


A Cost-Effectiveness Analysis of the 10-Valent Pneumococcal Non-Typeable *Haemophilus influenzae* Protein D Conjugate Vaccine (PHiD-CV) Compared to the 13-Valent Pneumococcal Conjugate Vaccine (PCV13) for Universal Mass Vaccination Implementation in New Zealand

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Abstract

Objectives Invasive pneumococcal disease (IPD), pneumonia and acute otitis media (AOM) still represent a significant medical burden in children < 5 years of age in New Zealand (NZ), with marked disparities across socioeconomic and ethnic groups. This cost-effectiveness evaluation aims to compare the potential impact of two childhood universal immunisation strategies: vaccination with a 3 + 1 schedule of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix*, GSK) and the 13-valent pneumococcal conjugate vaccine (PCV13, *Prevenar 13*, Pfizer).

Methods A static Markov-process cohort model was used to simulate the epidemiological and economic burden of pneumococcal diseases on a single-birth cohort over its lifetime. Costs and outcomes were discounted annually at

3.5%. Epidemiological and cost inputs were extracted from the most recently available NZ data, or derived from the most relevant reference countries' sources. The most updated evidence on the efficacies of the corresponding vaccines were used, particularly the significant effectiveness for PHiD-CV against IPD caused by serotype 19A.

Results The model estimated that both vaccines have a broadly comparable impact on IPD-related diseases and pneumonia. Due to the additional benefits possible through broader impact on AOM, PHiD-CV is estimated to potentially provide additional discounted cost offsets of approximately NZD 0.8 million over the lifetime of the birth cohort.

Conclusions To ensure health equity in children, given the substantial burden of pneumonia and AOM, decision-makers should also take into account the impact of PCVs on these diseases for decisions relating to routine infant immunization.

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Key Points for Decision Makers

Recently published evidence from well-designed studies in countries around the world that have used PHiD-CV in their national immunisation programmes point to a significant level of protection against invasive pneumococcal diseases caused by pneumococcal serotype 19A. Real-world evidence also points to protection against serotype 6A.

In light of the updated real-world evidence, both higher-valent pneumococcal conjugate vaccines (PHiD-CV and PCV13) were estimated to offer equivalent protection for infants against invasive pneumococcal diseases in New Zealand, in line with the findings by independent reviews conducted by PAHO and IVAC.

When considering the additional protection potentially offered by PHiD-CV against middle-ear disease caused by non-typeable *Haemophilus Influenzae*, PHiD-CV was estimated to produce greater health benefits while also being the less costly option compared to PCV13, assuming equivalent acquisition costs.

1 Introduction

Streptococcus pneumoniae (*Spn*) is a leading cause of acute otitis media (AOM), invasive pneumococcal disease (IPD) and pneumonia in children. Despite substantial reductions in IPD and pneumonia since the introduction of pneumococcal conjugate vaccines (PCVs), almost half a million deaths in children < 5 years old are still estimated to occur annually worldwide [1].

Spn may cause meningitis and bacteraemia, especially in children < 2 years of age, and is often the cause of bacteraemia with no obvious primary site of infection [2]. In New Zealand (NZ), IPD had a case-fatality ratio of 1.96% in the < 5-years age group in 2014 [3].

Otitis media (OM) is one of the most common disorders requiring medical care for children [4]. *Spn*, non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* are considered the major causative pathogens responsible for OM. In NZ children < 36 months of age who underwent ventilation tube (grommet) surgery, NTHi was detected in 43.5% of the middle ear fluid samples of cases with recurrent AOM and OM with effusion (OME) and *Spn* was detected in 23% [4]. OM can be debilitating and, if untreated, can impact hearing and result in significant

delays in learning and development [5, 6]. Prevention and prompt treatment of OM may help improve health equity. An analysis of NZ hospital admissions between 2000 and 2007 showed that children living in areas of higher socio-economic deprivation had twice the number of OM hospitalisations compared with children living in areas with the lowest socio-economic deprivation [7]. Furthermore, Maori and Pacific Island children with OM are less likely to have important surgical interventions, such as grommets [7, 8] and hence more likely to develop long-term sequelae.

Pacific children also had the highest childhood pneumonia rates, at 797 hospitalisations/100,000, which was 3.1 times higher than the rate in children of European descent [9]. The inequality in childhood pneumonia mortality also mirrored the hospitalisation rates. Socio-economic inequalities were even more marked with a clear trend of higher mortality with increasing socio-economic deprivation [9].

Since June 2008, vaccination with four doses of PCV has been fully funded in NZ for previously unvaccinated individuals up to the age of 59 months. The 7-valent PCV (PCV7, *Prevenar*, Pfizer) was the first conjugate vaccine funded in NZ. The 10-valent pneumococcal NTHi protein D conjugate vaccine (PHiD-CV, *Synflorix*, GSK) replaced PCV7 in October 2011. The 13-valent PCV (PCV13, *Prevenar 13*, Pfizer) replaced PHiD-CV from October 2014 onwards [10] and the latter replaced the former from July 2017 [11].

PCVs have had a significant impact on IPD in NZ. In children < 5 years of age, the rate of IPD due to the 10 serotypes included in PHiD-CV decreased by 95.6% (from 44.2/100,000 to 1.9/100,000 population from 2006 to 2014) [3]. The overall rate of IPD, irrespective of serotype, decreased by 66.7% (53.5–17.8/100,000) over the same period [3]. Due to the indirect effects of routine infant PCV immunisation, there have also been 60 and 70% reductions in IPD due to PHiD-CV serotypes in the 5–64-years and ≥ 65 -years age groups, respectively, between 2006 and 2014 [3].

The objective of this cost-effectiveness evaluation is to estimate and compare the potential impact of two childhood universal immunisation strategies in NZ: routine vaccination of infants with a 3 + 1 schedule of PHiD-CV or PCV13 (Fig. 1).

