Cost-Effectiveness Analysis of Pneumococcal Vaccination with the Pneumococcal Polysaccharide NTHi Protein D Conjugate Vaccine in the Philippines

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ABSTRACT

Objectives: To compare the cost-effectiveness of a universal mass vaccination (UMV) program with a 2 + 1 schedule of a 10-valent pneumococcal polysaccharide non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) against two strategies: 1) a no-vaccination strategy and 2) a pneumococcal 13-valent conjugate vaccine (PCV13) 2 + 1 strategy in the Philippines. Methods: A published Markov cohort model was adapted to simulate the epidemiological and economic burden of pneumococcal diseases (meningitis, bacteremia, pneumonia, and acute otitis media) within a projected birth cohort in 2012 of 1,812,137 newborns over lifetime. Analyses were conducted at an annual discount rate of 5% from the perspective of the Philippine government. The current evaluation was updated with the best available local/regional clinical epidemiological data and published efficacy evidence. Results: Compared with the no-vaccination strategy, the PHiD-CV 2 + 1 UMV program was projected to prevent 3,343 deaths due to invasive pneumococcal diseases and pneumonia and 326,862 cases of pneumococcal diseases, resulting in an incremental cost-effectiveness ratio of 50,913 pesos/quality-adjusted life-year gained, which was considered to be highly cost-effective according to the threshold recommended by the World Health Organization. In comparison with the PCV13 2 + 1 strategy, the PHiD-CV 2 + 1 strategy was estimated to have a substantial reduction in acute otitis media (127,680 cases) and therefore a cost saving of potential 92.5 million pesos assuming price parity between PHiD-CV and PCV13 (US $1 = 42.13 pesos in 2012). Conclusions: The PHiD-CV 2 + 1 UMV program is projected to be cost-effective, compared with no vaccination, and would provide substantial savings with higher quality-adjusted life-year gains as compared with the PCV13 2 + 1 strategy in the context of the Philippines.

Keywords: cost-effectiveness, PCV13, PHiD-CV, Philippines, vaccination.

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 Available online at www.sciencedirect.com

Background

The World Health Organization (WHO) estimated that 1.6 million people die every year from invasive pneumococcal diseases (IPDs), and an estimated 0.7 to 1 million of these are children younger than 5 years [3]. A study conducted in the Philippines showed that the peak incidence of IPDs is in children younger than 4 years. The same study estimated that one third of the children younger than 5 years with IPD would die [2].

Acute otitis media (AOM) is also a significant, although largely underestimated, public health burden among Filipino children. There is a paucity of good surveillance data regarding the extent of the burden of otitis media (OM) and/or AOM in Filipino children. A local study indicated that up to 25% of the children with pneumonia had concomitant OM [3]. In a recent national survey, the overall prevalence of clinically diagnosed AOM in children aged 0 to 12 years in the Philippines was estimated at 9.57%, with the 0 to 2 years age group having the most prevalent cases of AOM in the sample [4]. This prevalence rate is considered as high on the basis of the WHO classification for the prevalence of OM [5].

At present, two types of pneumococcal conjugate vaccines are available for use in children in the Philippines market. These are Synflorix™ (GlaxoSmithKline, Rixensart, Belgium), a pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) and Prevnar 13™ (Wyeth LCG, Madison, NJ, now part of Pfizer, Inc.), a pneumococcal 13-valent conjugate vaccine (PCV13). Both vaccines are licensed locally as a 2 + 1
scheme in the Philippines for the active immunization of infants and children aged 6 weeks to 5 years against disease caused by Streptococcus pneumoniae (including meningitis, sepsis, bacteremia, pneumonia, and AOM) [6,7]. In addition, PHID-CV is also licensed for use against OM caused by nontypeable Haemophilus influenzae (NTHi) and licensed for use in preterm infants [6].

Health economics has been increasingly incorporated into the comprehensive health technology assessment for formulary and vaccine policy decision making over the past decade. Published results from other countries might not be directly transferable because of the sensitivity of key local data inputs such as epidemiology, local treatment patterns, or prices [8].

The purpose of this study was to evaluate the epidemiological and economic consequences of pneumococcal conjugate vaccine(s) for a universal mass vaccination (UMV) program in addition to the current standard of care for pneumococcal diseases in the Philippines in 2012, using an adapted Markov cohort model. The two analyses presented in this article compared the cost-effectiveness of a UMV program with PHID-CV 2 + 1 versus no vaccination, and that of PHID-CV 2 + 1 versus PCV13, in the Philippines. The same model has been adapted for analyses in a number of different countries such as Norway and Sweden [9,10].

