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PCV20 for the prevention of invasive pneumococcal disease in the Mexican pediatric population: A cost-effectiveness analysis

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ABSTRACT

The introduction of a pneumococcal conjugate vaccine (PCV) covering 13 serotypes (PCV13) into the Mexican pediatric national immunization program (NIP) has substantially reduced the burden of pneumococcal disease (PD) since 2010. This study aimed to estimate the impact of replacing either PCV13 or 15valent PCV (PCV15) with 20-valent PCV (PCV20) in the Mexican pediatric NIP. A decision-analytic Markov model was developed to compare the cost-effectiveness of PCV20 versus lower-valent vaccines from a Mexican public health sector (payer) perspective over 10 years. Epidemiological and cost inputs were sourced from Mexican data. Direct and indirect vaccine effects were estimated using PCV13 clinical effectiveness, 7-valent PCV efficacy studies, and PCV13 impact data in Mexico. The estimated disease and cost impact of PCV20 was compared with PCV13 and PCV15, all under a 2 + 1 dosing schedule. A discount rate of 5% per annum was applied to costs and health outcomes. Model robustness was evaluated through sensitivity analyses, including deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and additional scenario assessments. PCV20 was estimated to provide considerably more health benefits than both comparators by averting more cases of PD compared with both PCV13 and PCV15, as well as a total cost saving of over 10 billion Mexican pesos. The DSA, PSA, and scenario assessments confirmed minimal deviation from the base case. Therefore, the introduction of PCV20 (2 + 1) into the Mexican pediatric NIP is expected to reduce the burden of PD and medical costs compared with lower-valent alternatives.

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Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is a commensal bacterium in the upper respiratory tract that significantly contributes to pneumococcal diseases, including invasive pneumococcal disease (IPD) and noninvasive conditions (e.g., pneumonia and otitis media).[1,2] With the greatest impact on infants, young children, the elderly, and individuals with underlying risk factors/comorbidities, pneumococcal diseases are associated with considerable mortality and morbidity burden globally.[3]

The first pneumococcal conjugate vaccine (PCV), covering 7 pneumococcal serotypes (PCV7), was introduced in 2006 as a pilot vaccination initiative targeting economically disadvantaged regions of Mexico and became a part of Mexico's pediatric national immunization program (NIP).[4,5] PCV7 targets serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F.[6] Between 2010 and 2011, PCV7 was replaced by 13-valent PCV (PCV13), which is offered to children aged <2 years as part of the Mexican NIP under a 2 + 1 schedule and remains the standard of care (SoC).[5,7] PCV13 covers an additional six serotypes (1, 5, 7F, 3, 6A, and 19A) compared with PCV7.[6] The introduction of PCVs into national routine vaccination programs has greatly reduced the disease incidence. Global observational impact data suggested that reductions in disease incidence occurred in both vaccinated and unvaccinated populations after the introduction of PCV7 and PCV13, which extended beyond the direct vaccine effects estimated from the original clinical PCV7 efficacy trials.[8–23] However, a review by Horn et al. 2021 suggested that the true impact of PCVs in published analyses might be underestimated, with realworld data on the number of averted cases of pneumococcal diseases from PCVs up to three times higher than those estimated in previous studies.[24]

Despite the introduction of PCV13 in 2011, pneumococcal disease remains a public health and economic burden in Mexico. Following the introduction of PCV13, an initial downward trend in overall pneumococcal disease was observed, followed by an upward trend in overall cases from 2016/2017, which might be the result of disease caused by non-vaccine type serotypes.[25]

The 20-valent PCV (PCV20) is a novel vaccine for active immunization for the prevention of pneumonia and IPD caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9 V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F. PCV20 received United States Food and Drug Administration (US FDA) approval in April 2023 to prevent IPD among individuals aged six weeks to <18 years.[26] Additionally, in March 2024, PCV20 received marketing authorization from the European

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Commission (EC) for active immunization to prevent IPD, pneumonia, and acute otitis media among individuals aged six weeks to <18 years.[27] Furthermore, market authorization was received in Mexico on August 1, 2024.[28] The 15-valent PCV (PCV15) has also been approved by the EC and is recommended by the US Advisory Committee on Immunization Practices (ACIP) as an option for childhood vaccination.[29–31]

Economic evaluation studies for PCVs in the Mexican pediatric population have previously shown that the introduction of PCV7, 10-valent PCV (PCV10), and PCV13 provided substantial cost-savings, with PCV13 providing superior health outcomes and cost-savings compared with lower-valent vaccines.[5,32] This study aimed to assess the cost-effectiveness of pediatric vaccination with PCV20 compared with the current SoC (PCV13), considering a 2 + 1 schedule for both, to prevent pneumococcal disease in the Mexican population. PCV15 2 + 1 was also considered as a comparator versus PCV20 due to its anticipated approval and potential as an alternative to the current SoC in Mexico.

