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A cost-effectiveness analysis of PHiD-CV compared to PCV13 in a national immunization program setting in Tunisia

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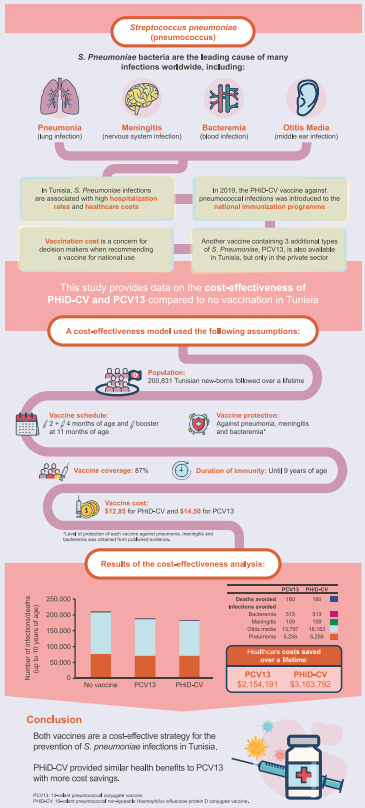
ABSTRACT

Background: In response to the substantial clinical and economic burden of diseases caused by *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NTHi) in Tunisia, the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) was recently introduced into the national immunization program. However, there has yet to be a full-scale health economic analysis comparing currently available pneumococcal conjugate vaccines (PCVs) in Tunisia.

Methods: A Markov model that simulated the disease processes of invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM) over a newborn cohort lifetime was used to evaluate the cost-effectiveness/utility of PHiD-CV and the 13-valent pneumococcal conjugate vaccine (PCV13) from payer's perspective, using 3% discounting. Vaccine effects were considered for up to 9 years of age.

Results: Vaccination with PHiD-CV or PCV13 was estimated to avert approximately 700 cases of IPD (200 meningitis, 500 bacteremia), and around 5,000 cases of all-cause pneumonia. However, PHiD-CV vaccination was estimated to avert around 4,000 additional AOM cases (18,000) versus PCV13 (14,000). Both PCVs were demonstrated to be cost-effective interventions, but PHiD-CV was estimated to generate additional cost savings of almost $1 million US dollars (USD) with similar levels of clinical benefits. An additional scenario which incorporated serotype-specific vaccine efficacy found no significant change in overall results.

Conclusion: PCVs are a cost-effective strategy to relieve the burden associated with diseases caused by *S. pneumoniae* and NTHi in Tunisia. PHiD-CV is more cost-effective than PCV13, generating similar health benefits, at a reduced net cost of almost $1 million USD per vaccinated cohort.



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Introduction

Streptococcus pneumoniae is a leading cause of invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM) in adults and children worldwide.[1] Similarly, in Tunisia, *S. pneumoniae* is one of the more frequently isolated bacteria in cases of bacterial meningitis,[2–4] and community-acquired pneumonia (CAP).[5] Pneumococcal meningitis, in particular, is associated with a high case fatality rate of approximately 14%, and neurological sequalae in a third of survivors.[6] The societal economic burden of pneumococcal infections is also substantial. In a prospective multicenter study across 15 pediatric departments in Tunisia, pneumococcal pneumonia and pneumococcal meningitis were estimated to cause 1,091 and 69 hospitalizations a year, respectively; incurring a total cost of 502,079.408 Tunisian dinars (TND) or $256,065.05 US dollars (USD).[7]

In response to the substantial prevalence, morbidity, and mortality of pneumococcal diseases, numerous countries have adopted pneumococcal conjugate vaccines (PCVs) into national immunization programs. A seven-valent pneumococcal conjugate vaccine (PCV7), which offers protection against the seven serotypes responsible for a high proportion of disease worldwide (4, 6B, 9V, 14, 18C, 19F, and 23F), was licensed in the US in 2000.[8] More recently, PCVs with broader serotype coverage have become available, including a 10-valent pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate (PHiD-CV; GlaxoSmithKline Biologicals SA) vaccine that includes three additional serotypes (1, 5, and 7F) and a 13-valent pneumococcal polysaccharide protein conjugate vaccine (PCV13; Pfizer Inc.) that includes six additional serotypes (1, 3, 5, 6A, 7F and 19A).[9,10]

Vaccination is a major pillar of public health policy in Tunisia, and in 2019, the Ministry of Health extended the previous national immunization program to include PHiD-CV, which has been available in the private market since 2011. PCV13 was also launched in Tunisia in 2011, but remains available only in the private sector. As vaccine serotypes of *S. pneumoniae* have been identified as a prominent cause of IPD in Tunisia,[11] the introduction of PCVs are expected to result in reduced disease burden and medical costs. However, cost of vaccination remains a major concern for decision makers in Tunisia.

There has yet to be a full-scale health economic analysis comparing currently available PCVs to assess their economic impact from a payer perspective in Tunisia. Therefore, the aim of the current study was to provide data on the cost-utility and cost-effectiveness of PHiD-CV and PCV13 from a payer perspective, in order to facilitate the decision-making process of immunization policy at a national level.

Materials and methods

Modeling description

A previously published Markov cohort model, implemented in Microsoft Office Excel (2007),[12] was adapted to simulate the health and economic impact of pneumococcal diseases in Tunisia (Figure 1). This model simulated the disease process of IPD, CAP, and AOM caused by *S. pneumoniae* and NTHi in a single birth cohort over a lifetime (1,128 monthly cycles or 94 years).

