Cost-effectiveness of pneumococcal conjugate vaccination in Georgia

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ABSTRACT

Objective: Financial support from the Global Alliance for Vaccines and Immunization (GAVI) to introduce the 10-valent pneumococcal conjugate vaccine (PCV10) into the routine childhood immunization schedule in Georgia is ending in 2015. As a result, the Interagency Coordination Committee (ICC) decided to carry out a cost-effectiveness analysis to gather additional evidence to advocate for an appropriate evidence-based decision after GAVI support is over. The study also aimed to strengthen national capacity to conduct cost-effectiveness studies, and to introduce economic evaluations into Georgia's decision-making process.

Methodology: A multidisciplinary team of national experts led by a member of the ICC carried out the analysis that compared two scenarios: introducing PCV10 vs. no vaccination. The TRIVAC model was used to evaluate 10 cohorts of children over the period 2014-2033. National data was used to inform demographics, disease burden, vaccine coverage, health service utilization, and costs. Evidence from clinical trials and the scientific literature was used to estimate the impact of the vaccine. A 3+0 schedule and a vaccine price increasing to US\$ 3.50 per dose was assumed for the base-case scenario. Alternative univariate and multivariate scenarios were evaluated.

Results: Over the 10-year period, PCV10 was estimated to prevent 7,170 (8,288 undiscounted) outpatient visits due to all-cause acute otitis media, 5,325 (6,154 undiscounted) admissions due to all-cause pneumonia, 87 (100 undiscounted) admissions due to pneumococcal meningitis, and 508 (588 undiscounted) admissions due to pneumococcal non-pneumonia and non-meningitis (NPNM). In addition, the vaccine was estimated to prevent 41 (48 undiscounted) deaths. This is equivalent to approximately 5 deaths and 700 admissions prevented each year in Georgia. Over the 10-year period, PCV10 would cost the government approximately US\$ 4.4 million (\$440,000 per year). However, about half of this would be offset by the treatment costs prevented. The discounted cost-effectiveness ratio was estimated to be US\$ 1,599 per DALY averted with scenarios ranging from US\$ 286 to US\$ 7,787.

Discussion: This study led to better multi-sectoral collaboration and improved national capacity to perform economic evaluations. Routine infant vaccination against *S. Pneumoniae* would be highly cost-effective in Georgia. The decision to introduce PCV10 was already made some time before the study was initiated but it provided important economic evidence in support of that decision. There are several uncertainties around many of the parameters used, but a multivariate scenario analysis with several conservative assumptions (including no

herd effect in older individuals) shows that this recommendation is robust. This study supports the decision to introduce PCV10 in Georgia.

Keywords: Georgia, cost-effectiveness analysis, Pneumococcal conjugate vaccine, decision-making process, evidence-based medicine

1. Introduction

Georgia has faced civil conflicts and economic and social decline since it gained independence from the Soviet Union in 1991. However, over the past decade, the socio-economic situation has improved due to substantial economic and social reforms. While economic growth was adversely affected by the August 2008 conflict, growth rebounded again in 2010 and the World Bank now classifies Georgia as a lower middle-income country. Similarly, over the last 10 years (2002-2012) the infant mortality rate was cut by nearly half, dropping from 20.1 to 10.8 deaths per 1,000 live births, according to national health statistics, and from 23.6 to 12.6 deaths per 1,000 live births, according to vital statistics.

Among the main causes of infant deaths are diseases of the respiratory system, certain conditions originating in the perinatal period, infectious and parasitic diseases, congenital malformations, and external causes such as accidents, injuries, and poisoning. The highest proportion of child morbidity is related to respiratory system diseases. Two efficacious and safe pneumococcal conjugate vaccines (PCV) are currently available to help reduce mortality and morbidity due to pneumonia, meningitis, and other invasive diseases caused by *Streptococcus pneumoniae* (Spn). Both vaccines can currently be procured with the financial support of the Global Alliance for Vaccines and Immunization (GAVI), but the support ends December 2015 and the government will then bear the total cost of the program. Georgia had planned to introduce the 10-valent pneumococcal conjugate vaccine (PCV10) in 2013 but due

