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RESEARCH PAPER

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Cost-effectiveness of a national immunization program with the 13-valent pneumococcal conjugate vaccine compared with the 10-valent pneumococcal conjugate vaccine in South Korea

Hye-Young Kim[a], Seong-Beom Park[a], Eun-Sil Kang[b], Sang-Min Lee[b], Hyun-Jin Kim[a], and Matt Wasserman[c]

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ABSTRACT

Introduction: Globally, pneumococcal disease represents a significant burden. South Korea implemented the 7-valent pneumococcal conjugate vaccine (PCV7) in 2003, replaced with the 10-valent (PCV10) and 13-valent (PCV13) vaccine in 2010. In 2014, both vaccines were introduced in the national immunization program (NIP) for infants with 3 primary doses and one booster dose We performed a cost-effectiveness evaluation to elucidate which vaccine may be expected to provide greater impact if included in a NIP.

Methodology: Using an established model, we estimated the impact of introducing either PCV13 or PCV10 into the South Korean NIP in 2015. Vaccine impact was based on historic observed impact of PCV13 from 2010 to 2015 in Korea given high uptake of PCV13, and PCV10 impact was estimated based on experiences in countries using PCV10. Incidence and costs for all ages and including invasive pneumococcal disease, pneumonia, and acute otitis media were derived from the literature and Health Insurance Review and Assessment database.

Results: In the base-case, over 5-years PCV13 was estimated to avert 550,000 more cases of pneumococcal disease compared to PCV10, driven by broader serotype coverage and less replacement due to serotypes 3 and 19A. This translated to a cost-savings of $47.4 million USD despite PCV13's higher cost. Sensitivity analysis found incremental cost-effectiveness ratios (ICERs) ranged from cost-saving to $7,300 USD per quality-adjusted life year (QALY).

Conclusion: A NIP using PCV13 was estimated to have a more substantial public health impact and be cost-saving compared to a program with PCV10 due to broader serotype coverage.

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Introduction

Streptococcus pneumoniae (S. pneumoniae) is a gram-positive bacterium with more than 90 serotypes associated with diseases such as acute otitis media (AOM), pneumonia, and invasive pneumococcal diseases (IPD), such as bacteremia and meningitis. Although IPD is more severe and has a greater chance of leading to mortality, pneumonia and AOM represent a significant portion of the burden of disease and associated medical costs.[1,2]

Since the early 2000s, pneumococcal conjugate vaccines (PCVs) containing 7 (PCV7, Prevnar/Prevenar®, Wyeth Lederle Vaccines S.A.), 10 (PCV10, Synflorix®, GlaxoSmithKline Biologicals S.A.), and 13 serotypes (PCV13, Prevnar 13®, Wyeth/Pfizer Vaccines) have been developed and implemented around the world for use in routine infant immunization programs. PCV10 contains antigens for original seven serotypes in PCV7 (4, 6B, 9 V, 14, 18 C, 19 F, and 23 F) plus provides protection against 1, 5 and 7 F, while PCV13 contains the serotypes in PCV10 plus serotypes 3, 6A, and 19A (Supplementary Material S1). The dissemination and implementation of these vaccines into national immunization programs (NIPs) have substantially reduced the burden of vaccine-type pneumococcal disease in both vaccinated children, as well as adults from their impact on reducing transmission of pneumococcal carriage.[3,4]

The prevalence of serotypes causing diseases varies over time, regions and age. In South Korea, from 1996 to 2005, *S. pneumoniae* was the most common cause of invasive bacterial disease in children aged 3 months to 4 years.[5] PCV7 was first approved in June 2002 in South Korea and was used voluntarily in the private sector in a 3 + 1 schedule with 3 priming doses in the first year of life and a booster at one year. Before and during the private use of PCV7, IPD isolates from numerous hospitals in Korea from 1996 to 2008, serotypes 19 F (9.8%), 23 F (8.3%), 19A (7.8%), 6A (7.5%), 3 (7.3%), 9 V (6.5%), 6B (6.2%), 14 (4.9%), 1 (3.9%), 11A (3.9%) and 4 (3.1%) represented 69.2% of all isolates.[6]

