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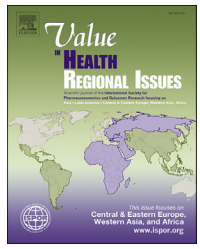

Economic Evaluation

Cost-Effectiveness Comparison of Pneumococcal Conjugate Vaccines in Turkish Children

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ABSTRACT

Background: The 13-valent pneumococcal conjugate vaccine (PCV13) is used for universal infant vaccination in Turkey. **Objectives:** To assess the cost effectiveness of replacing PCV13 with pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV). **Methods:** A Markov cohort model with monthly cycles following 1 cohort of infants over a 10-year time horizon was used. Local input parameters were obtained from published sources and expert consultation whenever possible. The model was adapted to estimate the health benefits and economic impact of each vaccine on invasive pneumococcal disease, pneumonia, and acute otitis media (AOM). An annual discount rate of 3% was used for benefits and costs (2016 euros). **Results:** Under base-case assumptions, vaccinating 1 birth cohort of 1 325 783 infants with PHiD-CV instead of PCV13 was predicted to have the same impact on meningitis and pneumonia, a similar impact on bacteremia (+30 cases), but greater reductions in AOM-related general practitioner visits (−34 955) and hospitalizations (−624). Assuming equal vaccine prices, PHiD-CV was predicted to be dominant over PCV13 (176 additional quality-adjusted life-years while saving €635 330 [discounted]). One-way sensitivity analysis indicated that varying the vaccine price differential had the largest effect on the incremental cost-effectiveness ratio, and then AOM parameters. Probabilistic sensitivity analysis predicted PHiD-CV to be dominant over PCV13 in 92.4% of simulations. **Conclusions:** Any difference in price between PHiD-CV and PCV13 is expected to be the key driver of vaccine choice for preventing childhood pneumococcal disease in Turkey. At price parity, PHiD-CV use is likely to be a dominant strategy over the use of PCV13.

Keywords: children, cost-effectiveness analysis, pneumococcal vaccine, Turkey

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Introduction

Pneumonia is the leading infectious cause of childhood morbidity and mortality worldwide, and *Streptococcus pneumoniae* is the most common etiological agent.[1] With more than 90 identified serotypes, *S pneumoniae* infections may also lead to severe invasive pneumococcal diseases (IPDs), for example, meningitis and bacteremia,[2] and less severe—but more common—acute otitis media (AOM). In Turkey, *S pneumoniae* is the most common cause of AOM, accounting for about 40% of all cases, followed by *Haemophilus influenzae* in about 21% of cases.[3]

Because of the high burden of disease, pneumococcal vaccination was introduced into the Turkish National Immunization Program in 2009, starting with a 7-valent pneumococcal conjugate vaccine (PCV7).[4] PCV7 was replaced by the 13-valent PCV (PCV13) in 2011.[4] Pneumococcal vaccination in Turkey is recommended at age 2, 4, 6, and 12 months.[5] Nevertheless, 2 PCVs are currently available in Turkey: the pneumococcal nontypeable *H influenzae* (NTHi) protein D conjugate vaccine (PHiD-CV) (containing *S pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F)[6] and PCV13 (with additional serotypes 3, 6A, and 19A).[7] PHiD-CV uses NTHi as the carrier protein for 8 of 10 pneumococcal serotypes, which appears to provide protection against NTHi AOM.[8-11]

A recent systematic review has shown that PHiD-CV and PCV13 have comparable impacts on reducing pneumonia and IPD.[12] This was confirmed by the International Vaccine Access Center (IVAC) PCV product assessment report[13] and the World Health Organization (WHO) Strategic Advisory Group of Experts recommendations.[14] Moreover, a recent comparison of vaccine effectiveness (VE) in Sweden, where some counties use PCV13 and others use PHiD-CV, found no significant differences in overall effect on IPD despite different serotype distributions.[15] Other Swedish data indicate that PHiD-CV may reduce outpatient AOM appointments and ventilation tube insertions, but this should be interpreted with caution because of geographical differences.[10]

Conflicts of interest: All authors are employees of the GSK group of companies.

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To guide vaccine budget allocation, health economic evaluations are increasingly recommended for evidence-based decision making.[16] Two studies have demonstrated the cost effectiveness of PCV programs in Turkey.[17,18] In 2012, Bakir et al[17] projected that either PHiD-CV or PCV13 would provide more quality-adjusted life-years (QALYs) while reducing costs compared with PCV7, and that PHiD-CV would provide more QALYs and cost savings than PCV13. In 2013, Turel et al[18] suggested that any of the 3 PCVs would be very cost-effective, with the lowest cost per life-year gained from PCV13. Nevertheless, they did not consider the evidence of cross-protection for PHiD-CV (eg, against serotype 19A) or against NTHi AOM, nor did they report outcomes in QALYs. Therefore, we assessed the differences in health and economic outcomes by comparing the current standard of care (PCV13) with PHiD-CV in 1 birth cohort. We considered the most up-to-date data while accounting for uncertainty and identifying key drivers of cost effectiveness. A no-vaccination arm was not considered because of the long-term use of PCVs in Turkey and the scarcity of prevaccination surveillance data.

