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Cost-effectiveness analysis of replacing the 10-valent pneumococcal conjugate vaccine (PCV10) with the 13-valent pneumococcal conjugate vaccine (PCV13) in Brazil infants

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ABSTRACT

Brazil currently has a 10-valent pneumococcal conjugate vaccine (PCV10) pediatric national immunization program (NIP). However, in recent years, there has been significant progressive increases in pneumococcal disease attributed to serotypes 3, 6A, and 19A, which are covered by the 13-valent PCV (PCV13). We sought to evaluate the cost-effectiveness and budget impact of switching from PCV10 to PCV13 for Brazilian infants from a payer perspective. A decision-analytic model was adapted to evaluate the clinical and economic outcomes of continuing PCV10 or switching to PCV13. The analysis estimated future costs ($BRL), quality-adjusted life-years (QALYs), and health outcomes for PCV10 and PCV13 over 5 y. Input parameters were from published sources. Future serotype dynamics were predicted using Brazilian and global historical trends. Over 5 y, PCV13 could prevent 12,342 bacteremia, 15,330 meningitis, 170,191 hospitalized pneumonia, and 25,872 otitis media cases, avert 13,709 pneumococcal disease deaths, gain 20,317 QALYs, and save 172 million direct costs compared with PCV10. The use of PCV13 in the Brazilian NIP could reduce pneumococcal disease, improve population health, and save substantial health-care costs. Results are reliable even when considering uncertainty for possible serotype dynamics with different underlying assumptions.

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Introduction

Pneumococcal diseases are caused by the bacterium *Streptococcus pneumoniae*, which has more than 90 immunologically distinct serotypes and is one of the most significant causes of morbidity and mortality worldwide.[1] Noninvasive pneumococcal diseases include otitis media (OM), sinusitis, and community-acquired pneumonia (CAP) and are highly prevalent illnesses in children under 5, adults over 65, as well as immunocompromised individuals. Invasive pneumococcal disease (IPD), such as meningitis, bacteremia, and sepsis, is the most severe presentations and can lead to death.[2]

Vaccination is the most effective strategy for the prevention of pneumococcal diseases. Pneumococcal conjugate vaccines (PCVs) are consistently managed by pediatric National Immunization Programs (NIPs) and have reduced the pneumococcal disease burden significantly since their introduction.[2-4] In Brazil's private sector, the 7-valent (PCV7) became available to children under 5 y of age at high-risk of pneumococcal diseases during 2002–2010. The 10-valent (PCV10) was introduced universally for all children 0–2 y of age as a 3 + 1 schedule in 2010 and later changed to 2 + 1 schedule in 2016.[5] In 2019, PCV13 was approved in Brazil's NIP exclusively for patients over 5 y of age with high-risk conditions.

Recently in Brazil, there have been significant progressive increases in 3 and 19A serotype IPD.[2,6] In 2018, approximately 40% of all registered IPD cases in children under 5 y were caused by serotype 19A and 52.3% were attributed to serotype 3, 6A, and 19A combined.[5] The editorial report from the Board of Directors of the Latin American Pediatric Association (ALAPE) revealed Latin American countries incorporating PCV10 in pediatric NIPs (Brazil, Chile, Paraguay, Peru, and Colombia) have subsequently experienced increases in serotype 19A.[7] Moreover, a recent World Health Organization (WHO) position regarding PCVs in 2019 advises that the choice of the appropriate vaccine in a country should be based on, among other factors, local and regional prevalence of serotypes and antimicrobial resistance patterns.[8]

Although several studies have reported efficacy and immunogenicity of PCV10 to serotype 19A,[1,9,10] epidemiologic surveillance from countries that use PCV10 universally shows increases of 3 and 19A serotype IPD, including cases in the vaccinated population.[11-15] In contrast, real-world effectiveness data have shown that PCV13 NIPs have reduced and stabilized the incidence of serotype 3, 6A, and 19A serotype disease cases.[16-21]

PCV NIPs require a significant amount of government resources to vaccinate large birth cohorts. Nevertheless, population disease trends, serotype replacement, herd effects, antimicrobial resistance, health-care system budget impact, and cost-effectiveness are all important factors that decision-makers need to factor in when choosing a PCV for pediatric NIPs. A cost-effectiveness analysis (CEA) quantifies the costs and health gains for a given population and compares alternatives. These analyses are often used as tools for prioritizing

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the allocation of resources to interventions which have the greatest gain in health for the least amount of resources.

There are several published studies evaluating the CEA of universal pediatric PCV NIPs in Brazil. One CEA study from 2006 found that a hypothetical universal PCV7 NIP for children aged <1 y compared with no vaccination program was cost-effective.[22] Another study assessed the historical cost-effectiveness of pre-vaccine (2006–2009) versus post-vaccine (2001–2014) era in one Brazilian state, Santa Catarina, and concluded that inclusion of PCV10 in the NIP had been cost-effective from the Brazilian federal government perspective.[23] Santori et al.[24] also concluded that PCV10 was cost-effective compared with no program; however, there was uncertainty in the estimated result due to quality and availability of data and long-term vaccine effects at the time of analysis.

