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Cost-effectiveness of introducing a domestic pneumococcal conjugate vaccine (PCV7-TT) into the Cuban national immunization programme

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of introducing a domestic pneumococcal conjugate vaccine (PCV7-TT) into the Cuban National Immunization Program (NIP).
Methods: We compared PCV7-TT given at two, four and six months of age to a scenario without PCV7-TT, over a ten-year period (2020–2029). We calculated the cost (Cuban pesos – CUP) per Disability Adjusted Life Year (DALY) averted from a Government perspective. We compared results from a static cohort model and a parsimonious prediction model informed by the serotype distribution among pneumococcal carriers and cases. We ran probabilistic and deterministic uncertainty analyses.
Results: PCV7-TT could prevent 6897 (95% uncertainty interval, 4344–8750) hospitalizations and 189 (115–253) deaths in children <5 years of age, over the period 2020–2029. This could cost around 25 million (20–31) discounted CUP but would be offset by treatment cost savings of around 23 million (14–31). A parsimonious model predicted less favourable impact and cost-effectiveness but the cost per DALY averted was still less than 0.4 times the current GDP per capita.
Conclusions: PCV7-TT is likely to be cost-effective in Cuba. The impact of the vaccine would need to be carefully monitored following its introduction into the NIP.

Background

Streptococcus pneumoniae is an important cause of severe bacterial infections in young children and the elderly (Valenzuela et al., 2009). In Cuba, high rates of nasopharyngeal colonization have been reported in children <5 years of age (Toledo et al., 2017) and pneumococcus is one of the main causes of meningitis, pneumonia, sepsis and acute otitis media (Wahl et al., 2018). The first licensed pneumococcal conjugate vaccine (PCV7) demonstrated substantial reductions in severe pneumococcal disease in both vaccinated and unvaccinated individuals (de Oliveira et al., 2016). Other vaccines covering more serotypes have subsequently been developed (PCV10 and PCV13) and introduced in several countries worldwide. The World Health Organization (WHO) recommends that all countries use PCVs in their national routine immunization programs (World Health Organization, 2012). Evidence from Latin America has demonstrated the significant impact of PCVs on hospitalizations in children due to radiograph-confirmed pneumonia, clinical pneumonia, meningitis, and invasive pneumococcal disease (IPD) (de Oliveira et al., 2016). In Cuba, the high cost of these vaccines has been an important barrier to introduction. Since 2006, the Cuban National Health Service (NHS) and state-owned biotechnology industry have been developing a domestic heptavalent pneumococcal

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conjugate vaccine. The main purpose of the Cuban heptavalent vaccine is the national market based on the principle of "vaccine for all, all the time". This vaccine, PCV7-TT, includes a 2.2 mg capsular polysaccharide of serotypes 1, 5, 14, 18C, 19F and 23F, and 4.4 mg of serotype 6B, conjugated with tetanus toxoid as a carrier protein and adsorbed in aluminum phosphate as an adjuvant (Linares-Pérez et al., 2017). The seven serotypes contained in the new vaccine candidate represent 42.3% of total IPD in Cuba in 2014 (Organización Panamericana de la Salud, 2015) and account for over 60% of isolated serotypes worldwide (International Vaccine Access, 2017). The safety and immunogenicity of PCV7-TT has been demonstrated in clinical trials of Cuban infants (Martinez et al., 2018) and preschool children (Dotres et al., 2014). In addition, PCV7-TT has demonstrated non-inferiority to the efficacy of PCV13 in a randomized double-blind clinical trial (Toledo-Romaní et al., forthcoming; Cuban Public Registry of Clinical Trials – code RPCEC00000243).

While PCV7-TT is expected to cost less than the two globally licensed vaccines (PCV10 and PCV13), an economic evaluation is still needed to assess whether it represents good value for money for the Cuban Government. This study aimed to evaluate the potential impact and cost-effectiveness of introducing PCV7-TT into the Cuban National Immunization Program (NIP).

