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Modeling the sustained use of the 13-valent pneumococcal conjugate vaccine compared to switching to the 10-valent vaccine in Mexico

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ABSTRACT

Introduction: Pneumococcal diseases caused by *Streptococcus pneumoniae* represent a significant health and economic burden. Mexico has benefited from the inclusion of the 7-valent (PCV7) and 13-valent pneumococcal conjugate vaccines (PCV13) since their inclusion in the National Immunization Program (NIP) in 2006 and 2010, respectively. The objective of this study is to estimate the impact of the existing program and predict future implications of a change in the current program.
Methods: A previously published model was updated to estimate the historic impact of the PCV programs relative to pre-PCV implementation. Future disease trends were forecasted based on historical serotype behaviors for each PCV13 serotype and non-vaccine serotypes across different age groups. Costs and outcomes were estimated over a 10-year period based on continued use of PCV13 compared to a switch to PCV10.
Results: The PCV7 and subsequent PCV13 NIP were estimated to prevent over 1.5 million cases of pneumococcal disease and 1,854 deaths, corresponding to a net savings of $34.50 Billion MXN. Continued use of PCV13 was estimated to save over 300 thousand cases of pneumococcal disease and 373 deaths compared to switching to PCV10 over a 10-year period. Despite a higher vaccine cost, maintaining PCV13 was cost-saving compared to PCV10, saving $6.71 billion MXN over 10 years.
Conclusion: The PCV program in Mexico has provided a significant return on investment. Sustained PCV13 use was estimated to provide the greatest healthcare and economic impact in Mexico. Changes to the pneumococcal vaccination program could result in serotype replacement and reduction in herd effects.

Introduction

Streptococcus pneumoniae is a gram-positive bacterium with more than 90 serotypes and is a pathogen known to cause invasive pneumococcal disease (IPD) such as bacteremia, and meningitis, as well as non-invasive infections such as pneumonia and otitis media (OM). Since the early 2000s, pneumococcal vaccines, in which capsular polysaccharides are conjugated to carrier proteins (PCVs), have been used in children to enhance immunogenicity. Pneumococcal conjugate vaccines (PCVs) containing 7 (PCV7, Prevnar®, Wyeth Lederle Vaccines), 10 (PCV10, Synflorix®, GlaxoSmithKline Biologicals S.A.), and 13 (PCV13, Prevnar 13®, Wyeth/Pfizer Vaccines) pneumococcal poly-saccharide antigens have been licensed and implemented in routine vaccination programs across the world (Supplementary Material S1). The use of these PCVs has substantially reduced the burden of vaccine-type pneumococcal disease in both vaccinated and unvaccinated populations through robust herd effects.[1–3]

In 2006 the vaccine was introduced as a pilot vaccination strategy for some of the poorest regions in Mexico, expanding the program to a full National Immunization Program (NIP)

in 2008 using a 2 + 1 schedule. In 2010, a switch to a higher valent PCV was made gradually. By the end of 2011, all children less than 2 years of age in Mexico were receiving PCV13 through the NIP. A study based on the National Health and Nutrition Survey in 2012[4] indicated that full schedule coverage for PCV13 was 80.8% for children below one year of age and 88% for children 15–23 months old.[5] The introduction of pneumococcal conjugate vaccines in the NIP in Mexico has been very successful in reducing the burden of disease, especially in children under 5 years of age. Decreased incidence of all-cause pneumonia (60.5% reduction), all-cause meningitis (59%) and OM (49%) were observed over a 10 year period.[6,7]

Even though immunization programs have proven to reduce the incidence of disease, they represent a significant budget impact for the government. For that reason, vaccine program funding bodies continuously look for ways to reduce expenditures. Currently, there are two pneumococcal conjugate vaccines registered in Mexico: PCV13 and PCV10. PCV13 has been in the NIP for almost 7 years, while PCV10 is available in the private market. While a change of the vaccine included in the NIP may result in lower vaccine

acquisition costs, PCV10 covers fewer serotypes which could lead to disease re-emergence of unprotected serotypes and result in an overall increase in incidence. This combined with lower herd effects could result in an additional overall net cost to the health system.

Several studies have evaluated the cost-effectiveness of pneumococcal vaccines in Mexico, but none of them have considered the economic impact that a switch on the immunization program strategy from a higher to a lower valent vaccine would have.[8,9] The aim of this study was to estimate the retrospective public health and economic impact that pneumococcal vaccination with PCVs has had in Mexico from 2006 to 2014, the last year complete data were available, and to prospectively estimate the potential public health and economic impact of changing vaccine programs from a higher to lower valent vaccine.

Results

Retrospective analysis

Results of the retrospective analysis demonstrated that between 2006 and 2014, the PCV7 and subsequent PCV13 program, averted over 1.5 million cases of pneumococcal disease, and prevented 1,840 deaths over a nine-year period (Table 1). This corresponded to a net cost-savings of $34.5 Billion MXN (Figure 1). Therefore, over the nine-year period where Mexico had a PCV7 and PCV13 program, there was a $2.21 MXN return on investment for each MXN invested in the PCV program.