Materials and methods

Model

A decision-analytic Markov cohort (state-transition) model was developed in Microsoft Excel® (Redmond, WA, US), populated with an annual cycle, to assess the costs and health outcomes associated with switching from SoC (PCV13) to PCV20, and from PCV15 to PCV20, all under a 2 + 1 schedule, in the Mexican pediatric population over a 10-year time horizon from Mexican public health sector perspective. The Markov framework has been considered appropriate in several costeffectiveness studies of PCVs globally.[33–39]

In each annual cycle, vaccinated and unvaccinated individuals had the potential to transition to a disease state (i.e., experiencing pneumococcal disease) or remain in a healthy state (i.e., not experiencing pneumococcal disease), with death as an absorbing health state. Within the disease state, individuals could suffer from different clinical events, such as IPD (meningitis or bacteremia); all-cause pneumonia (either non-hospitalized or hospitalized); all-cause acute otitis media (hereafter referred to as OM); or no pneumococcal disease from which all costs and quality-adjusted life year (QALY) decrements were considered (Figure 1). The probability of death in the model was incorporated as a blend of general mortality and case fatalities. Case fatalities were considered for either meningitis, bacteremia, or hospitalized pneumonia. The annual variation in transition probabilities for individual health states considered age and vaccination status. Multiple cohorts were considered to simulate temporal dynamics in the study, reflecting real-world childhood vaccination programs. Specifically, a new birth cohort was introduced at the start of

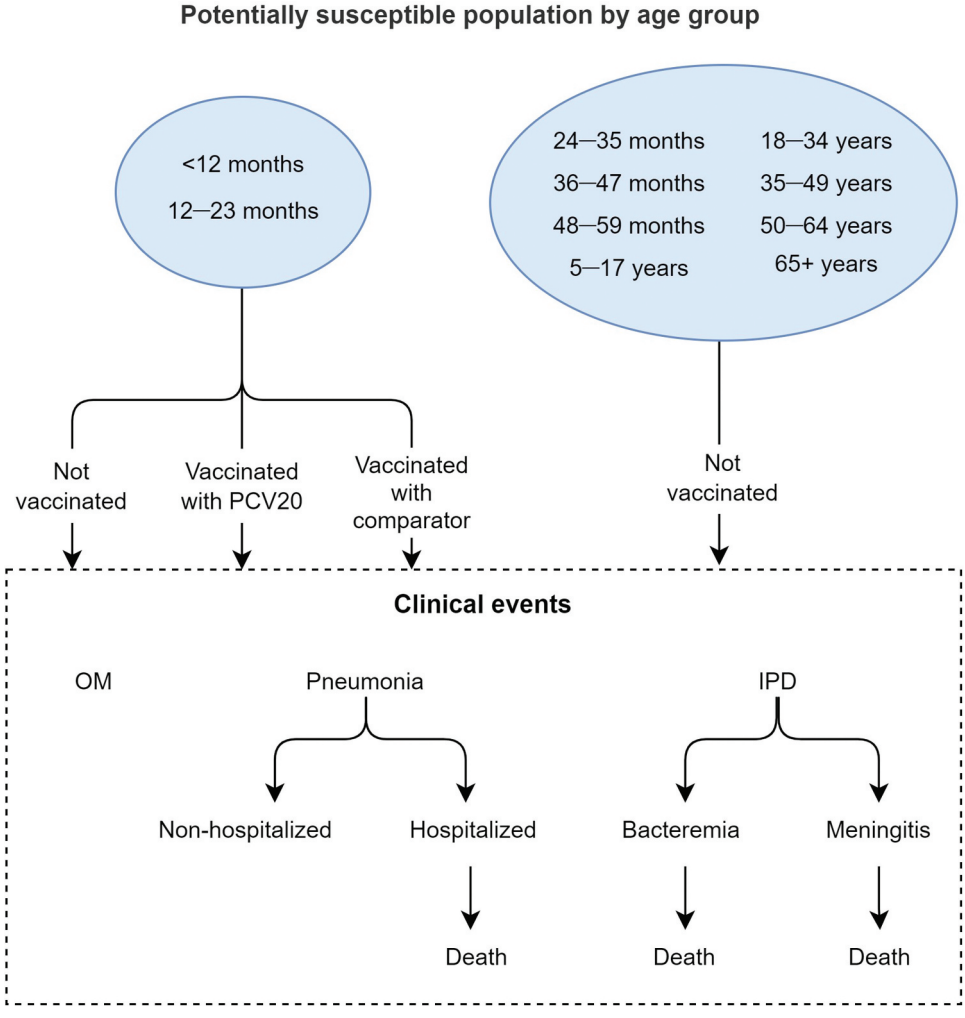

Figure 1. Model structure. Abbreviations: IPD, invasive pneumococcal disease; OM, otitis media; PCV20, 20-valent pneumococcal conjugate vaccine.

each annual cycle, becoming eligible for vaccination, a proportion of which was assumed to be vaccinated. The model followed these cohorts throughout the time horizon, alongside previously introduced cohorts, enabling the assessment of cumulative and dynamic effects of vaccination on newly vaccinated individuals and the broader population. The model examined costs and health outcomes associated with all included cohorts, enabling comprehensive vaccination assessment. The analysis did not account for the sequelae resulting from pneumococcal disease due to insufficient robust data on these rare conditions in Mexico.

Key model outcomes included costs and clinical outcomes (such as pneumococcal disease cases and deaths from disease), life-years (LYs), and QALYs. Incremental outcomes, such as incremental costs, incremental QALY, incremental LY, and incremental cost-effectiveness ratio (ICER), were considered in pairwise comparisons of PCV20 versus lower-valent alternatives.

Model population

The multi-cohort model included both vaccinated and unvaccinated cohorts, of which the targeted population (i.e., vaccinated cohort) consisted of children aged <2 years, with other age groups benefiting from indirect effects. Several age groups were considered to capture heterogeneity by age in epidemiology, disease probabilities, effectiveness of each vaccination strategy, costs, and quality of life. For children aged <5 years, one-year age groups (i.e., <12, 12–23, 24–35, 36–47, and 48–59 months) were adopted, whereas larger intervals were used to stratify individuals aged ≥5 years (5–17, 18–34, 35–49, 50–64, and ≥65 years). Population size and upcoming birth cohort data were sourced from Mexican-specific data (Proyecciones CONAPO data, 2023; Supplementary Table S1).[40]

At the start of each annual cycle, individuals who survived the previous annual cycle moved into the next corresponding age group, where relevant. As they transitioned, the relevant epidemiological characteristics of the new age group, including disease incidence, case fatality rates, and age-specific vaccine effects, were assigned accordingly.