Methods

We compared vaccination with PCV7-TT at two, four and six months of age to no vaccination, over the period 2020–2029. The primary outcome measure was the number of Cuban pesos (CUP) per Disability Adjusted Life Year (DALY) averted, from a Government perspective. We did not consider a broader societal perspective, so excluded all costs borne by households and caregivers e.g. out-of-pocket expenditures and lost wages. Consistent with the recommendations of the Cuban Guide to Health Economic Evaluations, a 3% discount rate was applied to all future costs and benefits (base year = 2020) (Gálvez-González, 2004). DALYs were calculated by combining years of life lost due to pneumococcal mortality (YLLs) and years of life lost due to living with pneumococcal disease (YLDs). YLLs were calculated using the estimated life expectancy at the age of pneumococcal death. YLDs were calculated by multiplying the average duration of illness by the disease disability (or disutility) weight. All costs were expressed in 2016 Cuban pesos (CUP). The official exchange rate for the business sector in Cuba of 1.00CUP = 1.00USD was used (Hidalgo de los Santos et al., 2000).

Modelling approach

An Excel-based static cohort model (UNIVAC version 1.4) was used to estimate numbers of pneumococcal cases and deaths in each week of age between birth and age 5.0 years (https://www.paho.org/provac-toolkit). For a given week (w) of age, the number of disease events D_w was calculated as:

$$D_w = P \times S \times A_w \times (1 - V_w)$$

where: $P \times D \times A_w$ is the number of disease events in week w of age; V_w is the effect of vaccination in week w of age; P is the number of person-years lived between birth and age 5.0 years in the birth cohort evaluated; S is the streptococcus pneumoniae (pneumococcal) disease event rate per 100,000 per year among children younger than 5 years before the introduction of vaccination; and A_w is the proportion of pneumococcal disease events in children younger than 5 years in week w of age.

Table 1
Input parameters for estimating the burden of pneumococcal disease in Cuban children aged <5 years

Parameter	Estimate	Low	High	Source
Annual case rate per 100,000 children aged <5 years				
Pneumococcal acute otitis media	11,664	9756	13,680	Bardach et al.
Pneumococcal non severe pneumonia	80	72	87	Linares-Pérez et al.
Pneumococcal severe pneumonia	149	112	170	Linares-Pérez et al.
Pneumococcal meningitis	9	4	18	Linares-Pérez et al.
Pneumococcal NPNM	36	16	76	Linares-Pérez et al.
Annual mortality rate per 100,000 children aged <5 years				
Pneumococcal severe pneumonia	3.83	2.71	3.99	Linares-Pérez et al.
Pneumococcal meningitis	1.58	0.68	3.28	Linares-Pérez et al.
Pneumococcal NPNM	1.40	0.60	2.92	Linares-Pérez et al.
% of healthy time lost living with disease				
Pneumococcal acute otitis media	1.3	0.7	2.4	Salomon J et al.
Pneumococcal non severe pneumonia[a]	5.1	3.2	7.4	Salomon J et al.
Pneumococcal severe pneumonia[a]	13.3	8.8	19	Salomon J et al.
Pneumococcal meningitis	13.3	8.8	19	Salomon J et al.
Pneumococcal NPNM[a]	13.3	8.8	19	Assumption
Mean duration of illness (in days)				
Pneumococcal acute otitis media	5	3	7	Marrero et al.
Pneumococcal non severe pneumonia	7	3	10	Marrero et al., Assumption
Pneumococcal severe pneumonia	10	7	21	Figueredo et al. and Marrero et al.
Pneumococcal meningitis	10	7	21	Figueredo et al. and Marrero et al.
Pneumococcal NPNM	10	7	21	Figueredo et al. and Marrero et al.
Age distribution of cases and deaths				
<1 m	0%	–	–	Russell et al
<2 m	2%	–	–	
<3 m	7%	–	–	
<6 m	23%	–	–	
<1 year	54%	–	–	
<2 year	84%	–	–	
<3 year	94%	–	–	
<4 year	98%	–	–	
<5 year	100%	–	–	

[a] The disability weights for moderate and severe lower respiratory infections were used as a proxy for non-severe and severe pneumococcal pneumonia, respectively. We further assumed NPNM would have the same disability weight as non-severe pneumonia.

Assuming vaccine coverage C and vaccine efficacy E, the effect of vaccination in each week of age (V_w) was calculated as:

$$C3_w \times E3_w + (C2_w - C3_w) \times E2_w + (C1_w - C2_w) \times E1_w$$

where: $C3_w \times E3_w$ is the effect contributed by infants that received all 3 doses; $(C2_w - C3_w) \times E2_w$ is the effect contributed by infants that received only 2 doses; $(C1_w - C2_w) \times E1_w$ is the effect contributed by infants that received only 1 dose; $C1_w$, $C2_w$, and $C3_w$ are coverage estimates for the first three doses of vaccination in week w of age; and $E1_w$, $E2_w$, and $E3_w$ are efficacy estimates for the first three doses of vaccination in week w of age. We assumed no waning of vaccine protection over time.