In the base case, three steady state scenarios were compared: no vaccination or vaccination of either PHiD-CV or PCV13 with a 2 + 1 schedule (defined as two doses at 2 and 4 months of

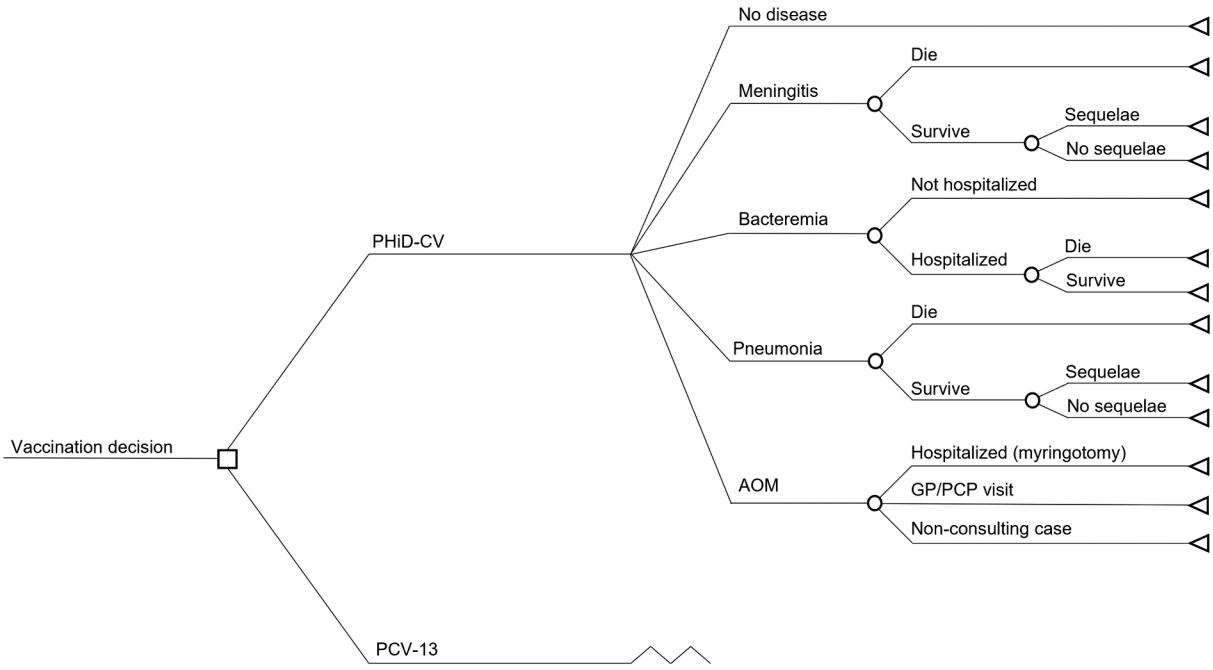

Figure 1. Markov cohort model design. The cohort model is Markov-based with exclusive health states: no disease, sequelae, and death. The transition from 'no disease' to 'sequelae' or 'death' is calculated based on this decision tree. In the model, only meningitis can lead to long-term sequelae and non-consulting AOM are accounted for in the quality-of-life impact calculation. AOM: acute otitis media; GP: general practitioner; PCP: primary care physician; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine.

age and a booster at 11 months of age). A direct vaccine effect was estimated as a reduction in the incidence of IPD, CAP, and AOM. Costs (from a payer perspective) and outcomes were discounted at 3%, consistent with a previously reported cost-effectiveness study of PCVs conducted for Tunisia and Algeria by Pugh et al.[13]

Epidemiological inputs

Demographic input for the birth cohort size (200,831) was extracted from the published birth rate for Tunisia, as applied to the size of the entire population.[14] Annual general mortality rates were obtained from the World Health Organization (WHO) Life Tables by country.[15]

The study's model required serotype data (i.e. incidence of *S. pneumoniae* serotypes) by age group. Pneumococcal serotype distribution data for Tunisia were available from six local studies. However, many of them contained a reduced number of strains without the adequate discrimination by age group.[11,16–20] As a result, data from one of the larger studies were used in this model,[18] providing the data by age as needed (Supplementary Table S1).

Age-specific incidence rates of IPD, as well as age-specific case-fatality ratios and proportions of cases with sequelae for IPD meningitis were obtained from the epidemiological parameter values reported by Pugh et al. 2019 for Tunisia.[13] These values were then adjusted accordingly using an epidemiological study specific to Tunisia by Sfar et al. 2012 (Supplementary Table S2 and S3).[21] All-cause pneumonia hospitalization rates, case fatality ratios and general practitioner consultations were also obtained from Pugh et al. 2019 (Supplementary Table S4).[13]

However, as Pugh et al. 2019 considered a very high incidence of AOM from a classic study conducted in Boston, US from 1989,[22] age-specific incidence of AOM was calibrated using values from a cost-effectiveness analysis of PCVs conducted for Taiwan (Supplementary Table S5).[23] Hospitalizations for tympanostomy tube placement procedures, sequelae data, and complications associated with AOM were not considered for this analysis, due to the lack of available data.