2 Methods

2.1 Model Description

A previously published static Markov cohort model [12] (Fig. 2) implemented in Microsoft Office Excel (2007) was adapted to estimate and compare the accumulated

Relevance of This Study

What is the context?

Streptococcus pneumoniae (*Spn*) is a leading cause of acute otitis media (AOM, defined as an infection and inflammation of the middle ear), invasive pneumococcal disease (IPD, defined as an infection confirmed by the isolation of *Spn* from a normally sterile site like blood or cerebrospinal fluid) and pneumonia in children. Despite the introduction of Pneumococcal Conjugate Vaccines (PCVs) in 2008 in New Zealand, these diseases continue to represent a significant burden in children <5 years of age; especially in those from socio-economically deprived households or ethnicities.

All wild strains of *Spn* have a thick, mucous-like polysaccharide capsule, primarily to protect the bacteria from the host's immune system. To date, 90 distinct capsular types (or serotypes) have been described for *Spn*; some of which are related to each other based on immune response system. For e.g., serotypes designated as 9A, 9L, 9N and 9V form one such group, 6A and 6B another, 19F and 19A yet another, etc. Conjugate vaccines work by attaching a polysaccharide which elicits a poor immune system response to another protein which elicits a much stronger response.

Two higher-valent PCVs (which contain more than seven serotype-specific polysaccharides of *Spn*) are available currently: the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix*, GSK) and the 13-valent PCV (PCV13, *Prevenar 13*, Pfizer).

What is new?

Updated evidence from studies around the world (especially around protection against serotype *Spn* 19A for PHiD-CV) was incorporated in a health-economic model to estimate the cost-effectiveness of PHiD-CV compared to PCV13.

The model estimated that the impact of PHiD-CV and PCV13 was broadly similar for IPD and pneumonia. However, PHiD-CV was projected to have a greater impact on AOM-related outcomes due to the potential to provide additional protection against AOM caused by non-typeable *H. influenzae*. At price-parity between the vaccines, PHiD-CV is expected to provide cost savings of approximately New Zealand Dollars (NZD) 0.8 million over the lifetime of a single birth cohort.

What is the impact?

Given the substantial burden of pneumonia and AOM in children, decision-makers should also take the impact of vaccination on these diseases into account when choosing a PCV for routine infant immunization in order to ensure health equity.

Fig. 1 Relevance of this study

outcomes of a single-birth cohort over a lifetime, using a monthly time-cycle, under two steady-state scenarios in the base-case: vaccinated with a 3 + 1 schedule (defined as a one primary dose each at months 2, 3 and 5 and a booster dose at 15 months of age) of either PHiD-CV or PCV13. The model structure and underlying assumptions were further validated using an expert panel (Leuven, September 2013). In the base-case, costs (from a payer perspective) and outcomes were discounted at 3.5% as per the NZ Pharmaceutical Management Agency (PHARMAC) cost-utility guidelines [13].

2.2 Demographics and Epidemiology

The size of the 2014 birth cohort for NZ (57,242) and age-specific overall mortality rates were obtained from national databases [14, 15].

Age-specific incidence rates of IPD were obtained from the annual Institute of Environmental Science and Research Ltd (ESR) surveillance report for 2014—the most recently available report for NZ (Supplementary Table 1) [3]. Cases of empyema, pneumonia, bacteraemia and other IPD were grouped as 'other IPD'. The age-specific serotype distribution of IPD cases was sourced from the 2014

ESR annual report (Supplementary Table 2) [3]. Age-specific case-fatality ratios (CFR) were calculated from the same report [3].

For IPD meningitis, the proportions of neurological sequelae and severe hearing loss were estimated based on Morrow et al. [16]. Due to lack of specific epidemiological data on sequelae following other IPD, no sequelae were assumed for these cases.

All-cause pneumonia hospitalisation rates (Supplementary Table 1) were taken from Milne and Vander Hoorn for children ≤ 5 years as the rates were presented by single-year age groups [7]. For children > 5 years, data were obtained from the publicly funded hospital discharges from July 2012 to June 2013 data for ICD-10 codes J12-J18 (the most recent data available) [17]. Age-specific CFRs were based on reported deaths in 2012 for ICD-10 codes J12-J18 [18]. General practitioner (GP) consultations were estimated as a ratio of 1:1 to hospitalisations based on the observations recorded in the UK using Hospital Episode Statistics (HES) database for 2013–2014 [19] as well as a cross-sectional analysis of the Medical Expenditure Panel Survey (MEPS) database between 2007 and 2011 in the USA [20].