Few studies report on the cost-effectiveness directly comparing PCV10 versus PCV13. One study assessed PCV10 compared with PCV13 over a 1-y time horizon and concluded that switching PCVs in the Brazilian infant NIP would not be cost saving.[25] However, the analysis did not consider life-years or quality-adjusted life-years (QALYs); assumed cross-protection against 19A for PCV10, although in recent years this has not been observed in Brazil; excluded serotype replacement in the analysis, which is regularly observed with PCV use; and did not include indirect effects in non-vaccinated individuals and the adult population. Outside the context of the Brazilian health-care system, there are several analyses from other countries that consider these factors when assessing the cost-effectiveness of PCV10 versus PCV13. Pugh et al. (2020) evaluated the clinical and economic benefit of replacing PCV10 with PCV13 in Colombia, Finland, and the Netherlands and determined that a PCV13 program would save costs and prevent more disease in Colombia and Finland, as well as be cost-effective in the Netherlands at 1 x GDP per capita (€34,054/QALY), compared with PCV10.[26] Another publication using a similar modeling technique estimated that PCV7 and PCV13 are estimated to have saved 1,840 lives due to pneumococcal disease in Mexico over an 8-y period.[27] Switching to PCV10 was estimated to result in 311,259 more cases of pneumococcal disease, 410 associated deaths, and cost over 6.7 USD billion MXN over a 10-y period compared to maintaining PCV13. In Malaysia, a country that has yet to adopt a PCV into its NIP, PCV13 compared with PCV10 was projected to avert an additional 190,628 cases of pneumococcal disease and 1126 deaths, gain 2,280 QALYs, with higher cost-saving potential.[28] Other examples are reported for Canada, demonstrating that switching to PCV10 from PCV13 was estimated to result in higher net costs due to increases in disease caused by uncovered serotypes;[29] as well as Italy, which concluded that Switching from PCV13 to PCV10 would increase the incidence of pneumococcal disease primarily linked to re-emergence of serotypes 3 and 19A.[30] Therefore, the aim of this study was to build upon previous cost-effectiveness analyses conducted in Brazil and to incorporate other critical evaluation factors, such as life-year and QALY outcomes, historical local serotype behavior, current epidemiology, serotype replacement, and herd effects. We evaluated the cost-effectiveness and budget impact of replacing PCV10 with PCV13 over a 5-y period in Brazil for vaccination of children up to 2 y of age after the implementation of a universal PCV10 program.

Methods

Model structure and assumptions

The incremental cost per QALY gained was calculated using a decision-analytic model to compare the cost-effectiveness of switching from a PCV10 NIP to a PCV13 NIP from a federal government perspective. The model structure has been described in detail elsewhere.[26,27,30] Briefly, the model uses retrospective country-level observed surveillance data on serotype-specific pneumococcal disease to estimate prospective serotype disease behavior. Therefore, for vaccine serotypes contained in both PCV10 and PCV13, as well as non-vaccine serotypes, the model predicts future disease behavior from retrospective real-world data in the population dependent on which vaccine is being evaluated. Given the observed historical serotype dynamics, the model calculates future IPD, pneumococcal pneumonia, and pneumococcal OM cases over a 5-y time horizon for the following scenarios: (1) maintaining PCV10 in the Brazilian NIP and (2) switching to PCV13 in the Brazilian NIP. We estimated the number of cases of IPD (meningitis and bacteremia), pneumococcal hospitalized pneumonia, pneumococcal OM, meningitis disease sequelae, deaths, direct health-care costs related to vaccine acquisition and disease burden, life-years gained, and QALYs gained, for both PCV13 and PCV10 over 5 y.

Epidemiology data

Population statistics were taken from the *Instituto Brasileiro de Geografia e Estatística* (IBGE) for years 2009 to 2018 and were stratified into 7 age groups, 0–<2 y, 2–4 y, 5–17 y, 18–34 y, 35–49 y, 50–64 y, and 65+ y (Table 1). Vaccine coverage was assumed to be 95% of infants using a 3-dose (2 + 1) vaccination schedule. The percent of infants vaccinated was tested in sensitivity analyses.

Invasive pneumococcal disease

To estimate historical trends, serotype-specific IPD distribution data and the proportion of IPD causing meningitis for all age groups were based on *Sistema Regional de Vacunas* (SIREVA) II, which is an international prospective surveillance program organized by the WHO, with the purpose of monitoring the epidemiology of bacterial pneumonia and meningitis.[31] The reference center in Brazil is the *Núcleo de Meningites, Pneumonias e Infecções* (NMPI) of the Bacteriology Center of *Instituto Adolfo Lutz* (IAL). It is worth noting that this is a passive, laboratory-based surveillance system, which captures the IPD serotype distribution in Brazil but contributes to a limited estimation of IPD incidence rates. Therefore, incidence data were obtained from the Colombian Individual Registration of Health Services (RIPS) database, a health benefit information system from all health maintenance organizations, which provides a good estimation of overall IPD rates,[26] and the data have been published elsewhere.[26] Colombia data were chosen since the countries share population and health-care assistance similarities and had first introduced a PCV10 program in 2010. Moreover, the Colombia surveillance system also showed an increase in non-PCV10 serotypes in recent years, mainly due to serotype 19A, which is mirrored in Brazil; therefore, we

Table 1. Population, clinical, and economic parameters

	Age Range (Years)						
Input Parameters at Start of Analysis (Year 2018)	0–2	2–4	5–17	18–34	35–49	50–64	≥65
Population	5,576,454	8,606,512	41,579,214	58,230,803	45,202,237	31,655,100	18,336,482
Incidence per 100,000							
IPD	21.0	9.9	5.6	6.2	7.6	13.0	41.8
Hospitalized Pneumonia	2,801	825	131	69	115	256	1,324
IPD Meningitis (%)	55%	55%	61%	61%	61%	35%	35%
Case Fatality Rate							
IPD	0.13	0.18	0.09	0.15	0.08	0.27	0.21
Hospitalized Pneumonia	0.01	0.01	0.00	0.02	0.04	0.06	0.11
Direct Costs ($BRL)							
Bacteremia	$2,314	$2,314	$1,138	$1,296	$1,387	$1,725	$1,893
Meningitis	$2,051	$2,051	$1,511	$1,758	$2,097	$2,742	$3,592
Hospitalized Pneumonia	$965	$965	$984	$1,109	$1,150	$1,256	$1,212
Baseline Utility	0.94	0.94	0.94	0.93	0.93	0.92	0.91

Abbreviations: BRL = Brazilian Real; IPD = invasive pneumococcal disease.

assume the incidence trends should be somewhat comparable between the two settings.[15] For the base case, the age group-specific serotype distributions in Brazil were applied to the overall incidence rates in Colombia by age-group.