Methods

Markov Cohort Model

A published Markov cohort model was adapted to simulate the epidemiological burden of pneumococcal and NTHi-related diseases, including IPDs, community-acquired pneumonia (CAP), and AOM, within a projected registered live birth cohort of 1,812,137 newborns in the Philippines in 2012 [11,12]. Cohort-based analyses represent one of the most common forms of health economic modeling and are particularly useful for determining the direct effect of medical interventions [13].

In the Markov cohort model, the individuals of the birth cohort move between the Markov states, as shown in Figure 1, according to estimated transition probabilities derived from the published incidence rates, over a projection of lifetime horizon. The model has a number of mutually exclusive disease-related outcomes, including meningitis, bacteremia, CAP, AOM, no pneumococcal infection, and death. Costs and quality-adjusted life-year (QALY) specific to each health state were estimated and summarized over the cohort’s lifetime to calculate total accumulated costs and QALYs. The incremental cost and QALY gained of the two different strategies were computed as an incremental cost-effectiveness ratio (ICER) for each set of comparison (PHiD-CV vs. no vaccination; PHID-CV vs. PCV13). The WHO-recommended thresholds for ICER were adopted in the study: 1) cost-saving: if the strategy costs less and provides higher QALYs; 2) cost-effective: the ICER is below three times the gross domestic product (GDP) per capita of the country; 3) highly cost-effective: the ICER is below one time the GDP per capita of the country; and 4) not cost-effective: the ICER is more than three times the GDP per capita of the country (GDP per capita of the Philippines in 2011 = 103,366 pesos) [14]. It was assumed in the base-case scenario that 100% of the birth cohort would be vaccinated according to the 2 + 1 schedule (dose 1 at 6 weeks, dose 2 at 14 weeks, and dose 3 at 13 months). Finally, it was assumed that there was no herd effect for the UMV program of both vaccines in the base-case scenario.

Epidemiological Data

The birth cohort size of 2012 used in the analysis was 1,812,137, which was projected from the 2010 Field Health Service Information System report using a 1.9% population growth annually (National Statistics Office, Average population growth rate

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Fig. 1 – Markov cohort model design. The cohort model is Markov-based with three exclusive health states: no disease, sequelae, and death. The transition from “no disease” to “sequelae” or “death” is calculated on the basis of this decision tree. In the model, only meningitis can lead to long-term sequelae; meningitis and bacteremia include NTHi meningitis and NTHi bacteremia, respectively; and nonconsulting AOM are accounted for in the quality-of-life impact calculation. AOM, acute otitis media; GP, general practitioner; NTHi, nontypeable Haemophilus influenzae; PCP, primary care physician; PCV13, pneumococcal 13-valent conjugate vaccine; PHiD-CV, pneumococcal polysaccharide nontypeable Haemophilus influenzae protein D conjugate vaccine.
2000–2010, www.nscb.gov.ph) [11]. Age-specific annual incidence data and case-fatality ratios for each pneumococcal/NTHi disease were obtained from the published literature or national databases from the pre-PCV7 period [2,15]. Table 1 and Appendix Tables 1 to 4 (in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004) present epidemiological data for IPD, bacteremia and sepsis, all-cause pneumonia, and AOM [2,4,15–21, Marcelo MJ. Case Series Report on Otogenic Complications of Chronic Otitis Media. Philippine Children’s Medical Center, unpublished data, 2004]. Local data were used wherever available. For certain parameters without local data, data from neighboring country Malaysia with similar developing country status, similar seasons, and similar epidemiology data were revalidated by clinical experts and used for extrapolation of local data if deemed suitable. For the long-term sequelae data of invasive diseases, because of the lack of local or regional data, published data were used for extrapolations.

### Vaccine Efficacy Parameters

The model assumed the vaccine efficacy to increase with the increasing number of doses a child would receive, until maximal efficacy was achieved after the booster dose at month 13. The duration of protection was assumed to be 10 years for the 2 + 1 regimen, with the linear waning of efficacy assumed to start at the age of 2 years. Vaccine efficacy against IPD was calculated as a sum product using distribution of local serotypes (Appendix Figure. 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004) and serotype-specific efficacy of each vaccine (Appendix Table 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Philippines value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of birth cohort (2012 projected; cohort model)</td>
<td>1,812,137 [11]</td>
</tr>
</tbody>
</table>

#### Pneumococcal meningitis

1. Incidence rate < 5 y (per 100,000) | 18.3 [2]  
2. CFR < 5 y (%) | 30.8 [2]  
3. % cases with long-term sequelae < 5 y (%) | 11 [47]  

#### Bacteremia

1. Incidence rate < 5 y (per 100,000) | 14.06 (≤1 y); 7.03 (2–4 y) [2]  
2. CFR < 5 y (%) | 53.3 [2]  
3. % cases with long-term sequelae < 5 y (%) | 10 [47]  