After this private use, from 2006 to 2010 invasive isolates from 8 centers found a reduction in PCV7 serotypes isolates (4, 6B, 9 V, 14, 18 C, 19 F, 23 F, and cross-reactive 6A) from 62.5% to 21.4%.[7] Similarly, there was an increase in disease caused by non-vaccine serotypes 3, 6A, and 19A from 18.8% to 42.9%.[7]

In March 2010, PCV10 and PCV13 were approved in Korea and gradually replaced the PCV7 also as an optional use in private sector. After this introduction, IPD cases collected from January 2011 to December 2013 across 25 hospitals in Korea found that the proportion of serotype

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19A decreased from 37.5% in 2011 to 22.2% of all isolates in 2013.[8] Nasopharyngeal aspirates from children diagnosed with AOM from seven centers reported serotype 19A (22.4%), serogroups 11 (14.7%), and 15 (13.5%) as the most common *S. pneumoniae* serotypes in 2011 to 2012,[7,9] and nasopharyngeal aspirates from infants and children with respiratory symptoms from a single center reported serotypes 19A (14.0%), 23A (12.8%), 15B/C (10.7%), 11A (10.1%), 6 C (7.8%), and 6A (6.3%) as the most common serotypes in 2010–2015.[10] Overall, PCV proportion decreased after the use of the vaccine but still 19A was reported as the most predominant serotype.[8] Even though PCV13 and PCV10 were only used in the private setting, a nationwide survey of immunization revealed that 83.4% of infants younger than 2 received one or more doses of PCV and 70.4% received all 4 doses.[10] In May 2014, the first Korean pediatric pneumococcal NIP was implemented with a 3 + 1 schedule in infants and both PCV10 and PCV13 were included as a physician choice; however, 88.6% of infants are vaccinated with PCV13.[11]

Although a recent cost-effectiveness study by Zhang et al. estimated that PCV10 would be cost-saving compared to PCV13 in Korea,[12] it did not capture the full spectrum of health outcomes associated with introducing PCVs. Notably, Zhang et al. did not account for population-level indirect effects in older age groups due to reductions in carriage circulation, therefore imply that both PCVs would induce the same herd protection and have no impact on the results.

The objective of our study is to expand upon this body of evidence and estimate the clinical and economic impact of introducing a PCV13 or PCV10 NIP in Korea, while considering the full population-level impact of pneumococcal vaccination.

Methods

Model structure

We adapted a previously published epidemiologic forecasting model to estimate the impact of introducing either a PCV13 or PCV10 NIP in South Korea.[13,14] Briefly, owing to the uncertainty of translating clinical effectiveness data into real-world population-based vaccine impact, this model leverages the real world observed trends in individual serotypes to estimate the continued impact of either PCV13 or PCV10 in the Korean NIP.

Age- and serotype-specific incidence for each of the 13-vaccine serotypes included in PCV13 are modeled independently for each vaccine under investigation (Supplementary Material S2). Non-PCV13 serotypes are grouped together given low incidence rates of individual serotypes and for model simplicity. Historical behavior of IPD is captured as the best fit trend line to observed increases or decreases of each serotype in each age group in the presence or absence of vaccine pressure. Each IPD incidence trend line is assumed to begin at the point where that serotype is being covered by vaccine in the specific country under investigation. These trend lines are then assumed to continue for each in the presence or absence of vaccine pressure when PCV13 or PCV10 is being forecasted, depending on the serotype trend lines being evaluated. Therefore, this methodology captures vaccine pressure and its observed effects in surveillance data. For example, as PCV10 has shown cross-reactivity between serotype 19 F (contained in the vaccine) and serotype 19A in case control studies,[15,16] therefore using surveillance data would inherently capture this serotype behavior under real-world vaccine pressure. In addition, under vaccine pressure, modeled incidence rates can climb due to non-vaccine type serotype replacement. However, modeled incidence rates are capped to never surpass pre-PCV incidence levels despite some countries observing potentially higher rates of disease after serotype replacement in certain age groups.[17]