The modeled historical estimates for incidence of IPD among children 0–2 y, 65 y and older, and for all ages combined are shown in Figure 1. Epidemiologic data are presented specifically for children 0–2 y and those 65 or older, since these

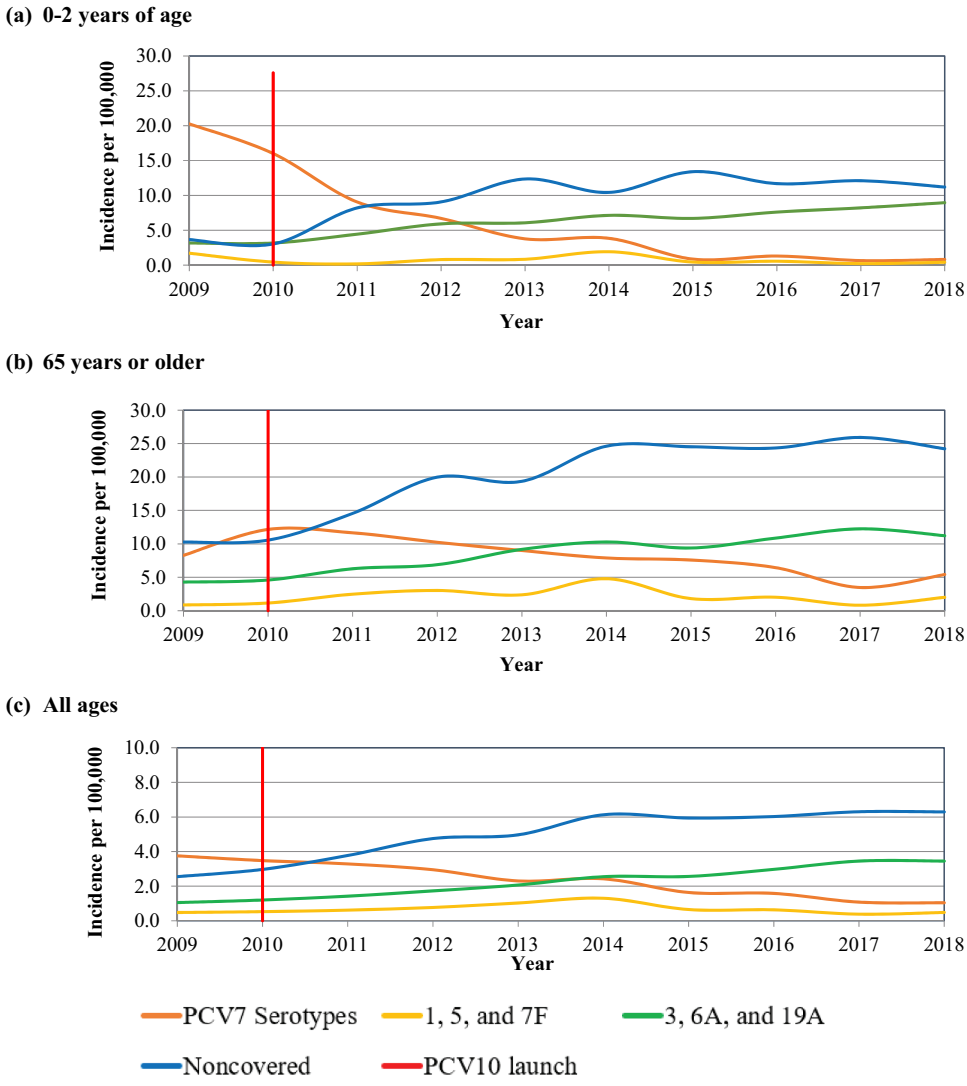

Figure 1. Base case historical invasive pneumococcal disease incidence (IPD) per 100,000 in infants 0–2 y of age in (a) 0–2 y of age, (b) 65 y or older, and (c) all ages. Data presented represent the launch of 10-valent pneumococcal conjugate vaccine (PCV10) and the historical serotype trends contained in 7-valent pneumococcal conjugate vaccine (PCV7); 1,5, and 7 F serotypes; 3, 6A, and 19A serotypes; and non-covered vaccine serotypes. Real-world data are based on the serotypes causing IPD reported annually in Brazil and incidence reported in Colombia.

populations are the most susceptible to pneumococcal disease and form a large proportion of the total disease burden. In the base case and start of the model (2018), 42% of disease in children 0–2 y of age and 26% for 65 y or older was caused by serotypes 3, 6A, and 19A, respectively. Given the uncertainty in the true incidence of IPD in Brazil, these data were tested in scenario analyses.

Noninvasive pneumococcal disease

The historical retrospective incidence of general OM from 2009 to 2014 was obtained from Santori et al.[24] for children 0–2 y of age. Santori et al.[24] included medical outpatient visits in children aged 2 to 23 months, from August 2008 through July 2015 in Goiania municipality, Brazil. The model and analysis used a conservative approach, and only included children in this age group for OM incidence rates. The incidence from 2014 to 2018 was assumed to be stable in Brazil in OM disease using data from 2014, with an annual incidence of 1,573 per 100,000 for all-cause OM. It was assumed that 20% of all-cause outpatient OM was caused by *Streptococcus pneumoniae* and was assumed to change proportionally to the changes in serotypes causing IPD. The percent of all-cause outpatient OM due to *Streptococcus pneumoniae* was tested in sensitivity analyses.