Pneumococcal disease burden inputs

For each birth cohort, estimates of person-years lived between birth and age 5.0 years (PY) were based on United Nations demographic projections (https://population.un.org/wpp/). We estimated disease event rates (D) separately for pneumococcal acute otitis media (AOM), non-severe pneumococcal pneumonia, severe pneumococcal pneumonia, pneumococcal meningitis and other non-pneumonia/non-meningitis pneumococcal disease (NPNM) (Table 1). Non-severe and severe NPNM cases were combined into one category. Pre-vaccination estimates from Linares et al. were used to estimate the incidence and mortality rates for severe pneumonia, meningitis and NPNM caused by pneumococcus (Linares-Pérez et al., 2019). In the same study 1.8 non-severe pneumonia cases were reported for every 1.0 severe pneumonia case, so this ratio was used to calculate the incidence of non-severe pneumococcal pneumonia. These estimates of pneumococcal disease incidence and mortality are consistent with separate published international estimates for Cuba (Wahl et al., 2018). We estimated 11,664 pneumococcal AOM cases per 100,000 per year <5 years based on a review of estimates from the Latin American region by Bardach et al. (2011), taking the upper estimate of all-cause AOM incidence (36,000 per 100,000 per year <5 years) and multiplying by the 32.4% (95% CI 27.1–38.0%) fraction estimated to be caused by pneumococcus.

Historical time-series estimates of pneumonia deaths have declined in the absence of vaccination (Liu et al., 2016). Thus, we assumed the pneumococcal pneumonia mortality rate would decrease over the 10-year period 2020–2029 at the same rate as the expected decline in overall under-five mortality i.e. from 5.7 to 4.5 under-five deaths due to any cause per 1000 live births. For consistency, we made the same assumption for all severe forms of pneumococcal disease.

The age distribution of pneumococcal disease cases and deaths <5 years of age was based on estimates for the Americas region (Russell et al., 2011). A 3-parameter *Burr* distribution was fitted to this age distribution (Clark et al., 2019) to calculate the expected number of cases and deaths in each week of age <5 years.

United Nations estimates of life expectancy by age and year were used to calculate YLLs from the age/year of pneumococcal disease death (https://population.un.org/wpp). Disability weights were taken from the 2015 global burden of disease (GBD) study (Salomon et al., 2015). The average duration of illness was estimated for each disease type using information reported in two Cuban health care utilization and costing studies (Figueredo Montes de Oca, 2016) (Table 2).

Pneumococcal economic burden inputs

Cuba has an integrated health system with universal coverage. We assumed one hospital admission per severe pneumococcal disease case (meningitis, severe pneumonia, NPNM). The average cost per hospitalization was estimated to be 1183, 2268 and 264 CUP for severe pneumonia, meningitis and NPNM, respectively, based on a study by Figueredo et al., conducted at

Table 2
Input parameters for estimating the health and economic impact of PCV7-TT introduction in Cuba