Methods

Model Structure

A previously published age-compartmental, static Markov cohort model with monthly cycles[19] was adapted to the Turkish setting (see Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). *S pneumoniae* infections were modeled in 1 Turkish birth cohort over a 10-year time horizon (because of the limited availability of local data for older age groups, ie, *S pneumoniae* serotype distribution in IPD and IPD burden of disease). Indirect effects (eg, herd effect and serotype replacement) were not accounted for because of the lack of data and the static modeling approach. The health and economic impacts of PHiD-CV versus PCV13 were assessed in terms of IPD (meningitis and bacteremia), all-cause pneumonia, and AOM.

Input Data

Cohort

There were 1 325 783 live births reported in Turkey in 2015,[20] and this formed the birth cohort for the model. Natural monthly mortality rates (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007) were based on Turkish annual mortality data.[21]

Epidemiological data

Age-specific *S pneumoniae* serotype distribution in Turkish children with IPD has been reported for 2008 to 2014[4] (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). Age-specific incidence and mortality due to pneumococcal meningitis (Table 1) were taken from a prospective study in Turkey,[22] and sequelae rates were based on expert opinion (M. Ceyhan, May 2017, written communication). Age-specific incidences of pneumococcal bacteremia were based on average incidences in children younger than 5 years in Turkey and the ratio of incidences in children younger than 5 years and between 5 and 9 years in the United Kingdom, as used in a previous Turkish cost-effectiveness model.[17,23,24] Age-specific case-fatality rates (CFRs) for bacteremia were based on expert opinion and local estimates used in previous economic studies.[18,25-28]

All-cause pneumonia incidence and CFRs were based on the lower respiratory tract infection estimates for Turkey, as reported by the Institute for Health Metrics and Evaluation for 2008.[29] Age-specific values were derived by adjusting the less than 5 years incidence rate to the age-specific distribution reported for the United Kingdom (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007).[30,31] The hospitalization rate due to all-cause pneumonia was assumed to be 5% (sensitivity analysis 2.5%-7.5%), as was used in a previous cost-effectiveness study in Turkey[18] (Table 1).

For AOM, age-specific general practitioner (GP) consultation rates were based on the number of episodes of suspected AOM in a retrospective, observational study from Turkey[32] (Table 1). In a 2004 burden-of-disease report, the Turkish Ministry of Health assumed that 3% of AOM cases would be treated at a hospital.[24] Nevertheless, on the basis of expert opinion, we assumed (more conservatively) that 1% of AOM cases would be hospitalized and 0.1% of all cases would result in hearing impairment. The distribution of AOM pathogens (*S pneumoniae*, 39.7%; *H influenzae*, 20.7%; other, 39.6%) was taken from a Turkish study published in 2006.[3] *S pneumoniae* serotype distribution in AOM was taken from a multinational study of AOM serotypes[33] (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007).

Vaccine effectiveness

WHO data indicate 97% vaccination coverage for the third dose in 2015.[5] It was assumed that all individuals receiving the third dose would receive the full 4-dose regimen. We applied a proportion of direct vaccine protection depending on the doses received. Direct vaccine protection was adjusted to 50%, 90%, 90%, and 100% of its maximum value after each of the 4 doses. No waning was assumed from age 13 months to 3 years, followed by an exponential decay to no direct protection at age 10 years.[9,34] This assumption was conservative because data do not indicate a rapid decrease in efficacy after 3 years.[9]

A direct comparison of VE is not available, and therefore a range of randomized controlled trials (RCTs) and effectiveness studies were used (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). VE against vaccine-serotype IPD was assumed to equal the average vaccine-serotype effectiveness of PCV7 from a matched case-control trial,[35] apart from serotype 3 for PCV13 (Table 2). This was due to a large number of immunogenicity, efficacy, and effectiveness studies reporting PCV13 to be less immunogenic/effective against serotype 3 than against the other serotypes.[36-45] Nevertheless, higher efficacies were tested in scenario analyses. Effectiveness and impact trials have reported cross-protection VEs of PHiD-CV against serotype 6A of 14.7%[46] and 100%.[47] Given the disparity of these results, cross-protection for PHiD-CV against serotype 6A IPD was assumed to be the same as for PCV7 in a matched case-control trial (76.0%),[35] on the basis of noninferiority immunogenicity data.[48,49] Reported cross-protections of PHiD-CV against serotype 19A from effectiveness trials were 62%,[47] 71%,[50] and 82%,[46] of which the lowest estimate was conservatively used. Because of the lack of data, PHiD-CV was assumed not to provide protection against NTHi invasive disease.

Estimating the impact of vaccination on pneumonia is more nuanced than applying a serotype-specific vaccine efficacy. It would be necessary to consider serotype replacement and synergies and competition between organisms.[51,52] Comparability of available evidence is also uncertain: PHiD-CV evidence is from 2 RCTs[9,53] and postmarketing surveillance,[54] whereas PCV13 data come primarily from postmarketing surveillance. Comparing studies with different case definitions, durations of PCV use, antibiotic use, and natural trends of pneumonia hospitalization rates is inherently biased. A recent systematic literature review and the IVAC assessment of PCVs found no difference in the impact on pneumonia between the 2 vaccines.[12,13] Therefore, VE for both vaccines against all-cause pneumonia GP visits and hospitalizations was assumed to be the same and was taken from a PHiD-CV RCT[9] (Table 2).

Table 1 – Input data for the base case (with values for the 1-way sensitivity analysis in parentheses).