#### All-cause pneumonia

1. Hospitalization rate < 5 y (per 100,000) | 7957 (<1 y) (Lucero MG, unpublished ARIVAC data, 2012); 5003 (1 year) (Lucero MG, unpublished ARIVAC data, 2012); 958 (2–4 y) [11,48,49]  
2. CFR < 5 y (%) | 6.4 [21]  
3. % cases with long-term sequelae < 5 y (%) | 10 [47]  

#### AOM

1. GP consultation rate < 5 y (per 100,000) | 98 (extrapolation based on expert opinion, 25% of the figure from the same age group [20])  
2. Total number of myringotomy procedures (per 100,000) | See Appendix, Figure. 1  

#### Note

See Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004.  
AOM, acute otitis media; ARIVAC, Acute Respiratory Infection Vaccine; CFR, case-fatality ratio; GP, general practitioner.
Table 2 – Vaccine-specific model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCV13 value</th>
<th>PHID-CV value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine efficacy against IPD</td>
<td>Serotype-specific efficacies were taken from a previous study of PCV7 efficacy [22]</td>
<td>Serotype-specific efficacies were taken from a previous study of PCV7 efficacy [22]</td>
</tr>
<tr>
<td>Vaccine efficacy against all-cause pneumonia</td>
<td>7.3% (assumed to be the same as PHID-CV, due to the lack of data)</td>
<td>7.3% [31]</td>
</tr>
<tr>
<td>Vaccine efficacy against AOM</td>
<td>23.4% (assumed to be the same as PHID-CV, due to the lack of data)</td>
<td>23.4% [31]</td>
</tr>
<tr>
<td>Vaccine efficacy against AOM due to S. pneumoniae vaccine serotypes</td>
<td>57.2% (95% CI 44%–67%) [38] (assumed to be the same as PCV7, due to the lack of data)</td>
<td>57.6% (95% CI 41.4%–69.3%) [37] (assumed to be the same as an earlier 11-valent formulation, supported by data from well-established animal models)</td>
</tr>
<tr>
<td>Serotype replacement for S. pneumoniae nonvaccine serotypes</td>
<td>−33.0% (−80.0%, 1.0%) [4,38]</td>
<td>−33.0% (−80.0%, 1.0%) [38]</td>
</tr>
<tr>
<td>Vaccine efficacy: reduction in AOM caused by NTHi</td>
<td>0</td>
<td>35.3% (95% CI 1.8%–57.4%) [37]</td>
</tr>
</tbody>
</table>

Note. See Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004.

AOM, acute otitis media; CI, confidence interval; GP, general practitioner; IPD, invasive pneumococcal disease; PCV13, pneumococcal 13-valent conjugate vaccine; PHID-CV, pneumococcal polysaccharide nontypeable Haemophilus influenzae protein D conjugate vaccine.

http://dx.doi.org/10.1016/j.vhri.2014.04.004). To date, the most robust data on serotype-specific efficacy are the PCV7 results reported by Whitney et al. [22]. To the best of our knowledge, so far there is no published meta-analysis comparing the efficacy of PHID-CV and PCV13. In addition, despite the fact that PHID-CV has been investigated in two large-scale randomized controlled trials (Clinical Otitis Media & Pneumonia Study and Finnish Invasive Pneumococcal disease trial), no published randomized controlled trial data are available for PCV13.

PHID-CV and PCV13 were assumed to have the same serotype efficacy as PCV7 for the seven serotypes covered by the latter. For the additional serotypes covered by PHID-CV (i.e., serotypes 1, 5, and 7F) or PCV13 (i.e., serotypes 1, 3, 5, 6A, 7F, and 19A), the average vaccine efficacy of PCV7 vaccine serotypes (e.g., 94.7%) was used as the default value (Table 2). Cross-protection for 6A (76%) and 19A (26%) were assumed on the basis of PCV7 vaccine efficacies. For PCV13 but not in PCV7. PCV13 appears ineffective against serotype 3” [29].

In the absence of PCV13-specific pneumonia vaccine efficacy estimates, the Clinical Otitis Media & Pneumonia Study efficacy estimates of 23.4% for inpatient pneumonia and 7.3% for outpatient pneumonia for PHID-CV were used for both PHID-CV and PCV13 vaccines [30]. Despite several pneumonia efficacy trials with vaccine formulations containing 7, 9, 10, and 11 serotypes [30–36], all the studies gave point efficacy estimates of between 20% and 35%, with no indication that vaccines with more serotypes provided greater protection against pneumonia. Vaccine efficacy against AOM was estimated on the basis of efficacy against pneumococcal vaccine serotypes and nonvaccine serotype disease and efficacy against disease caused by NTHi. For PHID-CV, the assumptions were based on the data reported in the Pneumococcal Otitis Efficacy Trial of an earlier 11-valent protein D-conjugate vaccine formulation in prevention of AOM caused by both S. pneumoniae and NTHi [37]. The assumptions of vaccine efficacy against AOM for PCV13 were based on an earlier randomized double-blinded, clinical trial for PCV7 [38].