Time horizon, perspectives, and discounting

The base-case analysis was conducted from a Mexican public health sector (i.e., payer perspective), the base-case settings are presented in Supplementary Table S2. The model time horizon was selected according to The Professional Society for Health Economics and Outcomes Research (ISPOR) guideline, which states that the time horizon should reflect the duration of vaccine effectiveness.[41] Observational studies of the PCV vaccination program have shown that both direct and indirect effects of PCV7 and PCV13 reached a plateau 5–10 years after PCV implementation.[8,42] Therefore, a 10 year time horizon was used, as this was considered long enough to capture all relevant costs and health benefits. The model discounted the costs and health benefits at a rate of 5% per annum, in line with Mexican economic evaluation guidelines.[43,44]

Epidemiology and vaccine effectiveness

Model inputs prioritized Mexican published literature and publicly available data sources where available. Key model inputs are presented in Table 1. The age-specific serotype coverage by each vaccine (PCV13, PCV15, and PCV20) and disease incidence data for IPD were derived from the Sistema Regional de Vacunas (SIREVA), utilizing the average data obtained between the years 2017–2021.[25] The use of average data in the model was argued to be a reasonable approach. Since SIREVA is a passive and laboratory-based regional surveillance system, where healthcare providers are not mandated to report cases directly to SIREVA but to national systems, which may subsequently contribute data to SIREVA. SIREVA data are therefore dependent on reports from sentinel hospitals and national reference laboratories. Due to several limitations, such as a limited hospital network and the exclusion of disease cases outside of sentinel sites/reference laboratories, IPD data are often underreported.[45,64] Accordingly, IPD incidence rates from SIREVA data were adjusted using an underestimation factor of 2%, as reported in a 2021 study.[45] The model categorized IPD as either meningitis or bacteremia, of which the distribution of cases was sourced from SIREVA 2019.[25] Data for noninvasive diseases such as hospitalized pneumonia, nonhospitalized pneumonia, and OM were retrieved from Mexican-specific sources and published literature. Statista 2019 data for the number of all-cause hospitalized pneumonia (inpatient) cases in Mexico were converted into incidence per 100,000 individuals.[46]

The incidence of all-cause non-hospitalized (outpatient) pneumonia was calculated based on the proportion of inpatients with all-cause pneumonia using data from Wasserman et al. 2019 for the pediatric population and adults aged ≤49 years, and from Buzzo et al. 2013 for age groups ≥50 years.[5,47] Incidence rates for all-cause OM in children ≤17 years were retrieved from Wasserman et al. 2019.[5] The analysis incorporated mortality using both general mortality and case fatality correspondent to meningitis, bacteremia, and hospitalized pneumonia.[5,65] It was assumed that no disease fatality was related to non-hospitalized pneumonia.

The safety of PCV13 was demonstrated in several studies across multiple countries with rarely reported treatment-related adverse events (AEs) and no serious AEs or deaths.[66] The highervalent vaccines, PCV15 and PCV20, were approved based on immunogenicity data, with safety profiles similar to PCV13.[67–69] Therefore, the analysis did not consider any AEs related to any of the assessed vaccines.

The assessment of outcomes spans the entire Mexican population, capturing the full benefits of the vaccine (direct and indirect effects). Direct effects occur immediately among the vaccinated population, while the indirect effects gradually accrue across the entire population, benefiting both the vaccinated cohort who were not fully protected as well as the unvaccinated cohort, over the model's time horizon. As there were no available data for the effectiveness and efficacy for PCV15 and PCV20 at the time of the study, parameters for vaccine effects were obtained from PCV13 effectiveness studies and PCV7 trial data as well as PCV13 impact data from Mexico.

Table 1. Key inputs.

	Age group							
	<12 mo	12–23 mo	24–59 mo	5–17 yrs	18–34 yrs	35–49 yrs	50–64 yrs	≥65 yrs
Serotype coverage, %[5]								
PCV13*	29.0	45.4	33.6	28.1	29.1	38.3	36.1	23.0
PCV15	30.8	45.4	33.6	28.5	31.6	39.2	39.2	26.9
PCV20	37.5	51.9	49.8	44.7	46.3	54.1	50.5	39.7
Disease incidence per 100,000 individuals								
IPD[25,45]	18.6	7.3	4.1	2.0	0.6	0.9	2.1	2.5
Hospitalized pneumonia[46]	801.5	271.1	271.1	42.9	26.8	54.1	128.1	370.5
Non-hospitalized pneumonia[5,47]	6412.0	2168.9	2168.9	343.4	214.1	433.0	638.7	654.9
Otitis media[5]	855.3	855.3	1081.8	1860.6	-	-	-	-
Proportion of IPD cases, %								
Meningitis[25]	30.43	30.43	30.43	14.29	0.00	0.00	38.90	38.90
Bacteremia	69.57	69.57	69.57	85.71	100.00	100.00	61.10	61.10
Fatality rate, %[5]								
Meningitis	14.7	14.7	14.7	14.7	14.7	14.7	20.0	25.3
Bacteremia	4.5	4.5	3.5	4.2	4.1	4.1	4.1	4.1
Hospitalized pneumonia	3.0	3.0	3.0	3.0	3.0	3.0	12.4	16.8
Direct medical costs (per episode), $MXN[5]								
Meningitis	267,282.68	267,282.68	267,032.47	188,184.13	193,654.94	197,711.37	209,617.51	296,368.71
Bacteremia	167,803.42	167,803.42	167,646.56	89,660.32	92,267.38	94,200.31	99,872.06	186,063.22
Hospitalized pneumonia	67,582.63	67,582.63	67,520.40	67,157.41	69,108.49	70,556.57	74,804.87	74,937.11
Non-hospitalized pneumonia	47,586.95	47,586.95	47,542.88	47,287.49	48,661.67	49,680.64	52,672.73	52,766.07
Otitis media	78,196.26	78,196.26	32,582.42	11,729.83	-	-	-	-