to healthcare system reorganization and the late introduction of a rotavirus vaccination (RV), a decision was made to postpone introducing PCV until 2014. Therefore, in consultation with the World Health Organization (WHO) Regional Office for Europe, the Interagency Coordination Committee (ICC), which is the national advisory committee on immunization, decided to conduct a cost-effectiveness analysis (CEA) on the introduction of PCV10 with support from the ProVac International Working Group (IWG). The aim of the study was to inform the government about the economic and epidemiological impact of introducing PCV10. A multidisciplinary team of national experts from several organizations (including and led by a member of the ICC), was established and met regularly to collect and review the best available national data. The team conducted the CEA to evaluate whether or not introduction of PCV10 would be cost-effective compared to no introduction, and through this process, to decide whether or not to advocate for an appropriate evidence-based decision after GAVI support has ended.

2. Methods

The ProVac Initiative was begun in the Americas by the Pan American Health Organization (PAHO) and during a two-year pilot phase, it was expanded to other regions through the ProVac IWG. [1]. Georgia was supported by the Agence de Médecine Préventive (AMP), an implementing partner of the ProVac IWG, in collaboration with WHO Europe. The TRIVAC decision support model, version 2.0, was used. This is an internationally recognized transparent Excel®-based model, described in detail elsewhere [2]. The parameters of the model required collection of data that included demography, burden of disease, health services utilization and costs, vaccine coverage, vaccine efficacy, and vaccination program costs.

2.1 Analytic framework

The analysis evaluated the costs and benefits of two alternative situations: (1) universal introduction of the PCV10 vaccination into the Georgian National Immunization Program and (2) no PCV vaccination. Ten consecutive birth cohorts were modeled over the period 2014- 2023. Following WHO recommendations, a 3% discount rate was used for both costs and health outcomes [3]. We assumed that PCV10 would be administered in three primary doses without a booster dose (3p+0). Realistic estimates of vaccination coverage and timeliness were based on estimates available for DTP vaccination. Four clinical outcomes related to *Streptococcus pneumoniae* were included: (1) outpatient visits due to all-cause acute otitis media (AOM), (2) inpatient admissions due to all-cause pneumonia, (3) inpatient admissions due to pneumococcal meningitis, and (4) inpatient admissions due to pneumococcal non-pneumonia non-meningitis (NPNM) invasive disease. It was the opinion of expert members of the team, in conjunction with a consensus among public health experts and pediatricians, that all cases of severe pneumonia, pneumococcal meningitis and pneumococcal NPNM would be admitted to a hospital in Georgia; as a result, it was practical and reasonable to focus on admissions rather than all cases in the community. A government perspective was taken, so no household costs were considered. In Georgia, the majority of providers are private and costs of treatment are partly or fully covered by the government. Three types of providers were taken into account: primary care providers (private individual entrepreneurs, who receive salaries from government), secondary care (polyclinics), and tertiary care (hospitals). All three providers handle outpatient visits for AOM, but only hospitals (tertiary care) handle inpatient admissions for invasive pneumococcal disease.

2.2 Demography

The National Statistics Office of Georgia (Geostat) provided all demographic data. The number of births for 2012 was 56,890. In the base-case scenario, a declining trend (based

on the projection of the United Nations Population Division [UNPOP]) was applied to this figure to estimate the number of births in future years. To take into consideration the uncertainty around the assumption of a declining population, a second scenario with no year-over-year trend was also evaluated. Estimates on mortality rates for infants and children younger than 5 years of age were provided by the National Centre for Disease Control and Public Health (NCDC). In 2012, 14 of every 1,000 live births died before the age of 1; 16 of every 1,000 live births died before the age of 5. The life expectancy for those born in 2012 was assumed to be 75. This was used to estimate the number of life-years lost and disability-adjusted life-years (DALY) due to mortality related to *Streptococcus pneumoniae*. The UNPOP projections for Georgia were applied to these estimates to generate a projection for the period 2014-2023 [3].