Using the Philippines epidemiology data and vaccine effectiveness data, a maximal effectiveness was calculated for each vaccine using the following equation (Appendix Table 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004):

\[ V_{\text{max}} = V_{\text{EVT}} \times \% \text{ of AOM cases due to vaccine serotypes} + V_{\text{EVT}} \times \% \text{ of AOM cases due to nonvaccine serotypes} + V_{\text{NTHi}} \times \% \text{ of AOM cases due to NTHi} \]

The AOM complications ratio and the long-term sequelae rate were based on unpublished local data from tertiary hospital. It is important to note that in the base-case scenario, we have taken a more conservative stand to exclude the AOM complications and long-term sequelae from the analysis. In the sensitivity analysis, the AOM complications and long-term sequelae were included.

Health Outcomes

The current model was designed to estimate the overall impact of disease by considering QALY loss in both acute and long-term
sequelae. Because of the lack of relevant local data, disutility weights, as shown in Table 3, which had been used in other published PHiD-CV cost-effectiveness analyses, were used in the current analyses [12,39,40].

Resource Use and Costs
The cost analyses were conducted from the perspective of the Philippine government. Only direct medical costs (e.g., hospitalization, inpatient/outpatient diagnostic tests and procedures, medication/vaccine costs, and health care professionals’ fees) were included. In the model, we have conservatively applied the same price of 800 pesos (US $1 = 42.13 pesos in 2012) per vaccine dose for both PHiD-CV and PCV13. The 800 pesos per vaccine dose price was derived from the indicative tendering offer price of GlaxoSmithKline for PHiD-CV in the Philippines. Cost data for acute episodes and related long-term sequelae of the IPD and CAP (Table 4) were based on expert validation of clinical treatment pathways and an average of the public and private hospitals costs. AOM costs were based on locally published data [42]. Only direct medical costs were counted in the study. Health effects and costs were both discounted at 5% per annum.

Sensitivity Analyses
For both comparisons, extensive one-way sensitivity analyses were performed to evaluate how robust the results are to the change in model variables. These were performed using ±20% (up to ±50% depending on the inputs) for each of the base-case value of most of the variables; the upper and lower limits of the 95% confidence interval were used for vaccine efficacy inputs. We also tested the effect of assuming the same steady herd effect of 30% for the cohort on year 11 and beyond because we assumed that the protection of both these vaccines lasts for 10 years. For

<table>
<thead>
<tr>
<th>Table 3 – Disutility weights of pneumococcal diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term</strong></td>
</tr>
<tr>
<td>Meningitis (inpatient)</td>
</tr>
<tr>
<td>Bacteremia (inpatient)</td>
</tr>
<tr>
<td>Pneumonia (inpatient)</td>
</tr>
<tr>
<td>Pneumonia (outpatient)</td>
</tr>
<tr>
<td>AOM (outpatient)</td>
</tr>
<tr>
<td>AOM hospitalized myringotomy</td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
</tr>
<tr>
<td>Neurological sequelae from meningitis</td>
</tr>
<tr>
<td>Hearing loss from meningitis</td>
</tr>
<tr>
<td>Meningitis long-term sequelae (children)</td>
</tr>
<tr>
<td>Meningitis long-term sequelae (adult)</td>
</tr>
<tr>
<td>Bacteremia long-term sequelae (children)</td>
</tr>
<tr>
<td>Short-term</td>
</tr>
<tr>
<td>AOM, acute otitis media.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 – Costs for pneumococcal diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumococcal disease</strong></td>
</tr>
<tr>
<td>Meningitis—first year (acute episode)</td>
</tr>
<tr>
<td>Meningitis long-term sequelae annual cost for subsequent years</td>
</tr>
<tr>
<td>Bacteremia—hospitalized (acute episode)</td>
</tr>
<tr>
<td>Bacteremia—outpatient (acute episode)</td>
</tr>
<tr>
<td>Bacteremia long-term sequelae annual cost for subsequent years (children)</td>
</tr>
<tr>
<td>(adult) 18,170</td>
</tr>
<tr>
<td>Pneumonia—hospitalized (acute episode)</td>
</tr>
<tr>
<td>Pneumonia—outpatient (acute episode)</td>
</tr>
<tr>
<td>AOM hospitalized myringotomy</td>
</tr>
<tr>
<td>AOM GP consultations (acute episode)</td>
</tr>
<tr>
<td>AOM, acute otitis media; GP, general practitioner; IV, intravenous; PHP, Philippine pesos.</td>
</tr>
<tr>
<td>* US $1 = 42.13 pesos.</td>
</tr>
</tbody>
</table>
the comparisons of PHiD-CV versus PCV13, three alternative scenario analyses were performed with
1. different price of PCV13;
2. unpublished local AOM etiology with a high proportion of NTHi-attributed AOM versus S. pneumonia–attributed AOM as compared with the internationally published data; and
3. inclusion of AOM long-term sequelae and complications.