Finally, the frequency of NTHi and *S. pneumoniae* (32.3% for NTHi and 35.9% for *S. pneumoniae*) and the distribution of pneumococcal serotypes in AOM were obtained from international reviews, as Tunisia-specific epidemiological data for AOM were not available (Supplementary Table S6).[24,25]

Vaccine efficacy assumptions

As in the previously described Markov model, this analysis assumed that vaccine efficacy (VE) increased from 2–12 months with the increasing number of doses; had full effectiveness from 12 months–3 years; and then declined until age 9. To simulate waning over these time periods, the model linearly adjusted VE each month.[12]

PCV13 includes three additional *S. pneumoniae* serotypes compared to PHiD-CV. However, there is no systematic evidence of differences in VE when comparing these PCVs. In line with this, and the conclusions of independent reviews conducted by the Pan American Health Organization (PAHO), the International Vaccine Access Center (IVAC) and the WHO, the same VE in the base case scenario was used for both PHiD-CV and PCV13 against IPD and all-cause pneumonia (Table 1).[26–28]

VE against all-types IPD were provided by a study conducted by Deceuninck et al. 2015 in Canada, as this study contained a comparison of the effectiveness of both PCVs in the same population setting. This study estimated that the point effect against all-types of IPD was 72% for PHiD-CV and 66% for PCV13, with overlapping 95% confidence intervals (CIs).[29] For the base case scenario, the higher point estimate (72% [95% CI: 46–85%]) was used in order to consider other studies which report higher VE against IPD for these vaccines.[33,34]

VE data against all-cause pneumonia generated from this PHiD-CV clinical trial were also used for both PCVs. In this case, VE reported against consolidated CAP (21.8% [7.7–33.7%]) was used as a proxy to vaccine effect against hospitalized pneumonias, and VE reported against suspected CAP (8.7% [3.8–13.4%]) was used as a proxy to vaccine effect against ambulatory pneumonias.[30]

Table 1. Vaccine efficacies used in the base case scenario (WHO recommendation scenario).

Outcome	Agent	PHiD-CV	PCV13
IPD	All *Sp.* types[29]	72% (95% CI: 46–85%)	72% (95% CI: 46–85%)
CAP	Hospitalized cases[30]	21.8% (95% CI: 7.7–33.7%)	21.8% (95% CI: 7.7–33.7%)
	Ambulatory cases[30]	8.7% (95% CI: 3.8–13.4%)	8.7% (95% CI: 3.8–13.4%)
AOM[a]	*Sp.* Vaccine types[30, 31]	69.9% (95% CI: 29.8–87.1%)	69.9% (95% CI: 29.8–87.1%)
	Sp. Non-vaccine types[31]	−33% (95% CI: −80–1%)	−33% (95% CI: −80–1%)
	NTHi[30–32]	21.5% (95% CI: −43.4–57.0%)	−11% (95% CI: −34–8%)

[a]The final effectiveness against all AOM for PHiD-CV was 23.4% and PCV13 17.2%. AOM: acute otitis media; CAP: community acquired pneumonia; CI: confidence interval; IPD: invasive pneumococcal disease; NTHi: non-typeable *Haemophilus influenzae*; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; *Sp*: *Streptococcus pneumoniae*; WHO: World Health Organization.

VE against AOM were taken from clinical trials related for both PCVs.[30,32] As both the PHiD-CV clinical trial and the Finnish Otitis Media trial showed high VE against AOM associated with *S. pneumoniae* vaccine-types for both PCVs with overlapping CIs, a VE of 69.9% (29.8–87.1%) was assumed for both vaccines.[30,31] VE against AOM associated with non-vaccine types of *S. pneumoniae* was taken from the Finnish Otitis Media Vaccine Trial and also considered equal for both vaccines.[31] Lastly, VE against NTHi AOM for PHiD-CV and PCV13 were taken from the PHiD-CV clinical trial and Finnish Otitis Media Vaccine Trial, respectively.[30–32]

Cost-effectiveness analysis

Cost-effectiveness was compared between PHiD-CV, PCV13, and no vaccination. For this analysis, vaccine coverage of 87% was used for both vaccines, in line with the official vaccine coverage reported by Tunisia for the 3rd dose of the pneumococcal vaccine and reported to the WHO for the year 2020.[35] Vaccine prices per dose in USD were obtained from the 2020 PAHO Revolving Fund for PHiD-CV ($12.85) and PCV13 ($14.50) as they are publicly available on the PAHO web page.[36] Vaccine costs also included a 10% wastage cost and a $1 administrative cost per dose for either vaccine.[37]

Following the recommendations of the commission on Macroeconomics and Health of the WHO, cost-effectiveness thresholds of one gross domestic product (GDP) per capita were used.[38,39] GDP per capita for the cost-effectiveness threshold was obtained from the World Bank National Accounts ($3,317 USD per capita for Tunisia, 2019).[40] The PCVs with incremental cost-effectiveness ratios (ICERs) lower than one GDP per capita were considered cost-effective for Tunisia.

Cost inputs

Average costs of treatment for the different outcomes were estimated for Tunisia using the values previously reported by Pugh et al. 2019,[13] which were compared with results of a local study by Sfar et al.[21] As treatment costs of sequelae were not reported for this model, these costs were taken from a local study.[7,21]

Average treatment costs were then updated to USD using the consumer price index per year between 2016 and 2020 for Tunisia,[41] and the 2020 exchange rate for USD and TND.[42] Adult costs were based on the same cost reported for children plus 20% (Supplementary Table S7). Indirect costs, such as productivity losses, were not included.

Utility inputs

Due to the lack of local data, normative utilities and disutility values used in the model were obtained from international sources (Supplementary Table S8).[43–45] These values were then used to estimate population quality-adjusted life year (QALY) loss. Losses in future utilities due to premature death or long-term sequelae associated with events occurring during the study year were assigned to the present year at an annual discount rate of 3% in order to estimate the net present value.[13] Life expectancy was estimated using normative utilities according to age.