Parameter	Estimate	Low	High	Source
Vaccination coverage (%)				
Dose 1	99.5	98.8	100	López-Ambrón et al.
Dose 2	99.5	98.8	100	López-Ambrón et al.
Dose 3	99.5	98.8	100	López-Ambrón et al.
Vaccine efficacy after 3 doses				
Pneumococcal AOM	37	21	49	Pavia et al
Pneumococcal non-severe pneumonia	17	6	22	Assumption based on Lucero et al
Pneumococcal severe pneumonia	69	24	87	Lucero et al.
Pneumococcal meningitis	69	24	87	Lucero et al.
Pneumococcal NPNM	69	24	87	Lucero et al.
Relative efficacy of partial doses				
Ratio of 1-dose VE to 3-dose VE	0.51	–	–	Mahon et al.
Ratio of 2-dose VE to 3-dose VE	0.92	–	–	Mahon et al.
Government cost per clinic visit (CUP)				
Pneumococcal AOM	81.80	51.65	110.99	Marrero et al.
Pneumococcal non-severe pneumonia	163.99	120.00	208.50	Marrero et al.
Pneumococcal severe pneumonia[a]	137.55	79.99	193.43	Marrero et al.
Pneumococcal meningitis[a]	147.70	105.69	189.97	Marrero et al.
Pneumococcal NPNM[a]	147.70	105.69	189.97	Marrero et al.
Government cost per hospital admission (CUP)				
Pneumococcal severe pneumonia	1182.74	682.77	1953.73	Figueredo et al.
Pneumococcal meningitis	2268.3	1513.81	3163.67	Figueredo et al.
Pneumococcal NPNM	263.83	208.8	318.87	Figueredo et al.
Vaccination programme cost (CUP)				
Vaccine dose price	7.00	5.00	10.00	Finlay Vaccine Institute
Syringe fixed price per dose	0.05	0.05	0.05	Ministry of Health
Safety box price per dose	0.01	0.01	0.01	Ministry of Health
Wastage (% of doses discarded)	0.10	0.10	0.10	Ministry of Health
Incremental system cost per dose	1.27	1.07	1.47	De la Hoz-Restrepo et al.

[a] Follow up post-discharge.

the University Pediatric Hospital "Paquito González Cueto". This study included 45 patients who required hospital admission and in whom pneumococcus was microbiologically isolated between January 2010 and December 2015 (Figueredo Montes de Oca, 2016) (Table 2). The number and type of resources used by each patient was calculated based on a review of medical records, consultation with key informants and direct observation. All resources were valued using official prices. Total and average costs were estimated in Cuban pesos. Mean values and confidence intervals were calculated using the non-parametric bootstrap method.

For all pneumococcal diseases we assumed one clinic visit per case. For severe diseases this was assumed to represent a follow-up visit following discharge from hospital. The average cost per clinic visit ranged from 82 to 164 CUP. These costs were based on a 2016 study by Marrero et al., at the Policlinico Docente de Playa, a unit that forms part of the Sentinel Network of Clinical Research, Surveillance and Impact Assessment of new preventive vaccines (VacCuba) (Marrero-Araújo et al., 2020). Flow charts were developed for each clinical outcome of the disease, based on care guidelines and the expert opinion of 9 physicians (convenience sample) with experience of diagnosing and treating childhood diseases in primary health care. The experts estimated the type of resources and quantities used (average, minimum and maximum) and official (unpublished Ministry of Health) prices were assigned to each. A mean, minimum and maximum cost was estimated and reported in Cuban pesos (Table 2).

Vaccination schedule and coverage

The target group for vaccine introduction was infants in the first semester of life who would receive the vaccine in a 3-dose schedule, given at 2, 4 and 6 months of age. We did not evaluate a catch-up campaign or a schedule with booster doses. Following advice from the Cuban NIP, we assumed that all vaccines were administered on time. We used the coverage of the first three doses of pentavalent vaccine Heberpenta® (DPT-HB-Hib) in 2016 as a proxy for PCV vaccination coverage over the ten-year period 2020–2029 (López Ambrón et al., 2018) (Table 2).

Vaccination program costs

The number of doses to be procured was calculated by multiplying the mid-year population aged <1 year in the birth cohort of interest by dose-specific coverage and wastage rates. Vaccine wastage was estimated using data from the NIP. Total numbers of procured doses were then multiplied by the cost per dose (assuming a single-dose presentation of 0.7 ml). A PCV7-TT price of 7.00 CUP per dose was provided by the state-owned vaccine manufacturer. Cost of syringes and safety boxes were then added. There was no specific information on the expected incremental cost to the health system of introducing PCV7-TT (expansion of cold chain, transportation, materials, training, supervision and monitoring), so we assumed 1.27 CUP per dose, based on a systematic review of incremental non-vaccine costs associated with PCV introduction, by De la Hoz-Restrepo et al. (2013).