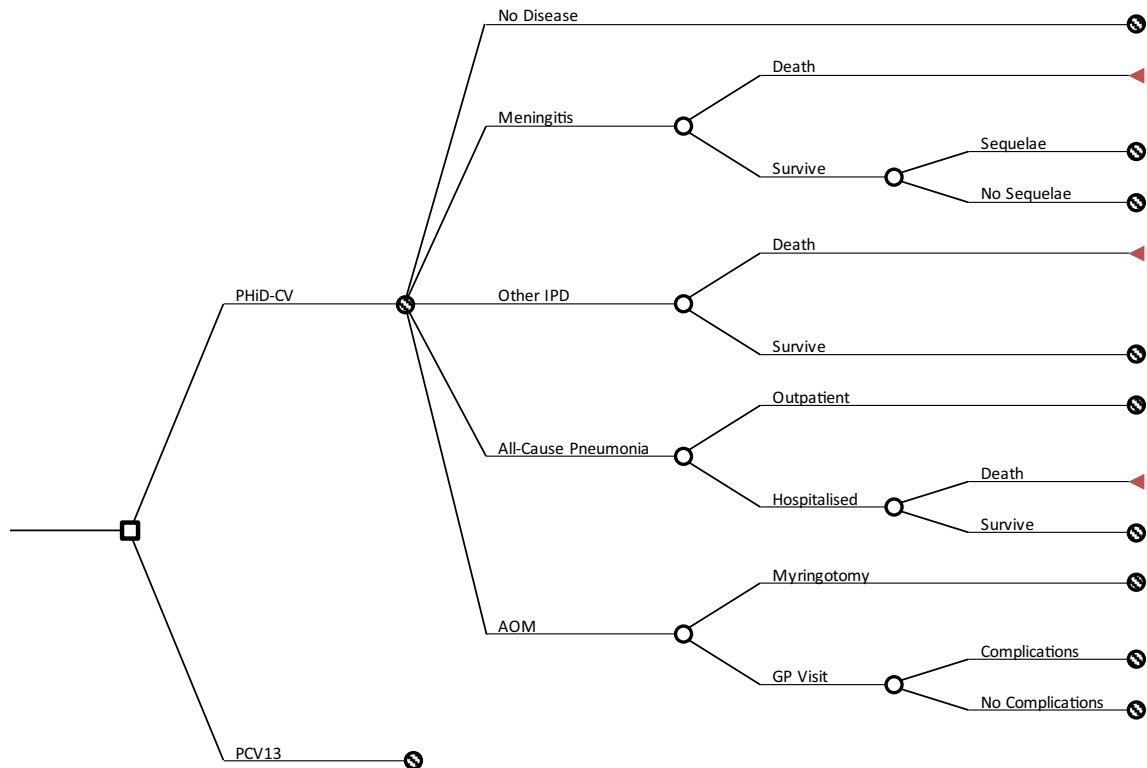


Fig. 2 Model structure. AOM acute otitis media, IPD invasive pneumococcal disease, PCV13 13-valent Pneumococcal conjugate vaccine, PHiD-CV 10-valent pneumococcal non-typeable

Haemophilus influenzae protein D conjugate vaccine, Other IPD empyema, pneumonia, bacteraemia without focus and other IPD

AOM incidence rates (Supplementary Table 1) in primary-care settings for the < 5-years age group were sourced from Gribben et al. [21]. Since NZ-specific data for children ≥ 5 years were not available, GP consultation rates from the UK were used [22]. It was assumed that there were no AOM consultations beyond the age of 14 years. The number of myringotomy procedures performed in NZ was obtained from the publicly-funded hospital discharges and procedures database of the Ministry of Health (MoH) using ICD-10 code 309 [17]. For the proportion of AOM cases with complications, hospital discharges for ICD-10 codes H65 (Non-suppurative otitis media) and H66 (Suppurative and unspecified otitis media) were used [17].

2.3 Vaccine Effectiveness

The model assumed that vaccine efficacy (VE) increased with the increasing number of doses until the maximum efficacy was achieved after the booster dose based on the observed effectiveness values observed with PCV7 [23]. The model assumed that protection persisted up to 3 years of age for the 3 + 1 regimen. A long-term efficacy study for the 9-valent PCV conducted in South African children observed that VE against vaccine-serotype IPD following

6.16 years of follow-up persisted in HIV non-infected children (77.8% compared to 83% after 2.3 years of follow-up) [24]. Additionally, a meta-regression analysis of PCV VE against nasopharyngeal carriage (NPC) estimated a 23.6% reduction in VE against carriage of PCV7 serotypes 5 years following the completion of vaccination [25]. Based on these evidences, VE in the current model was assumed to, conservatively, decline exponentially up to the age of 10 years.

2.4 IPD Effectiveness

The overall effectiveness of each vaccine against IPD is a function of the age-specific serotype distribution and the serotype-specific efficacy (Table 1). A post-marketing matched case-control study demonstrated that PCV7, on average, was 94.7% effective against vaccine serotypes while also offering significant protection of 76% (95% confidential interval [CI]: 39–90) against serotype 6A [23]. Both PHiD-CV and PCV13 were licensed based on non-inferiority immunogenicity trials versus PCV7 [26–28], so serotype-specific efficacy of both against IPD caused by the seven common serotypes contained in all three vaccines, and the three additional common to both PHiD-CV and PCV13 were assumed to be 94.7%.

Table 1 Vaccine efficacy estimates for IPD and AOM

Spn serotypes	IPD Vaccine efficacy		AOM causative agent distribution (%)	AOM vaccine efficacy	
	PHiD-CV (%)	PCV13 (%)		PHiD-CV (%)	PCV13 (%)
VT	94.7 [23]	94.7 [23]	64.3 ^a [47]	69.9 [44]	69.9 [44]
1					
4					
5					
6B					
7F					
9V					
14					
18C					
19F					
23F					
3	0.0	26.0 [29]	4.0 ^a [47]	0.0	19.2
6A	76.0 [23]	94.7 [23]	7.3 ^a [47]	29.0 [44]	69.9 [44]
19A	71.3 [38]	94.7 [23]	6.6 ^a [47]	29.0 [44]	69.9 [44]
Other NVT	0.0	0.0	17.8 ^a [47]	– 33.0 [48]	– 33.0 [48]
Spn			35.9	43.4	49.4
NTHi			32.3 [51]	21.5 [44]	0.0
Others			31.8	0.0	0.0
Total				22.5	18.0

^aValues are reported as a proportion of Spn AOM

AOM acute otitis media, IPD invasive pneumococcal disease, NTHi non-typeable *Haemophilus influenzae*, NVT non-vaccine type, PCV13 13-valent pneumococcal conjugate vaccine, PHiD-CV 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, Spn *Streptococcus pneumoniae*, VT vaccine-type

Despite the introduction of PCV13 into many national immunisation programmes (NIP) for several years, there is a wide range of estimated effectiveness against IPD caused by serotype 3 [29–35]. We assumed a 26% base-case efficacy for PCV13 in the model [29] while assessing values of 0% and 79.5% in the sensitivity analysis [34].