	Cost of dose	Administration cost per dose
Vaccination costs, $MXN**		
PCV13 2 + 1	183.78[48]	291.69
PCV15 2 + 1	183.78*	291.69

	IPD[49]	Hospitalized pneumonia[50]	Non-hospitalized pneumonia[51]	Otitis media[52]
Direct effects, %#	88.7	25.5	6.0	7.8

	IPD[25]	Hospitalized pneumonia[23–53–55]	Non-hospitalized pneumonia[54,55]	Otitis media[18,53]	Excluded population from adult vaccination program§ [40,56]
Indirect effect – maximum reduction, %					
<5 y	50.3	43.8	32.3	28.0	-
5–17 y	50.3	35.6	26.2	28.0	-
18–34 y	57.8	22.5	0.0	-	-
35–49 y	48.9	22.5	0.0	-	-
50–64 y	51.2	25.2	0.0	-	16.8
≥65 y	69.1	26.9	0.0		47.9

	Year(s)					
	1	2	3	4	5	6–10
Indirect effect – ramp-up (PCV15/PCV20), %[53,57]	0.0	37.5	52.8	67.7	82.7	100.0

	0–19 yrs	20–49 yrs	50–64 yrs	≥65 yrs
Baseline utilities[5]	0.94	0.93	0.92	0.91

	0–17 yrs[58–60]	≥18 yrs[61–63]
Utility decrements		
Meningitis	0.023	0.13
Bacteremia	0.008	0.13
Hospitalized pneumonia	0.006	0.13
Non-hospitalized pneumonia	0.004	0.045
OM	0.005	N/A

*Assumption: same cost as PCV13. **Assumption: PCV20 cost is 10% higher than the PCV13. #Direct vaccine efficacy data were adjusted using serotype coverage pre-PCV7 to pre-implementation (various years before implementation depending on source data) of higher-valent vaccines: 80.6% PCV7, 47.5% PCV20, 17.8% PCV15, and 12.8% PCV13 – Pfizer data on file. Abbreviations: $MXN, Mexican peso; IPD, invasive pneumococcal disease; mo, months; N/A, not applicable; OM, otitis media; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; yrs, years.

In Mexico, under the 2 + 1 schedule for PCVs, the priming doses are given at ages 2 and 4 months, with a booster dose given at 12 months. Based on data reported from Gobierno de Mexico, vaccine uptake was assumed to be equivalent for all vaccines, with 83.5% of individuals completing the full schedule by age 12 months.[70]

The direct vaccine effect against IPD was defined as the expected reduction in vaccine serotype IPD incidence among

vaccinated children aged <2 years using data on the effectiveness of PCV13 against IPD (88.7%, 95% confidence interval [CI]: 81.7–92.7).[49] The base-case assumed that all vaccine serotypes had the same direct effect, regardless of vaccine. The reduction in all-cause noninvasive disease incidence was estimated by multiplying the effectiveness estimates of all-cause hospitalized pneumonia (25.5%), non-hospitalized pneumonia (6.0%), and OM (7.8%) from the PCV7 pivotal trials with the ratio of current serotype coverage level for each vaccine to the serotype coverage level for PCV7 at the time the trials were conducted.[50,51,71] To reflect the vaccine schedule in which the two primary doses are given in the first year of life, the direct effect within the first year was assumed at 67% of the full direct effect (i.e., two-thirds of the full effect of a complete 2 + 1 schedule). Based on real-world effectiveness data from Savulescu et al. 2022, direct effects were assumed to remain unchanged for the first five years after the final dose and then would gradually wane over time.[49] The direct vaccine effects were assumed to reduce by 10% annually from Year 6 post-vaccination, reaching 58% in Year 10, which represented the maximum protection duration of all vaccines. However, since the maximum modeling time horizon is 10 years, only the first vaccinated birth cohort enter at the onset of the modeling year would be benefited for the maximum protection. The duration of the direct protection for all other sequential vaccinated birth cohorts would only last to the end of modeling horizon.