2.3 Burden of disease

Data concerning AOM and pneumonia were based on national statistical reports published in the statistical yearbook 2012. Two types of reports were available to estimate AOM incidence; therefore, two estimates of incidences were calculated. Both report types gather data from health facilities based on the International Classification of Diseases (ICD) 10th revision codes. However, one is from the Tbilisi-level case-based reporting system and the other one is from the national reporting system of notifiable diseases. These two reporting systems were used to estimate a Tbilisi annual incidence of 1,695 cases of AOM per 100,000 under 5 years old and a national annual incidence of 3,073 per 100,000 under 5 years. The more conservative Tbilisi incidence was used in the base-case analysis; the national incidence was used in the scenario analysis. The national-level reporting was sufficient to estimate the incidence of pneumonia admissions, 1,603 per 100,000 under 5 years old. For pneumococcal meningitis and pneumococcal NPNM, no national data were available; instead, WHO 2008

estimates for Georgia were used [4], with annual incidences, respectively, of 10 and 62 per 100,000 under 5 years.

Data on the number of pneumonia deaths was based on the national reporting system. A case fatality ratio (CFR) was calculated by dividing the number of pneumonia deaths by the estimated number of pneumonia admissions. The CFR of 25% for pneumococcal meningitis was based on estimates from sentinel surveillance for bacterial meningitis. The CFR for pneumococcal NPNM was based on the WHO estimate for Georgia. No national data were available on the proportion of children with long-term sequelae following meningitis; instead, global estimates from Edmond et al. were used [5]. In order to estimate DALYs, each syndrome was assigned a disability weight provided by the WHO global burden of disease (GBD) [4]. The age distribution of pneumococcal disease was based on estimates for Europe by Sanderson et al. [14] and mean duration of illness was estimated after consulting national experts.

2.4 Health services cost related to Streptococcus pneumoniae (Spn)

Only government expenditures were taken into consideration. Based on data from Ministry of Health (MoH) state health programs, the weighted average cost of a visit for AOM was equivalent to US\$ 11.84. This sum was calculated from two costs: professional services and lab exams. In addition, the costs of AOM-related visits were inflated to reflect the fact that some of the AOM cases are indeed hospitalized and incur substantial cost. The visit cost was assumed to be equal for all three types of providers. According to the MoH, the cost of one hospital admission for pneumonia was estimated at US\$ 301.18, for pneumococcal meningitis at US\$ 494.12, and for pneumococcal NPNM at US\$ 800.00. Sequelae costs borne by the government were not considered due to lack of data.

2.5 Vaccine coverage, efficacy, and other impact assumptions

Coverage of PCV1 over the 2014-2023 period was assumed to be 67%, 75%, 87%, 90%, 94%, 96%, and 98% thereafter. This was based on data on DTP immunization coverage for 2013 obtained from the national immunization reporting system and provided by the NCDC immunization department. Rotavirus vaccine coverage was used to inform the estimates of PCV coverage in the first few years, as this vaccine was introduced relatively recently. Estimated coverage of DTP doses 1, 2, and 3 was used as a proxy for the expected drop-out rate between PCV doses 1, 2, and 3. The timeliness of PCV doses 1, 2, and 3 was based on estimates for the European region by Clark and Sanderson [14].

Two studies were considered for PCV10 vaccine efficacy against all-cause AOM. One was from Czech and Slovak Republic [6]; the second was a study nested [7] within a recent clinical trial from Finland [8]. The evidence from the study in the Czech and Slovak Republic, 33.6% (20.8%; 44.3%), was assumed for the base case. For efficacy against all-cause pneumonia, 26.2% efficacy was assumed based on a meta-analysis of the fraction of radiological pneumonia (proxy for pneumonia admissions) prevented in clinical trials in California, the Philippines, and South Africa [4]. The estimate from the Gambian trial was much higher than in the other three trials and since it was not considered relevant to the Georgian context, it was excluded. For pneumococcal meningitis and NPNM, we used 81% vaccine efficacy based on the Cochrane review [9] and we considered the uncertainty around these estimates in the scenario analysis.