Vaccine efficacy

PCV7-TT was found to have non-inferior vaccine efficacy to PCV13 in a double-blind phase II-III clinical trial that included 1135 children (Toledo-Romaní ME et al., forthcoming; Cuban Public Registry of Clinical Trials - code RPCEC00000243). Efficacy values for PCV7-TT were therefore based on the reported efficacy of other pneumococcal conjugate vaccines (PCVs) in the scientific literature (Table 2). All efficacy values were based on published meta-analyses (random effects) of per protocol vaccine efficacy. We assumed 3-dose vaccine efficacy of 37% (95% CI 21–49) against pneumococcal AOM based on the pooled efficacy against *all-serotype* pneumococcal AOM from two heptavalent PCVs studied in Finnish infants (Pavia et al., 2009). We assumed 3-dose efficacy of 69% (95% CI 24–87) against all severe pneumococcal outcomes (meningitis, severe pneumonia and NPNM) based on pooled efficacy against *all-serotype* invasive pneumococcal disease (IPD) from four PCV studies – Gambia, Philippines, USA and USA (American Indian) (Lucero et al., 2009). We assumed 3-dose vaccine efficacy of 17% (95% CI 6–22) against non-severe pneumococcal pneumonia, which is one quarter of the efficacy value assumed for severe pneumococcal pneumonia. This reflects the relative efficacy of PCVs against all-cause clinical pneumonia (6%, 4 studies) compared to X-ray defined pneumonia (24%, 5 studies) (Lucero et al., 2009). Thus, the relative difference in efficacy against these two outcomes was considered a reasonable proxy for the relative difference in efficacy against non-severe and severe pneumococcal pneumonia.

We assumed that one dose would have half the efficacy of three primary doses, and that the ratio between two and three doses would be 0.92, based on the dose-specific effectiveness of PCV7 against *vaccine-serotype* IPD in the USA (Mahon et al., 2006).

Vaccine impact inputs for parsimonious prediction model

The proportion of carriage due to vaccine serotypes (C_V) and non-vaccine serotypes (C_N) was estimated to be 0.26 (50/187) and 0.73 (137/187) respectively, based on a carriage study of Cuban children aged 2–18 months conducted between October and December 2013 in Cienfuegos municipality (Toledo et al., 2017). The proportion of pneumococcal disease due to vaccine serotypes (D_V) and non-vaccine serotypes (D_N) was estimated to be 0.48 (11/23) and 0.52 (12/23) respectively, based on national hospital sentinel surveillance of invasive pneumococcal disease among children aged <24 months in the year 2014 (Toraño-Peraza et al., 2017). The impact of the vaccine (percentage reduction is all pneumococcal disease cases and deaths aged <5 years), based on the parsimonious prediction model described above, was predicted to be 28.8%. The uncertainty interval was estimated to be 2.2–54.2% based on the 2.5th and 97.5th percentiles of 1000 resampled impact estimates, after resampling C_V and D_V from binomial distributions.

Uncertainty analyses

We ran 1000 probabilistic simulations to generate 95% uncertainty intervals (2.5th and 97.5th percentiles). For simplicity, all ranges used a Beta-PERT distribution centered around the mid estimate and using the low and high estimates as the range. These simulations were also used to calculate the probability that the vaccine would be cost-effective at different willingness-to-pay thresholds.

Pneumococcal vaccination is associated with potentially important but uncertain indirect effects such as herd immunity and serotype replacement. We therefore re-ran the probabilistic analysis assuming overall impact from a parsimonious prediction model rather than the static cohort model. The parsimonious prediction model has been validated to real-world PCV7 impact in 13 high-income countries (Flasche et al., 2015). This method, proposed by Flasche et al., assumes full replacement of vaccine-type carriage with (less invasive) non-vaccine-type carriage, following introduction of the vaccine. The overall impact of the vaccine (% reduction in pneumococcal disease <5 years of age) is

Table 3
Undiscounted numbers of disease cases, clinic visits, hospitalisations and deaths with and without PCV7-TT in Cuba over the ten-year period 2020–2029.

	No vaccination	PCV7-TT	Averted
Cases <5 years	676,038	446,533	229,505
Pneumococcal Acute Otitis Media	660,502	438,592	221,910
Pneumococcal non-severe pneumonia	4530	3831	699
Pneumococcal severe pneumonia	8444	3153	5290
Pneumococcal meningitis	497	186	312
Pneumococcal NPNM	2065	771	1294
Deaths <5 years	302	113	189
Severe pneumococcal pneumonia	170	63	106
Pneumococcal meningitis	70	26	44
Pneumococcal NPNM	62	23	39
Clinic visits	676,038	446,533	229,505
Pneumococcal Acute Otitis Media	660,502	438,592	221,910
Non-severe pneumococcal pneumonia	4530	3831	699
Severe pneumococcal pneumonia	8444	3153	5290
Pneumococcal meningitis	497	186	312
Pneumococcal NPNM	2065	771	1294
Hospital admissions	11,006	4110	6896
Severe pneumococcal pneumonia	8444	3153	5290
Pneumococcal meningitis	497	186	312
Pneumococcal NPNM	2065	771	1294