For all-cause hospitalized pneumonia incidence, data were obtained from Andrade et al.[32] from the years 2005 to 2015. Data reported by Andrade et al.[32] were representative of the full Brazilian population taken from the Unified Health System (SUS) in the National Hospitalization Information Database (SIH) stratified by age groups. This cost-effective analysis only included inpatient pneumonia cases in the calculations. Hospitalized incidence data were assumed constant from 2016 to 2018, using 2015 annual all-cause hospitalized pneumonia incidence. The same assumption was taken for inpatient pneumonia comparable to OM, that approximately 20% of all-cause inpatient pneumonia cases were caused by *Streptococcus pneumoniae* and assumed to change proportionally to IPD. Given the uncertainty in this percentage, it was varied in the sensitivity analyses.

Mortality and sequelae

Age-specific all-cause mortality rates per 100,000 for each age group were taken from IBGE 2018 data.[30] Age-specific case-fatality rates (CFR) for bacteremia, meningitis, and hospitalized pneumonia were taken from the most recent year of Novaes et al.[33] which calculated CFR from the number of deaths/confirmed cases for each clinical syndrome registered in the SIH-SUS. The analysis used CFR from SIH-SUS for hospitalized pneumonia and meningitis (Table 1). It was assumed that bacteremia had the same CFR as meningitis. Two long-term sequelae associated with meningitis were included in the model, which were neuromotor disorders and hearing loss, and probabilities for both were taken from a cost-effectiveness analysis of PCVs in Brazil, 0.17 and 0.13, respectively.[22] Base case CFRs and long-term sequelae assumptions were tested in scenario analyses.

Costs data

Direct costs were taken from publicly available sources and were inflated to 2019 Brazilian Reals (BRL). The direct costs for bacteremia, meningitis, OM, and hospitalized pneumonia were taken from SIH/SUS, calculated by taken the total cost value to the health-care system and dividing it by the number of hospitalizations recorded in 2017.[34] The calculation was performed for each disease state and age group (Table 1). The cost of OM was calculated using the same method as IPD and pneumonia and taken from SIH/SUH, but only for the 0–2 y age group, which was estimated to be 312 USD BRL per episode.[34] Cost for the two-long term sequelae due to meningitis was taken from a cost-effectiveness analysis of PCVs in Brazil, 16,200 USD for a lifetime neurologic disorder and 14,464 USD for lifetime hearing loss.[22]

The last vaccine prices practiced by the Ministry of Health and published on the Federal Official Gazette were considered, 57.22 USD and 58.94 USD per dose for PCV10 and PCV13, respectively.[35,36] The cost of immunization per child was based on the price per dose in a 2 + 1 schedule, as per guidance on the respective vaccine labels. All administration costs were assumed equal across vaccines.

Utility and decrements data

To calculate QALYs, individuals who did not experience a disease event had a baseline utility that was age-specific taken from a healthy population, shown in Table 1.[37] A utility decrement was applied for each case of disease experienced annually. Decrements of 0.0070 and 0.0232 were assumed for bacteremia and meningitis, respectively.[38] Decrements of 0.0050 and 0.0060 were assumed for OM and hospitalized pneumonia, respectively.[39] Long-term sequelae involving neurologic impairment and hearing loss following a case meningitis carried a lifetime utility decrement of 0.40 and 0.20.[40,41] Long-term sequelae input parameters were tested by excluding them in a scenario analysis, thereby omitting their associated negative utility decrements.

Analysis

Base case analysis

Clinical outcomes, direct costs, and QALYs were estimated assuming PCV10 was maintained in the NIP or where PCV10 was replaced with PCV13. In a switch from PCV10 to PCV13, disease trends began to change upon introduction of the PCV13 program. Vaccine and non-vaccine serotypes were separately modeled by age group and based on historical surveillance data. The PCV13 switch scenario was predicted using the United States (US) historical data in the base case, and additional scenarios were tested using surveillance from other countries. For PCV10, the base case analysis used the serotype distribution from Brazil and applied this to the incidence of IPD in Colombia. Sensitivity analyses were run using PCV10 NIP country case counts of IPD from Brazil and Chile.

An annual 5% discount rate was chosen based on Brazil's National Committee for Health Technology Incorporation (CONITEC) guidelines for economic evaluation[42] and was applied to costs and effectiveness outcomes beyond the first year. The analysis was from the Brazilian federal government perspective over a 5-y time horizon.

Scenario analyses

Scenario analyses were performed to assess uncertainty in Brazil IPD incidence. For historical data and subsequent

projections, the Colombia IPD data were tested in sensitivity analysis using Chilean IPD case data given that PCV10 was implemented in the NIP over multiple years. The incidence data for Chile were taken from Chilean laboratory surveillance system for IPD from 2011 to 2016.[14] This scenario analysis assumed a stable incidence rate from 2016 to 2018, using the 2016 IPD incidence rate. Moreover, a scenario analysis was run using Brazilian IPD case data reported by SIREVA II from 2009 to 2018.[2]

Separate scenario analyses were run for PCV13 future serotype dynamic projections. We conducted scenario analyses where serotype behavior was predicted using the United Kingdom (UK), Canada, and Quebec historical trends, rather than US trend data. In order to test the influence of including sequelae due to meningitis in the model, we conducted a scenario omitting the probability of incurring lifetime hearing loss and neurologic disorders, and thus omitting their associated incurred costs and negative utility weights. Vaccination coverage was tested by assuming only 89% of infants in Brazil were vaccinated starting in 2019 and projecting forward. The percentage of all-cause pneumonia and all-cause OM due to *Streptococcus pneumoniae* was conservatively assumed to be 10% for both parameters in scenario analyses. Finally, case-fatality rates were changed to assess the impact on results using case-fatality rate data from a cost-effectiveness analysis of PCV10 compared with PCV13 in Mexico.[27]

To assess the cost-effectiveness over a different time horizon, the model was run using a 10-y time horizon. Moreover, a scenario analysis was run to assess the cost-effectiveness using a 1% discount rate applied to future costs and outcomes.