We also conducted probabilistic sensitivity analysis to assess the overall effect on results from simultaneous uncertainties around input parameters, and present the results in a cost-effectiveness plane. Point estimates used in the base case as input data were replaced by appropriate choice of distributions, for example, lognormal distribution for efficacy parameters, triangular distribution for cost inputs, and beta distribution for disutility weights.

### Results

**Predicted Effect of Vaccination on Disease Burden and Costs**

For the projected birth cohort of 1,812,137 in the Philippines in 2012, it was estimated that without a UMV there would be a total of 11,919 cases of IPD (3,513 cases of meningitis and 8,406 cases of...

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### Table 5 – Estimated effect of PHiD-CV and PCV13 on lifetime disease burden (projected number of cases) in the Philippines.

<table>
<thead>
<tr>
<th>Health outcomes</th>
<th>No-vaccination program (A)</th>
<th>PCV13 2 + 1 vaccination program (B)</th>
<th>PHiD-CV 2 + 1 vaccination program (C)</th>
<th>Difference PHiD-CV vs. no-vaccination program (C - A)</th>
<th>Difference PHiD-CV vs. PCV13 (C - B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPD cases (acute episode)</td>
<td>11,919</td>
<td>10,768</td>
<td>10,818</td>
<td>-1,102</td>
<td>50</td>
</tr>
<tr>
<td>All-cause pneumonia cases</td>
<td>2,342,129</td>
<td>2,277,482</td>
<td>2,277,466</td>
<td>-64,664</td>
<td>-16</td>
</tr>
<tr>
<td>AOM cases (acute episode)</td>
<td>3,691,038</td>
<td>3,510,803</td>
<td>3,383,123</td>
<td>-261,096</td>
<td>-127,680</td>
</tr>
<tr>
<td>IPD cases (long-term sequelae)</td>
<td>3,378</td>
<td>3,299</td>
<td>3,302</td>
<td>-75</td>
<td>3</td>
</tr>
<tr>
<td>All deaths</td>
<td>39,574</td>
<td>1,773,057</td>
<td>1,773,057</td>
<td>-3,343</td>
<td>0</td>
</tr>
</tbody>
</table>

AOM, acute otitis media; IPD, invasive pneumococcal disease; PCV13, pneumococcal 13-valent conjugate vaccine; PHiD-CV, pneumococcal polysaccharide nontypeable *Haemophilus influenzae* protein D conjugate vaccine.

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### Table 6 – Direct costs by disease and vaccination program in the Philippines (2012 Philippine pesos).

<table>
<thead>
<tr>
<th>Cost category</th>
<th>No-vaccination program (A)</th>
<th>PCV13 2 + 1 vaccination program (B)</th>
<th>PHiD-CV 2 + 1 vaccination program (C)</th>
<th>Difference PHiD-CV vs. no-vaccination program (C - A)</th>
<th>Difference PHiD-CV vs. PCV13 (C - B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination costs</td>
<td>0</td>
<td>4,331,835,868</td>
<td>4,331,835,868</td>
<td>4,331,835,868</td>
<td>0</td>
</tr>
<tr>
<td>Acute episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD</td>
<td>903,957,346</td>
<td>804,351,625</td>
<td>808,699,878</td>
<td>-95,257,468</td>
<td>4,238,253</td>
</tr>
<tr>
<td>All-cause pneumonia</td>
<td>13,432,362,973</td>
<td>12,304,532,946</td>
<td>12,304,464,588</td>
<td>-1,127,898,385</td>
<td>-68,358</td>
</tr>
<tr>
<td>AOM</td>
<td>3,145,091,640</td>
<td>3,031,573,906</td>
<td>2,917,838,591</td>
<td>-227,253,049</td>
<td>-113,735,315</td>
</tr>
<tr>
<td>Long-term sequelae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD</td>
<td>2,835,267,365</td>
<td>2,643,669,639</td>
<td>2,652,113,618</td>
<td>-183,153,747</td>
<td>8,443,979</td>
</tr>
<tr>
<td>Total discounted costs</td>
<td>10,273,482,597</td>
<td>13,219,953,924</td>
<td>13,127,492,075</td>
<td>2,854,009,477</td>
<td>-92,461,849</td>
</tr>
<tr>
<td>Total discounted QALYs gained</td>
<td>31,268,126</td>
<td>31,323,884</td>
<td>31,324,182</td>
<td>56,056</td>
<td>298</td>
</tr>
<tr>
<td>Incremental cost-effectiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50,913</td>
</tr>
</tbody>
</table>

AOM, acute otitis media; IPD, invasive pneumococcal disease; PCV13, pneumococcal 13-valent conjugate vaccine; PHiD-CV, pneumococcal polysaccharide nontypeable *Haemophilus influenzae* protein D conjugate vaccine; QALY, quality-adjusted life-year.