Sensitivity analysis

Univariate sensitivity analysis was completed for all model input (73 parameters). Here, each parameter was varied up and down from the base-case value using realistic ranges, following which the new incremental cost-utility ratio (ICUR) obtained was compared to the cost-effectiveness/utility threshold.

In addition, probabilistic sensitivity analysis (PSA) of the ICURs for the comparisons of PHiD-CV versus no vaccine, and PHiD-CV versus PCV13, was performed by recording the results of 1,000 Monte Carlo iterations, each of which simultaneously sampled each of the model's input parameters from an appropriate probabilistic distribution (normal distribution for VE, triangular distribution for disease incidence and costs, and beta distribution for disutility). The list of model parameters and their associated sampling uncertainty are shown in Supplementary Table S9.

Alternative scenario

In the alternative scenario, VE against IPD was calculated as a sum product of local serotype distribution and the serotype-specific efficacy of each vaccine to account for the three additional serotypes included in PCV13 (Table 2). The sensitivity analysis for the alternative scenario used similar parameters as listed in Supplementary Table S9 but considered the VEs included in Table 2.

Protection against vaccine-type IPD

Randomized control trials of PHiD-CV and real-world effectiveness data of PCV13 against IPD in children have shown that both PHiD-CV and PCV13 reduce the incidence of vaccine-types IPD.[29,30,34,50] However, evidence of the serotype-specific VE of PHiD-CV and PCV13 is limited, given the low incidence of the serotypes common to PCV7 due to prior mass vaccination programs.

Therefore, serotype-specific effectiveness data were largely extrapolated from estimates of vaccine effectiveness developed from a CDC case-control study conducted in the US for PCV7 and reported by Whitney et al.[55] It was assumed that the ten common types covered by both PHiD-CV and PCV13 (1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F) would have a VE of 94.7% (95% CI: 93.0–98.0%), which is the mean of the serotype-specific estimates (≥1 dose) for the serotypes covered by PCV7.[34]

Protection against serotype 6A

Evidence for cross-protection of PCV7 against serotype 6A (through the inclusion of the cross-reactive 6B serotype) has been demonstrated in many countries.[55,56] PHiD-CV, which also contains serotype 6B, was assessed to be immunologically noninferior to PCV7 and real-world protection against 6A has been observed from PHiD-CV use in Finland.[49,57] Based on the above evidence, cross-protection for 6A was assumed at 76.0% for PHiD-CV.[29,33,49] For PCV13, VE against serotype 6A was assumed to be the same as that of other vaccine-type serotypes (94.7% [95% CI:93.0–98.0%]).[34]

Table 2. Vaccine efficacies used in the alternative scenario.

Outcome	Agent	PHiD-CV	PCV13
IPD	PHiD-CV *Sp.* types[34]	*Type specific VE assumed* 94.7% (95% CI: 93–98%)	*Type specific VE assumed* 94.7% (95% CI: 93–98%)
	Non-vaccine types 19A	*Cross protection assumed*[29] 72.0% (95% CI: 46–85%)	*Type specific VE assumed*[29,46–48] 80.0% (95% CI: 70–90%)
	Non-vaccine types 6A	*Cross protection assumed*[29,33,49] 76.0% (95% CI: 39–90%)	*Type specific VE assumed*[34] 94.7% (95% CI: 93–98%)
	Non-vaccine types 3[47,48,50–54]	*No efficacy assumed* 0%	*No efficacy assumed* 0%
CAP	Hospitalized cases[30]	21.8% (95% CI: 7.7–33.7%)	21.8% (95% CI: 7.7–33.7%)
	Ambulatory cases[30]	8.7% (95% CI: 3.8–13.4%)	8.7% (95% CI: 3.8–13.4%)
AOM[a]	*Sp.* Vaccine types[30,31]	69.9% (95% CI: 29.8–87.1%)	69.9% (95% CI: 29.8–87.1%)
	Sp. Non-vaccine types[31]	−33% (95% CI: −80–1%)	−33% (95% CI: −80–1%)
	NTHi[30–32]	21.5% (95% CI: −43.4–57.0%)	−11% (95% CI: −34–8%)

[a]The final effectiveness against all AOM for PHiD-CV was 23.4% and PCV13 17.2%. AOM: acute otitis media; CAP: community acquired pneumonia; CI: confidence interval; IPD: invasive pneumococcal disease; NTHi: non-typeable *Haemophilus influenzae*; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; *Sp*: *Streptococcus pneumoniae*; VE: vaccine efficacy.

Protection against serotype 19A

While the serotype 19A is not included in PHiD-CV, real-word effectiveness data from post-marketing case-control studies in Canada and Brazil, a population-based study in Finland and a surveillance study from the Netherlands, have all demonstrated a substantial impact of PHiD-CV on IPD caused by serotype 19A.[29,49,58,59] The case-control study from Canada additionally demonstrated no substantial difference in VE against 19A IPD between PHiD-CV and PCV13.[29] Consequently, a VE of 72.0% was assumed for PHiD-CV in this alternative scenario.[29]

On the other hand, real-world evidence on the effectiveness against serotype 19A showed a lower value than the estimates for the serotypes shared with PCV7.[29,46–48] For example, while the highest reported VE against 19A IPD for PCV13 was 86% (US study) the Canadian case-control study reported a VE of 66%.[29,47] As a result, an estimate of 80% was used as an optimal assumption for PCV13.[29,46–48]

Protection against serotype 3

There is conflicting evidence on the effectiveness of PCV13 for protecting against serotype 3 IPD infections.[47,48,50–53] Based on recent data from the UK for a 2 + 1 schedule, a statistically non-significant effectiveness estimate of 26% (95% CI: -69–68%) was observed for PCV13 against serotype 3.[48] This lack of effectiveness of PCV13 against serotype 3 was highlighted by the UK Joint Committee on Vaccination and Immunization (JCVI).[54] As a result, a VE of 0% was assumed for both vaccines.