Results

The public health and economic impact of PCV13 use in the Brazilian NIP for all children was predicted over 5 y from a direct health-care government perspective.

Base case results

Epidemiologic results

Base case results for IPD are presented in Figures 2 and 3. Considering that 43% of IPD was caused by 19A, 6A, and 3 serotypes in children 0–2 y of age in 2018, we estimated that this absolute percentage could increase to 48% by 2023 if maintaining a PCV10 NIP, whereas by implementing PCV13 this percentage could decrease the absolute percentage to 24% of IPD (Figures 2(a) and 3(a)). Based on epidemiologic assumptions, IPD incidence could decrease from 21 per 100,000 to 15 per 100,000, a 26% relative decrease, if PCV13 is implemented. However, if PCV10 is continued universally, IPD incidence could have a relative increase by 19% with an overall incidence of 25 per 100,000 in children 0–2 y of age.

For adults aged 65 or older, approximately 27% of all IPD was caused by the three additional serotypes in PCV13 in 2018 at the start of the analysis. The use of PCV13 was estimated to decrease the contribution of these serotypes to 17% of all IPD after 5 y (Figures 2(b) and 3(b)). However, continuing PCV10 use universally in infants for 5 y was predicted to increase 19A, 6A, and 3 IPD in adults 65 or older, with these serotypes causing 31% of all IPD. Thus, adults over 65 could see a relative decrease in IPD by 15% with a corresponding incidence of 36 per 100,000 if PCV13 replaced PCV10 in the pediatric NIP. However, this population could also see a relative increase in IPD by 10% after 5 y if PCV10 is maintained.

In general, serotypes not covered by PCV13 were predicted to cause substantial IPD burden for all age groups and this estimated burden was similar across vaccines. In the full population comprising all ages, the burden of 19A was a key driver of IPD (Figures 2(c) and 3(c)). The use of PCV13 was estimated to reduce 19A disease to 3% of all IPD after 5 y, whereas maintaining PCV10, 19A disease could increase to 20% of all IPD in the full population.

Cost-effectiveness results

Results for the base case are shown in Table 2. Using PCV13, we estimated 24,934 life-years gained and 20,317 QALYs gained over 5 y compared with PCV10. PCV13 was estimated to prevent an additional 12,342 bacteremia cases, 15,330 meningitis cases, 25,872 otitis media cases, and 170,191 hospitalized pneumonia cases over a 5-y period compared with PCV10. It was estimated that 6,979 IPD and 6,730 hospitalized pneumonia deaths could be avoided by a switch from PCV10 to PCV13. Moreover, the use of PCV13 in Brazil was estimated to be a cost-saving strategy compared with maintaining PCV10. Despite higher vaccine-related costs associated with PCV13, switching to PCV13 was estimated to save the Brazilian government approximately 172 USD million BRL over 5 y due to direct costs avoided by prevention of substantial pneumococcal disease burden.

Scenario analyses results

Three alternative scenarios were used to predict PCV13 IPD serotype dynamics based on the UK, Canada, and Quebec historical trends (Figure 4). Each scenario's trendline predictions mirrored the US base case, showing a range of predictions, all with decreasing IPD incidence, mainly due to decreases in 19A, 6A, and 3 serotype IPD.

Overall cost-effective results and cost savings for the use of PCV13 compared with PCV10 did not change when altering major assumptions in the base case. PCV13 remained cost saving compared with PCV10 across several scenario analyses (Table 3).

The scenarios included varying the trend line estimates used to forecast vaccine impact given experiences in different countries, changing the incidence of IPD using both Brazil and Chile case data from passive surveillance reports, altering the time horizon to 10 y, lowering the percentage of all-cause pneumonia and all-cause OM due to *Streptococcus pneumoniae* to 10%, omitting long-term sequelae from the analysis, changing the vaccination coverage to 85%, using Wasserman et al.[27] CFRs instead of Novaes et al.[33] and changing the discount rate to 1% for all future costs and outcomes.

Discussion

The goal of this study was to conduct a cost-effectiveness analysis using a decision-analytic model and real-world data to predict the potential public health and economic impact of