Prospective analysis

In 2014, the most recent data that was available for the model, incidence of disease caused by PCV13 serotypes was 3.7 per 100,000 in children < 2 year old and represented 52% of the total burden of IPD. Based on our forecasting model, after 10 years, in children < 2 years old PCV13-type IPD was estimated to increase to 4.9 per 100,000 when switching to PCV10, representing 54% of the total IPD burden, but was estimated to drop to 1.7 per 100,000 while maintaining PCV13 (Figure 2A and 2B). While serotype replacement of non-vaccine type disease occurred in the PCV13 estimation, this was smaller than the PCV13-10 type (serotypes 3, 6A, and 19A) replacement in the PCV10 scenario, specifically due to serotype 19A. After 10 years, incidence of IPD in < 2 year olds caused by any serotype was estimated at 9.1 and 6.0 per 100,000 with PCV10 and PCV13, respectively. A similar

Table 1. Historic impact of pneumococcal vaccination programs.

| Parameter	PCV Program	No PCV Program	Difference
Outcome			
Estimated Cases of:			
IPD	16,138	23,382	−7,244
OM	6,612,647	7,372,469	−759,822
Nonhospitalized pneumonia	3,052,273	3,777,884	−725,612
Hospitalized pneumonia	436,039	539,698	−103,659
Total cases	10,117,097	11,713,433	−1,596,337
Disease-related deaths	11,661	13,501	−1,840
Costs			
Vaccine-related	$15,617,279,631	$0	$15,617,279,631
IPD direct medical	$2,009,753,583	$2,974,119,745	-$964,366,163
Pneumonia direct medical	$139,723,616,475	$172,736,278,355	-$33,012,661,879
OM direct medical	$97,950,395,460	$113,908,778,235	-$15,958,382,775
Indirect (lost productivity)	$872,914,311	$1,037,818,140	-$164,903,829
Total costs	$256,173,959,460	$290,656,994,474	-$34,483,035,014