Results

Public health and economic results

The modeled health burden of pneumococcal and NTHi-related diseases during the first 10 years of life in Tunisia for the base case is shown in Table 3. For the projected birth cohort of 200,831, it was estimated that without vaccination, there would be 1,708 cases of IPD (400 cases of meningitis and 1,308 cases of bacteremia) with 32 cases of long-term sequalae, 76,594 cases of all-cause pneumonia and 130,863 cases of AOM.

All-cause pneumonia was estimated to be responsible for the majority of deaths. However, disease burden with meningitis was highest, accounting for 2,706 QALYs lost due to morbidity compared to 1,261, 1,151 and 36 for pneumonia, AOM and bacteremia, respectively. Total lifetime direct medical costs (undiscounted) to the Tunisian healthcare system were $112,355,166 USD.

Base case (WHO recommendation scenario)

For the base-case scenario, vaccination with either PHiD-CV or PCV13 was estimated to avert 672 cases of IPD during the first 10 years of life (159 meningitis, 513 bacteremia), as well as 5,256 cases of all-cause pneumonia. However, PHiD-CV vaccination was estimated to avert 4,386 additional AOM cases (18,183) compared to PCV13 (13,797). Both vaccines were estimated to prevent 180 deaths.

Between the two PCVs, PHiD-CV was estimated to result in 20 QALYs gained due to the decrease in QALYs associated with AOM morbidity in comparison to PCV13. Total lifetime direct medical costs saved with PHiD-CV and PCV13 (including vaccine cost) were $3,163,792 USD and $2,154,191 USD, respectively. Costs were around $1 million USD less for PHiD-CV, due to the lower cost of the vaccination program and savings in AOM treatments.

Alternative scenario

When taking into account the serotype-specific VE of each vaccine, the alternative scenario estimated that PCV13 would avert two further cases of pneumococcal bacteremia compared to PHiD-CV. Nevertheless, the differences described in the base case with regards to averted cases of AOM and vaccine cost remained consistent across scenarios (Table 4).

Table 3. Public health and economic results of PCVs in the base case (WHO recommendation scenario; undiscounted).

Health outcomes (cases)[a]	No Vaccine	PHiD-CV	PCV13
Hospitalized pneumonias	6,314	5,318	5,318
Ambulatory pneumonias	70,280	66,020	66,020
AOM medical visits	130,863	112,680	117,066
Streptococcus meningitis	400	241	241
Streptococcus meningitis sequela	32	21	21
Streptococcus bacteremia	1,308	795	795
Health outcomes (deaths)[a]			
Pneumonias	365	306	306
Streptococcus meningitis	154	80	80
Streptococcus bacteremia	102	55	55
Total deaths	621	441	441
QALY lost[b]			
Pneumonias (morbidity)	1,261	1,228	1,228
Streptococcus meningitis (morbidity)	2,706	2,274	2,274
Streptococcus bacteremia (morbidity)	36	32	32
AOM (morbidity)	1,151	1,061	1,083
QALYs lived by the cohort (mortality effect)	13,098,247	13,109,750	13,109,750
LY lived by the cohort (mortality effect)	15,299,502	15,312,966	15,312,966
Direct medical costs (USD)[c]			
Pneumonias	$48,006,592	$46,905,274	$46,905,274
Streptococcus meningitis	$2,471,159	$2,174,875	$2,174,875
Streptococcus meningitis sequela	$47,603,392	$40,082,962	$40,082,962
Streptococcus bacteremia	$3,778,846	$3,396,648	$3,396,648
AOM medical visits	$10,495,177	$9,717,748	$9,906,338
Direct medical treatment costs	$112,355,166	$102,277,507	$102,466,097
Vaccination costs	$0	$6,913,868	$7,734,878
Total direct medical costs	$112,355,166	$109,191,374	$110,200,975

[a]Data report the number of cases observed after the follow-up of the Tunisian birth cohort (n=220,831) until 10 years of age.
[b]Reported QALYs after the lifetime follow up of the Tunisian cohort.
[c]Lifetime costs are reported in USD from 2020. AOM: acute otitis media; LY: life years; PCV: pneumococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life year; USD: US dollar; WHO: World Health Organization.

Table 4. Public health and economic results of PCVs in the alternative scenario.