2.5 Protection Against 6A and 19A for PHiD-CV

Despite both PCV7 and PHiD-CV containing serotype 19F, Poolman et al. observed that PHiD-CV induced higher levels of functional antibodies against 19F and 19A than PCV7. They postulated that the processes (reductive amination vs. cyanylation) used to conjugate the polysaccharides to the corresponding vaccine carrier proteins could possibly explain the variation in immunological responses [36]. Effectiveness studies performed in various countries point to significant protection for PHiD-CV against IPD caused by 6A and 19A. A matched case–control study performed in Brazil following the introduction of PHiD-CV into the NIP showed an effectiveness of 82% (95% CI 10.7–96.4) against 19A IPD [37]. Verani et al. estimated an effectiveness of 71.3% (95% CI 16.6–90.1) [38] using the

indirect cohort method on the same Brazilian data. These results from Brazil have been corroborated by additional studies from Canada, 71% (95% CI 24–89) [39], and Finland, 62% (95% CI 20–85) [40]. As the average value of the effectiveness results fell close to the estimate obtained by Verani et al., we assumed an effectiveness of 71.3% for PHiD-CV against 19A IPD.

For 6A IPD, a value of 76% was used based on the efficacy estimated for PCV7 [23].

2.6 All-Cause Pneumonia Effectiveness

The model uses VE against WHO-defined X-Ray confirmed Community-Acquired Pneumonia (WHO-CAP) as a surrogate measure of efficacy against hospitalised pneumonia. VEs of PCVs against WHO-CAP and suspected-CAP have been assessed in several large-scale, randomised trials [41–44]. Despite differences in study design, setting and vaccine formulation, efficacies were between 20–35 and 6–8%, for WHO-CAP and suspected-CAP, respectively.

A recent systematic review on the effectiveness of PHiD-CV and PCV13 on hospitalisations due to

pneumonia in Latin American and Caribbean countries found no evidence of the superiority of one vaccine over the other in children < 5 years old [45]. In the absence of PCV13-specific pneumonia VE clinical trials in children, estimates of 21.8% (95% CI 7.7–33.7) for inpatient pneumonia and 8.7% (95% CI 3.8–13.4) for outpatient pneumonia were used for both vaccines based on the Clinical Otitis Media and Pneumonia Study (COMPAS, NCT00466947) [44].

2.7 AOM Effectiveness

VE against AOM is estimated based on the corresponding efficacies against pneumococcal vaccine serotypes, non-vaccine serotypes and AOM caused by *NTHi* (Table 1).

The model assumed that 35.9% of the AOM cases were attributable to *Spn* and 32.3% to *NTHi* [46]. The percentage of *Spn* AOM cases caused by vaccine serotypes is assumed to be 78.2% (assuming protection against 6A and 19A) [47].

VE against clinically-confirmed AOM (C-AOM) was obtained from COMPAS [44]: 69.9% (95% CI 29.8–87.1) against vaccine-type serotypes and 29.9% (95% CI – 123.7 to 77.5) against cross-reactive serotypes. A – 33% (95%

CI – 80 to 1) efficacy was assumed for non-vaccine serotypes to account for serotype replacement [48].

Although the COMPAS trial was not powered to provide conclusive evidence for PHiD-CV efficacy against *NTHi* AOM, the positive point estimate of 21.5% (95% CI – 43.4 to 57) [44] is consistent with the statistically significant efficacy observed with the predecessor protein D conjugate formulation in the Pneumococcal Otitis Efficacy Trial (POET) study (35.3%; 95% CI 1.8–57.4) [49].

Black et al. reported an efficacy of 20.1% in preventing myringotomies and an efficacy of 7.0% in preventing AOM for PCV7 [50], implying that PCV7 was 2.87 times more effective at preventing myringotomy than AOM episodes. This ratio was used to estimate the reduction in myringotomy for each vaccine.

2.8 Herd Effects

Pneumococcal vaccination has been consistently followed by significant decreases in both vaccine-type (VT) carriage and VT-IPD in unvaccinated groups [52]. However, the benefits from reduction in VT-disease also have to be considered in the context of serotype replacement.

Jokinen et al. showed that in the Finnish Invasive Pneumococcal disease (FinIP) vaccine trial, PHiD-CV

Table 2 Utility estimates

Short-term disutilities (per event)	QALY losses	Elicitation method; country
IPD meningitis [60]	0.0232	Chained Standard Gamble; USA
Other IPD [60]	0.0079	
All-cause pneumonia (hospitalised) [61]	0.0060	SF-36 and QWB index; USA
All-cause pneumonia (outpatient) [61]	0.0040	
AOM GP consultations [62]	0.0050	Visual analogue scale; Canada
AOM myringotomy ^a	0.0050	
AOM complications ^b [62]	0.0093	
Long-term disutilities (per year)		
Neurological sequelae from meningitis [16]	0.4000	No information available
Hearing loss from meningitis [63]	0.2000	Meta-analysis of QoL studies from various countries using different instruments
Meningitis long-term sequelae (children)	0.2690	Estimated based on the proportion of hearing loss to neurological sequelae following meningitis as described by Morrow et al. [16] and the corresponding disutilities presented above
Meningitis long-term sequelae (adults)	0.2857	

^aAssumed to be the same as AOM requiring GP visit

^bAssumed to be the same as AOM with first treatment failure in the reference

AOM acute otitis media, GP general practitioner, IPD invasive pneumococcal disease, QoL quality of life, QALY quality-adjusted life-year, QWB Quality of Well-being index, SF-36 36-Item Short Form Survey

Table 3 Direct and indirect costs

Costs (in NZD)	Direct costs (per event)	Indirect costs (per event)
IPD meningitis	7180.42	532.86
Other IPD	8256.40	694.19
All-cause pneumonia (hospitalised)	4853.41	465.74
All-cause pneumonia (outpatient)	300.00	232.87
AOM GP consultations	75.00	54.02
AOM myringotomy	1536.07	109.07
AOM complications	2140.47	167.50
Long-term meningitis sequelae (net present value)	21,330.83 ^a	2160.65 ^a

AOM acute otitis media, GP general practitioner, IPD invasive pneumococcal disease, NZD New Zealand dollars

^aPer year

demonstrated an efficacy against VT-NPC of 29% (95% CI 6–47) in the siblings (aged 3–7 years) of the vaccinated children [53]. A population-based observational study in Finland also reported a 48% (95% CI 18–69) reduction in IPD among unvaccinated children aged 2–5 years with PHiD-CV [40]. Additionally, surveillance data from a number of countries using PHiD-CV clearly demonstrate VT herd effects in all age groups of older adults following the introduction of childhood vaccination programmes [54–56].

