048 | $15,418,324 | $22,548,868 | $21,666,504 |
| Pneumococcal meningitis | $5,476,527 | $3,566,810 | $1,909,718 | $2,792,909 | $2,683,619 |
| Pneumococcal NPNM (sepsis)[b] | $24,530,849 | $15,976,707 | $8,554,142 | $12,510,194 | $12,020,655 |
| Total sequelae costs* | $3,742,384 | $2,457,121 | $1,285,263 | $1,900,560 | $1,841,824 |
| Auditory sequelae | $1,999,473 | $1,312,767 | $686,706 | $1,015,427 | $984,046 |
| Neurological sequelae | $1,742,911 | $1,144,355 | $598,557 | $885,133 | $857,778 |

[a] Government perspective includes [all bed day and disease-specific drug/diaganostic costs borne by the Government of Peru at the following health providers: Ministry of Health and Social Security]. Costs are discounted at 3% per year
[b] All pneumococcal sepsis refer to non-pneumonia non-meningitis invasive disease (NPNM).




(a) Favorable scenario = High incidence and high case fatality ratio, high efficacy, a decrease in the price of annual vaccination of 10%, a herd effect (direct effect x 110%), no adjustment for relative coverage, higher outpatient and hospital costs, serotype replacement of 1% per year for PCV10. This would be a cost saving escenario i.e. the Pneumococcal disease health services costs averted exceed the cost of introducing PCV.
(b) Unfavorable scenario = Lower incidence, mortality and vaccine efficacy, lower vaccination coverage, a relative coverage adjustment of 80%, lower inpatient and outpatient costs and no change in the price of the vaccine over time.
(c) DALY = Disability adjusted life years.
(d) GDP= Gross Domestic Product
(e) WHO = World Health Organization.

**Fig. 3.** Cost per disability adjusted life year (DALY) averted for base case 10-valent Pneumoccocal Conjugate Vaccine scenario and alternative "what if" scenarios: Government of Peru perspective.

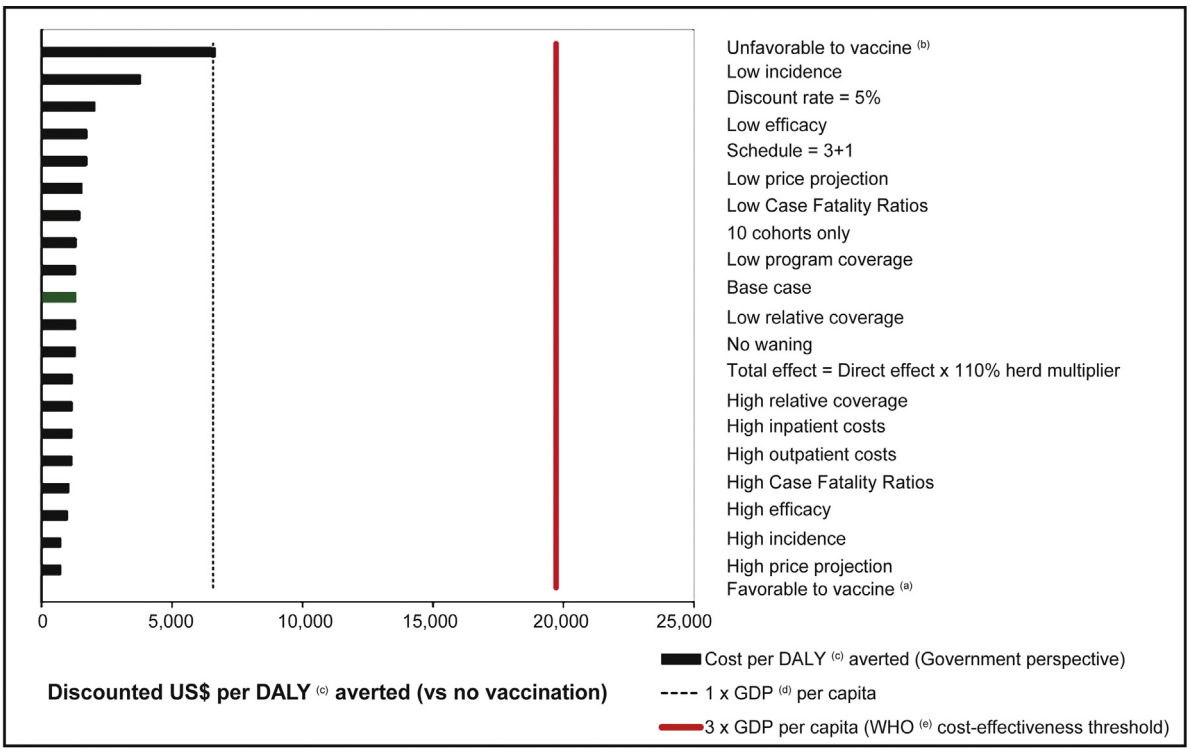
**Table 8**
Discounted cost-effectiveness of pneumococcal conjugate vaccine-10 (PCV10) versus PCV13 in Peru (20 cohorts vaccinated over the period 2012–2031)[a]