There is a good deal of uncertainty around assumptions for herd effects, serotype replacement, waning vaccine-induced protection, and relative coverage (i.e., the extent to which high-risk children are covered by the vaccine). We therefore varied these assumptions in scenario analyses to assess their influence on the cost-effectiveness result. For the base case, we assumed 95% relative coverage by dividing DTP2 coverage in the poorest quintile

by DTP2 coverage in the entire birth cohort. Overall program coverage was then multiplied by 95% to provide a more realistic estimate of coverage for children at the highest risk of mortality from invasive pneumococcal disease. The 95% value was based on estimates from Demographic and Health Surveys (DHS) in other middle-income countries [15]. We assumed that the direct effectiveness in children younger than 5 could be multiplied by 120% to reflect the observed herd effect in this age group with PCV7 in the USA [10]. We did not consider herd effects in older age groups. Waning vaccine-induced protection and type replacement were assumed to be 5% and 5.5% per year, respectively, but these were both varied in scenario analyses.

2.6 Vaccination program cost

To estimate the price of the vaccine and injection supplies, we used NCDC data and the country GAVI proposal for introducing PCV. In the base-case scenario we used a per-dose vaccine price of US\$ 3.50, which was then adjusted for the initial years because national co-financing is progressive (see Table 4). The additional freight cost was taken at 5% of the vaccine price. Based on the NCDC data, the wastage rate for the two-dose vaccine presentation was assumed to be 10%. Prices for safety boxes and administering syringes were also considered.

The incremental system cost per dose for introducing PCV vaccine was estimated based on the country comprehensive multi-year plan (cMYP) 2010-2015. The per-dose spending was estimated to be US\$ 0.63. For the first year of introduction, the team calculated the difference between expected costs in 2012 and in 2013; the only difference between these two years was the expected introduction of PCV10. This cost was divided by the number of doses (with a 3+0 schedule) expected in the first year of introduction. Using this data, we

estimated the operational cost of the launch to be US\$ 1.06 in the first year and US\$ 0.60 in subsequent years.

2.7 Scenario analysis

A scenario analysis was performed to evaluate the uncertainty of results due to the shortage of reliable national data. The scenarios tested were: (1) high and low burden of disease (i.e., incidence and deaths), (2) no change in the number of births over time, (3) high and low vaccine efficacy, (4) waning vaccine-induced protection, (5) high and low health services costs (i.e., outpatients and inpatients), (6) no discount rate, (7) worst case (unfavorable for introduction), (8) best case (favorable for introduction), and (9) high and low coverage. We also considered a scenario in which no adjustment was made for herd effects or type replacement.

3. Results

3.1 Without vaccination

With no introduction of PCV10 over the period 2014-2023, we estimate 34,444 (39,838 undiscounted) outpatient visits due to all-cause AOM, 32,578 (37,680 undiscounted) admissions due to all-cause pneumonia, 213 (247 undiscounted) admissions due to pneumococcal meningitis, and 1,250 (1,446 undiscounted) admissions due to pneumococcal NPNM. In addition, there would be 4,744 discounted DALYs and US\$ 11.33 million discounted health service costs borne by the government.

3.2 With vaccination

Clinical benefits expected with the vaccination program for the ten cohorts are summarized in Table 6. In brief, over the period 2014-2023, PCV10 is estimated to prevent

7,170 (8,288 undiscounted) outpatient visits for all-cause AOM, 5,325 (6,154 undiscounted) admissions for all-cause pneumonia, 87 (100 undiscounted) admissions for pneumococcal meningitis and 508 (588 undiscounted) admissions for pneumococcal NPNM. In addition, the vaccine is estimated to prevent 41 (48 undiscounted) deaths. This is equivalent to preventing approximately 5 deaths and 700 admissions each year in Georgia.

Over the 10-year period, PCV10 would cost the government approximately US\$ 4.4 million (US\$ 440,000 per year). However, about half of this would be offset by averted treatment costs of approximately US\$ 2.14 million. (Of that figure, US\$ 1.6 million are averted treatment costs for pneumonia.) The net cost borne by government would be equal to US\$ 2.30 million. This amount is derived from the total cost of vaccination minus the savings from averted treatment (Table 8). The incremental cost-effectiveness ratio (i.e., the cost per DALY averted) from governmental perspective is equal to US\$ 1,599 per DALY averted. According to the WHO recommendation of using the gross domestic product (GDP) per capita as thresholds to interpret this ratio, the introduction of PCV in Georgia is highly cost-effective, which means that taking into account the end of GAVI's support, the intervention is still a valuable investment for the government [12].