Given the complexity of accurately predicting the extent of herd protection, in the base-case analysis no indirect effect was applied, whereas net indirect effect was applied only to IPD in a scenario analysis. In the steady state, an indirect protection (corrected for serotype replacement) of 30% for PHiD-CV and 32% for PCV13 [57] was assumed.

2.9 Quality of Life

Normative utility values for the whole population were based on EQ-5D index value for NZ [58]. Annualised disutility values reported in a UK cost-effectiveness analysis of PCV7 based on several reported studies were used in the model (Table 2) [59].

2.10 Costs

All costs are expressed in 2015 NZ Dollars (NZD).

In line with the PHARMAC guidelines for pharmacoeconomic analysis [13] and the cost resource manual [64], hospital inpatient costs were estimated using Diagnostic Related Group (DRG) prices. For each DRG code, the corresponding inlier multiday weight was obtained from the weighted inlier separations dataset for 2015/16 published by the MoH [65]. The PHARMAC cost resource manual for 2015 states a unit price of NZD 4751.58 [64]. Data on the discharges for each DRG code for 2012/13 were obtained from the MoH. The weighted average costs

for each health state was subsequently estimated (Table 3 and Supplementary Table 3).

IPD and pneumonia outpatient costs are assumed to be NZD 300 each (initial outpatient physician consultation costs for 2015) while AOM GP visits are assumed to cost NZD 75 [64]. An AOM or pneumonia event is assumed to require one consultation only.

Milne et al. estimated the long-term costs associated with survivors of paediatric pneumococcal meningitis who had severe disability [66]. The net present value (NPV) longitudinal cost (inflated to 2015 NZD) from 12 months to 64 years of age was obtained from the total of age-specific disability funding discounted annually at 3.5%. An age-independent annual cost was calculated by estimating the yearly payments that would result in the same NPV after 65 years discounted at 3.5% (assuming an annuity costing methodology). The estimated annual cost was NZD 21,331 (Supplementary Table 4).

Price-parity per dose is assumed for PHiD-CV and PCV13 with an administration cost (per dose) of NZD 22.93 [64]. While the vaccine price chosen for each vaccine will significantly affect the outcomes and acknowledging that the final price in an NZ universal mass vaccination setting is a result of a complex tendering process, price-parity was assumed to focus on the clinical differences between both vaccines.

Both vaccines are considered to have an acceptable safety profile and serious adverse events (SAE) are estimated to be rare [67, 68]. Hence, we have not considered the impact of SAEs in our analysis.

Indirect costs are considered in a scenario analysis. The 2015 median income data was obtained from the NZ statistics website [69]. It was assumed that only 20–49-year-olds will be affected in terms of indirect costs and the average of the median monthly income is estimated (NZD 3286). It was further assumed that the time taken off work is equal to the average length of stay (ALoS) for the

outcome as obtained from the NZ MoH weighted inlier separations dataset for 2015/2016 (Table 3) [65].

2.11 Sensitivity Analyses

A one-way sensitivity analysis was performed to explore the individual impact of uncertainties in model parameters on the model results. The sensitivity analysis was performed using pre-defined ranges or published 95% CI values for each parameter (Supplementary Table 5). A multivariate sensitivity analysis was also performed using a Monte Carlo simulation over 1000 iterations and the results are presented on the cost-effectiveness plane.

3 Results

3.1 Base-Case

The model estimated that the impact of PHiD-CV and PCV13 was broadly similar for meningitis, other IPD and all-cause pneumonia in the base-case analysis (Table 4).

However, PHiD-CV was projected to have a more pronounced impact than PCV13 on AOM-related outcomes by preventing over 3600 incremental AOM-related cases. This resulted in an incremental AOM-related savings of over NZD 1 million and overall savings of NZD 0.8 million from a payer perspective. Assuming price-parity, PHiD-CV dominated PCV13.

3.2 Herd-Effect Impact

Assuming a net indirect effect of PHiD-CV and PCV13 of 30% and 32%, respectively, on IPD across all age-groups, PHiD-CV dominated PCV13. PCV13, compared to PHiD-CV, prevented 2.0, 17.8 and 0.5 cases of IPD meningitis, other IPD and meningitis sequelae, respectively (Table 4). The disproportionate impact on other IPD can be explained by the fact that the incidence in the > 65-year-old population is 24 times higher than IPD meningitis. Overall, the use of PHiD-CV would still result in 11.6 quality-adjusted life-years (QALYs) gained and cost savings of NZD 721,478 compared to PCV13 (discounted) (Table 4).