As herd immunity is an important benefit of the implementation of a pediatric NIP, the analysis considered vaccine indirect effects for unique serotypes covered in higher-valent vaccines, PCV15 and PCV20, against all disease states.[24] Indirect effects against serotypes covered by all vaccines are reported in Supplementary Table S3. Indirect effects were assessed based on the change in incidence rate (i.e., percent reduction) in unvaccinated age groups since the implementation of the PCV13 pediatric NIP in 2010.[5] The indirect effects were assumed to occur gradually until a steady state was attained, following the same approach as other studies of the PCV20 pediatric vaccine.[72–74] IPD and hospitalized pneumonia indirect effects were applied to all age groups; whereas, non-hospitalized pneumonia and OM indirect effects were applied to children only (aged ≤17 years). Individuals covered under the adult vaccination program (17% of those aged 50–64 years and 62% of those aged ≥65 years) were excluded from receiving vaccine indirect effects.[56] The indirect effect against IPD (i.e., the maximum reduction in IPD incidence following the introduction of PCV15 or PCV20) was estimated based on the maximum reduction in IPD incidence from Mexican surveillance data post PCV13 implementation from SIREVA.[25] For noninvasive diseases, due to the lack of robust data from PCV13 effectiveness and impact studies, efficacy data from PCV7 pivotal trials were used to estimate the reduction in disease incidence for inpatient/outpatient pneumonia and OM. Due to the limited availability of Mexican data, the model utilized impact data from European countries to estimate noninvasive disease indirect effects.[18,23,53,54,57] Due to use of PCV13 for over a decade, an assumption was made that the indirect effects of the vaccine-type serotypes covered by PCV13 had stabilized. Therefore, implementing higher-valent vaccines such as PCV15 or PCV20 would not yield additional indirect effects for PCV13-unique serotypes. The indirect effects of PCV15 and PCV20 were calculated only for the newly covered serotypes, assuming these effects would be realized gradually over the model's time horizon. To inform the accrual time of the indirect effects for PCV15 and PCV20, IPD surveillance data from the United Kingdom (UK; Ladhani et al., 2018) were used, with the sixth year of the PCV13 infant program designated as the steady-state year, in line with Perdrizet et al., 2023.[53,57] Specifically, for individuals in age groups other than the vaccination eligible age group, the discounted indirect protection started to count in the modeling year 2 and gradually increase along with the modeling year increase. The full indirect effect, as specified above, took effect at the modeling year 6 and thereafter.

Costs and utilities

Cost categories considered in this analysis included vaccine costs, vaccine administration costs, and direct medical costs (per episode) of pneumococcal diseases (Table 1). All costs were calculated in Mexican pesos (MXN) inflated to January 2024 using the Índice Nacional de Precios al Consumidor (INEGI) tool.[75] In this study, as we aimed to provide evidence to aid policymakers in Mexico regarding the implementation of higher-valent PCV into the NIP for infants and children, using local currency (i.e., MXN) to ensure that the results are relevant and applicable to the local context. Age-specific baseline utility values, informed by Wasserman et al. 2019, were assumed for healthy individuals.[5] QALY decrements for pneumococcal diseases were sourced from published literature.[33,58,61,62,76]

Sensitivity and scenario analyses

Through a series of deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses, uncertainties around model inputs and structural assumptions were assessed. The DSA was conducted to identify key model influencers on costs and QALYs by varying relevant parameters individually at a default variance of 10% to estimate the upper and lower bounds. In the PSA, all relevant model parameters were randomly distributed using different distributions based on recommendations described by Briggs et al. 2006, such as beta for proportion, serotype coverage, gamma for incidence and costs, and normal distribution for population size or doses.[77] A standard error of 10% was used and the analysis was performed with 1,000 iterations.

Additionally, a series of scenario analyses were conducted to assess uncertainty around the structural and methodological assumptions, as well as the data sources used to inform model inputs. Scenarios 1a and 1b examined the impact of varying discount rates: Scenario 1a applied no discount rate for benefits and a 3% discount rate for costs, while Scenario 1b applied a 7% discount rate for both benefits and costs. Scenarios 2a – c focused on the assumptions related to vaccine indirect effects. These included estimating indirect effects for the unvaccinated cohort only (2a), assuming all adults benefit from indirect effect (2b), and a scenario in which indirect effects were only considered against IPD (2c). Scenario 3 adopted an "efficacy-based approach" using PCV7 clinical trial data to

estimate direct effect against IPD (93.9%).[71] In Scenario 4, the percentage of pneumonia cases attributable to *S. pneumoniae* (18%) was applied to estimate health state outcomes for pneumonia.[78] Scenario 5 explored a societal perspective by including productivity loss in the total costs. Lastly, scenarios 6a and 6b tested the assumptions around serotype replacement, applying a linear reduction of 5% or 10% annually for PCV15- and PCV20-unique serotypes (i.e., those newly covered versus PCV13) until a steady state is reached to account for potential serotype distribution changes over time. While PCV13 serotypes were assumed to have reached a steady state, PCV15- and PCV20-unique serotypes were expected to decline, leading to an increase in non-vaccine-type serotypes. As a result, the direct and indirect effects of PCV15 and PCV20 on pneumococcal diseases diminished over the 10-year horizon. A summary of the explored scenarios are provided in Table 2. Indirect cost inputs for the scenario exploring societal cost are reported in Supplementary Table S4.

Results

Base case

The discounted results for pairwise comparisons of PCV20 versus PCV13 and PCV20 versus PCV15 over a 10-year time period are presented in Table 3. In the base-case analysis, PCV20 was the dominant vaccination strategy compared with both SoC (PCV13) and PCV15 from a Mexican public health sector perspective over 10 years. Compared with PCV13, the implementation of PCV20 was estimated to result in a reduction of 2,068 IPD cases 55,720 hospitalized pneumonia cases, 150,959 nonhospitalized pneumonia cases, 244,124 OM cases, and 3,536 deaths due to disease across all ages. Similarly, in the pairwise comparison with PCV15, a considerable number of disease cases were averted by PCV20: 1,863 IPD cases 49,578 hospitalized pneumonia cases, 142,428 nonhospitalized pneumonia cases, and 237,771 OM cases, plus 2,943 deaths due to disease.

As a result, the incremental QALY gain with PCV20 versus PCV13 was 65,774, and with PCV20 versus PCV15 was 56,647. Replacing PCV13 with PCV20 was estimated to result in a total cost saving of $MXN −11,046,591,714 and replacing PCV20 with PCV15 was estimated to result in a total cost saving of $MXN 10,264,306,296.