calculated as:

$$1 - [(C_V/C_N + 1)/(D_V/D_N + 1)]$$

where: C_V is the proportion of carriage due to vaccine serotypes, C_N is the proportion of carriage due to non-vaccine serotypes, D_V is the proportion of pneumococcal disease cases due to vaccine serotypes and D_N is the proportion of pneumococcal disease cases due to non-vaccine serotypes.

Uncertainty intervals (2.5th and 97.5th percentiles) were calculated by bootstrapping from binomial distributions.

Results

Vaccine effects

Over the ten-year period 2020–2029, we estimate around 11,000 pneumococcal hospitalizations and 300 deaths aged <5 years in Cuba, without vaccination (Table 3). We estimate that vaccination could lead to a 63% reduction in hospitalizations and deaths, preventing 6896 (4344–8750) hospitalizations and 189 (115–253) deaths. In addition, we estimate that the vaccine could prevent around 34% of all pneumococcal disease cases and clinic visits, with the majority of prevented disease cases being acute otitis media (around 220,000 disease cases averted).

Costs and cost-effectiveness

Introducing PCV7-TT is estimated to cost around 25 million discounted CUP over the ten-year period 2020–2029 (Table 4). Without vaccination, we estimate the cost of disease treatment to be 58,628,969 discounted CUP (48,572,128 for clinic visits and 10,056,841 for hospitalizations). Equivalent estimates with vaccination are 35,784,420 (32,016,246 for clinic visits and 3,768,175 for hospitalizations). Thus, a large proportion of the costs of vaccination are estimated to be offset by averted treatment costs (around 23 million discounted CUP). Most of these averted treatment costs are associated with avoided clinic visits (around 17 million discounted CUP), of which pneumococcal AOM represents the largest share. The cost per DALY averted is estimated to be 374 CUP per DALY averted (cost-saving – 3465) from a Government perspective.

Uncertainty analysis

Figure 1 shows the probability that PCV7-TT will be cost-effective at different willingness to-pay (WTP) thresholds. Based on a GDP per capita of CUP/USD 8822 for Cuba in the year 2018 (https://data.worldbank.org), there is a 100% probability that the vaccine would be cost-effective at a willingness-to-pay threshold set at 0.5 times the current GDP per capita. We also ran several what-if scenarios. Our results were less favorable to the vaccine (3300 versus 374 per DALY averted) when we assumed impact based on the parsimonious prediction model (29% reduction in all pneumococcal disease outcomes, versus 34–63% for the static cohort model), but the cost-effectiveness ratio was still less than 0.5 times the current GDP per capita. The dose price at which PCV7-TT would be cost-saving was estimated to be around 6.25 CUP per dose using the static cohort model, and 4.25 CUP per dose using the parsimonious prediction model. We estimated less favourable cost-effectiveness (2248 vs 374) when assuming the low estimate for all rates of cases, visits, admissions and deaths, and when assuming the low estimates for all clinic visit and hospitalization costs (2116 vs 374). Finally, we estimated less

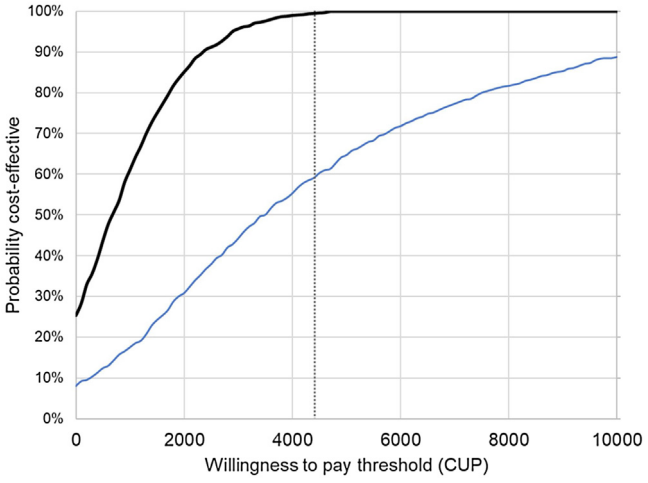

Figure 1. Probability that PCV7-TT will be cost-effective at different willingness-to-pay thresholds in Cuba.
The thick black line represents the results based on the static cohort model. The thin blue line represents the results based on a pseudo-dynamic algorithm adjusted for local serotype distribution among carriers and cases. The dashed vertical line represents 0.5 times the current GDP per capita in Cuba.