All results of the scenario analysis are shown in Figure 1. Almost all are below the GDP per capita threshold (i.e., highly cost-effective). Even the worst-case scenario, which gathers unfavorable figures of several parameters, still results in a cost-effective intervention. Therefore, from the governmental perspective, the results of this analysis are robust.

4. Discussion

This study assessed the potential impact of introducing the vaccine in terms of health benefits, incremental costs to the immunization program, health system costs averted, and cost-effectiveness of the introduction of the pneumococcal vaccine. These criteria are all

relevant to the decision-making process in Georgia. This analysis shows that introduction of PCV10 is likely to be highly cost-effective in Georgia. It also provides evidence about the clinical and economical burden of the *Streptococcus pneumoniae* in Georgia, and about the benefit of introducing PCV10 to the national immunization program. The introduction of PCV10 is estimated to cost approximately US\$ 4-5 million over a decade, but about half this cost would be offset by savings from reduced hospital admissions and outpatient visits.

This cost-effectiveness analysis is the first country-led economic evaluation of a vaccine in Georgia. Utilization of a transparent model to perform the study made it possible to obtain useful evidence and multiple relevant results. The methodology used to collect data included several experts from different fields and was an effective way to produce a snapshot of the current economic and epidemiological burden associated with pneumococcal disease in Georgia.

However, the study faced some limitations. (1) Data on community pneumonia were not available, so no outpatient visits were assumed for pneumonia; this resulted in underestimating the burden of disease. (2) Only expert opinion was available for estimates of parameters such as duration of illness or health service utilization; because no local data were available for sequelae and associated costs, the benefits of vaccination were underestimated. (3) The societal perspective was not explored due to lack of available data and also due to the recent change in the health financing system. (4) Herd immunity effect among people older than 5 years old, especially elderly people, was not modeled although the herd effect is likely to have a significant impact on the cost-effectiveness and would make the result even more favorable. (5) Although global estimates used for incidence of pneumococcal meningitis and NPNM are reasonable placeholders, a good quality national source would be more appropriate.

Nonetheless, as much as possible, many of these limitations were evaluated in the scenario analyses and the fact that the vaccine remained cost-effective despite very conservative assumptions (e.g., no herd effect in older individuals) suggests that the conclusion is robust. In addition, it should also be mentioned that AOM inclusion would improve CE ratio further.

Other benefits of the national study included the identification of important gaps in national data, such as health service utilization and costs, and the increased capacity of the national team to conduct economic evaluations in the future.

5. Conclusion

The decision to introduce PCV10 was already made some time before the study was initiated but this study provides important economic evidence in support of that decision. Not only is it highly cost-effective, it is also likely to prevent approximately 5 child deaths and a substantial number of hospital admissions annually. This analysis also created the opportunity to identify some gaps in national data, especially on health care utilization, for which we relied mainly on expert opinion. It is important to work on the collection of these data. This analysis was a good capacity building process and led to better understanding of cost-effectiveness, better multi-sectorial collaboration and an improved national capacity to perform the economic evaluations. In conclusion, it would be interesting to extend this type of evaluation to other health interventions in order to compare their cost-effectiveness and provide a new source of information for decision-makers.

Conflict of interest

Authors declare no conflicts of interest for this work. The current manuscript was supported by the ProVac IWG, which is funded entirely by a grant from the Bill & Melinda Gates Foundation.