* US $1 = 42.13 pesos.
bacteremia), with 3,378 cases with long-term sequelae, 2,342,129 cases of all-cause pneumonia, and 3,691,038 cases of AOM over their lifetime under the current standard of care for pneumococcal diseases (Appendix Table 7 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.04.004). The associated economic burden (discounted) amounted to be 10,273.48 million pesos. For the base-case scenario, it was found that UMV with PHID-CV 2 + 1 was highly cost-effective as compared with the no-vaccination strategy for the 2012 birth cohort (n = 1,812,137), with an ICER of 50,913 peso/QALY gained, which is less than one time the GDP per capita of the Philippines as recommended by the WHO (equivalent to 103,366 pesos). In another comparison using the same cohort, it was projected that compared with PCV13, PHID-CV 2 + 1 would have a substantially greater reduction in the AOM cases (127,680 cases) and comparable reduction in IPD and CAP-related cases and IPD long-term sequelae (Table 5). Both vaccines would provide a broadly similar effect on reduction in the number of IPD-related and CAP-related deaths in the Philippines. The estimated financial projections based on the same analysis showed that the PHID-CV 2 + 1 vaccination program can reduce the financial burden of IPD, CAP, and AOM of the 2012 birth cohort (n = 1,812,137) over lifetime (Table 6) by approximately 1.54 billion pesos against no vaccination. In comparison against the PCV13 vaccination program, the PHID-CV vaccination program was estimated to result in total savings of approximately 92.5 million pesos while having an additional gain of 298 QALYs, meaning 298 additional years in the perfect health state. Therefore, the PHID-CV 2 + 1 vaccination program was evaluated to be a cost-saving and dominant strategy as compared with the PCV13 2 + 1 vaccination program for the Philippines. This was indeed a conservative estimation without taking into account the complications and long-term sequelae associated with AOM. If the complications and long-term sequelae were incorporated into the base-case scenario, the total savings of PHID-CV 2 + 1 as compared with PCV13 would be around 267 million pesos, with a higher QALY gained of 364.

### Sensitivity Analyses

The tornado diagram in Figure 2 shows the effect of the 10 most influential input parameters around the base-case value on the discounted ICER (descending order), based on the extensive one-way sensitivity analyses. It was found that most of the model variables had very little influence over the conclusion that the PHID-CV 2 + 1 vaccination program as compared with the no-vaccination strategy was a highly cost-effective strategy for the Philippines. Among all the variables, only one variable (% reduction in CAP hospitalizations) had a greater effect on the final conclusion. When the lower limit of the 95% confidence interval was selected, the ICER was increased to 151,012 pesos/QALY gained, less than three times the GDP per capita of the Philippines (equivalent to 310,098 pesos). As expected, PHID-CV 2 + 1 became even more cost-effective than the no-vaccination strategy when a herd effect of 30% was assumed, resulting in a lower ICER of 46,568 pesos/QALY.

The presentation of a one-way sensitivity analysis for a dominant base case can be difficult to interpret using a traditional tornado diagram because of the inability to calculate an ICER. Therefore, Figure 3 presents the effect of the nine most influential variables on a cost-effectiveness plane generated by comparing the PHID-CV 2 + 1 vaccination program with the PCV13 2 + 1 vaccination program in the Philippines. It was found that most of the model variables had little influence over the cost-saving conclusion of the PHID-CV 2 + 1 vaccination program. As seen in Figure 3, there are two variables/assumptions changing the conclusion. These two observations, however, are not
unexpected either. First, when the PhiD-CV efficacy was adjusted to the lower limit of the 95% confidence interval for PCV7 for IPD, it was expected that fewer IPD cases could be prevented, resulting in a lower gain in QALY of the PhiD-CV strategy although the overall costs were still lower with PhiD-CV due to the substantial savings by the prevention of AOM cases. Second, when the percentage of AOM cases due to S. pneumoniae and NTHi was adjusted from 25.7% and 32.3% to 56% and 22%, respectively, the result showed less favorable QALYs of PhiD-CV with lower cost savings compared with PCV13. This change was in line with the key difference between the two vaccines that PhiD-CV provides better protection against AOM caused by NTHi. However, as anticipated, the herd effect of 30% assumed for both vaccines did not alter the ICER result in the base-case analysis.