Table 4 Lifetime model outcomes

	Direct effects only (base-case)			Direct and herd effects		
	PCV13 (3 + 1)	PHiD-CV (3 + 1)	Difference	PCV13 (3 + 1)	PHiD-CV (3 + 1)	Difference
Cases of IPD meningitis	42.8	44.0	1.1	27.8	29.9	2.0
Cases of other IPD	702.1	705.5	3.5	473.1	490.9	17.8
Cases of all-cause pneumonia	76,299.7	76,299.6	- 0.1	76,312.7	76,311.8	- 0.9
Cases of AOM	121,499.8	117,868.8	- 3631.0	121,500.2	117,869.2	- 3631.0
Cases of meningitis sequelae	15.5	15.7	0.2	10.3	10.8	0.5
Deaths from IPD	4188.6	4188.6	0.1	4174.6	4175.5	0.9
Total LYs gained (undiscounted)	5340,808.8	5340,802.9	- 5.9	5341,143.5	5341,116.7	- 26.8
Total LYs gained (discounted)	1,591,621.7	1,591,620.1	- 1.6	1,591,656.2	1,591,652.5	- 3.8
Total QALYs gained (undiscounted)	4,332,135.9	4,332,143.5	7.6	4,332,447.7	4,332,435.9	- 11.8
Total QALYs gained (discounted)	1,378,211.2	1,378,225.2	14.1	1,378,249.9	1,378,261.5	11.6
IPD meningitis cost	307,649	315,596	7947	199,832	214,519	14,686
IPD meningitis sequelae cost	14,354,448	14,824,108	469,660	9,211,354	10,002,473	791,119
Other IPD cost	5,796,591	5,825,127	28,536	3,906,196	4,052,897	146,701
All-cause pneumonia cost	195,975,919	195,975,705	- 214	196,009,413	196,007,106	- 2307
AOM cost	24,191,518	23,136,727	- 1,054,791	24,191,607	23,136,809	- 1,054,798
Total direct costs (undiscounted)	257,110,757	256,561,897	- 548,860	250,003,035	249,898,436	- 104,599
Total direct costs (discounted)	65,774,152	64,977,560	- 796,592	64,572,348	63,850,870	- 721,478
Indirect costs (undiscounted)	21,118,443	20,930,110	- 188,333	20,660,675	20,501,021	- 159,654
Indirect costs (discounted)	9,368,651	9,172,732	- 195,918	9,267,461	9,077,917	- 189,544

AOM acute otitis media, GP general practitioner, IPD invasive pneumococcal disease, LY life year, NZD New Zealand dollars, PCV13 13-valent Pneumococcal conjugate vaccine, PHiD-CV 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine, QALY quality-adjusted life-year

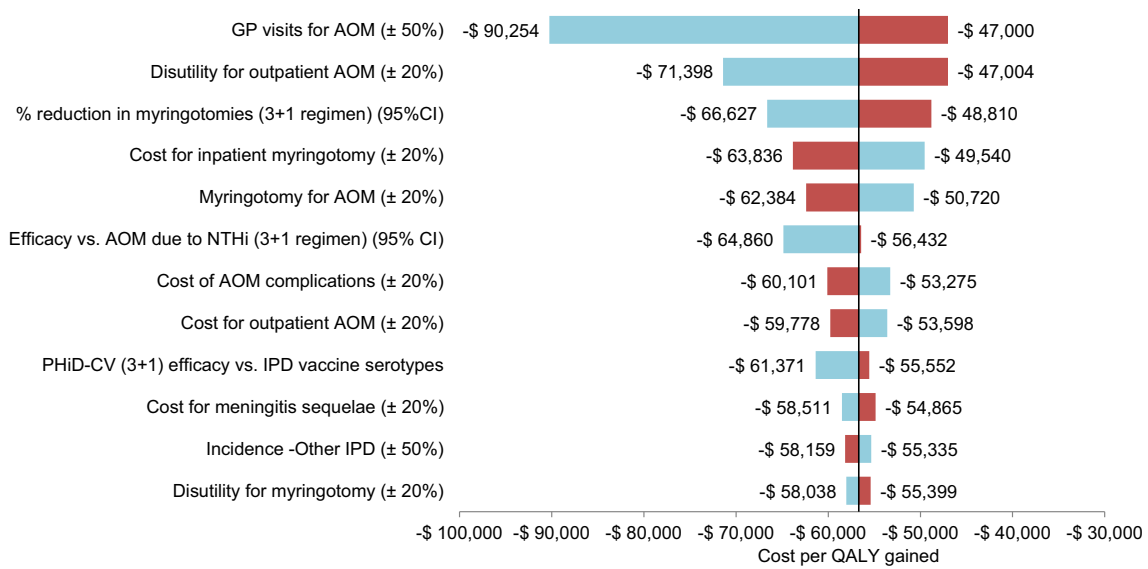
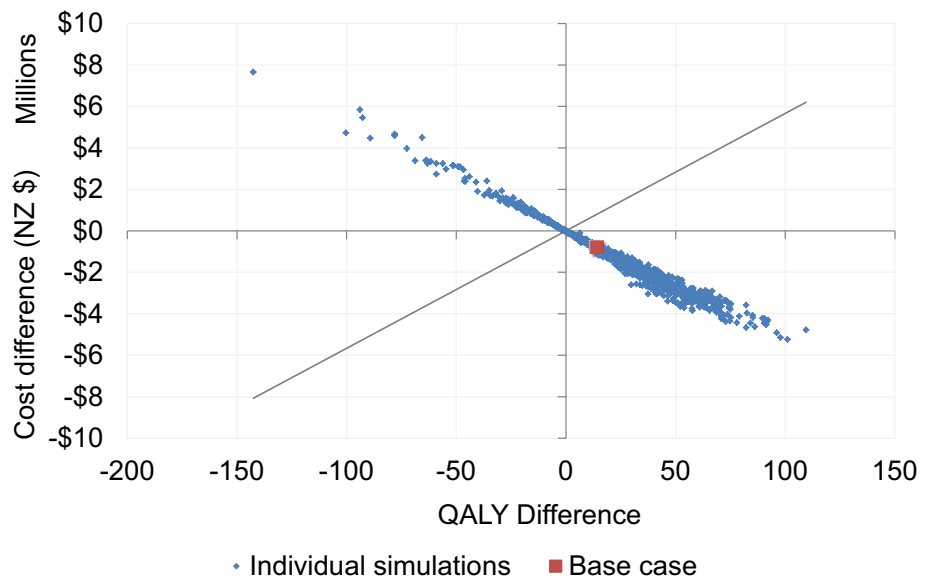