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Table 1. Input parameters for estimating disease burden

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1-59m:				
All-cause acute otitis media	1,695	1,695	3,073	National reporting system
All-cause pneumonia admissions	1,603	1,603	1,603	Estimate
Pneumococcal meningitis admissions	10.5	5.8	17.4	GBD 2000
Pneumococcal NPNM admissions	61.5	33.8	102.1	GBD 2000
% case fatality ratios (CFRs) in ages 1-59m:^a				
All-cause pneumonia admissions	0.20%	0.16%	0.24%	NCDC Georgia
Pneumococcal meningitis admissions	25.0%	12.96%	29.87%	Sentinel surveillance (NCDC Geo)
Pneumococcal NPNM admissions	2.6%	2.33%	5.14%	GBD 2000 (adjusted to 2014)
% sequelae in pneumococcal meningitis survivors				
% Major sequelae (single)	20.2%	-	-	Edmond 2010
% Major sequelae (multiple)	4.5%	-	-	Edmond 2010
Disability weight for DALY calculations				
All-cause acute otitis media	0.02	-	-	WHO GBD 1990
All-cause pneumonia admissions	0.28	-	-	WHO GBD 1990
Pneumococcal meningitis admissions	0.62	-	-	WHO GBD 1990
Pneumococcal NPNM admissions	0.28	-	-	Assumption (Griffiths PhD, page 107)
% Major sequelae (single)	0.24	-	-	Assumption (Griffiths PhD, page 107)
% Major sequelae (multiple)	0.63	-	-	Assumption (Griffiths PhD, page 107)
Mean duration of illness (in days)				
All-cause acute otitis media	6	-	-	Expert opinion (2)
All-cause pneumonia admissions	6	-	-	Expert opinion (2)
Pneumococcal meningitis admissions	10	-	-	Expert opinion (2)
Pneumococcal NPNM admissions	6	-	-	Expert opinion (2)
Age distribution of disease cases and deaths				
<3m:	9.4%	-	-	Sanderson 2013, WHO IVR Schedule Report
3-5m:	13.0%	-	-	Sanderson 2013, WHO IVR Schedule Report
6-8m:	13.3%	-	-	Sanderson 2013, WHO IVR Schedule Report
9-11m:	12.2%	-	-	Sanderson 2013, WHO IVR Schedule Report
12-23m:	32.5%	-	-	Sanderson 2013, WHO IVR Schedule Report
24-35m:	13.3%	-	-	Sanderson 2013, WHO IVR Schedule Report
36-47m:	4.7%	-	-	Sanderson 2013, WHO IVR Schedule Report
48-59m:	1.6%	-	-	Sanderson 2013, WHO IVR Schedule Report

^a In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in mortality under 5 years of age. This is done by assuming that the fraction of deaths under age 5 that are caused by the disease remains fixed over time.

Table 2. Input parameters for estimating health service utilisation and costs (all costs are presented in US \$) 2013

Parameter	Estimate	Scenarios		Source/s
		Low	High	
OUTPATIENT VISITS				
Government cost per outpatient visit ^a				
All-cause acute otitis media	\$12	\$9	\$14	MoH (mix of inpatient and outpatient)
INPATIENT ADMISSIONS				
Government cost per inpatient admission ^b				
All-cause pneumonia admissions	\$301	\$241	\$361	MoH
Pneumococcal meningitis admissions	\$494	\$395	\$593	MoH
Pneumococcal NPNM admissions	\$800	\$640	\$960	MoH

^a Government costs per outpatient visit for AOM included professional services and a lab exam. The costs of AOM visits were also inflated to account for some of these cases being hospitalized. Outpatient visits are distributed as follows: 50% polyclinic 10% hospital, 40% private individual entrepreneur (PIE). The cost presented is the weighted average of the provider-specific costs.

^b Government costs per inpatient admission include the cost per bed-day multiplied by the expected length of stay, the cost of disease-specific drugs and diagnostics. Inpatient admissions are 100% hospital.

Table 3. Input parameters for estimating PCV vaccine coverage and timeliness

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for PCV doses given with DTP1)				
3m	69.9%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
6m	86.4%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
9m	91.6%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
12m	93.9%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
24m	97.8%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
Coverage of DTP2 by age in year 2014 (proxy for PCV doses given with DTP2)				
3m	6.7%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
6m	70.5%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
9m	82.4%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
12m	87.0%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
24m	94.3%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
Coverage of DTP3 by age in year 2014 (proxy for PCV doses given with DTP3)				
3m	0.1%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
6m	41.4%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
9m	68.0%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
12m	78.9%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009
24m	91.4%	-	-	www.provac-olives.com , Clark and Sanderson Lancet 2009

Coverage projections over the period 2014-2023 were estimated by assuming that PCV will achieve the same coverage and timeliness as RV in the early period of introduction, and the same coverage as DTP thereafter.