Sensitivity analyses

DSA results are presented in Figure 2 for PCV20 versus PCV13 and Figure 3 for PCV20 versus PCV15. For both comparisons, the top five most powerful cost drivers were vaccine coverage of the comparator (PCV13 or PCV15) and PCV20, overall serotype coverage by vaccine, and administration cost per dose for each PCV. The top five key drivers of QALYs in both pairwise comparisons followed the same order, from maximum indirect effect of hospitalized pneumonia with PCV20, overall serotype coverage by vaccine, baseline utilities, and the incidence and case fatality rate of hospitalized pneumonia. In all DSAs, PCV20 remained dominant compared with both PCV13 and PCV15.

The cost-effectiveness plane from the PSA based on 1,000 simulations is presented in Supplementary Figure S1 for comparison of PCV20 versus PCV13 and Supplementary Figure S2 for PCV20 versus PCV15. In the PSA, despite variation in base-case parameter inputs, all of the incremental costeffectiveness ratios fell in the lower-right hand quadrant, indicating that PCV20 vaccination was less costly and more effective than PCV13 and PCV15 vaccination (dominant) in all 1,000 simulations.

Scenario analyses

The results from different scenario analyses did not change the conclusions, with PCV20 remaining the dominant strategy in

Table 2. Explored scenarios.

Settings/parameters	Base case	Scenarios
S1. Discount rates	5% for both costs and benefits.	1a. No discount rate (0%) for benefits and 3% discount in costs. 1b. 7% discount in both effects and costs.
S2. Indirect effects	• Applied to the whole population. • Consider indirect effects against all disease states. • Data source for PCV20 2 + 1 and PCV15 2 + 1: use indirect effect from SoC. • Exclude vaccinated adults from indirect effect.	2a. Estimated for unvaccinated cohort only. 2b. Assume all adult population benefiting from indirect effects. 2c. Only consider indirect effects against IPD.
S3. Direct effect	• Invasive pneumococcal disease: the "effectiveness-based approach" (vaccine type) 88.7%. • Non-invasive disease: the "efficacy-based approach" 25.5%, 6%, and 7.8% for hospitalized pneumonia, non-hospitalized pneumonia, and otitis media, respectively.	• Invasive pneumococcal disease: the "efficacy approach" of 93.9%. • Non-invasive disease: same as the base case.
S4. Health state outcomes	All-cause disease. Unknown percentage of cases by *S. pneumoniae*.	If known percentage of cases by *S. pneumoniae* (18% for community-acquired pneumonia (Lansbury et al., 2022).[78]
S5. Perspective	Payer perspective.	Societal perspective.
S6. Serotype replacement	No replacement.	6a. Linear reduction at 5% in PCV15 and PCV20 newly covered serotypes. 6b. Linear reduction at 10% in PCV15 and PCV20 newly covered serotypes.

Abbreviations: IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; *S. pneumoniae, Streptococcus pneumoniae*; SoC, standard of care.

Table 3. Discounted results by vaccine over a 10-year period.

Model outcomes	SoC: PCV13 2 + 1	PCV15 2 + 1	PCV20 2 + 1	PCV13 versus PCV20	PCV15 versus PCV20
Cases of IPD	26,426	26,221	24,358	−2,068	−1,863
IPD cases which are meningitis	6,356	6,299	5,873	−483	−426
IPD cases which are bacteremia	20,071	19,922	18,486	−1,585	−1,437
Cases of hospitalized pneumonia	1,552,278	1,546,136	1,496,557	−55,720	−49,578
Cases of non-hospitalized pneumonia	8,408,580	8,400,049	8,257,621	−150,959	−142,428
Cases of otitis media	6,361,537	6,355,184	6,117,413	−244,124	−237,771
Number of deaths due to disease	133,383	132,789	129,846	−3,536	−2,943
Total QALYs	2,403,377,370	2,403,386,497	2,403,443,144	65,774	56,647
Total LYs	2,631,411,629	2,631,416,724	2,631,447,459	35,380	30,735
Total costs, $MXN	540,265,516,104	539,483,230,686	529,218,924,390	−11,046,591,714	−10,264,306,296
Total direct cost of doses, $MXN	20,837,130,672	20,837,155,004	21,642,652,942	805,522,270	805,497,938
Total direct cost of disease, $MXN	519,428,385,432	518,646,075,682	507,576,271,448	−11,852,113,984	−11,069,804,234
ICER per QALY	-	-	-	**PCV20 is dominant**	**PCV20 is dominant**

Abbreviations: $MXN, Mexican peso; ICER, incremental cost-effectiveness ratio; IPD, invasive pneumococcal disease; LY, life-year; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life year; SoC, standard of care.