Input data	Value	References
Epidemiological data		
Pneumococcal meningitis		
Incidence rate (per 100 000)	Age: <1 y, 1.0 (0.7-1.2); 1-3 y, 0.2 (0.1-0.2); 4 y, 0.3 (0.2-0.4); 5-9 y, 0.3 (0.2-0.4)	Ceyhan et al[22]
CFR (%)	All ages: 5.8 (3.2-9.0)	Ceyhan et al[22]
Meningitis sequela (% of cases)		
Hearing impairment	All ages: 20.0 (16.0-24.0)	*
Convulsive disorder	All ages: 5.0 (4.5-5.5)	*
Learning disability	All ages: 1.0 (0.5-1.5)	*
Pneumococcal bacteremia		
Incidence rate (per 100 000)	Age: <1 y, 45.0 (36.0-54.0); 1-2 y, 25 (20.0-30.0); 3-4 y, 12.5 (10.0-15.0); 5-9 y, 0.5 (0.4-0.6)	Bakir et al[17]
CFR (%)	Age: <1 y, 2.0 (1.6-2.4); 1-9 y, 1.4 (1.1-1.7)	Turel et al,[18] Melegaro and Edmunds,[25] Lloyd et al,[26] Butler et al,[27] Tilson et al[28]
Pneumonia		
GP consultation rate (per 100 000)	Age: <1 y, 2189 (1739-2689); 1-4 y, 2047 (1625-5514); 5-9 y, 638 (507-784)	Institute for Health Metrics and Evaluation[29,†]
Hospitalization rate (per 100 000)	Age: <1 y, 109 (55-164); 1-4 y, 102 (51-154); 5-9 y, 32 (16-48)	Turel et al[18,‡]
CFR (%)	All ages: 0.28 (0.19-0.38)	Turel et al[18]
AOM		
GP consultation rate (per 100 000)	Age: <1-2 y, 9300 (6800-12 500); 3-4 y, 10 700 (7600-14 700); 5-9 y, 6546 (4650-8993)	Mustafa et al[32,†]
Hospitalization rate (per 100 000)	Age: <1-2 y, 93 (0-279); 3-4 y, 107 (0-321); 5-9 y, 65 (0-196)	Ministry of Health[24,§]
Hearing impairment (% of AOM cases)	All ages: 0.1	*
AOM pathogens (%)	NTHi: 20.7 (13.9-28.5); *S pneumoniae*: 39.7 (31.0-48.7)	Guven et al[3,‖]
Vaccine serotypes (%)	83.2 (82.1-84.5)	Hausdorff et al[33]
Nonvaccine serotypes (%)	16.8 (15.5-17.9)	Hausdorff et al[33]
Costs (2016 €)		
Vaccine (per dose)		
PHiD-CV	23.78 (23.19-24.37)	Turkish Medicine and Medical Device Agency,[57] OANDA[62,¶]
PCV13	23.78	¶
Meningitis (acute episode)	7776 (495-35 905)	Ceyhan et al[58,60,#]
Bacteremia (hospitalized)	3370 (508-7761)	Ceyhan et al[58,#]
Pneumonia (outpatient)	42.8 (4.5-192.6)	Ceyhan et al[58,#]
Pneumonia (hospitalized)	1102 (71-15 576)	Ceyhan et al[58,60,#]
AOM (GP consultation)	17.3 (13.1-41.8)	Ceyhan et al[58,#]
AOM (hospitalized)	318.5 (77.2-559.8)	Turkish Medicine and Medical Device Agency[57,#,**]
AOM hearing loss	NA	NA
Utilities		
Meningitis (acute episode)	0.023 (0.010-0.042)	Bennett et al[64]
Meningitis sequelae	0.246 (0.177-0.322)	Morrow et al[66,††]
Bacteremia (hospitalized)	0.008 (0.003-0.015)	Bennett et al[64]
Pneumonia (outpatient)	0.006 (0.002-0.013)	Bennett et al[64]
Pneumonia (hospitalized)	0.008 (0.003-0.015)	Bennett et al[64,‡‡]
AOM (GP consultation)	0.005 (0.003-0.007)	Melegaro and Edmunds,[25] Oh et al[65]
AOM (hospitalized)	0.005 (0.003-0.007)	Melegaro and Edmunds,[25] Oh et al[65]
AOM hearing loss	0.090 (0.070-0.110)	Oostenbrink et al[67]

AOM indicates acute otitis media; CFR, case-fatality rate; GP, general practitioner; NA, not available; NTHi, nontypeable *Haemophilus influenzae*; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine.

* Expert opinion (M. Ceyhan, May 2017, written communication).

† Ratios from UK data[30,31] were used to estimate the incidence in 5- to 9-y-old children.

‡ Based on Turel et al,[18] who reported that 5% of pneumonia cases were hospitalized.

§ It was assumed that 1% of AOM cases would be hospitalized (expert opinion).

‖ Based on the reported proportion of *H influenzae* cases.

¶ Price for both vaccines is based on the PHiD-CV published price to wholesaler in Turkey (2016)[57] and converted into euros (1 Turkish lira = €0.24622).[62]

Unpublished 2014 Turkish lira data (M. Ceyhan, May 2017, written communication) associated with a published abstract.[58] Cost estimates were inflated to 2016 Turkish lira on the basis of the consumer price index for health,[61] and then converted to 2016 euros.[62]

** Assumed to be the cost of a patient hospitalized for myringotomy.

†† Estimated using the ratio of hearing loss to neurological sequelae in children and adults (77% and 23%, respectively) and disutility values from Morrow et al.[66]

‡‡ Long-term disutility considered only for the 10-y time horizon.

Table 2 – Vaccine effectiveness for the base case (and the 1-way sensitivity analysis).