Health outcomes (cases)[a]	No Vaccine	PHiD-CV	PCV13
Hospitalized pneumonias	6,314	5,318	5,318
Ambulatory pneumonias	70,288	66,021	66,021
AOM medical visits	130,863	112,681	117,067
Streptococcus meningitis	400	245	245
Streptococcus meningitis sequela	32	21	21
Streptococcus bacteremia	1,308	809	807
Health outcomes (deaths)[a]			
Pneumonias	365	306	306
Streptococcus meningitis	154	81	80
Streptococcus bacteremia	102	56	56
Total deaths	621	443	442
QALY lost[b]			
Pneumonias (morbidity)	1,261	1,228	1,228
Streptococcus meningitis (morbidity)	2,706	2,294	2,292
Streptococcus bacteremia (morbidity)	36	32	32
AOM (morbidity)	1,151	1,061	1,083
QALYs lived by the cohort (mortality effect)	13,098,247	13,109,693	13,109,731
LY lived by the cohort (mortality effect)	15,299,502	15,312,899	15,312,943
Direct medical costs (USD)[c]			
Pneumonias	$48,006,592	$46,905,172	$46,905,296
Streptococcus meningitis	$2,471,159	$2,182,757	$2,181,476
Streptococcus meningitis sequela	$47,603,392	$40,426,950	$40,398,786
Streptococcus bacteremia	$3,778,846	$3,407,161	$3,405,515
AOM medical visits	$10,495,177	$9,717,750	$9,906,367
Direct medical treatment costs	$112,355,166	$102,639,790	$102,797,439
Vaccination costs	$0	$6,913,890	$7,734,906
Total direct medical costs	$112,355,166	$109,553,680	$110,532,344

[a]Data report the number of cases observed after the follow-up of the Tunisian birth cohort (n=220,831) until 10 years of age.
[b]Reported QALYs after the lifetime follow up of the Tunisian cohort.
[c]Lifetime costs are reported in USD from 2020. AOM: acute otitis media; LY: life years; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life year; USD: US dollar; WHO: World Health Organization.

Base case cost-effectiveness and cost-utility analysis results

Base case (WHO recommendation scenario)

Overall, for the base case scenario, both vaccines were shown to have a ICUR below the cost-effectiveness threshold for Tunisia (1 GDP per capita or $3,317 USD per QALY gained). However, PHiD-CV was estimated to generate 20 more QALYs gained over a lifetime than PCV13, with a reduced investment of $982,016 USD in the cost-utility analysis (Table 5). Moreover, although both vaccines are predicted to save the same number of life years (LYs), PHiD-CV is predicted to conserve these with a reduced investment of $982,016 USD in the cost-effectiveness analysis (Supplementary Table S10). Therefore, PHiD-CV was predicted to be the most cost-effective vaccine, whether costs per QALY or costs per LY are considered.

Alternative scenario

As in the base case scenario, both vaccines were shown to have an ICUR and ICER below the cost-effectiveness threshold for Tunisia (1 GDP per capita or $3,317 USD per QALY gained). PHiD-CV was estimated to generate five more QALYs gained than PCV13, with a reduced investment of $971,031 USD in the cost-utility analysis (Table 6). However, in the cost-effectiveness analysis, PCV13 was estimated to generate 16 more LYs gained than PHiD-CV, with an increased investment of $971,031 USD (Supplementary Table S11).

Sensitivity analysis of the cost-utility analysis

The one-way sensitivity analyses found that the most influential parameters for the cost-effectiveness results for PHiD-CV and PCV13 were incidence of meningitis, VE for IPD, and the vaccine administration and wastage costs (Figure 2). However, no parameter was able to move the ICUR result close to the 1 GPD per capita threshold of cost-effectiveness, confirming that the conclusion that both vaccines are cost-effective for Tunisia is robust in the scenarios analyzed.

The PSA on the ICUR of PHiD-CV versus no vaccination in the base-case scenario also confirmed PHiD-CV as a cost-effective intervention, with 100% of the iterations resulting in an ICUR below the cost-effectiveness threshold for Tunisia (Figure 3(a)). When comparing PHiD-CV versus PCV13 in the PSA, the differences between QALYs generated were not significant between vaccines as iterations were equally distributed around the x-axis zero value, with 50% of iterations resulting in a QALY benefit for each vaccine. However, the savings generated by PHiD-CV of almost $1 million USD was robust in the PSA comparison and confirmed with 98% of PSA iterations below the y-axis zero value (Figure 3(b)).

Alternative scenario

The one-way sensitivity analyses found that the most influential parameters for the cost-effectiveness results for PHiD-CV and PCV13 in the alternative scenario were incidence of meningitis, vaccine administration and wastage costs, and VE for hospitalizations due to pneumonia (Supplementary Figure S1). Similar to the base case scenario, the PSA for the alternative scenario showed that the difference in QALYs and LYs between vaccines was not significant. However, the difference between PCVs with respect to cost ($971,031 USD savings favoring PHiD-CV) was significant and robust (Supplementary Figure S2)

Table 5. Cost-utility analysis for PCVs in Tunisia for the base case (WHO recommendation scenario).

			Incremental difference		
	QALYs[a]	Costs (USD)[b]	QALYs	Costs (USD)	ICUR[c]
No Vaccine	5,260,275	$38,784,439	–	–	–
PCV13	5,264,901	$42,013,506	4,626	$3,229,067	dominated
PHiD-CV	5,264,921	$41,031,491	20	−$982,016	484

[a]Reported discounted QALYs after the lifetime follow up of the Tunisian cohort.
[b]Lifetime discounted costs reported in USD from 2020.
[c]ICUR was calculated by dividing incremental costs by incremental QALYs gained.
ICUR: incremental cost-utility ratio; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life year; USD: US dollars; WHO: World Health Organization.

Table 6. Cost-utility analysis for PCVs in Tunisia for the alternative scenario.