Fig. 3 One-way sensitivity analysis results. Red bars denote the change from the baseline ICER when the upper limit of the parameter is used in the analysis and the blue bars when the lower limit of the parameter is used. AOM acute otitis media, CI confidence interval, ICER Incremental Cost-Effectiveness Ratio, IPD invasive

pneumococcal disease, GP general practitioner, NTHi non-typeable *Haemophilus influenzae*, PHiD-CV 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, QALY quality-adjusted life-year

Fig. 4 Probabilistic sensitivity analysis (PSA). NZD New Zealand dollars, QALY quality-adjusted life-year. Blue markers represent individual probabilistic simulations; the red marker represents the base-case estimate; and the grey line represents a hypothetical threshold for the maximum willingness-to-pay of NZD 56,637 (2016 1xGDP per capita) for illustrative purposes (since PHARMAC does not use a cost-effectiveness threshold for decision-making)



3.3 Indirect Costs Impact

The inclusion of indirect costs into the base-case analysis results in incremental (discounted) cost savings of NZD 992,510 for PHiD-CV over PCV13 (Table 4).

3.4 Sensitivity Analysis

The results of the one-way sensitivity analysis (ranges presented in Supplementary Table 3) (assuming no net

indirect effect) are presented in Fig. 3. The key differentiators for PHiD-CV over PCV13, namely those relating to AOM, are the major drivers of the results.

The results of the probabilistic sensitivity analysis (PSA) are presented in Fig. 4. PHiD-CV dominated PCV13 in 80.5% of the 1000 runs, while being dominated by PCV13 in 18.8% of the simulations.

4 Discussion

Our analysis estimated a similar impact of PHiD-CV and PCV13 against IPD and all-cause pneumonia in the base-case analysis. PHiD-CV was, however, projected to result in cost-savings from a payer-perspective of approximately NZD 0.8 million over PCV13 by preventing over 3600 incremental AOM-related cases.

For this economic assessment comparing PHiD-CV with PCV13 in NZ, we incorporated the most robust clinical trial data available and supplemented data gaps with real-world effectiveness data. Model inputs regarding VE have been validated through expert reviews and advisory boards and are based on studies of PCV7 [23, 48], PHiD-CV [40, 44] and its precursor [49]. All epidemiological and cost inputs are either direct extracts of the most recently available NZ data, or derived from the most relevant source in reference countries (usually the UK).

Since price-parity was assumed, in an effort to focus on the clinical differences between the two vaccines, along with no change in the schedule, the model outcome is highly dependent on the specifics of VE attributed to each vaccine. While the simplest expectation that differences in VE would correspond to the serotype coverage of each vaccine, the available data indicate the reality is more complex.

For the ten common serotypes, both vaccines are considered to be more or less equal, but for the three additional serotypes it is important to look at the available effectiveness data for both vaccines. There is still no conclusive evidence that PCV13 prevents IPD caused by serotype 3 [29–33, 35]. For 19A, full (94.7%) efficacy is assumed for PCV13 despite observed evidence of a lower protection compared to other vaccine types [29, 34, 70–72]. Early economic assessments assumed little or no cross-reactivity by PHiD-CV for 19A; however, recent data strongly support the basis for the inclusion of protection [37–40]. These studies were considered robust enough for the European Medicines Agency (EMA) and NZ Medicines and Medical Devices Safety Authority (Medsafe) to update the PHiD-CV summary of product characteristics (SmPC) in Europe and the product data sheet, respectively, to include protection against 19A [73, 74]. Furthermore, a recent systematic review of PCV effectiveness in children < 5 years of age in Latin America and the Caribbean concluded that both vaccines offered similar protection not just for pneumonia, but also for IPD [45].

However, substantial differences exist between these two vaccines for the prevention of AOM. The efficacy of PCV7 against AOM in the Finnish Otitis Media (FinOM) study [48] was much lower than that of the PHiD-CV precursor in the POET study [49] (7 vs. 34%), and the

recent COMPAS trial demonstrated a 19% efficacy against clinical AOM for PHiD-CV [44]. While these trials are not directly comparable, PHiD-CV would be expected to have a greater impact on AOM due to its novel protein D carrier by providing the opportunity to reduce the two leading causes of OM, *Spn* and *NTHi* [75, 76]. The positive point estimate of PHiD-CV efficacy against *NTHi* observed in COMPAS (22%; 95% CI – 43 to 57) [44] and the significant efficacy observed with the 11-valent vaccine formulation in POET (35%; 95% CI 2–57) [49] are in stark contrast with the negative estimates observed for non-protein D containing PCVs [48, 77]. While the vaccine formulations used in the POET and COMPAS trials are different, Schuerman et al. observed that antibody responses against protein D for the 11-valent Pneumococcal Protein D (11Pn-PD) conjugate vaccine formulation were in the same range as those measured with the 10-valent PHiD-CV vaccine [78]. Given the burden of AOM in NZ, it is not surprising that this difference in vaccine effectiveness weighs heavily on the results.

The current comparison indicates that there are simultaneous cost and QALY benefits to be expected with PHiD-CV use over PCV13. There are a small number of IPD cases (and even smaller numbers of sequelae and deaths) potentially saved through PCV13 use; however, the large reductions in AOM-related events with PHiD-CV use are expected to result in costs and QALY benefits. These benefits were observed over all the scenarios tested in the one-way sensitivity analysis. These reductions in AOM are particularly relevant given the disproportionate burden of disease afflicting Maori and Pacific Island children in NZ [7, 8]. Recurrent OM can also potentially lead to hearing impairment if left untreated and has been associated with social and developmental problems [5, 6, 79] and the use of PHiD-CV over PCV13 could, potentially, help address the health equity gap in NZ.