Parameters	PHiD-CV	PCV13	References
IPD (%)			
10 common serotypes	94.7 (87.0 to 99.9)*	94.7 (87.0 to 99.9)*	Whitney et al[35]
Serotype 3	0.0 (0.0 to 0.0)	0.0 (0.0 to 26.0)	Andrews et al,[36] Ben-Shimol et al,[37] Dagan et al,[39] Government of Canada,[40] Demczuk et al,[41] Harboe et al,[42] Moore et al,[43,44] Steens et al,[45] Vesikari et al[48]
Serotype 6A	76.0 (39.0 to 90.0)†	94.7 (87.0 to 99.9)*	Whitney et al,[35] Vesikari et al,[48] van Hoek et al[49]
Serotype 19A	62.0 (20.0 to 85.0)	94.7 (87.0 to 99.9)*	Jokinen et al[47]
Other serotypes	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Pneumonia (%)			
Reduction in GP visits	7.3 (2.1 to 12.3)		Tregnaghi et al[9]
Reduction in hospitalizations	23.4 (8.8 to 35.7)		Tregnaghi et al[9]
AOM (%)			
Vaccine serotypes (including serotypes 3, 6A/C, 19A)	63.2 (55.8 to 70.7)‡,§	66.5 (59.0 to 73.9)‡	Prymula et al,[8] Tregnaghi et al,[9] Andrews et al,[36] Joint Committee on Vaccination and Immunisation Pneumococcal Subcommittee,[38] Saez-Llorens et al[56] (calculated)
Nonvaccine serotypes	−33.0 (−80.0 to 1.0)‖	−33.0 (−80.0 to 1.0)‖	Eskola et al[55]
NTHi	21.5 (0.0 to 35.3)‖	−11.0 (−34.0 to 8.0)	Prymula et al,[8] Tregnaghi et al,[9] Eskola et al[55]
Overall AOM base case	23.1	17.5	Calculated
Hospitalized AOM	41.2 (20.4 to 56.6)	31.1 (6.7 to 49.2)	Fireman et al,[96] Palmu et al,[97,98] Black et al[99],¶

AOM indicates acute otitis media; GP, general practitioner; IPD, invasive pneumococcal disease; NTHi, nontypeable *Haemophilus influenzae*; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine; RCT, randomized controlled trial.

* Assumed to be the same as the average effectiveness of the 7 PCV7 serotypes in a PCV7 study.

† Cross-protection for PHiD-CV against serotype 6A IPD was assumed to be the same as for PCV7 from Whitney et al,[35] on the basis of non-inferiority immunogenicity data from Vesikari et al.[48]

‡ Not varied individually.

§ Cross-protection of 45.8% against serotype 19A was set for PHiD-CV, on the basis of the ratio of VE against serotype 19A IPD and vaccine strain IPD: (PHiD-CV VE against vaccine-serotype AOM [69.9%] [Tregnaghi et al[9]]) × (PHiD-CV VE against serotype 19A IPD [62%] [Jokinen et al[47]])/(PHiD-CV VE against vaccine-serotype IPD [94.7%]) (Whitney et al[35]).

‖ Assumed to be the same as for PCV7.

¶ VE against inpatient AOM was extrapolated using an exponential function based on the results of PCV7 clinical trials and the relative ratio of overall AOM VE, in line with the findings of the Finnish Invasive Pneumococcal disease study.[97] The vaccine efficacy estimates used in this model have been chosen by a panel of independent experts (Leuven, Belgium, 2013) using data available from RCTs.[96,97,99]

VE against vaccine-serotype AOM was based on a PHiD-CV RCT.[9] The same value was used for PCV13 serotypes, excluding serotype 3, for which no effect was assumed in the base case. Cross-protection of PHiD-CV against serotype 6A AOM was taken from an 11-valent PHiD-CV predecessor RCT.[8] This trial also reported cross-protection against serotype 19A AOM, but because of the very low number of cases, a more conservative estimate was calculated, as presented in Table 2. Both vaccines were assumed to cause replacement of nonvaccine-serotype AOM, whereas PCV13 could also lead to NTHi AOM replacement in the base case, on the basis of a PCV7 RCT.[55] PHiD-CV was assumed to provide protection against NTHi AOM, on the basis of a PHiD-CV RCT (21.5%; 95% confidence interval [CI] −43.4% to 57.0%)[9,56] and the aforementioned predecessor trial (35.3%; 95% CI 1.8% to 57.4%).[8] Conservatively, the lower of these estimates was used. Overall, VEs against AOM of 23.1% and 17.5% were used for PHiD-CV and PCV13, respectively, in the base case (Table 2; see also Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). Different scenarios analyzed the impact of higher VEs of PCV13 on serotype 3 and no NTHi replacement (overall VEs of 20.0% and 20.7% for PCV13).

Cost parameters

Direct medical costs were considered from the public payer perspective. Both vaccines were assumed to cost €23.78 per dose (the published price to wholesaler of PHiD-CV from March 2016 through January 2017; Table 1).[57] Vaccine administration and wastage costs were not considered because they were assumed to be the same for both vaccines. Disease-related costs were taken from published sources[58-60] and expert consultation (M. Ceyhan, May 2017, written communication). No costs were associated with meningitis sequelae, because suitable data were not available. Indirect costs were not considered, because the analysis was from the public payer perspective. All costs were inflated to 2016 values based on the Turkish consumer price index for health and converted into euros (1 Turkish lira = €0.24622),[61,62] as presented in Table 1.