			Incremental difference		
	QALYs[a]	Costs (USD)[b]	QALYs	Costs (USD)	ICUR[c]
No Vaccine	5,260,275	$38,784,439	–	–	–
PCV13	5,264,895	$42,111,099	4,620	$3,326,660	dominated
PHiD-CV	5,264,900	$41,140,068	5	−$971,031	509

[a]Reported discounted QALYs after the lifetime follow up of the Tunisian cohort.
[b]Lifetime discounted costs reported in USD from 2020.
[c]ICUR was calculated by dividing incremental costs by incremental QALYs gained.
ICUR: incremental cost-utility ratio; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life year; USD: US dollars.

Discussion

Globally, and in Tunisia, pneumococcal diseases have been found to result in substantial medical costs.[7] In line with these findings, this study estimated substantial health and economic burden of pneumococcal and NTHi-related diseases over the first 10 years of life in Tunisia. For the projected Tunisian birth cohort of 200,831, it was estimated that there would be a total of 1,708 cases of IPD (400 cases of meningitis and 1,308 cases of bacteremia) with 32 cases of long-term sequalae, 76,594 cases of all-cause pneumonia and 130,863 cases of AOM. Total lifetime, direct medical costs of pneumococcal and NTHi diseases in an unvaccinated birth cohort to the Tunisian healthcare system were $112,355,166 USD.

Compared with no vaccination, PCVs were demonstrated to have a substantial impact on pneumococcal and NTHi-related diseases between 0–10 years of age in Tunisia, reducing the burden associated to IPD, pneumonia and AOM.

Furthermore, both PCVs provided similar levels of health benefits, whether measured as QALYs or LYs. Finally, both PCVs were demonstrated to be highly cost-effective interventions for Tunisia in any of the scenarios analyzed, consistent with results of previous studies of the region.[13] The sensitivity analyses further demonstrated that these conclusions were robust, even when all uncertainties in the parameters used were considered.

When comparing PHiD-CV and PCV13 vaccination strategies, PHiD-CV was estimated to avert 4,386 additional AOM cases compared to PCV13. Moreover, PHiD-CV was estimated

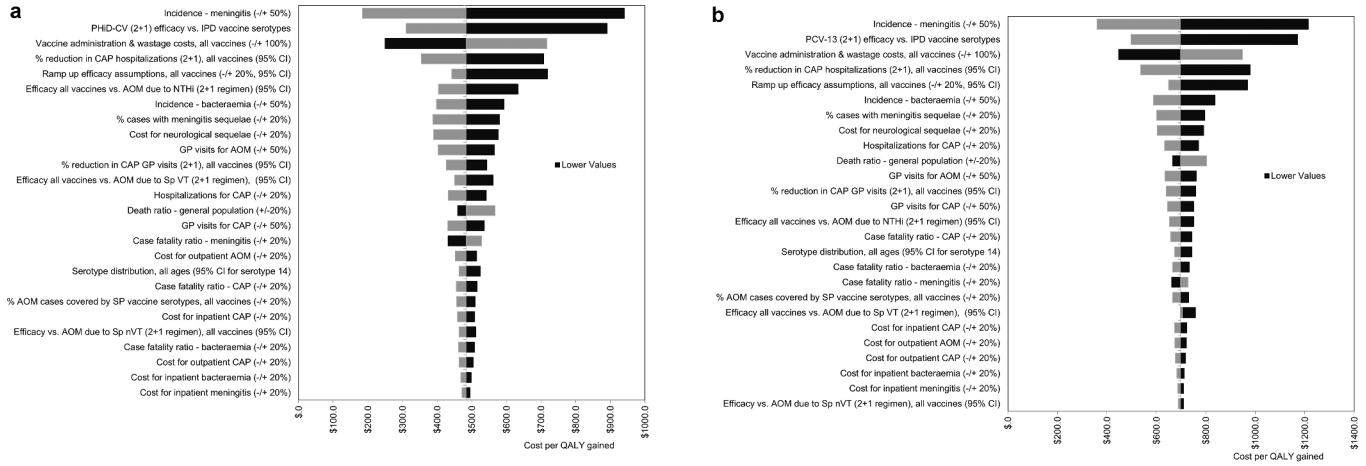

Figure 2. Univariate sensitivity analysis of ICURs for the base case (WHO recommendation scenario). (a) PHiD-CV versus no vaccine; (b) PCV13 versus no vaccine. Only the most influential parameters are shown. AOM: acute otitis media; CAP: community acquired pneumonia; GP: general practitioner; IPD: invasive pneumococcal disease; ICUR: incremental cost-utility ratio; NTHi: non-typeable *Haemophilus influenzae*; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; *Sp* VT: *Streptococcus pneumoniae* vaccine-type; WHO: World Health Organization.