Results are presented in $MXN ($19.7 MXN = $1 USD)
OM = Otitis Media; IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine
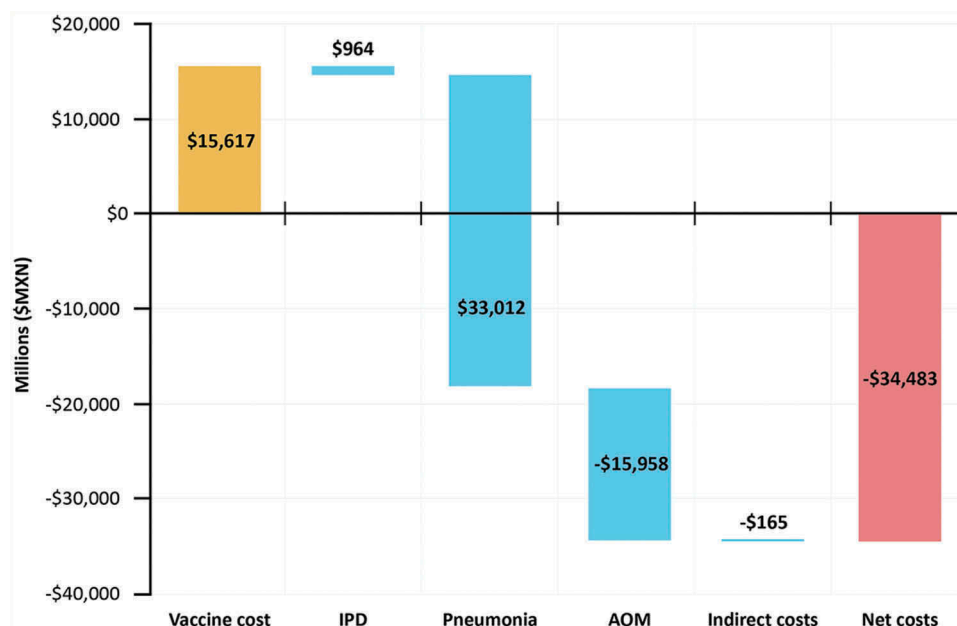
Figure 1. Historic cost of PCV program and cost-savings from cases of disease averted (millions of $MXN). summarizes the historic vaccine investment costs and the cost savings from observed reductions in IPD, Pneumonia, OM, and indirect costs between 2006 and 2014 in Mexico.
Results are presented in $MXN ($19.7 MXN = $1 USD)OM = Otitis Media; IPD = invasive pneumococcal disease
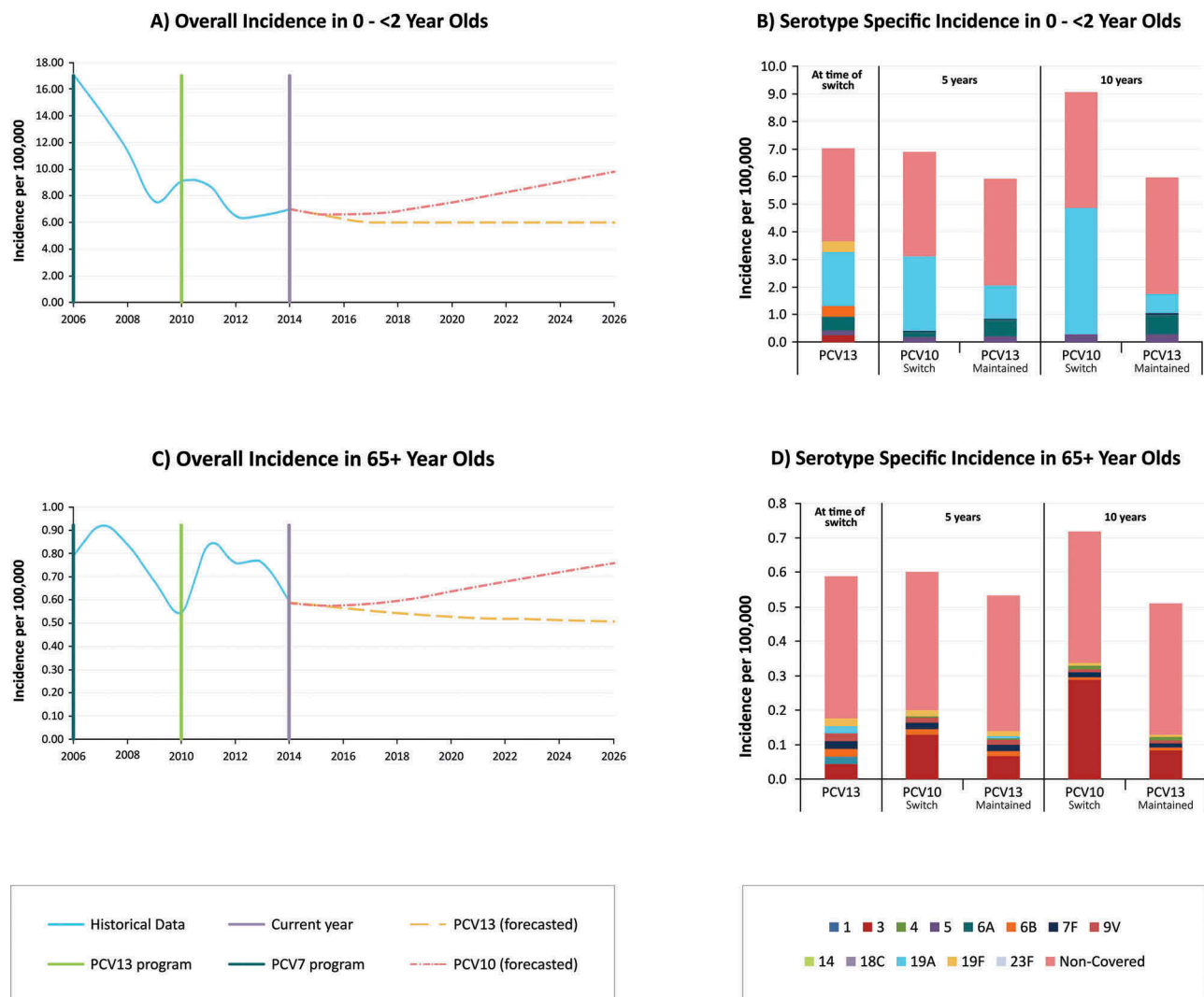
Figure 2. Forecasted incidence of invasive pneumococcal disease in 0–2 and 65 year Olds. presents the (A) forecasted all-cause IPD in 0–2 year olds using trend line estimates from Mexico, (B) the incidence of IPD in 0–2 year olds by serotype at the time of switch, and 5 and 10 years post switch with PCV10 or PCV13,(C) the forecasted all-cause IPD in 65+ year olds using trend line estimates from Mexico, (D) and the incidence of IPD in 65+ year olds by serotype at the time of switch, and 5 and 10 years post switch with PCV10 or PCV13.

trend was observed in other age groups, with a higher level of replacement from serotype 3 observed in 65+ in the PCV10 arm compared to the PCV13 arm (Figure 2C and 2D).

Based on the most recent incidence of pneumococcal disease, in the hypothetical scenario where Mexico switched to a PCV10 vaccination program, over the next 10 years there would be an estimated 310,034 additional cases of pneumococcal disease and 373 additional deaths compared to maintaining PCV13 (Table 2). Maintaining use of PCV13 in Mexico was estimated to be a cost-saving strategy compared to switching to PCV10. Despite the higher vaccine cost, maintained use of PCV13 was estimated to save the Mexican government over $6.71 Billion MXN over a 10 year period due to greater disease averted.