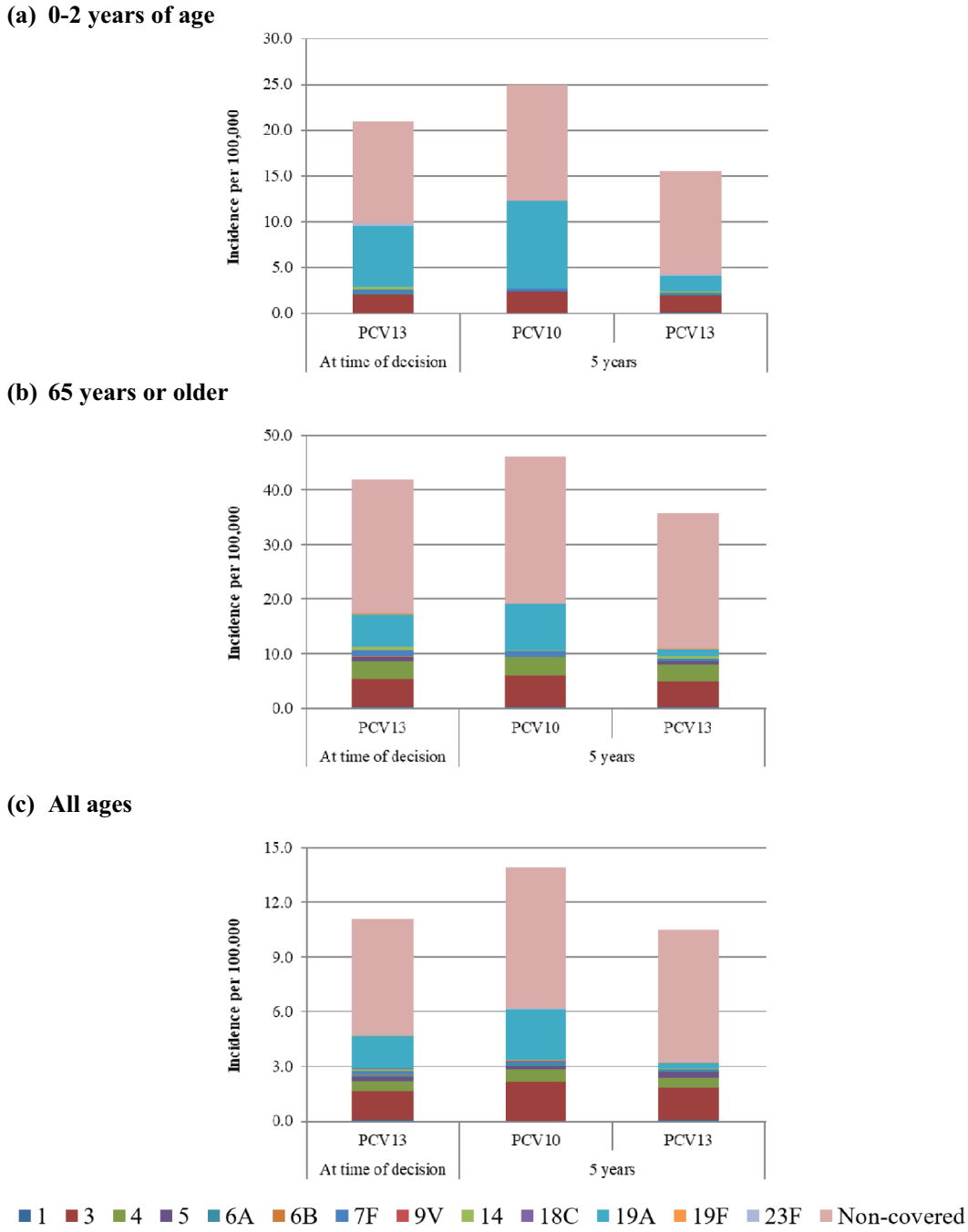

Figure 2. Base case invasive pneumococcal disease (IPD) serotype distribution at time of decision to switch and forecasted at 5 y with implementing either PCV10 or PCV13 on the Brazilian NIP in (a) 0 to 2 y of age, (b) 65 y of age or older, and (c) all ages. "At time of decision" indicates the "current state of pneumococcal disease considering the switch to the PCV13 strategy".

switching from PCV10 to PCV13 in the Brazilian NIP. This study will help enrich the cost-effectiveness literature regarding PCVs in Brazil and is the first to estimate the cost-effectiveness of switching vaccination programs from PCV10 to PCV13 for the full population over 5 y. The analysis showed that even with its higher acquisition cost, PCV13 could ultimately have a greater public health impact by preventing more pneumococcal disease.

We demonstrated that the use of PCV13 could decrease pneumococcal disease primarily due to serotypes 3, 6A, and 19A in those aged 0–2 and those 65 y or older, given that a large burden of the remaining disease in Brazil are caused by these serotypes. Moreover, serotype 19A is associated with antimicrobial resistance, the need for longer treatment, and thus the use of more health-care resources.[43] This expansion of multidrug resistance among invasive 19A strains after PCV10 introduction has been observed in Brazil.[6] While this cost-effectiveness analysis did not incorporate data on vaccine prevention for antimicrobial resistance, antimicrobial resistance is another important aspect to consider when choosing a PCV for a NIP locally, according to a recent WHO publication.[8]

This analysis was tailored to the Brazilian population by using data on the complex nature of real-world historical PCV use (serotype distribution, disease trends, vaccine type, herd