Utility parameters

A normative utility value of 0.91 was used on the basis of UK data for young adults.[63] Short-term disutility values for hospitalized meningitis (0.023), hospitalized bacteremia (0.008), and outpatient pneumonia (0.006) were taken from parents of children with

bacteremia in a US study[64] (Table 1). The disutility due to hospitalized pneumonia was assumed to equal that of hospitalized bacteremia. A short-term disutility of 0.005 was used for AOM.[25,65] Long-term disutilities were 0.400 for meningitis neurological sequelae (convulsive disorder or learning disability),[66] 0.200 for meningitis hearing loss,[66] and 0.090 for AOM hearing loss.[67]

Outcomes

Health outcomes are reported as disease cases and aggregated QALYs gained, whereas costs are reported in 2016 euros. A discount rate of 3% was applied to health outcomes and costs, on the basis of Turkish guidelines.[68] The threshold for high cost effectiveness was set at less than the 2016 gross domestic product (GDP) per capita for Turkey (€9730) per QALY gained.[69,70]

One-Way Sensitivity Analysis

Each parameter was varied to the minimum and maximum values of its range. Parameters included epidemiological data (eg, IPD serotype distribution, AOM causal pathogens, disease incidences, hospitalization rates, CFRs, and probabilities of sequelae), VE, costs, disutilities, and vaccine price. Their ranges are presented in Tables 1 and 2 and in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007. Incremental cost-effectiveness ratios (ICERs) were recorded for each iteration, and the 12 parameters with the strongest impact on the ICER are reported.

Multivariate Sensitivity Analysis

The different scenarios for the multivariate sensitivity analysis were as follows:

- *Scenario 1:* UK epidemiology inputs for IPD and pneumonia were used to address the uncertainty related to the burden-of-disease estimates[30] (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007).
- *Scenario 2:* Higher PCV13 VE against serotype 3 IPD (26%[36]), serotype 3 AOM (19.2% [calculated]), and NTHi AOM (0% [assumption]) was assumed (Table 2).
- *Scenario 3:* The highest PCV13 VE against serotype 3 IPD (79.5%[43]), serotype 3 AOM (58.7% [calculated]), and NTHi AOM (0% [assumption]) was assumed (Table 2).

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted by recording the results of 10 000 Monte-Carlo simulations. Values of uncertain parameters were randomly assigned from their 95% CIs and associated probability distributions (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). Each considered parameter was simultaneously sampled for each iteration.

Results

Base Case

Vaccination with PHiD-CV versus PCV13 in Turkey was estimated to result with no differences in meningitis or pneumonia, 30 more bacteremia cases, but nearly 35 000 fewer cases of AOM (Table 3). Overall, the model showed PHiD-CV vaccination to result in an incremental gain of 176 QALYs while saving €635 340 in direct costs to the public payer (discounted) over the 10-year time horizon in 1 birth cohort, making the use of PHiD-CV the dominant strategy.

One-Way Sensitivity Analysis

In the 1-way sensitivity analysis, the variation of the price of PHiD-CV by ±2.5% that of PCV13 had the largest effect, followed by parameters related to AOM (outpatient cost, hospitalized incidence, and disutility) and VE against vaccine-serotype IPD (Fig. 1; see also Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007). For all variations, apart from a higher vaccine price, PHiD-CV was estimated to remain dominant over PCV13. When PHiD-CV was 2.5% more expensive than PCV13, the ICER was €13 387 per QALY, higher than the GDP per capita, but less than 3 times the GDP per capita. Threshold

Table 3 – Base-case results (over a 10-y time horizon).

Outcomes	PCV13	PHiD-CV	Difference
Health outcomes (cases)			
Meningitis	28	28	0
Bacteremia	819	849	+30
Pneumonia (outpatient + inpatient)	176 519	176 519	0
AOM (outpatient)	965 996	931 040	−34 956
AOM (inpatient)	8815	8191	−624
Deaths due to meningitis, bacteremia, and pneumonia	37	37	0
Total QALYs gained, undiscounted	11 904 248	11 904 443	+195
Total QALYs gained, discounted	10 320 697	10 320 873	+176
Costs, undiscounted (€)			
Vaccine*	121 647 611	121 647 611	0
Meningitis	216 713	220 587	+3874
Bacteremia	2 758 515	2 858 322	+99 807
Pneumonia (outpatient and inpatient)	15 489 462	15 489 458	−4
AOM (outpatient and inpatient)	19 559 617	18 754 746	−804 871
Total direct cost, undiscounted (€)	159 671 918	158 970 724	−701 194
Total direct cost, discounted (€)	153 690 046	153 054 706	−635 340

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

* In the base case, we assume price parity. However, on the basis of global observations, PCV13 is standardly more expensive than PHiD-CV.