Sensitivity analysis

PCV13 remained cost saving compared to PCV10 across a number of scenario analyses (Table 3). These included: varying the trend line estimates used to forecast vaccine impact

given experiences in different countries, changing the time horizon (5 and 20 years), lengthening the time before serotype replacement began with PCV10 (2 and 3 years), and reducing the total level of replacement that occurs (See Table 3). In only one scenario was PCV13 more costly than PCV10 (assuming trend lines from the UK for PCV13 and the Netherlands for PCV10). However, in this scenario, PCV13 remained highly cost-effective. Results were also robust in one-way and probabilistic sensitivity analyses, as PCV13 remained cost-saving in all individual parameter variation and in 100% of simulations (Supplementary Material S3).

Discussion

This study highlights the significant health benefit that PCV7 and PCV13 have provided in Mexico. Our results indicate that over an 9 year period, PCV7 and PCV13 have saved 1,840 lives and provided an overall net savings to the Mexican Health System of approximately $34.5 Billion MXN. Despite a lower vaccine acquisition cost, changing the NIP to PCV10

Table 2. Prospective impact of maintaining PCV13 versus switching to PCV10 over 10 years.

Parameter	PCV13 Program	PCV10 Program	Difference
Outcome			
Number of cases of:			
IPD	16,807	17,247	−440
OM	7,023,033	7,245,033	−222,000
Nonhospitalized pneumonia	3,542,791	3,619,435	−76,644
Hospitalized pneumonia	506,113	517,062	−10,949
Total cases	11,088,743	11,398,777	−310,034
Disease-related deaths	48,795	49,168	−373
QALYs	747,041,374	747,040,067	1,307
Costs			
Vaccine-related	$12,941,913,312	$11,325,571,425	$1,616,341,887
IPD direct medical	$1,593,612,279	$1,657,311,997	-$63,699,718
Pneumonia direct medical	$124,389,694,990	$126,775,360,463	-$2,385,665,473
OM direct medical	$68,335,620,605	$74,195,721,482	-$5,860,100,877
Indirect (loss of productivity)	$737,920,604	$755,540,600	-$17,619,996
Total costs	$207,998,761,791	$214,709,505,967	-$6,710,744,176
Incremental cost-effectiveness			
Incremental cost per QALY gained			PCV13 Cost-saving

Results are presented in $MXN ($19.7 MXN = $1 USD)

OM = Otitis Media; IPD = invasive pneumococcal disease; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; QALY = quality-adjusted life-year.

Table 3. Scenario analyses of maintaining PCV13 compared to switching to PCV10.

Parameter	Incremental Cost	Incremental QALYs	ICER
Base case	-$6,710,744,176	1,307	PCV13 Cost-saving
Alternate trend line estimates[a]			
PCV13 UK/PCV10 Finland	-$15,031,003,157	5,380	PCV13 Cost-saving
PCV13 US/PCV10 Finland	-$35,322,154,172	10,012	PCV13 Cost-saving
PCV13 UK/PCV10 Netherlands	$2,068,788,272	1,371	PCV13 More effective
PCV13 US/PCV10 Netherlands	-$14,104,202,560	4,792	PCV13 Cost-saving
Time horizon			
5 Years	-$1,326,122,906	298	PCV13 Cost-saving
20 Years	-$20,847,243,294	4,765	PCV13 Cost-saving
Years until disease re-emergence begins after switch of vaccine[b]			
2 Years	-$4,873,592,852	1,111	PCV13 Cost-saving
3 Years	-$3,297,027,160	963	PCV13 Cost-saving
Maximum replacement to Pre-PCV levels			
75% of pre-PCV incidence	-$6,717,284,575	1,325	PCV13 Cost-saving

Results are presented in $MXN ($19.7 MXN = $1 USD)

PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine

[a] Alternate trend lines apply trends from each country to serotype distribution in the year of switch in Mexico to estimate sensitivity of potential serotype replacement

[b] These scenarios assume that serotype replacement may take several years to occur given sustained use of PCV13 in years before switch.

was estimated to cause a higher burden of disease in Mexico due to serotype replacement, specifically due to higher circulation of non-covered serotypes such as serotypes 3 and 19A. The health resource utilization associated with these additional disease cases negated the savings from a lower priced vaccine, therefore maintaining PCV13 in the NIP was estimated to result in better health outcomes at a lower cost to the Mexican health system. This result was consistent across all sensitivity analyses, and PCV13 remained cost-effective or cost-saving in all scenario analyses.

This analysis is important for decision makers given that the majority of disease replacement was estimated to be caused by serotype 19A. This outcome has been seen in a number of settings which use PCV10 as the vaccine does not provide protection against 19A carriage.[10] For example, Belgium switched from PCV13 to PCV10 between 2015 and 2016, and has since seen an increase in cases of 19A from 2 cases in 2016 to 21 cases in 2017, suggesting our results may underestimate potential replacement.[11] This is important because disease caused by serotype 19A has often been shown to be more invasive and highly resistant to antibiotics.[12,13] Given the increasing risk of antibiotic resistance, using a vaccine with greater serotype coverage is paramount to ensure the broadest protection of infants in Mexico reducing overall antibiotic use and associated costs of resistant episodes. While some early case-control studies did demonstrate that PCV10 may have cross-protection against 19A,[14,15] more recent studies have shown that cases of 19A have been increasing in both vaccinated and unvaccinated individuals in countries using PCV10.[10,16,17] Our analysis mitigates for any uncertainty around cross-protection by using data from Finland and the Netherlands, countries that use PCV10, in sensitivity analysis. These scenarios thus would capture any observed cross

protection. Despite this, PCV13 remained cost-saving across the majority of scenarios.