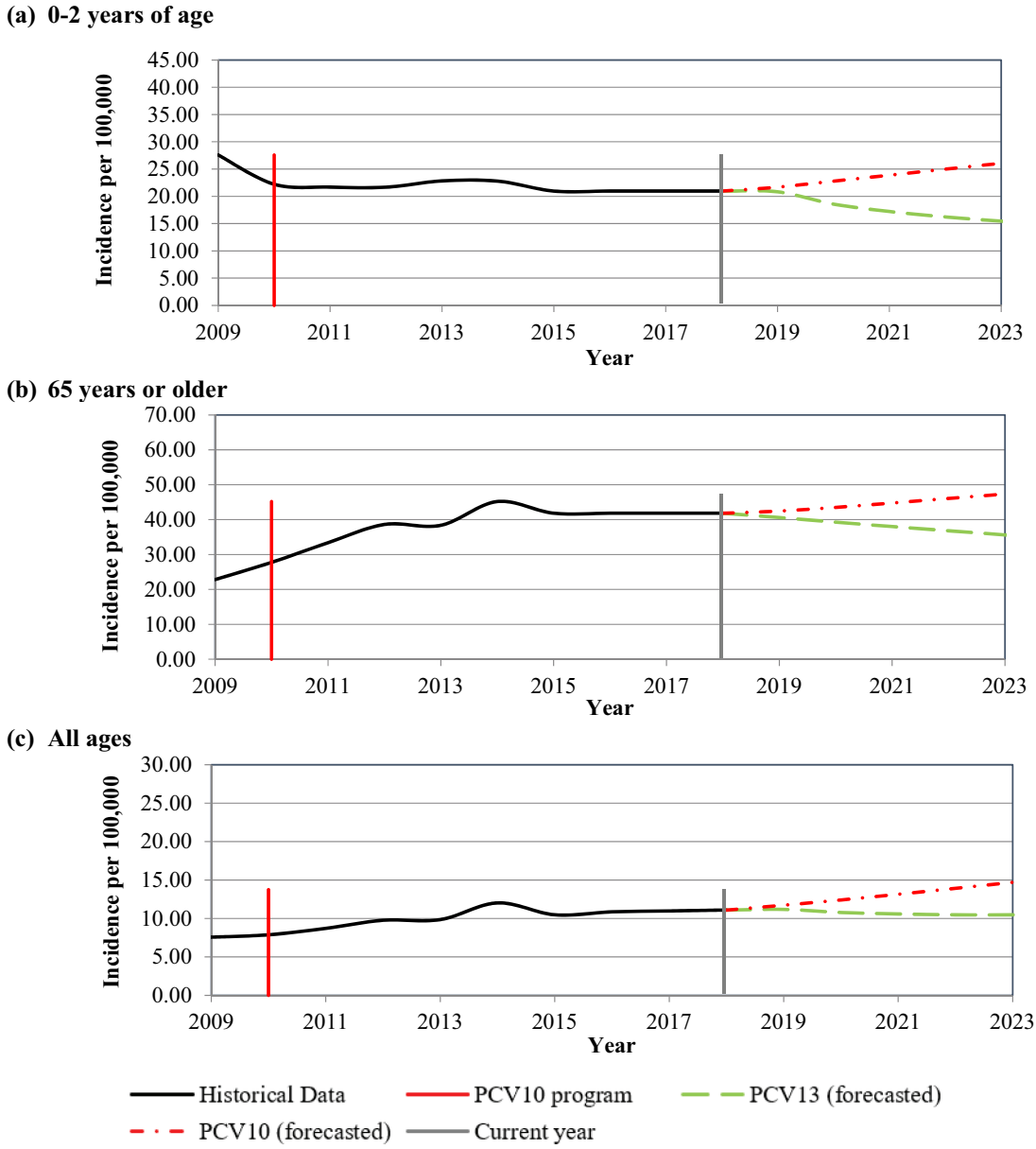

Figure 3. Base case predicted invasive pneumococcal disease incidence (IPD) based on observed real-world data per 100,000 in (a) 0–2 y of age, (b) 65 y or older, and (c) all ages. Data presented represent Historical Data for overall IPD incidence, the year 10-valent pneumococcal conjugate vaccine (PCV10) program was implement in Brazil, the current year reflecting the year the choice was made between maintaining PCV10 on the NIP or switching to PCV13, and predicted IPD for PCV10 (forecasted) and PCV13 (forecasted) depending on the choice made in the current year.

effects, uptake, etc.) to predict future disease behavior. A strength of this study was testing the serotype dynamics by using trendlines from multiple countries to predict how PCV13 could impact pneumococcal disease. Under these various scenarios using the US, UK, Canada, and Quebec serotype dynamics, the use of PCV13 followed similar serotype trends and was shown to be cost saving compared with maintaining PCV10. Additionally, by using real-world effectiveness data to predict future IPD, the framework inherently incorporates IPD indirect herd effects in projections, whereas most other cost-effectiveness studies may miscalculate these effects and/or serotype replacement by only using point estimates of vaccine efficacy.[44]

Vaccine serotype coverage was the main driver of the clinical and economic results in this analysis. The analysis demonstrated that estimated rates of total IPD, pneumococcal pneumonia, and pneumococcal OM could be further reduced in children and adults if PCV13 is included in the NIP, shedding light on the added public health impact that higher-valent vaccines provide to the population directly and indirectly. Higher valent-vaccines may soon be available, a 15-valent (PCV15, PCV13 serotypes + 22 F and 33 F) and a 20-valent (PCV20, PCV15 serotypes + 15B/C, 12 F, 11A, 10A, and 8),[45,46] which contain several of the new emerging serotypes causing IPD globally.[47-49] These higher-valent PCVs that cover additional serotypes in their formulations may add even more clinical and economic benefit by preventing more pneumococcal disease burden compared with lower-valent PCV alternatives. Thus, considerable increases in serotype protection may be obtained with the highest-valent PCV, which can ultimately

Table 2. Base case results on incremental cost, outcomes, and cost-effectiveness of PCV13 compared with PCV10 Brazil national immunization program over a 5-year time horizon

Base Case Results	National Immunization Program Intervention		
Direct Costs ($BRL)	PCV13	PCV10	Difference
Vaccine-related	$2,023,719,454	$1,964,644,829	$59,074,625
Invasive pneumococcal disease	$316,368,297	$388,210,331	-$71,842,034
Pneumococcal hospitalized pneumonia	$670,239,802	$822,856,507	-$152,616,704
Pneumococcal otitis media	$20,066,970	$26,783,938	-$6,716,968
Total Costs	$3,030,394,523	$3,202,495,604	-$172,101,081
Outcomes			
Life-years	945,651,735	945,626,801	24,934
QALYs	765,872,165	765,851,848	20,317
Cases (n)			
Bacteremia	52,502	64,844	−12,342
Meningitis	65,216	80,546	−15,330
Pneumococcal otitis media	73,815	99,687	−25,872
Pneumococcal hospitalized pneumonia	686,877	857,068	−170,191
Deaths (n)			
Invasive pneumococcal disease	31,933	38,912	−6979
Pneumococcal hospitalized pneumonia	41,847	48,576	−6730
Incremental Cost-Effectiveness (PCV13 vs PCV10)			
Incremental cost per life-year gained		PCV13 cost-saving	
Incremental cost per QALY gained		PCV13 cost-saving	

Abbreviations: BRL = Brazilian Real; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; QALY = quality-adjusted life-year.