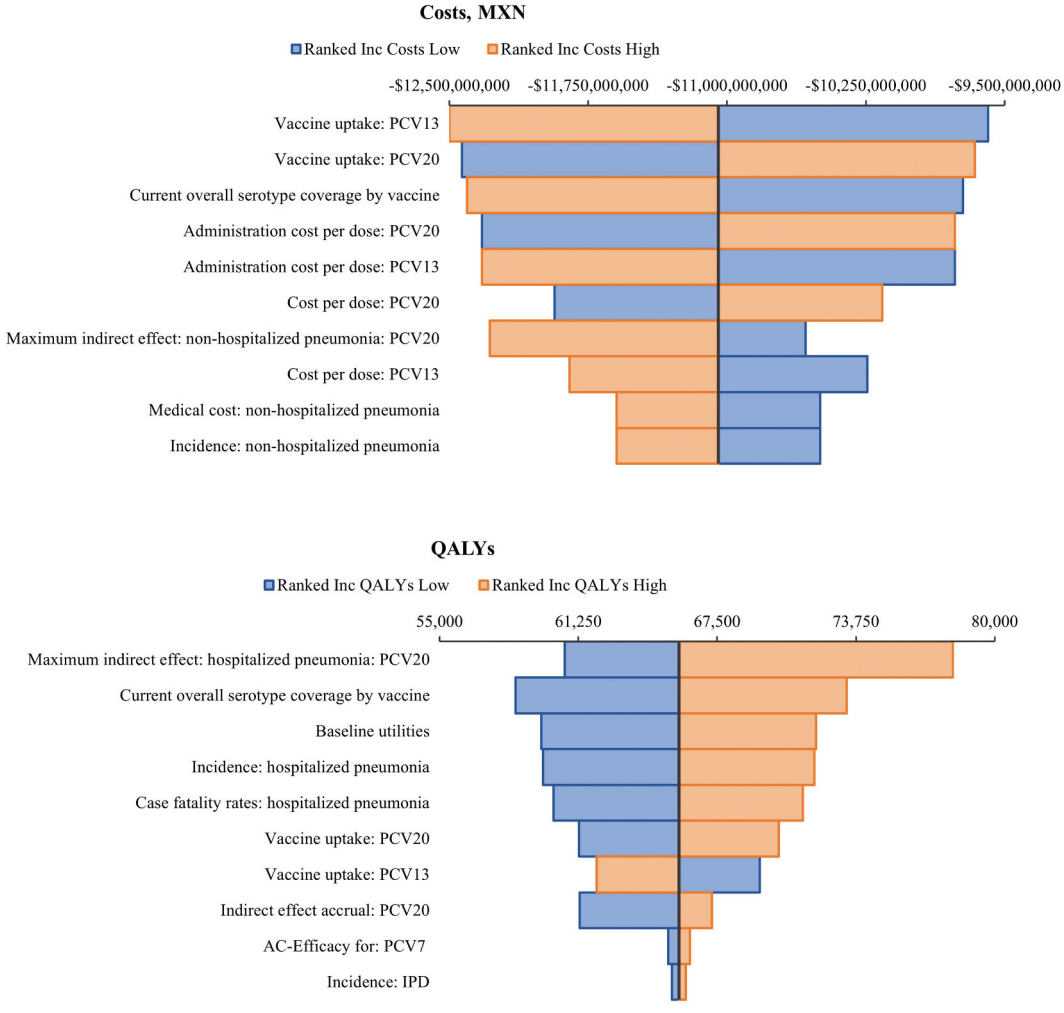

Figure 2. DSA results: SoC (PCV13) versus PCV20, (a) costs (10% bounds), (b) QALYs (10% bounds). Abbreviations: AC-efficacy, all-cause efficacy; DSA, deterministic sensitivity analysis; IPD, invasive pneumococcal disease; MXN, Mexican peso; PCV13, 13valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life year; SoC, standard of care.

all scenario analyses versus PCV13 and PCV15 (Supplementary Table S5). Specifically, using different discount rates led to similar total cost savings and similar or higher QALYs gained with PCV20 as in the base case. Assuming all adults benefited from indirect effects and a scenario with a societal perspective both also led to similar findings. However, lower cost savings and QALY gain versus the base case were found in the scenario that only considered indirect effects against IPD. Examining the assumptions for serotype replacement, as well as a scenario in which health