Previous economic evaluations of PCVs in Mexico have a number of important limitations that this analysis improves upon.[8,9] An early study by Mucino-Ortega and colleagues (2010) determined PCV13 was cost-saving compared to PCV10. However this analysis did not consider the impact of herd effects.[8] Furthermore this study evaluated the impact of replacing PCV7 with a higher valent PCV program (PCV10 or PCV13) rather than switching from a higher to lower-valent vaccine as was done in this analysis.

A more recent analysis by Gomez and colleagues (2016) determined that PCV10 would be the cost-saving option compared to PCV13.[9] The results from this study however were driven entirely by the benefits of PCV10 preventing OM caused by non-typable *Haemophilus influenza* (NTHi) based on evidence from an investigational PCV11 vaccine. However, recent studies have shown PCV10 did not demonstrate any statistically significant effect on NTHi-clinically confirmed

OM.[18,19] This study also did not fully account for the benefits of PCV13 on serotype 3 and assumed cross- protection for PCV10 protecting against IPD and OM caused by serotype 6A and 19A. These assumptions are not consistent with the most up to date literature[20] and so the results should be interpreted with caution.

Both of these cost-effectiveness analyses in Mexico have also underestimated the potential impact of serotype replacement and indirect effects due to the static nature of their design.[8,9] They also rely on assumptions around the efficacy of specific serotypes and cross-reactivity. The study presented here improves upon previous estimates by taking into consideration the potential for serotype replacement due to changes in vaccine pressure as well as any potential cross-reactivity by using real world data as opposed to data from case control studies which may not reflect how serotypes behave in the real world.[15,21] This has been shown to be of significant importance, as examples exist around the world where reduction of vaccine pressure of important serotypes such as 19A results in increases in disease in both vaccinated and unvaccinated populations.[10] Similarly, recent studies in Spain have shown rapid return of both invasive and non-invasive disease when vaccine pressure is reduced,[22,23] further justifying the need to maintain sustained high levels of uptake with the broadest coverage.

As with any modelling exercise, the model is subject to some limitations. The most important assumption is that the historical serotype trends determine disease incidence prospectively. In other words, we assumed that disease will behave similarly to what was observed in the past. This assumption has the benefit of being a conceptually simple and intuitive approach, but it is subject to limitations. Furthermore, because IPD is relatively rare, in most cases the predictive trends were estimated using small sample sizes and therefore could be over or under estimated. These trends in Mexico are also limited in that they rely on passive surveillance data and that, depending on where isolates originated, may over or underestimate the historic serotype distribution.[24–28] This could be a reason for 52% vaccine type disease in the baseline year of this analysis, therefore potentially overestimating future disease impact if vaccine type disease were actually lower. However, this would reduce the impact and replacement for both vaccines and thus would unlikely change the incremental difference significantly.

Second, the model does not allow trends in serotype emergence and reductions to vary over time. It is possible that disease could behave differently over different periods of time when vaccination uptake changes, or due to epidemiologic shifts. For example, following the introduction of PCV7, replacement with 19A was observed given the opening of the pneumococcal niche to other serotypes. Trends developed immediately after the introduction of PCV7 would not have predicted emergence of 19A. Comparably, the model is unable to account for the possible emergence of a serotype that has not yet started to increase. To date, no serotype(s) have emerged in the several years following introduction of PCV13 in Mexico in the way that 19A did after the introduction of PCV7. Thus, this limitation may not have substantial impact for several more years. However, as more data become available on emerging serotypes, these could be modelled separately.

Third, our model assumes that the proportion of pneumococcal OM and pneumococcal pneumonia change proportionally with IPD . This methodology may over or underestimate the impact on OM and pneumonia if the serotypes causing OM and pneumonia are not consistent with IPD; however it has been used in several studies to extrapolate non-invasive disease outcomes associated with PCV introduction.[29–32] Previous economic evaluations have instead used clinical effectiveness data from PCV10 and PCV13 given that both vaccines have demonstrated an impact on all-cause OM and all-cause pneumonia.[33–38] However, translating these vaccine effectiveness parameters from other countries to Mexico may be more vulnerable to overestimation given differences in underlying epidemiology, vaccine uptake, and antibiotic use.[20] Therefore our proportional approach may be conservative in that it only accounts for changes in disease caused by S. pneumoniae.