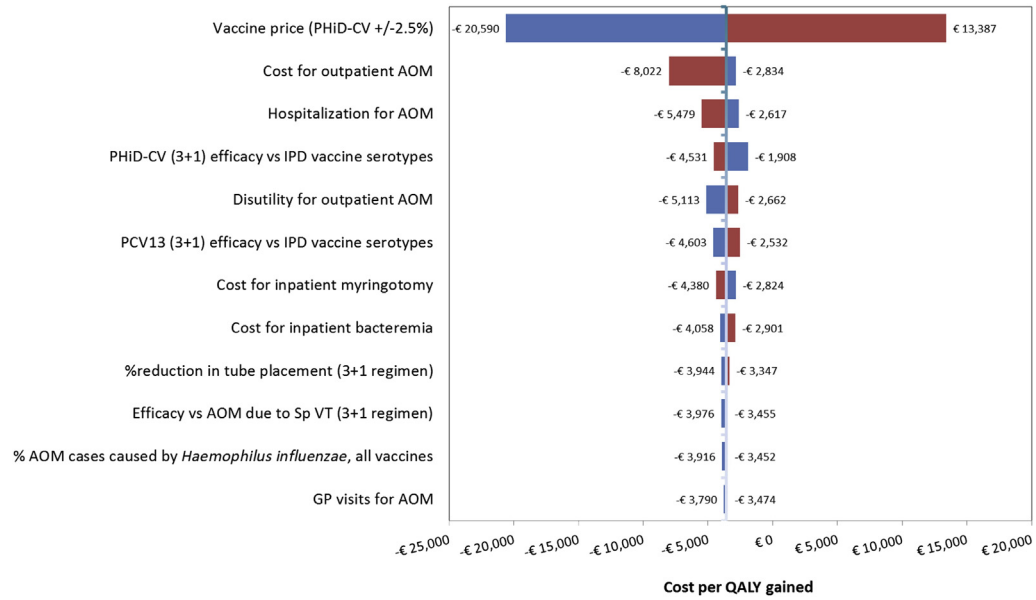

Fig. 1 – One-way sensitivity analysis results. Blue bars are generated from the minimum values and red bars from the maximum values. AOM indicates acute otitis media; GP, general practitioner; IPD, invasive pneumococcal disease; NTHi, nontypeable *Haemophilus influenzae*; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine; QALY, quality-adjusted life-year; Sp, *Streptococcus pneumoniae*; VT, vaccine type.

analysis to determine the extreme cost-effective values of PHiD-CV vaccine price showed a price premium of +€0.46 per dose for GDP per capita and +€1.15 per dose for 3 times GDP per capita.

Multivariate Sensitivity Analysis

In scenario 1 (UK IPD and pneumonia estimates), results were very similar to the base case: PHiD-CV was estimated to result in 178 QALYs gained and €711 709 saved (discounted), showing dominance over PCV13. In scenarios 2 and 3 (the higher and highest efficacies of PCV13 against serotype 3 IPD/AOM), there were fewer QALYs gained (92 and 67, respectively) and reduced cost savings (€223 732 and €10 453, respectively) (discounted) with PHiD-CV versus PCV13. In each scenario, PHiD-CV was the dominant option compared with PCV13 at price parity (Table 4).

Table 4 – Multivariate sensitivity analysis.

Parameters	Outcomes	Scenario analysis 1 (UK epidemiology data*)		Scenario analysis 2 (vaccine efficacy)		Scenario analysis 3 (vaccine efficacy)	
		PHiD-CV	PCV13	PHiD-CV	PCV13	PHiD-CV	PCV13
IPD	Serotype 3	0.0%	0.0%	0.0%	26.0%[36]	0.0%	79.5%[43]
AOM							
Caused by NTHi (20.7%)		21.5%	−11.0%	21.5%	0.0%†	21.5%	0.0%†
Caused by *S pneumoniae* (39.7%)	Serotype 3	0.0%	0.0%	0.0%	19.2%‡	0.0%	58.7%‡
Overall AOM VE§		23.1%	17.5%	23.1%	20.0%	23.1%	20.7%
Price difference		Price parity		Price parity		Price parity	
PHiD-CV vs PCV13							
QALYs gained, discounted		178		92		67	
Total direct cost, discounted		−€711 709		−€223 732		−€10 453	
ICER, discounted		PHiD-CV is dominant		PHiD-CV is dominant		PHiD-CV is dominant	

Note. Underlined vaccine efficacy values represent changes compared with the base case.
AOM indicates acute otitis media; GP, general practitioner; ICER, incremental cost-effectiveness ratio; IPD, invasive pneumococcal disease; NTHi, nontypeable *Haemophilus influenzae*; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine; QALY, quality-adjusted life-year; VE, vaccine efficacy.
* UK epidemiology data for IPD meningitis, bacteremia, and pneumonia.
† Assumption.
‡ Calculated, (VE against vaccine-serotype AOM) × (VE against serotype 3 IPD)/(VE against vaccine-serotype IPD).
§ Calculated, on the basis of base-case VE calculations described in Table 2.