Table 4
Discounted cost-effectiveness of PCV7-TT introduction in Cuba over the ten-year period 2020–2029.

	No vaccine	PCV7-TT	Difference (95% uncertainty interval)
Cost (CUP) of vaccination	–	24,701,818	24,701,818 (20,004,232–31,367,257)
Cost (CUP) of disease treatment	58,628,969	35,784,420	22,844,548 (14,488,066–30,581,844)
DALYs	7990	3026	4964 (2998–6662)
Cost (CUP) per DALY averted	–	–	374 (cost saving – 3465)

favorable cost-effectiveness (3546 vs 374) when acute otitis media was removed completely from the analysis.

Discussion

We estimate that introduction of PCV7-TT could prevent a substantial number of pneumococcal disease cases, clinic visits, hospitalizations and deaths among Cuban infants over the period 2020–2029. We also estimate substantial treatment cost savings, with a large share of these costs saved due to averted cases of acute otitis media. The cost of introducing the vaccine would be around 2.8 million CUP each year, but it is likely that a substantial proportion of these costs will be offset by disease treatment cost savings.

Our best estimate of the potential cost-effectiveness of the vaccine is 374 CUP per DALY averted, from a Government perspective. This is around 0.05 times the current GDP per capita in Cuba. Cuba does not have an established willingness-to-pay threshold for health interventions, but Ochalek et al. have suggested a threshold for middle-income countries in the region of 0.4 times GDP per capita, with wide variation between countries (range 0.1–1.0) (Ochalek et al., 2015). Our analysis indicates that PCV7-TT is likely to be cost-effective across most values in this range. When using estimates of vaccine impact based on a parsimonious prediction model (accounting for local serotype distributions and potential serotype replacement) our results were less favorable to the vaccine, but the cost-effectiveness ratio was still less than 0.4 times GDP per capita. Had we included herd immunity benefits to unvaccinated individuals in older age groups (e.g. the elderly) (Kieninger et al., 2015), and averted disabilities among meningitis survivors, then our results would have been even more favorable to the vaccine.

A strength of our study is that we were able to use national data for several input parameters, including the serotype distribution of carriers and disease cases, the non-inferiority of PCV7-TT to PCV-13, the expected price of PCV7-TT, and the costs of treating pneumococcal disease. The decision-support model used in this analysis allowed a national multidisciplinary team to easily review and build consensus on all input parameters and scenarios. This strengthened the national ownership of the analysis and increases the likelihood that our results will inform national decision-making.

An important limitation of our analysis is that the model did not explicitly simulate the transmission dynamics of pneumococcal infections in Cuba. In the absence of good-quality local evidence on the age-specific patterns of social mixing and transmission, we compared our estimates of impact to a parsimonious prediction model (Flasche et al., 2015) informed by local evidence on the serotype distribution among carriers and cases. This predicted a lower impact on pneumococcal disease than our model (29% versus 34–63%). However, the serotype distributions for pneumococcal carriers and cases were not taken from the same geographical location within Cuba. There were also relatively few pneumococcal disease cases ($n = 23$) after matching the age range and period of the disease surveillance data to the age range and period of the carriage study. As a result, there was a good deal of uncertainty about the predicted impact using this approach (95% CI: 2–54%). It is somewhat reassuring that our base case (best) estimates based on the static cohort model were similar to a separate analysis by Chen et al. In this study the authors estimated potential impact of 50% (95% CI: 42–57%) for the Latin America and Caribbean region, using the same parsimonious prediction model, although it should be noted that this analysis was done for PCV13 rather than PCV7-TT (Chen et al., 2019). The uncertainty associated with both approaches (static cohort model and parsimonious prediction model) emphasizes the need for accurate post-introduction surveillance to establish the real-world impact of the vaccine. This would allow cost-effectiveness to be revisited as new data emerges.