Finally, as of 2018, Belgium is the only example of a switch from a higher to lower valent vaccine.[11] Historical vaccine use, antibiotic prescriptions, vaccine uptake, schedules, and catch-up vaccination policy choices all may have an impact on both the time to and extent of serotype replacement. We have attempted to mitigate this by evaluating several trend lines and how these might impact disease re-emergence. Further we test a number of constraints and limitations on potential serotype replacement. However, further research is necessary to understand the potential parameters that may influence changes in serotype replacement. The time to and degree of disease re-emergence may vary in each country depending on a number of factors.

Conclusion

This modelling exercise shows the public health and economic impact the introduction of PCVs has had in Mexico. It is the first evaluation in Mexico to estimate the impact of serotype replacement when considering a change in pneumococcal vaccination allowing decision makers to understand what may happen when changing from a higher to lower valent vaccine. This type of model has not been used in the past in Mexico but can help in providing the scenarios that could be faced if considering a change in the NIP. Previous steady state models did not fully account for the impact of changes in serotype dynamics, therefore underestimate the potential risks involved in changing vaccination policy. This is important, as past experience has shown that removal of vaccine pressure has severe effects on both vaccinated and unvaccinated populations. Specifically, serotypes 3, 6A, and 19A remain a burden in Mexico; therefore continued vaccination with PCV13 will continue to provide an important public health benefit. As non-vaccine serotypes continue to increase, it will be essential to protect populations against all pneumococcal serotypes with higher valent PCVs.

Methods

Model structure

A published decision analytic model was updated to estimate the historic public health and economic impact of the PCV7 and PCV13 NIP in Mexico, as well as evaluating a potential change from the current immunization program using PCV13 to using PCV10.[29] The structure is therefore split in two parts: a retrospective impact analysis and a prospective forecasting model.

In the retrospective analysis, we estimated the total impact of pneumococcal vaccination compared with a hypothetical scenario in which no vaccine program existed. To do this, the number of cases of IPD, pneumonia, and OM as observed during the retrospective period using real world data (described below) were estimated. The observed cases were compared to an estimated incidence of disease based on pre-PCV incidence. The cumulative vaccine impact was estimated based on the resulting difference between pre-PCV incidence carried forward and the observed incidence in the presence of PCVs. To ensure we do not overestimate the historic impact of the vaccines, and that some change is due to natural fluctuation, we assume that only the 8.2% of pneumonia cases caused by *S. pneumoniae* are due to the introduction of PCVs (discussed below).[24]

The prospective forecasting model used historic real world passive surveillance data on IPD in Mexico to estimate the potential future disease scenarios with either PCV13 or PCV10. For each serotype contained within PCV13, a trend was estimated based on the historical behavior when it was covered or uncovered by a vaccine (Supplementary Material S2). A similar approach has been proposed in the literature to examine changes in serotype dynamics in Canada[39] and the Netherlands.[31] In Mexico, these trends were estimated between 2006 to 2010 for PCV7 serotypes, and 2010 to 2014 for PCV13 serotypes. Because PCV10 does not contain the 3 additional serotypes in PCV13 (3, 6A, and 19A), in the base case we assumed that these serotypes behaved as they did prior to the introduction of PCV13 (2006–2010) in the event of a switch to PCV10. Given these forecasts, the incidence of IPD, pneumococcal pneumonia, and pneumococcal OM were estimated for a 10 year time horizon into the future maintaining PCV13 or switching to PCV10. It was assumed that serotype replacement would not begin until 1 year following the switch of a program given historic PCV13 use and remaining stock of the vaccine. Total life years, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios were estimated.

Population

According to Consejo Nacional de Población (CONAPO), in 2014 the Mexican population was 120,285,089, with a birth cohort of 4,425,280 eligible for pneumococcal vaccination (see Table 4).[40] Vaccine coverage was assumed for 85% of infants using a 3-dose (2 + 1) vaccination schedule. The remaining individuals comprised the non-vaccinated cohorts. The population was stratified into 6 age groups: 0-< 5 years, 5–17 years, 18–34 years, 35–49 years, 50–64 years, and 65 + years.

Epidemiology

Ipd

Incidence of IPD was retrieved from data published by the Epidemiological Surveillance System Platform (SUIVE[7] for the years 2004 to 2014 (See Table 5). This incidence data were weighted based on the serotype distribution data provided by SIREVA to estimate the trends of both covered and uncovered serotypes for PCV10 and PCV13 forecasts.[24–28]

IPD surveillance data included all invasive disease and the model considered IPD as combination of meningitis and bacteremia. To estimate the economic and clinical impact of IPD, the proportion of IPD due to meningitis was estimated based on the average number of cases reported during 2011 to 2014 from the SIREVA (Secretaría de Salud) passive surveillance system.[24–28]

Pneumonia

The incidence of all-cause inpatient pneumonia was obtained from the Epidemiological Surveillance System Platform (SUIVE.[7] Due to a lack of data on non-hospitalized pneumonia in Mexico, cases were estimated to occur relative to hospitalized pneumonia at a rate of 7:1 based on data used in other studies.[8]