In addition, an alternative scenario analysis showed that if the price of PCV13 per dose was increased from 800 pesos to 900 pesos, the discounted financial savings of PhiD-CV versus PCV13 would be significantly increased to close to 620.34 million pesos because of the substantial increase in the vaccination costs.

Another scenario analysis was also performed with the unpublished local etiology data (2012) from Dr. Gretchen Navarro-Locsin on AOM cultures collected from Philippine General Hospital, Philippine Children’s Medical Centre, and St. Luke’s Medical Centre, with the NTHi-attributed AOM of 32.3%; S. pneumoniae-attributed AOM: 35.9%) [43]. The results showed that as compared with PCV13, PhiD-CV would save 162.1 million pesos, with incremental QALYs gained of 739.

The third scenario analysis showed that if the AOM long-term sequelae and complications were counted into the analysis, the total savings would be close to 267 million pesos, with incremental QALYs gained of 364.

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**Fig. 3** – Univariate sensitivity analysis comparing PhiD-CV with PCV13 in the Philippines. The effect of the nine most influential variables on cost-effectiveness results of the PhiD-CV 2 + 1 vaccination program versus the PCV13 2 + 1 strategy. AOM, acute otitis media; CI, confidence interval; GP, general practitioner; LL, lower limit; NTHi, nontypeable *Haemophilus influenzae*; PCV13, pneumococcal 13-valent conjugate vaccine; PhiD-CV, pneumococcal polysaccharide nontypeable *Haemophilus influenzae* protein D conjugate vaccine; QALY, quality-adjusted life-year; UL, upper limit.

**Fig. 4** – Cost-effectiveness plane of probabilistic sensitivity analysis comparing PhiD-CV 2 + 1 with the no-vaccination strategy in the Philippines. PhiD-CV, pneumococcal polysaccharide nontypeable *Haemophilus influenzae* protein D conjugate vaccine; QALY, quality-adjusted life-year.
In the probabilistic sensitivity analysis, 99.9% of the simulations fell below the three times the GDP per capita threshold, indicating a high level of certainty that the PHID-CV vaccination program is cost-effective compared with the no-vaccination strategy (Fig. 4). In comparison against the PCV-13 vaccination program, the PHID-CV strategy was estimated to be very likely a dominant strategy (74.2% of the simulations located in the southeast quadrant in Fig. 5: additional QALY gains with cost savings).

**Discussion**

Globally, pneumococcal and NTHi-associated diseases continue to result in substantial direct medical and caregiver costs despite current PCV7 vaccination programs [43]. The evaluation shows substantial health and economic burden of pneumococcal diseases on the health care system over the lifetime of the birth cohort without pediatric vaccination program against pneumococcal diseases. For the projected birth cohort of 1,812,137 newborns in the Philippines in 2012, there would be a total of 11,919 cases of IPD (3,513 cases of meningitis and 8,406 cases of bacteremia), with 3,378 cases with long-term sequelae, 2,342,129 cases of all-cause pneumonia, and 3,691,038 cases of AOM over their lifetime under the current standard of care for pneumococcal diseases without a UMV program in the Philippines. The associated economic burden (discounted) amounted to 10,273.48 million pesos.

If the government were to adopt the PHID-CV (2 + 1 schedule) vaccination program as compared with the no-vaccination strategy, potentially 3,343 deaths due to IPD and CAP and 326,862 cases of pneumococcal diseases (1,102 IPD cases, 64,664 pneumonia cases, and 261,096 AOM cases) would be prevented over the lifetime horizon of the study cohort. The cost-effectiveness analysis also shows that the discounted ICER of the PHID-CV 2 + 1 vaccination versus the no-vaccination program was 50,913 pesos/QALY gained, which is considered to be cost-effective because it is less than one time the GDP per capita of the Philippines.

When the PHID-CV (2 + 1) vaccination program is compared with the PCV13 (2 + 1) strategy, the results show that an additional 127,646 cases would be prevented with a reduction in AOM cases due to NTHi AOM and a comparable reduction in IPD and CAP-related cases. This would further result in substantial financial savings of 92.5 million pesos with higher QALYs gained (298 additional years in perfect health state). Therefore, the study shows that PHID-CV is a cost-saving and dominant strategy as compared with PCV13. It is also interesting to note that although the incremental QALYs gained of 298 for the entire cohort over lifetime appear to be small, this improvement actually reflects a significant disease burden reduction in AOM (n = 127,680 cases) of PHID-CV versus PCV13 because the disutility per episode we assumed in the data input for the AOM acute cases was quite minimal (disutility of AOM = 0.005).