We did not include a direct comparison between PCV7-TT and other PCV products such as PCV10 or PCV13. However, PAHO Revolving Fund prices for PCV10 and PCV13 are not available for Cuba so PCV7-TT will be competitively priced for the domestic market. PCV7-TT has also been found to be non-inferior to PCV13 in studies of Cuban children (Toledo-Romaní et al., forthcoming; Cuban Public Registry of Clinical Trials – code RPCEC00000243). However, given the well documented serotype replacement observed with previous lower-valency pneumococcal conjugate vaccines, the real-world impact of PCV7-TT will need to be closely monitored following introduction in order to detect any increase in pneumococcal disease caused by types not included in the vaccine. As more post-vaccination evidence emerges, more sophisticated transmission dynamic models may offer insights into the expected longer-term impact of the vaccine.

Despite several uncertainties around some of the parameters used, our probabilistic uncertainty analysis indicates that PCV7-TT is likely to be cost-effective in Cuba. Scenarios with assumptions that were unfavourable to the vaccine did not dramatically alter the cost-effectiveness ratio (all were less than 0.4 times GDP per capita) and in all scenarios we excluded DALYs and costs associated with long-term sequelae among pneumococcal meningitis survivors. AOM was influential in our analysis because of high associated health care costs averted (23 million averted with AOM included, versus 7 million averted without AOM). Because vaccine program costs (25 million) were so finely balanced with health care costs averted (23 million), excluding AOM was particularly influential on the cost per DALY (374 with versus 3546 without). This is an interesting result. Although most published studies have included AOM (Wu et al., 2015; Saokaew et al., 2016), it has not been particularly influential on the results. Our estimates of the incidence of AOM, treatment costs and efficacy, were uncertain, and better evidence is needed to validate these assumptions. It is reassuring therefore that the results remain cost-effective (below the GDP per capita of CUP/USD 8822) when AOM is excluded from the analysis.

In general, better parameters should be sought to validate our inputs. For example, the costs of disease treatment were based on just one hospital and one polyclinic. However, in the Cuban health system, clinical management guidelines are standardized across the country for pneumonia and meningitis so these estimates should be a good indication of the costs in other Cuban health facilities.

We used a government perspective and incorporated only direct costs. The government perspective was selected because 100% of the Cuban population receives health care services from governmental institutions. The study allowed us to estimate the direct medical costs that would be saved by the government if the vaccine were introduced nationwide. We excluded out-of-pocket expenses and lost productivity incurred by households because they would be difficult to estimate at the national level and including them would only make the case for vaccination more favourable.

Cuba operates in an economic environment characterized by a considerable degree of dualism and segmented markets. Three currencies are currently in circulation: the Cuban peso (CUP), the US dollar (USD) and the Cuban convertible peso (CUC). There is no exchange market for CUC into dollars, but in commercial and financial transactions companies operate with a one-to-one exchange rate, and do not have bank accounts or separate accounting for these two types of currency. Companies prepare their balance sheets using the official exchange rate (one CUP to

one USD or CUC). There is an overvaluation of the CUP that affects the entire economy. On this basis, cost-effectiveness comparisons with other countries should be made with caution, but the results when compared with the threshold defined by the country's GDP are not affected because GDP is also affected by this structural issue of the current Cuban economy.

In conclusion, PCV7-TT is likely to be cost-effective in Cuba. The real-world impact of PCV7-TT would need to be closely monitored following introduction in order to detect any increase in pneumococcal disease caused by types not included in the vaccine.

Contributions of authors

AGF, NLP, AC and MET participated in the design, analysis, interpretation of data and writing this paper. IPG, MMA, ARJ, LLA and GTP participated the conception of the study and acquisition of data of the model. NEO reviewed the methodology and discussion of the results of paper. All authors were involved as experts in the discussion, review and final approval of the version to be submitted.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AGF, NLP and IPG work at the *Finlay Vaccine Institute*, a state-owned vaccine manufacturer based in Havana, Cuba. All other authors declare no conflicts of interest. All authors had full access to the data and had final responsibility for the decision to submit the paper.

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Ethical approval

This study was submitted to the Tropical Medicine Institute "Pedro Kourí" Institutional Ethics Committee (IPK-IEC) and was approved under the agreement IPK IEC # 17-14/37-16. In addition, the Scientific Council of the Finlay Vaccine Institute approved the study.

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