Assuming the ratios of all-cause inpatient pneumonia to IPD and outpatient pneumonia to IPD were constant over time, we estimated the prospective change in the number of pneumococcal hospitalized and non-hospitalized pneumonia cases by multiplying these ratios by the forecasted number of IPD cases each year. Rates of pneumococcal pneumonia were assumed to change proportionally to IPD based on the assumption that comparable serotypes would cause both invasive and non-invasive disease. This assumption has been used in previous evaluations and documented in the literature.[30–32] The proportion of all-cause pneumonia that was assumed to be pneumococcal was estimated at 19% for the retrospective analysis and 8.2% in the most recent year based on data from SIREVA.[24] The historic percentage was used as a weight to estimate the proportion of pneumonia that was assumed to decrease due to PCV implementation. The direct and indirect effects of vaccination are implicitly considered in the serotype data for the 0-< 5 age group.

Otitis media

Incidence rates of OM were retrieved from the Epidemiological Surveillance System Platform (SUIVE).[7] Because no serotype specific data for OM was available in Mexico, rates of pneumococcal OM were assumed to proportionally change relative to IPD similar to pneumonia. Historically, all changes in OM incidence were assumed to be due to PCV implementation.

Table 4. Population and economic parameters.

Parameter (source)	Age range (years)						
	0 to < 2	2 to 4	5 to 17	18 to 34	35 to 49	50 to 64	65+
2014 population [22]	4,425,280	6,636,434	29,146,268	33,864,877	23,663,980	14,420,395	8,127,855
% IPD presenting as meningitis [23]	46.8%	37.8%	40.6%	38.8%	50.0%	47.4%	33.3%
Direct costs ($MXN) [38]							
Bacteremia	$129,438	$129,317	$69,161	$71,172	$72,663	$77,038	$143,523
Meningitis	$206,173	$205,980	$145,159	$149,379	$152,508	$161,692	$228,609
Hospitalized pneumonia	$52,131	$52,083	$51,803	$53,308	$54,425	$57,702	$57,804
Nonhospitalized pneumonia	$36,707	$36,673	$36,476	$37,536	$38,322	$40,630	$40,702
Otitis media	$60,318	$25,133	$9,048	-	-	-	-
Hours of lost productivity per case [39]							
Bacteremia	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Meningitis	5.90	5.90	5.90	5.90	5.90	5.90	5.90
Hospitalized pneumonia	7.96	7.96	7.96	7.96	7.96	7.96	7.96
Nonhospitalized pneumonia	7.96	7.96	7.96	7.96	7.96	7.96	7.96
Otitis Media	2.84	2.84	2.84				
Age-specific baseline utility [40]	0.94	0.94	0.94	0.93	0.93	0.92	0.91
General mortality							
Mortality per 100,000	690.56	44.68	53.12	148.77	321.40	964.52	4,753.06
Case-fatality rates [31–34]							
Meningitis	14.7%	14.7%	14.7%	14.7%	14.7%	20.0%	25.3%
Bacteremia	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%	12.4%	16.8%

Results are presented in $MXN ($19.7 MXN = $1 USD)

Table 5. Epidemiologic parameters (per 100,000 population).

Parameter	2006	2007	2008	2009	2010	2011	2012	2013	2014
Invasive pneumococcal disease (age) [7]									
< 2	17.04	14.36	11.37	7.58	9.11	8.80	6.50	6.54	7.04
2 to 4	2.02	2.03	1.71	1.23	1.42	1.21	1.00	1.12	0.94
5 to 17	1.90	1.91	1.70	1.42	1.39	1.47	1.37	1.57	1.13
18–34	1.05	1.15	0.93	0.76	1.11	1.18	1.65	1.22	0.91
35–49	0.90	0.93	0.88	0.81	0.79	1.26	1.35	1.27	0.73
50–64	1.73	2.02	1.70	1.30	1.35	1.88	2.17	1.32	1.22
≥ 65	0.79	0.92	0.84	0.68	0.55	0.84	0.76	0.76	0.59
Otitis Media (age) [7]									
< 2	1,554.5	1,445.6	1,479.7	1,377.4	1,244.0	1,212.3	940.8	913.0	855.3
2 to 4	1,615.5	1,538.2	1,535.5	1,430.4	1,455.0	1,425.4	1,142.6	1,159.8	1,081.8
5 to 17	2,215.2	2,110.1	2,088.6	2,085.0	2,070.2	2,086.4	1,877.0	1,889.7	1,860.6
Nonhospitalized pneumonia (age) [1]									
< 2	11,889.2	12,532.0	11,001.1	9,127.5	10,037.4	10,559.1	7,310.8	8,429.3	6,760.8
2 to 4	3,302.7	3,185.4	2,883.0	2,977.9	3,165.7	3,043.3	2,347.5	2,482.0	2,412.3
5 to 17	1,180.4	1,103.6	1,014.1	1,344.2	1,160.0	963.6	922.5	920.1	1,090.1
18–34	433.9	448.7	448.0	665.6	522.3	429.4	482.1	491.9	605.9
35–49	652.4	678.8	697.9	936.0	741.1	598.9	703.7	756.0	968.1
50–64	2,182.5	2,222.1	2,308.5	2,591.6	2,451.2	2,108.4	2,276.0	2,333.6	2,834.3
≥ 65	2,964.9	3,287.3	3,428.3	3,253.1	3,627.6	3,184.4	3,166.0	3,512.3	3,922.1
Hospitalized pneumonia (age) [7]									
< 2	1,698.5	1,790.3	1,571.6	1,303.9	1,433.9	1,508.4	1,044.4	1,204.2	965.8
2 to 4	471.8	455.1	411.9	425.4	452.2	434.8	335.4	354.6	344.6
5 to 17	168.6	157.7	144.9	192.0	165.7	137.7	131.8	131.4	155.7
18–34	62.0	64.1	64.0	95.1	74.6	61.3	68.9	70.3	86.6
35–49	93.2	97.0	99.7	133.7	105.9	85.6	100.5	108.0	138.3
50–64	311.8	317.4	329.8	370.2	350.2	301.2	325.1	333.4	404.9
≥ 65	423.6	469.6	489.8	464.7	518.2	454.9	452.3	501.8	560.3