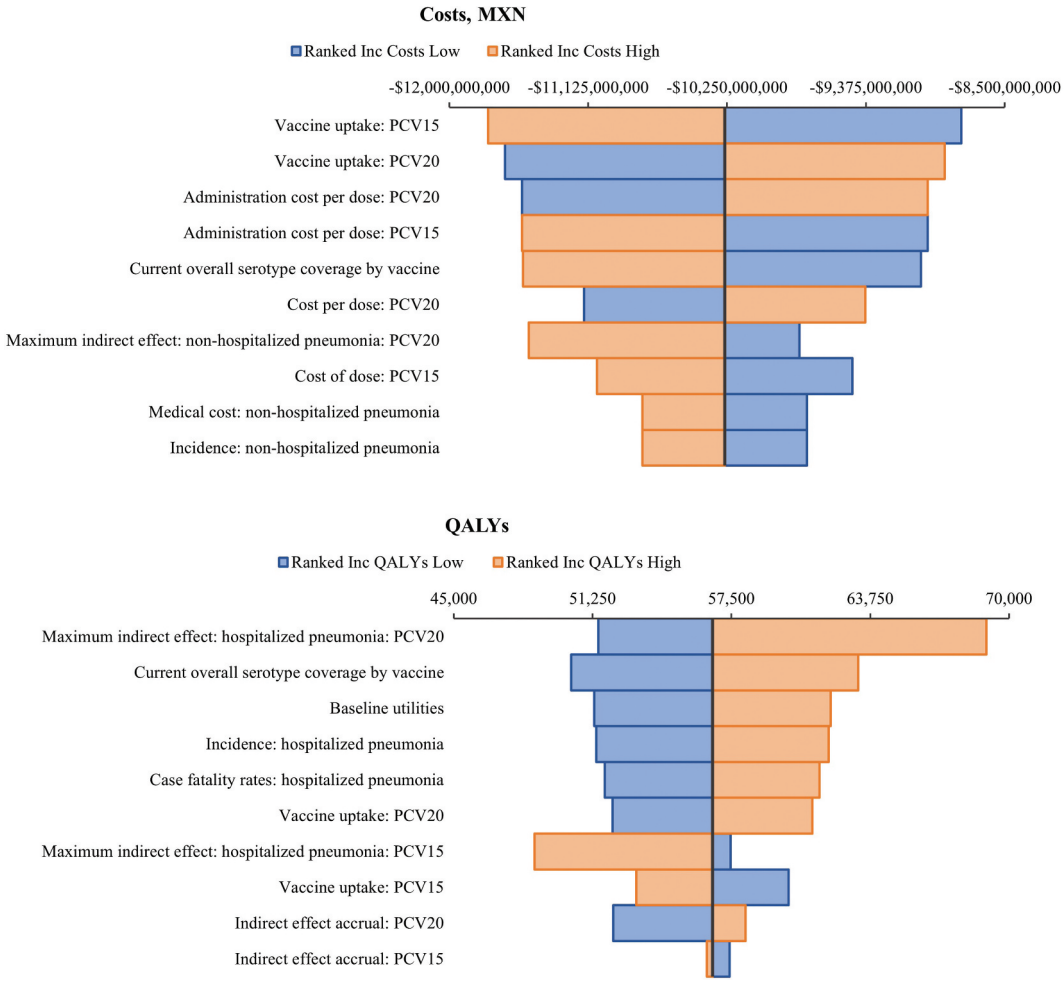

Figure 3. DSA results: PCV15 versus PCV20, (a) costs (10% bounds), (b) QALYs (10% bounds). Abbreviations: MXN, Mexican peso; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

outcomes for pneumonia were estimated based on 18% of cases being caused by *S. pneumoniae*, led to lower cost savings and QALY gain versus the base case; however, PCV20 remained the dominant strategy in all scenarios.

Discussion

This cost-effectiveness analysis assessed the impact of switching from the current SoC (PCV13) or PCV15 to PCV20 in the Mexican pediatric NIP over 10 years from a Mexican public health sector perspective. The results suggested that PCV20 would be the dominant strategy (i.e., providing cost savings and higher QALYs) over both comparators. The model predicted that PCV20 would avert more cases of disease, resulting in lower medical costs related to disease, compared with lowervalent alternatives across all disease states. The findings suggest that with greater health benefits, likely due to its broader serotype coverage, implementation of PCV20 into the Mexican pediatric NIP was predicted to lead to cost savings versus lowervalent comparators.

In this study, we prioritized the most recent Mexican-specific input data, where possible. In addition, we explored multiple scenarios and sensitivity analyses to examine uncertainties around the base case and evaluate the robustness of the results. All scenario analyses estimated that PCV20 would be the dominant strategy compared with both PCV13 and PCV15, consistent with the results from the basecase analysis. The DSA and PSA indicated robust results in all iterations. The finding that PCV20 is dominant versus lower-valent alternatives is consistent with previously published economic evaluations in other countries, such as studies in the UK, Germany, Canada, Greece, and the Netherlands.[73,74,79–82]

Despite being consistent with previous studies and robust in all sensitivity and scenario analyses, the results of this study should be considered with the following limitations. Firstly, no real-world data were available to inform the public health impact of including PCV20 and PCV15 in pediatric NIPs at the time the analyses were conducted. These next-generation PCVs also did not have available efficacy data from clinical studies for ethical reasons. Therefore, vaccine direct effect estimates were derived from lower-valent PCVs (i.e., from PCV13 effectiveness for IPD and PCV7 efficacy for noninvasive diseases); additional serotypes covered by PCV15 and PCV20 were accounted for via inclusion of assumptions. However, this approach has been considered appropriate and widely used in costeffectiveness analyses for higher-valent vaccines.[34,38,83,84] Evaluating vaccine indirect effects was challenging due to the lack of available data for higher-valent

PCVs, since these effects require the longterm implementation of vaccination programs. The model was based on observational data from countries that have implemented PCV13 in infant NIPs, including IPD data from Mexico. Data from higherincome countries such as France and the UK were used for noninvasive disease data, due to large sample size and stable impacts, where no Mexican data were available. Furthermore, in the base-case analysis, serotype replacement was not included. However, the impact of increasing non-vaccine serotypes over time was tested, the results of which were consistent with the base case.

Conclusions

The results of the current cost-effectiveness study projected that PCV20 would be less costly and more effective compared with both PCV13 (the current SoC) and PCV15 in the Mexican pediatric NIP from a public health sector perspective over a 10-year time horizon. The results were stable and robust in all sensitivity and scenario analyses. As such, replacing the current SoC with PCV20, or implementing PCV20 instead of PCV15, would be regarded as a cost-saving strategy in the Mexican pediatric NIP, likely due to its broader serotype coverage compared with lower-valent alternatives.

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Disclosure statement

Jose Luis Huerta, Gustavo Ivan Torres, Warisa Wannaadisai, and Liping Huang report employment by Pfizer, the sponsor of this study and manufacturer of PCV20. An Ta and Elizabeth Vinand report consulting fees from Pfizer to their employer (Cytel) at the time of the study for the development of the model for the submitted work. An Ta and Elizabeth Vinand are employees of Cytel, which received funding from Pfizer in connection with the development of this manuscript.

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The study was sponsored by Pfizer. The sponsor was involved in the study design, analysis, and interpretation of the data.

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Author contributions

Liping Huang, Jose Luis Huerta, Gustavo Ivan Torres, and Warisa Wannaadisai were involved in the study conceptualization and methodology. An Ta and Elizabeth Vinand conducted the formal analysis (data analysis and interpretation). All authors drafted, edited, critically reviewed, and approved the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article/as supplementary information files.

Ethical approval

As this study used publicly available or anonymized data, ethical approval was not necessary.

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