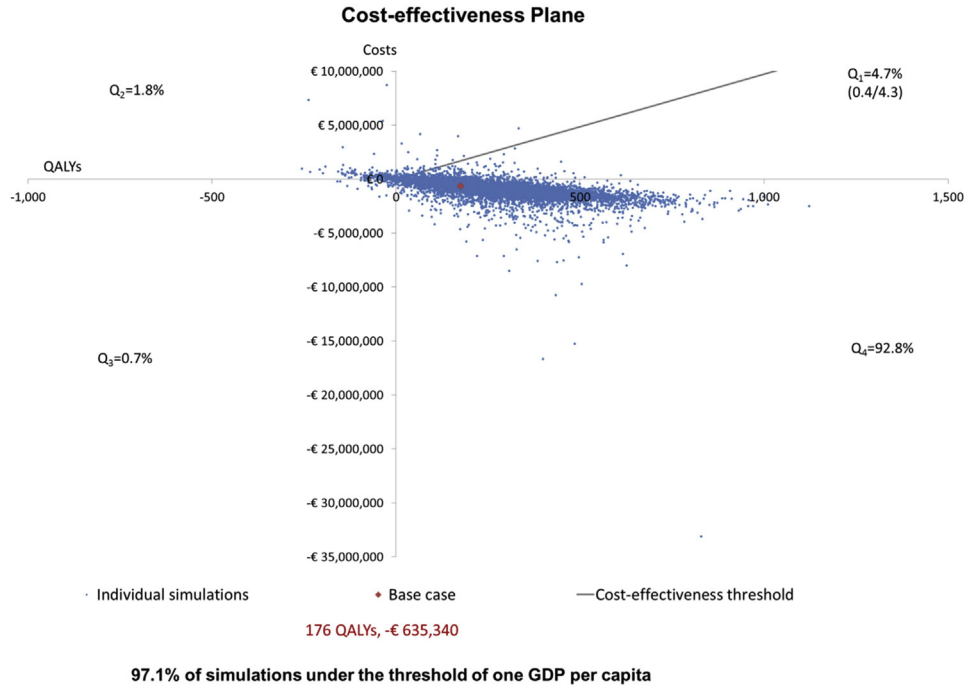

Fig. 2 – Cost-effectiveness plane (10 000 PSA simulations). GDP indicates gross domestic product; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years.

Probabilistic Sensitivity Analysis

PHiD-CV was dominant in 92.4% of PSA simulations, meaning that the ICER fell into the fourth quadrant of the cost-effectiveness plane, estimating more QALYs gained at a lower cost than with PCV13 (Fig. 2). The cost-effectiveness acceptability curve (see Appendix Figure 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2018.11.007) shows that 97.1% of the PSA iterations fall below the GDP per capita threshold (€9730 per QALY), indicating high cost effectiveness of PHiD-CV.

Discussion

This cost-effectiveness analysis of PCVs in Turkey shows PHiD-CV to be a dominant option over PCV13 under base-case assumptions, yielding 176 more QALYs gained with a cost saving of €635 340 (discounted; over a 10-year time horizon). Extensive scenario and sensitivity analyses show the same outcome in most cases.

A previous cost-effectiveness model from Turkey also predicted the dominance of PHiD-CV over PCV13, considering children aged between 0 and 9 years during a 1-year period after steady state had been reached (933 QALYs gained and a direct cost saving of $8 235 010 [undiscounted]).[17] QALYs gained and costs saved were both estimated to be much higher than in the current model, but there are a number of important differences. First, Bakir et al[17] estimated lifetime outcomes for the population up to age 10 years (10 age cohorts), whereas we followed up 1 cohort to the age of 10 years. Second, we used a Markov model with monthly cycles over 10 years, rather than a decision-tree cohort model with a 1-year time horizon. Finally, our analysis used some important new data: inclusion (vs not) of meningitis sequelae; approximately 3-fold lower incidence of AOM; excluded VE of PHiD-CV against NTHi invasive disease or pneumonia; updated VE of PCV13 against serotype 3 IPD/AOM; included cross-protection of PHiD-CV against serotypes 6A and 19A IPD/AOM (vs only serotype 6A IPD); higher VE against vaccine-serotype AOM for both vaccines (69.9% vs 57.6%); a lower VE of PHiD-CV against NTHi AOM (21.5% vs 35.3%); replacement of NTHi AOM with PCV13; and updated medical cost estimates.

The only other cost-effectiveness analyses of these 2 PCVs in Turkey predicted that either vaccine would be very cost-effective, with the lowest cost per life-year gained for PCV13.[18] Nevertheless, they measured outcomes only as life-years and did not estimate QALYs. Moreover, they did not consider serotype-specific VE for IPD meningitis and bacteremia, but assumed the same efficacy for any vaccine serotype and adjusted the overall VE by the nominal serotype coverage of each vaccine. This assumption overestimates the effectiveness of PCV13 on serotypes 3 and 19A and does not consider any cross-protection of PHiD-CV. Their analysis also assumed a higher burden of AOM and a marginally higher efficacy of PHiD-CV against AOM. This led to a higher AOM case difference than in this analysis, but because only life-years were considered, it did not have any impact on the qualitative outcome. Furthermore, cases of hospitalized AOM were not considered.

Although local results of cost-effectiveness analyses should not be regarded as generalizable to other countries, our results showing PHiD-CV as dominant over PCV13 are in line with previous studies in Turkey,[17] other European countries,[19,30,71-73] Asia,[74-76] and the Americas.[19,77] Nevertheless, some studies have predicted that PCV13 would be dominant over PHiD-CV.[78-82] Notable difference between these 2 sets of studies is the inclusion of VE based only on vaccine-serotype coverage for PCV13 or marginally higher effectiveness of PHiD-CV against AOM, on the basis of NTHi AOM.[17,19,30,71-82] Other articles have not reported dominance of either vaccine, but have reported a lower ICER for PHiD-CV compared with PCV13 when efficacy against NTHi AOM was included,[83,84] or lower ICERs for PCV13 when it was not.[18,85-88] Interestingly, 1 article that included PHiD-CV efficacy against NTHi AOM reported a lower ICER for PCV13,[89] whereas 3 articles

that did not include PHiD-CV efficacy against NTHi AOM reported a lower ICER for PHiD-CV.[90-92] Clearly, the assumption on PHiD-CV efficacy against NTHi AOM is important, as is the local burden of disease and serotype-specific VE. Our decision was to allow a conservative estimate in the base case and conduct extensive sensitivity/multivariate analyses. This allows testing of extreme ranges and estimating the impact of parameter uncertainty for disease- and vaccine-related inputs.