Table 4. Input parameters for estimating PCV10 program costs

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine dose price projection				
2014	\$0.70	-	-	User override
2015	\$1.40	-	-	User override
2016	\$2.10	-	-	User override
2017	\$2.80	-	-	User override
2018	\$3.50	-	-	Model derived
2019	\$3.50	-	-	Model derived
2020	\$3.50	-	-	Model derived
2021	\$3.50	-	-	Model derived
2022	\$3.50	-	-	Model derived
2023	\$3.50	-	-	Model derived
Other vaccine dose costs				
International handling (% of vaccine price)	0.0%	-	-	
International delivery (% of vaccine price)	5.0%	-	-	Freight costs from GAVI proposal
Wastage (% of doses discarded, etc) ^a	10.0%	-	-	Estimate - measles vaccine
Safety box cost (80 syringes per box)				
Price of each safety box	\$0.55	-	-	NCDC Geo
International handling (% of vaccine price)	0.0%	-	-	
International delivery (% of vaccine price)	10.0%	-	-	Freight costs from GAVI proposal
Wastage (% of doses discarded, etc) ^a	5.0%	-	-	NCDC Geo
Incremental system costs of introduction ^b				
Incremental system cost per dose	\$0.63	-	-	Calculations based on cMYP Georgia 2010-2015

^a The % wastage is converted into a factor $[1 / (1 - \% \text{ wastage})]$ which is multiplied by the expected number of doses required to meet the anticipated level of coverage.

^b Estimated incremental system costs per-dose spending was estimated to be US\$ 0.63. The operational launch cost was estimated to be US\$ 1.06 in the first year, with costs of US\$ 0.60 thereafter

Table 5. Input parameters for estimating the health impact of PCV10

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine efficacy vs all-cause AOM outpatient visits				
Dose 1	17.0%	10.5%	34.0%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 2	30.9%	19.1%	44.3%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 3	33.6%	20.8%	44.3%	Prymula 2006, Czech & Slovak Reps.
Vaccine efficacy vs all-cause pneumonia admissions				
Dose 1	14.4%	14.4%	20.1%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 2	24.1%	24.1%	26.2%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 3	26.2%	19.0%	33.0%	O'Brien Lancet 2009 Web Appendix page 12 (meta analysis)
Vaccine efficacy vs vaccine type pneumococcal meningitis / NPNM				
Dose 1	41.0%	31.9%	69.2%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 2	74.5%	58.0%	90.0%	Mahon 2006 ratio (Mahon-20%, Whitney 2006 ratio)
Dose 3	81.0%	63.0%	90.0%	Lucero 2009, Gambia; SA; Philippines; USA (Nat.); USA (Cal.)
% vaccine serotype coverage				
Pneumococcal meningitis admissions	81.0%	78.0%	82.0%	Johnson, 2010
Pneumococcal NPNM admissions	81.0%	78.0%	82.0%	Johnson, 2010
Other vaccination impact assumptions				
% relative coverage ^a	95%	80%	100%	www.provac-olives.com
% decrease in dose efficacy per yr ^b	5.0%	0.0%	5.0%	Assumption
% contribution of herd effect in <5yrs ^c	120%	100%	120%	Reingold/CDC (based on PCV7)
Decline in vaccine type coverage / yr ^d	5.5%	0.0%	5.5%	Assumption

^a Relative coverage is the coverage of those at risk of getting the disease (i.e., effective coverage) compared to coverage of the entire birth cohort (i.e. overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

^b To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3m, 4-5m, 6-8m, 9-11m, 12-23m, 24-35m, 36-47m, 48-59m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

^c Rather than endogenous modeling of transmission dynamics, the % of direct protection for <5 yrs is multiplied by a herd effect multiplier (e.g., 120%) to give the % of total protection in the cohort of interest <5 yrs. This excludes any herd effect in individuals aged 5 yrs+ and is therefore very conservative.