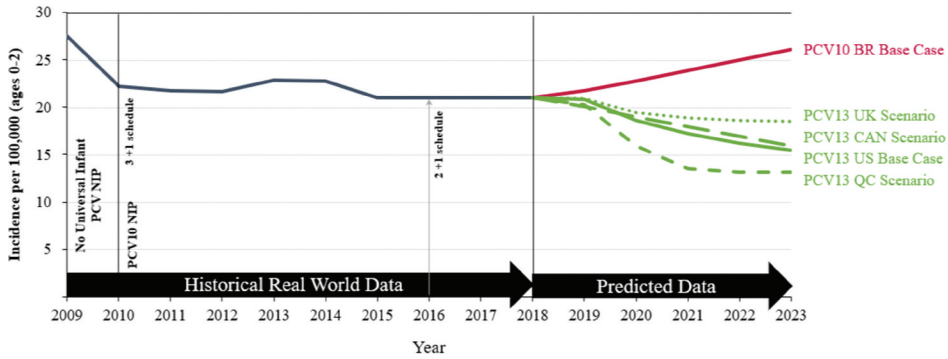

Figure 4. Scenario analyses showing the predicted invasive pneumococcal disease incidence based on observed real-world data per 100,000 in children 0–2 y of age in Brazil. Scenario analyses were run where 13-valent pneumococcal conjugate vaccine (PCV13) serotype dynamics were predicted using the United Kingdom (UK), Canada (CAN), and Quebec (QC) historical trends. For reference, the base case serotype dynamics are presented for PCV13 using historical United States (US) trends and 10-valent pneumococcal conjugate vaccine (PCV10) using historical Brazil (BR) trends. Implementation of PCV10 on the Brazilian national immunization program (NIP) and schedule changes are shown.

drive cost-effectiveness analysis results as shown in this analysis.

Like all cost-effectiveness analyses, there are some limitations mainly related to issues with the quality and underreporting of incidence rates, as many countries in Latin America have passive laboratory-based surveillance systems. For example, we applied the serotype distribution derived from Brazil IPD isolates of *Streptococcus pneumoniae* serotypes reported to Colombia's incidence rate. However, we tested the incidence data in scenario analyses using both Brazil and Chile IPD isolate case data. Results showed that the use of PCV13 would remain cost saving compared with maintaining PCV10 in the Brazilian NIP, even when using other assumptions for IPD incidence rates. For all-cause OM, data were taken from one municipality, Goiania. However, Santori et al. (2017) used the electronic Outpatient Visit Information System (OVIS), in which all outpatient visits occurring in SUS facilities in Goiania are recorded in real time, and likely reflect an accurate capture of all-cause OM reflective of the Brazilian population.[24] This study did not examine schedule adherence (two primary infant doses and one booster), something that is variable across Brazil. Without strong adherence, there can be resurgent outbreaks of the disease which subsequently weakens herd immunity. Therefore, in this analysis, uncertainty remains on how much pneumococcal burden could be influenced by adherence to the schedule and how adherence to the priming doses compared with the booster dose influences resurgence.

In conclusion, this cost-effectiveness analysis showed the use of PCV13 in the Brazilian NIP could reduce pneumococcal disease rates and improve population health. Additionally, the Brazilian government could save substantial health-care costs due to greater disease cases averted. We demonstrated that the results are consistent even when considering uncertainty for other possible serotype dynamics with different underlying assumptions.

Table 3. Scenario analyses results for total direct costs, total quality-adjusted life-years gained, incremental difference between PCV13 and PCV10, and the cost-effectiveness of PCV13 compared with PCV10 Brazil national immunization program

	PCV13		PCV10		PCV13 vs PCV10		PCV13 vs PCV10
Scenario Analysis Conducted	Total Cost ($BRL)	Total QALY	Total Cost ($BRL)	Total QALY	Cost Difference	QALY Difference	ICER
Base Case	$3,030,394,523	765,872,165	$3,202,495,604	765,851,848	-$172,101,081	20,317	Cost-saving
IPD incidence using Chile cases	$2,775,818,677	765,921,572	$2,792,646,977	765,916,820	-$16,828,300	4,752	Cost-saving
IPD incidence using Brazil cases	$2,690,940,597	765,943,240	$2,819,482,762	765,924,284	-$128,542,165	18,956	Cost-saving
PCV13 trend using UK historical	$3,125,010,042	765,863,362	$3,202,495,604	765,851,848	-$77,485,562	11,514	Cost-saving
PCV13 trend using Canada historical	$3,056,837,665	765,870,216	$3,202,495,604	765,851,848	-$145,657,940	18,368	Cost-saving
PCV13 trend using Quebec historical	$3,050,404,341	765,865,766	$3,202,495,604	765,851,848	-$152,091,263	13,918	Cost-saving
Excluding long-term sequelae	$2,925,050,221	765,874,302	$3,072,430,995	765,854,486	-$147,380,773	19,816	Cost-saving
10% of all-cause OM due to *S. pn.*	$3,020,361,038	765,872,326	$3,189,103,635	765,852,063	-$168,742,597	20,263	Cost-saving
10% of all-cause PNA due to *S. pn.*	$2,695,340,776	765,911,344	$2,800,104,584	765,894,716	-$104,763,808	16,628	Cost-saving
Alternative case-fatality rates	$3,030,336,396	765,860,502	$3,202,416,606	765,838,668	-$172,080,211	21,834	Cost-saving
Alternative vaccine coverage 89%	$2,902,979,885	765,872,165	$3,078,800,341	765,851,848	-$175,820,457	20,317	Cost-saving
Ten-year time horizon	$5,436,117,048	1,284,387,358	$6,027,867,541	1,284,295,364	-$591,750,493	91,994	Cost-saving
Discount rate set to 1%	$3,395,749,417	957,823,186	$3,596,488,854	957,795,898	-$200,739,437	27,288	Cost-saving

Abbreviations: BRL = Brazilian Real; ICER = incremental cost-effectiveness ratio; IPD = invasive pneumococcal disease; OM = otitis media; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PNA = pneumonia; *S. pn.* = *Streptococcus pneumoniae*; QALY = quality-adjusted life-year; UK = United Kingdom.

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