Some limitations in the analysis proposed here need to be highlighted. Dynamic transmission models to assess the impact of vaccination against pneumococcal disease have the benefit of incorporating the indirect benefits of vaccination as well as more accurately modelling the dynamic nature of the disease [80–82]. The choice of a static cohort model for our analysis was driven by factors such as simplicity of modelling and its accessibility despite being non-optimal for dealing with the dynamic nature of pneumococcal diseases and the temporal impact of the vaccine in the overall population. While NZ-specific hospitalization data are available for IPD, pneumonia and AOM over the period of PCV usage [17], such observational data are prone to a variety of biases given the complex nature of pneumococcal diseases, the lack of detailed reporting and the change of PCVs every 3-year period [83]. We, thus, used data obtained from randomised trials and other

robustly designed studies in a prospective static model to estimate the comparative life-time benefits of either vaccine for a single birth cohort.

Given the disproportionate burden of IPD in Maori and Pacific Islander children the use of aggregated cost and epidemiological data for the analysis, may not be able to estimate the value of either vaccine in these groups. A further detailed analysis using patient-level data and vaccine impact across various ethnic or income groups will be consequently necessary.

We estimated the herd effect in a static model using a fixed approach. There are currently not enough data available on PCVs to estimate when a steady-state is expected to be reached in a population and what the net effect could be over time. IPD serotype replacement has been observed in various countries that have implemented mass-vaccination with PCVs—the extent of which in both the vaccinated and unvaccinated vary considerably across studies [84]. Given the limitations of observational studies, it is not possible to predict accurately how much of the variance in the effect can be attributed to true differences or to surveillance artefacts. Our analysis has not taken into account this phenomenon but since we expect a similar level of serotype replacement to occur for both higher-valent vaccines, the impact of serotype replacement on the incremental effects is expected to be small.

Surveillance reports of IPD during periods of use of PHiD-CV in various countries have shown that IPD caused by 19A has not decreased in line with the protection estimated from well-designed studies [55, 85]. The exact reasons for this contrast are not exactly known, but it is important to note that the analysis of secular trends from surveillance reports may be biased by differences in the ascertainment of disease, changes in diagnostic criteria and other confounding factors. A similar phenomenon can be observed in Australia where PCV13 replaced PCV7 in the NIP in 2011. While a significant drop of 61% was seen in 19A cases in children < 5 years of age (from 7.05/100,000 in 2011 to 2.76/100,000 in 2012), 19A continues to cause IPD in this age group with approximately 30 cases annually [86]. Reports from the UK and Ireland, both of which have used PCV13 over a long period of time, have also observed similar trends [87, 88]. To account for the potential variability in the effectiveness of PHiD-CV against 19A IPD, the 95% CI estimated by Verani et al. (16.6–90.1) were used in the sensitivity analysis. Owing to the relatively low incidence of 19A in NZ, PHiD-CV still came out as the dominant option compared to PCV13.

Robust evidence on the protection conferred by PHiD-CV against *NTHi* AOM is sparse. However, the available evidence points to a protective effect [44, 49, 75, 76, 89]. In a study that looked at NPC and middle-ear discharge (ED) microbiology in indigenous Australian children

vaccinated with PCVs, the prevalence of *NTHi*-infected ED was lower in PHiD-CV vaccinated children (34%) compared to PCV7 vaccinated children (61%) [89]. Concurrently, there was no substantial difference in the NPC of children vaccinated with PCV7 compared to PHiD-CV [89]. The authors hypothesised that vaccine-induced immune responses could deliver protection in the middle ear where the numbers of organisms were likely to be lower, without eliminating NPC [89]. A follow-up study in the same population following a switch from PHiD-CV to PCV13 showed that while children vaccinated with PCV13 had significantly lower carriage of combined *Spn* and *NTHi*, there was no change in disease severity or OM prevalence. In non-mixed PCV schedules, children receiving PCV13 had lower *NTHi* carriage as well. An analysis of ED swabs, however, showed a higher prevalence of middle ear co-infection with *NTHi* and *Spn* in children vaccinated with PCV13 compared to PHiD-CV [90]. Further studies are required to robustly estimate the effect of PHiD-CV on *NTHi* AOM.

5 Conclusion

In our analysis both vaccines are predicted to provide a broadly comparable impact on IPD-related diseases and pneumonia. Importantly, due to the additional benefits possible through a broader impact on AOM, PHiD-CV is estimated to potentially provide additional cost offsets of approximately NZD 0.8 million over the lifetime of a single birth cohort at equal vaccine acquisition costs. The results of this analysis have been reflected in PHARMAC's decision to replace PCV13 with PHiD-CV in 2017 [11].

Direct comparison of the antigenic content of PHiD-CV and PCV13 should not be used on its own to differentiate the potential benefits of the two vaccines. While PCV13 contains antigens for an additional three *Spn* serotypes, the incremental value of serotype 3 is unclear for PCV13 and significant cross-reactive protection for PHiD-CV against 6A [40] and 19A [37–40] has been demonstrated.

OM is a significant driver of healthcare costs, and is responsible for approximately 70% of the net present lifetime cost of PCV-preventable diseases in children [7, 21, 66]. PHiD-CV has the potential to provide protection against AOM caused by *NTHi* [44, 49]. A vaccine with the potential for dual protection against both *Spn* and *NTHi* could offer substantially greater benefits than a vaccine covering *Spn* only [91]. Importantly, vaccination against key otopathogens is not only expected to reduce the burden of OM [92], but preventing OM in the first year of life is likely to have the greatest impact as these early episodes are more likely to lead to recurrence [93].

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Data Availability Statement Data that are detailed in the methods or in the supplementary material can be found in the list of references contained in the manuscript.

Author Contributions All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. BM, LT and XHZ conceived and designed the study. The data were acquired and analysed by all authors. All authors participated in the development of this manuscript and gave final approval before submission.

Compliance with Ethical Standards

Conflict of interest All authors are employees of the GSK group of companies. BM and XHZ hold shares in the GSK group of companies. GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and agreed with the submission of the publication.

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