^d Vaccine type disease replacement is handled by reducing the expected vaccine type coverage in successive vaccinated cohorts by a fixed % each year, thus reducing overall expected impact of the program in each successive vaccinated cohort by a similar amount. Thus, for a given vaccinated cohort, the % vaccine type coverage is equal to: $[T * (1-R) ^ N]$ where, T = % of disease caused by vaccine types in the year of vaccine introduction, R = % reduction in vaccine type coverage per year following vaccine introduction, and N = number in the sequence of vaccinated birth cohorts.

Table 6. Discounted health benefits (10 cohorts vaccinated over the period 2014-2023)

	No vaccine (Status quo)	PCV10 With vaccine	Averted
Total outpatient visits	34,444	27,274	7,170
All-cause acute otitis media	34,444	27,274	7,170
Total inpatient admissions	34,042	28,122	5,919
All-cause pneumonia admissions	32,578	27,253	5,325
Pneumococcal meningitis admissions	213	127	87
Pneumococcal NPNM admissions	1,250	742	508
Total deaths <5yrs	137	96	41
All-cause pneumonia admissions	59	50	10
Pneumococcal meningitis admissions	49	29	20
Pneumococcal NPNM admissions	29	17	12
Total children with permanent disability	41	24	17
Sequelae group A	33	20	14
Sequelae group B	7	4	3
DALYs Lost	4,744	3,305	1,438
YLDs - DALYs due to morbidity	666	458	208
YLLs - DALYs due to mortality	4,078	2,848	1,230

Health benefits are discounted at 3% per year

Table 7. Discounted economic benefits (10 cohorts vaccinated over the period 2014-2023)

	No vaccine (Status quo)	PCV10 With vaccine	Averted
TOTAL GOV. HEALTH SERVICE COSTS ^a	\$11,325,355	\$9,187,383	\$2,137,972
Total outpatient visit costs	\$407,915	\$323,006	\$84,909
All-cause acute otitis media	\$407,915	\$323,006	\$84,909
Total inpatient admission costs	\$10,917,440	\$8,864,377	\$2,053,063
All-cause pneumonia admissions	\$9,811,714	\$8,208,083	\$1,603,631
Pneumococcal meningitis admissions	\$105,341	\$62,524	\$42,817
Pneumococcal NPNM admissions	\$1,000,385	\$593,770	\$406,615

Costs are discounted at 3% per year

^a Government perspective includes bed days covered by the government and disease-specific diagnostic costs borne by the government at the following health providers: polyclinic, hospital and private individual entrepreneur (PIE).

Table 8. Discounted cost-effectiveness of PCV (10 cohorts vaccinated over the period 2014-2023)

	PCV10
	Government perspective
<i>Cost-effectiveness compared to no vaccine</i>	
Net cost of vaccine introduction	\$2,300,242
Costs of vaccine introduction	\$4,438,214
Health service costs avoided	\$2,137,972
DALYs averted	1,438
YLDs averted - DALYs due to morbidity	208
YLLs averted - DALYs due to mortality	1,230
US\$ per DALY averted	\$1,599
<i>Cost-effectiveness threshold</i>	
1 x GDP per capita (2012) - WHO threshold for 'highly cost-effective'	\$3,508
3 x GDP per capita (2012) - WHO threshold for 'cost-effective'	\$10,525

Costs and DALYs are discounted at 3% per year

Figure 1. US\$ per DALY averted for base case PCV10 scenario and alternative 'what-if' scenarios: Government perspective

- (1) Favorable scenario = High annual incidence rates, high CFRs, low vaccine price projections, low systems costs, high efficacy parameters, 0% waning in dose efficacy, high serotype coverage parameters, a 125% herd effect multiplier, a high vaccine coverage projection, high inpatient and outpatient costs.
- (2) Unfavorable scenario = Low annual incidence rates and CFRs, high vaccine price projections and system costs, low efficacy parameters, a 10% yearly waning in dose efficacy, low serotype coverage parameters, low vaccine coverage projections and low outpatient and inpatient costs.