1 Nonhospitalized pneumonia cases were assumed to be proportional to hospitalized pneumonia based on a 7:1 ratio consistent with previous publications[8]

Mortality

A general risk of mortality was assumed for the entire population based on published estimates (Table 4).[41] For each case of disease, there is a risk of mortality based on case fatality rates. These rates were sourced from the published literature for meningitis, bacteremia, and hospitalized pneumonia.[42–45] No mortality risk was included for non-hospitalized pneumonia and OM.

Disease sequelae

As a result of contracting pneumococcal disease, clinical sequelae such as neurologic impairment and hearing loss may occur. For meningitis, we assumed hearing loss and neurological impairment for 13% and 7% of patients, respectively.[46,47] For OM, 5% of patients were assumed to require myringotomy procedures.[47] Sequelae of bacteremia or pneumonia were not considered in this analysis.

Costs

Mexican vaccine procurement requires confidential pricing, therefore prices for PCV10 ($12.85 USD) and PCV13 ($14.50 USD) were derived from published Pan American Health

Organization (PAHO) Expanded Program of Immunization Vaccine Prices for 2017.[48]

Direct medical costs were considered from the perspective of the public Mexican health system using clinical tabulators costs published by the Instituto Mexicano de Seguro Social (IMSS), a social security health system, in Mexico in 2014 (the latest edition.[49] These lists include the average fees that a patient could go through per disease case, such as, laboratory analyses, hospital stay, specialists' visits, nurse fees, etc. The last version was published on 2014, therefore the amounts where inflated to 2018 dollars.[49] Indirect costs were estimated based on the numbers of hours productivity lost for each case of disease multiplied by the estimated average hourly wage of a working adult ($18.70 MXN).[50]

Utility inputs

Utility weights range from 0.0 to 1.0, where 1.0 represents perfect health and 0.0 represents death. We assumed an age-specific baseline utility weight for individuals in each age group who do not experience a case of pneumococcal disease.[51] Utility decrements were applied for each occurrence of disease as well as long term sequelae. Specifically, decrements of 0.0070 and 0.0232 were assumed for a case of bacteremia and meningitis respectively[52] . Decrements of 0.0050, 0.0040, and 0.0060 were assumed for OM, inpatient pneumonia, and outpatient pneumonia respectively.[53] Finally, a lifetime decrement of 0.40 and 0.20 were included for neurological impairment or hearing loss, respectively.[47]

Sensitivity analysis

To test the robustness of results, several sensitivity analyses and scenarios were tested. First, given the variation in PCV implementation and the potential variation in trend line estimations, trend forecasts were applied from countries with established PCV programs and robust surveillance. In these analyses, disease cases were forecasted based on historical surveillance data from the United Kingdom and the United States in which PCV13 is used in the infant immunization program following PCV7 in a 2 + 1 and 3 + 1 schedule, respectively, as well as the Netherlands and Finland, in which PCV10 is used in the infant vaccination program, both in a 2 + 1 schedule.[1,2,54–56] These scenarios were meant to reflect potentially varying serotype dynamics under different situations to ascertain the robustness of serotype forecasts. For example, any potential cross-protection or changes in indirect effect that could be observed with either vaccine would be captured within these trend lines. Since Mexico has never used PCV10 in the NIP, trends observed from the Netherlands and Finland were of specific importance to extrapolate the impact of the vaccine. Additional scenarios were also tested varying the time horizon and the impact of a lag in serotype re-emergence.

In addition to scenario analyses, one-way, and probabilistic sensitivity analyses (PSA) (second order monte-Carlo simulations with 10,000 simulations) were undertaken to evaluate specific parameter uncertainty. These results are included in the Supplementary Material.

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