In the base case of the present study, we assumed price parity for both vaccines. This approach has been widely used in previous studies comparing PHiD-CV and PCV13,[17-19,30,71,72,74-76,78,81-84,86] whereas other studies have used a lower cost for PHiD-CV.[73,77,79,80,85,87-92] In our 1-way sensitivity analysis, a marginal vaccine price difference had the greatest impact on the predicted ICER, much more so than VE or any other input parameter. Surprisingly, many previous studies do not appear to have examined the impact of a vaccine price differential, but of those that did, all reported that reducing the cost of PHiD-CV relative to PCV13 had a large effect on the ICER.[30,71,76,79,80] Therefore, the cost of both vaccines is a key component to consider when making public health decisions because every €1 difference would directly lead to more than €5 million annual savings to the Turkish government (based on the 3 + 1 schedule for 1 325 783 births[20]).

Other parameters with the largest impact on the predicted ICER (after vaccine price difference) occurred for inputs related to AOM (outpatient cost, hospitalized incidence, disutility, and myringotomy cost) and efficacies against vaccine-serotype IPD. This is largely in line with other studies, which have reported important factors to be AOM pathogen split, GP visits, and disutility; PCV13 myringotomy reduction; PHiD-CV VE against NTHi AOM; and PHiD-CV and PCV13 VEs against vaccine-type IPD.[17,19,30,71,72,74-76] Nevertheless, extreme ranges of these parameters did not have an impact on the overall study result of PHiD-CV being the dominant option.

In the multivariate analyses, we assumed an increasing range of PCV13 VE against serotype 3 IPD/AOM, but even at the highest PCV13 serotype 3 efficacy, the predicted dominance of PHiD-CV was maintained. The highest VE estimate for serotype 3 is, however, very improbable, because IVAC review demonstrated no consistent impact on serotype 3 disease,[13] with most studies showing no impact.

These results are in line with the most recent WHO Strategic Advisory Group of Experts recommendations,[93] which state no overall net difference between PHiD-CV and PCV13 on IPD, while considering the recent Swedish publication showing a trend toward AOM reduction in counties using PHiD-CV versus PCV13.[10,15]

Study Limitations

As with all modeling studies, there are some limitations of this study. The model outcomes are highly dependent on the input approximations and assumptions. When possible, we used data from Turkey, but when these were not available, we used data from another country or assumed no cost (eg, vaccine administration and meningitis sequelae costs). Although accounting for administration costs would have had an impact on the cost effectiveness of vaccine introduction, it would have had no impact on the comparison between vaccines.

Unfortunately, we could not find suitable data for AOM and pneumonia GP-consultation rates in the age group of 5 to 9 years, and so we extrapolated data from 4-year-olds on the basis of the ratios used by Bakir et al.[17] We did not consider that this would have had much impact on the results and tested different ranges in the sensitivity analysis. Moreover, we did not have data on costs related to long-term sequelae, which would add to the value of vaccination, but would have little effect on the comparison between vaccines. Regarding serotype distribution, we used average serotype distribution data from Turkey for 2008 to 2014.[4] Assessing serotype competition and replacement would require a dynamic modeling approach, for which not enough data are available. The serotype distribution was applied to the age-specific incidence rates from a prospective study of childhood meningitis in Turkey conducted in 2005/2006.[22] Although a 1-year period might underestimate the overall burden of pneumococcal meningitis, the modeled outcomes predicted 28 cases in the birth cohort, corresponding to an annual incidence of 0.2 per 100 000 as reported for 2011/2012.[94]

There are no head-to-head studies of the PCVs, and there is a paucity of RCT data of both vaccines, particularly PCV13. Therefore, we had to estimate the VEs of both vaccines against IPD and AOM on the basis of serotype distributions and serotype-specific efficacies (from PCV7 or PHiD-CV [or its predecessor] studies). We decided to include the impact of PHiD-CV against NTHi AOM. Although the available data were not conclusive,[8,9] they indicated that there is likely a beneficial effect. We did not, however, include any efficacy of PHiD-CV against NTHi invasive disease or pneumonia. Obviously, if such data were to become available, this would improve the relative cost effectiveness of PHiD-CV versus PCV13.

We did not account for indirect effects, such as herd protection and serotype replacement. Had we included herd protection, this would have improved the cost effectiveness of both vaccines, whereas including serotype replacement would have reduced their cost effectiveness. On balance, we feel that the lack of inclusion of indirect effects is unlikely to have had an important effect on the vaccine comparison in children. Of course, our model ran only for 10 years and the benefits of herd protection would most likely be greater among older adults.[95]

Finally, we did not include societal costs, for example, time lost from work for caregivers to take care of their child. Had societal costs been considered, the relative cost effectiveness of PHiD-CV versus PCV13 would have been even higher.

Conclusions

This analysis confirms that PHiD-CV is expected to be a dominant option compared with PCV13 in Turkey when NTHi AOM is considered. The introduction of PHiD-CV is estimated to result in no difference in mortality and a small increase in IPD, offset by a large reduction in AOM costs and cases. This is predicted to result in more QALYs gained with PHiD-CV while saving the public payer a substantial budget, which can be used to implement other life-saving interventions. Extensive sensitivity analyses of all uncertain parameters at price parity showed the base-case results to be robust. When a small difference in vaccine price was included, it proved to be an overpowering driver of the relative cost effectiveness of the 2 vaccines.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2018.11.007.

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