| | PCV10 Government perspective | PCV13 Government perspective |
|---|---|---|
| Cost-effectiveness compared to no vaccine | | |
| Net cost of vaccine introduction | $363,268,692 | $408,264,249 |
| Costs of vaccine introduction | $400,653,860 | $455,484,409 |
| Health service costs avoided | $37,385,167 | $47,220,160 |
| DALYs averted[b] | 226,370 | 313,119 |
| YLDs averted – DALYS due to morbidity | 3673 | 5075 |
| YLLs averted – DALYs due to mortality | 222,696 | 308,044 |
| US$ per DALY averted | $1605 | $1304 |
| Cost-effectiveness of PCV13 compared to PCV10 | | |
| Net cost of vaccine introduction | – | $44,995,556 |
| Costs of vaccine introduction | – | $54,830,549 |
| Health service costs avoided | – | $9,834,992 |
| DALYs averted | – | 86,749 |
| YLDs averted – DALYS due to morbidity | – | 1402 |
| YLLs averted – DALYs due to mortality | – | 85,347 |
| US$ per DALY averted | – | $519 |
| Cost-effectiveness threshold | | |
| 1× GDP per capita (2012) – WHO threshold for 'highly cost-effective' | $6573 | $13,227 |
| 3× GDP per capita (2012) – WHO[c] threshold for 'cost-effective' | $19,719 | $39,681 |

[a] Costs and DALYs are discounted at 3% per year.
[b] DALYs= Disability adjusted life years.
[c] WHO = World Health Organization.

cross-sectional SUPREMES model [67]. However, such static models do not account for realistic changes over time in positive (herd) and negative indirect effects (serotype replacement) [16]. TRIVAC does not currently include indirect effects and only considers a herd-effect scenario for children <5 years of age. There is evidence that older individuals could also benefit indirectly from the vaccination of infants, but the duration of this effect is unclear. The development of a dynamic model could provide a better approximation of the infectious disease pattern and a more accurate estimate of its prevention through vaccination [70]. Dynamic modeling, however, is complex and requires good quality, primary data, e.g., reproductive rates for *S. pneumoniae* colonization and age-specific burden of disease in older age groups [16,50,71]. Also, when a vaccine is cost-effective in a static model, usually a dynamic model would only make it appear more so. In the case of pneumococcal disease, however, there is concern that the negative indirect effects could outweigh the positive ones [16].

Second, we found deficiencies in primary epidemiological data without etiological reports from health service providers and lack of evidence about head-to-head clinical efficacy related to the syndromes studied. Thus, we have extrapolated data from meta-analyses and others primary studies, and this could lead to an inaccurate estimation of disease burden and efficacy. Third, we utilized a public health care system perspective and incorporated only direct cost. However, expenses and lost income incurred by households during hospitalization, plus the cost to society can affect CEA results. Estimating such costs is difficult at the national level. Fourth, TRIVAC generates a specific model




(a) Favorable scenario = High incidence and high case fatality ratio, high efficacy, a decrease in the price of annual vaccination of 10%, a herd effect (direct effect x 110%), no adjustment for relative coverage, higher outpatient and hospital costs, and the same case base serotype replacement for PCV13. This would be a cost saving scenario i.e. the pneumococcal disease health services costs averted exceed the cost of introducing PCV.
(b) Unfavorable scenario = Lower incidence, mortality and vaccine efficacy, lower vaccination coverage, a relative coverage adjustment of 80%, lower inpatient and outpatient costs and no change in the price of the vaccine over time.
(c) DALY = Disability adjusted life year.
(d) GDP= Gross Domestic Product.
(e) WHO= World Health Organization.

**Fig. 4.** Cost per disability adjusted life year (DALY) averted for base case 13-valent Pneumoccocal Conjugate Vaccine scenario and alternative "what if" scenarios: Government of Peru perspective.

for each vaccine, contrasting PCV impact versus no new vaccine state; so the model assumes that benefits from a new vaccine are not influenced by a preceding PCV any other additional health intervention [16]. However, this was probably not an issue in the current study since PCV7 had been taken off the market. Fifth, the analysis was restricted to children <5 years of age, though there is evidence that the vaccine could have effects later; however, the greatest pneumococcal disease burden occurs in this age group [5]. Finally, we did not include a probabilistic sensitivity analysis for evaluating the extended dominance, which was found in the case base scenario, nevertheless the "what if" scenario analysis is a relevant approach specially in making decision process.

## 5. Conclusions

In the Peruvian context, PCV13 has shown better health outcomes, but PCV10 would have lower introduction costs. Whit this results, PCV13 would be the preferred policy; and PCV10 would also be reasonable (and cost-saving relative to the status quo) if for some reason 13-valent were not feasible. MINSA must consider the Government priorities when deciding on the best option. Since this study constituted a national and inter-institutional effort to provide the best available evidence for vaccine decision-making in Peru, its results are an important scientific component for improving this process on the health of the population, especially among its youngest and most vulnerable, with actions that are fiscally responsible.

## Conflict of interest statement

The authors declare that they have no conflict of interests.

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## Additional information

Official and comprehensive version (Spanish) of this study can be visited at: http://www.ins.gob.pe/repositorioaps/0/4/jer/evidencias/Nota%20T%C3%A9cnica%202012%20-%203_%20Estudio%20de%20costo%20efectividad%20de%20las%20vacunas%20deca-%20y%20trece-valente%20para%20la%20prevenci%C3%B3n%20de%20enfermedad%20asociada%20a%20Streptococcus%20pneumoniae%20en%20ni%C3%B1os.pdf