Our findings are in line with those of the other published cost-effectiveness analysis to compare PHID-CV vaccination programs with PCV13. By et al. [9] used a Markov cohort model to compare the PHID-CV 2 + 1 strategy versus the PCV13 2 + 1 strategy in Sweden from a societal perspective. It was found that the PHID-CV strategy would generate an additional 45.3 QALYs with a substantial savings of estimated 62 million Swedish kroner (close to US $9.3 million) for a cohort of 112,120 children [9]. Robberstad et al. [10] have also applied a Markov model to evaluate the cost-effectiveness of pneumococcal conjugate vaccines (PCV7, PCV13, and PHID-CV) for a specific birth cohort (n = 61,152) in Norway; PHID-CV was also found to be a dominant strategy as compared with PCV13 with substantial savings of 24 million Norwegian kroner (close to US $4.15 million), with an additional 49 QALYs gained [10]. In the study published by Knerer et al. [12], it was found that PHID-CV was also a dominant strategy as compared with PCV13, offering an additional savings of Can $9 million (close to US $9.2 million) in the birth cohort size of approximately 33 million newborns in Canada, and additional savings of £4.9 million (close to US $7.2 million) in the United Kingdom with the birth cohort size of approximately 61 million newborns [15].

It is important to note that a conservative approach was adopted in the base-case scenario analysis. It was assumed that PHID-CV possessed an efficacy against NTHi-derived AOM, but not on IPD or CAP, the inclusion of which would result in higher financial savings with higher QALYs gained as compared with PCV13. The AOM-associated complications and long-term sequelae were also not included in the base-case scenario. As mentioned in the Results section, if AOM complications and long-term sequelae were included on the basis of local data reported by Marcelo [Case Series Report on Otogenic Complications of Chronic OM. Philippines Children’s Medical Center, unpublished data, 2004], the total savings of PHID-CV compared with PCV13 would be close to 267 million pesos, with a higher QALY gained of 364 [9]. On a separate note, we believe that more total cost savings would be estimated if the analysis was conducted from a societal perspective in which there is less productivity loss of parents or caregivers for taking care of children suffering from AOM for UMV with PHID-CV. Similarly, the same trend of analyses would be observed if costs for other related expenses, for example, transport to and from the hospitals and clinics, were included.

As is the case with all the modeling exercises, there are a number of limitations to the current analysis as well. First, ideally, a dynamic model should be considered for the evaluations of vaccination against infectious diseases. In the absence of reliable and published data required for constructing a dynamic model, however, an established Markov model for vaccination against pneumococcal diseases was used. Given that recent data tend to suggest a similar herd effect between the two vaccines [44-46], we believe that the study analyses and findings would not likely be much different from those reported in this article should a dynamic model be developed and used in this study. This assumption, however, may be changed with the availability of newer data. In this analysis, best locally published data were
used wherever available, yet there were still some specific clinical epidemiology variables that were not available locally. Similarly, local utility data, ideally, should be used in the analyses. As always, it is not available in many developing countries including the Philippines. So, published disutility weights have been considered and used. Given that the relatively small values of the disutility weights applied and also the relatively short episode of each of the infections included, we believe that the effect of disutility weights on QALY and hence cost-effectiveness ratios is negligible. Furthermore, only a small proportion of patients was assumed to have long-term disease sequelae and differences between these proportions were small between the two vaccinated groups. Published data or regionally available data sets were therefore reviewed by local clinical experts, and reasonable adjustments were made from these.

Conclusions

This economic modeling study showed that a PhID-CV 2 + 1 universal vaccination program could potentially prevent a substantial number of deaths and cases of pneumococcal diseases as compared with the no-vaccination strategy. The results also suggested that the PhID-CV 2 + 1 vaccination program is likely to be a cost-effective strategy and could potentially provide savings with higher health gain measured in QALYs as compared with the PCV13 2 + 1 strategy. Monetary estimates based on Markov cohort analyses could be used to assess the return on investment from vaccination programs of the national government and they could be considered in policy making.

Acknowledgments

We thank Emmanuelle Delgize from GlaxoSmithKline Vaccines for critical review of the manuscript; Lakshmi Hartharan, Jesse Quigley Jones, and Irene Chen from GlaxoSmithKline Vaccines for manuscript coordination; and Seng Chuen Tan from IMS Health Asia for his help in preparing the manuscript.

Source of financial support: GlaxoSmithKline Vaccines funded this study and was involved in all stages of the study and analysis. GlaxoSmithKline Vaccines also took in charge all costs associated with the development and the publishing of the present article. All authors had full access to the data and retained full independence in preparing the article. Publication of the study results was not contingent on sponsor’s approval.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2014.04.004 or, if a hard copy of article, at www.valueinhealthjournal.com/issue (select volume, issue, and article).

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