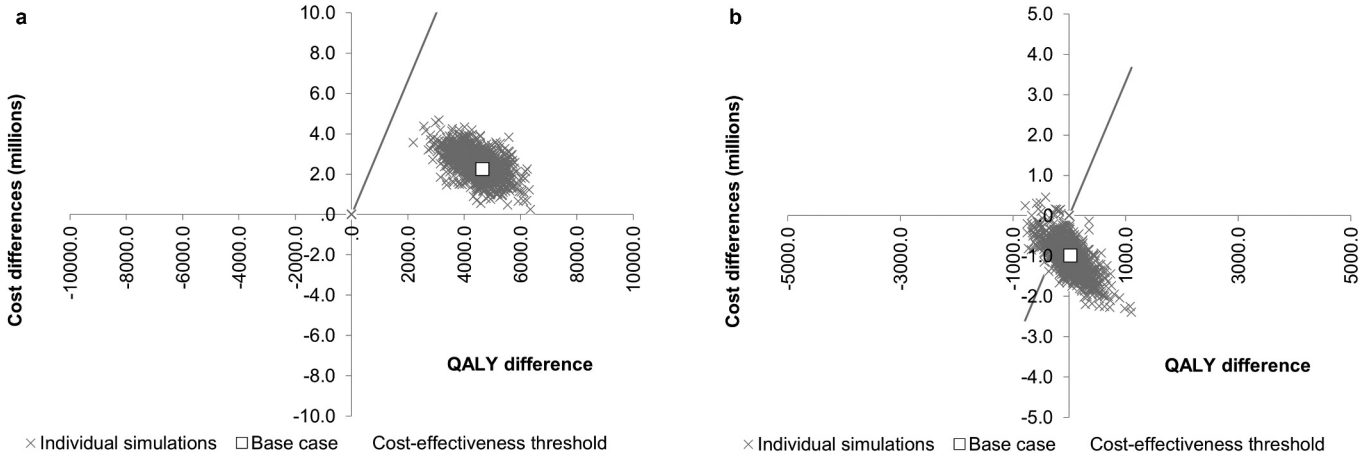

Figure 3. Probabilistic sensitivity analysis of ICURs for the base case (WHO recommendation scenario). (a) PHiD-CV versus no vaccine; (b) PCV13 versus no vaccine. The diagonal grey line indicated the cost-utility threshold for Tunisia. ICUR: incremental cost-utility ratio; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life year; WHO: World Health Organization.

to result in 20 QALYs gained due to the decrease in QALYs lost associated with AOM morbidity. This, along with a lower price per dose of $12.85 USD compared with $14.50 USD, would result in financial savings of almost $1 million USD per cohort vaccinated with PHiD-CV versus PCV13. With respect to the cost-utility and cost-effectiveness analyses, the PSA demonstrated that both vaccines had similar health effects, however, the difference of almost $1 million USD savings in direct medical costs with PHiD-CV versus PCV13 was shown to be robust.

These findings are consistent with those of other cost-effectiveness analyses conducted around the world, including Peru,[60] the Philippines,[61] Canada[12] and Europe,[12,62,63] which estimate that PHiD-CV is a dominant intervention when compared to PCV13. However, the previous cost-effectiveness analysis conducted by Pugh et al. 2019, which compared the cost-effectiveness of these PCVs for Algeria and Tunisia, reported that PCV13 versus no vaccination was more cost-effective when compared to PHiD-CV versus no vaccination.[13]

While many of the parameters used for this analysis were taken from Pugh et al. 2019, there are key differences in considerations between these studies that may have led to the conclusions of Pugh et al. 2019 being different to those reported in the current study. Namely, Pugh et al. 2019 calculated VE of both PCVs against IPD, pneumonia and AOM based on VE estimates from PCV7 clinical trial data, adjusted based on country-specific serotype coverage proportional to the additional serotypes covered by either PHiD-CV or PCV13. Therefore, cross-protection of PHiD-CV against serotypes included in PCV13 as reported across various real-world evidence studies was not accounted for.[13,49,55,58,59] Pugh et al. also assumed that PCV13 would provide serotype-specific VE against all-cause pneumonia, while various systematic reviews have concluded that all PCVs have similar effects against pneumonia cases.[13,26–28] Moreover, VE against AOM was estimated to be higher for PCV13 despite PHiD-CV containing protein D of NTHi, the second most prevalent agent of AOM worldwide.[64] Finally, Pugh et al. 2019 assumed indirect effects

of vaccination with PCV13 based on those observed in the US, with no indirect effects assumed for PHiD-CV.[13] Given the differences in the features of the PCV programs between the US and Tunisia, this assumption may not be adequate.

However, several limitations must be addressed when interpreting these results of the current study. Firstly, while local data were used wherever possible, the information required for some variables was not available for Tunisia. As a consequence, some data from other countries had to be used to calibrate the model. Secondly, this study used the vaccine costs provided by the 2020 PAHO Revolving Fund as they were publicly available. As Tunisia is not a part of PAHO, the actual vaccine costs of PHiD-CV and PCV13 may differ from what is reported here. Lastly, this model did not account for herd effects. While such data are available for other countries, due to the differences in many aspects of the PCV vaccination program of Tunisia, the epidemiologic and intervention scenarios between countries were not considered comparable. Therefore, the benefit of both PCVs in terms of reducing pneumococcal and NTHi-related diseases and the cost-effectiveness of these interventions may be underestimated in this analysis.

Finally, although this analysis of pneumococcal vaccines for Tunisia demonstrated a good economic profile for the country, authorities have to consider these data alongside data on affordability, budget impact, fairness, feasibility and other important criteria for the local context.

Conclusions

The results of this study predict that PCVs are a very cost-effective strategy to relieve the epidemiological and economic burden associated with pneumococcal and NTHi diseases in Tunisia. Furthermore, PHiD-CV is more likely to be the dominant intervention, with similar health gains at a reduced net cost, when compared to PCV13.

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Author's contributions

Substantial contributions to study conception and design: YL, MTS, JG; substantial contributions to analysis and interpretation of the data: YL, MTS, JG; drafting the article or revising it critically for important intellectual content: YL, MTS, JG; final approval of the version of the article to be published: YL, MTS, JG.

Disclosure statement

YL and **JG** are employees of the GSK group of companies and hold GSK shares. **MTS** reports personal fees from GSK during the conduct of this study.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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