The benefit of this methodology is that it can capture changing serotype dynamics which has not been possible in models using "steady state" frameworks in the past.[12,18,19] These "steady state" models assume that serotype epidemiology is either constant, or has reached an equilibrium, which has shown not to be the case in numerous countries using PCVs given the consistency of serotype replacement of non-vaccine serotypes. One proposed approach to capture these dynamics is a transmission dynamic model; however, these models are extremely complex requiring numerous assumptions and have been shown to produce comparable results as static models.[20] In contrast, the methodology used in this study also allows a more simplified approach and dataset than alternative transmission dynamic models.[21,22]

Incidence rates of noninvasive disease are based on a proportional change relative to the forecasted changes in IPD. This is based on the assumption that increases or decreases in circulating carriage would equally be likely to cause IPD as noninvasive outcomes such as pneumococcal AOM or pneumococcal pneumonia. This methodology has been used in the pneumococcal modeling space both in a static forecasting framework similar to this model,[23] as well as in a dynamic modeling framework.[24,25] This methodology could be considered conservative as it does not consider the changes in all-cause pneumonia or AOM given the complexities of disentangling the etiology of disease and relative impact of each PCV on these outcomes.

Incidence rates of invasive and noninvasive disease are then used to calculate the number of cases of diseases expected with each vaccination program each year, and for each case a disutility, cost, and risk of mortality is estimated to derive the overall impact of each vaccine as well as the incremental cost-effectiveness ratio (ICER). All costs and outcomes are discounted at a rate of 5% and ICER was calculated over a 5-year time horizon in the base case.

Epidemiologic parameters

Incidence of IPD across all ages was derived from the Korean Center for Disease Control (KCDC) from 2005 through 2015 and is summarized in Table 1.[26] As this data is not serotype specific, incidence for each age group was weighted based on circulating serotypes reported in the literature. IPD cases in both infants and adults were assumed to be either pneumococcal meningitis, or pneumococcal bacteremia based on historical rates of disease.[5,7,8,26,27] Patients experiencing a case of pneumococcal meningitis also carry a risk of long-term sequelae from either epilepsy or hearing loss at a rate of 7% and 13%, respectively.[28,29]

Table 1. Epidemiologic inputs used in cost-effectiveness analysis.

Parameter	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Invasive Pneumococcal Disease[26]											
<2	1.92	1.30	2.26	1.54	2.36	1.53	2.70	1.35	1.61	1.64	1.64
2 to 4	1.18	0.72	0.96	1.57	0.55	0.84	1.50	0.55	0.75	0.94	0.94
5 to 17	0.28	0.36	0.35	0.43	0.34	0.30	0.33	0.24	0.28	0.38	0.38
18–34	0.42	0.40	0.41	0.37	0.35	0.32	0.42	0.33	0.48	0.39	0.39
35–49	0.42	0.40	0.41	0.37	0.35	0.32	0.42	0.33	0.48	0.39	0.39
50–64	1.11	0.89	1.02	0.92	0.96	0.98	0.83	0.95	0.87	0.80	0.80
≥65	2.24	2.66	3.17	3.20	2.70	2.00	2.61	2.66	2.48	2.33	2.33
Acute Otitis Media (age)*[12]											
0 to <2	57,785	57,785	57,785	57,785	57,785	57,785	57,785	53,162	48,909	44,996	41,397
2 to 4	80,011	80,011	80,011	80,011	80,011	80,011	80,011	73,610	67,722	62,304	57,320
Hospitalized Pneumococcal Pneumonia (age)[26]											
<2	201	123	100	71	63	54	59	50	45	63	63
2 to 4	306	276	190	115	105	101	110	90	64	100	100
5 to 17	70	72	39	37	53	45	42	30	22	26	26
18–34	17	21	10	12	21	19	15	10	10	12	12
35–49	21	21	13	13	14	14	12	11	9	13	13
50–64	27	27	21	21	19	15	14	12	9	15	15
≥65	53	52	43	43	42	22	23	18	15	19	19

*AOM incidence rates were reduced by 40.6% based on observed effectiveness in the US to account for sustained PCV use in lieu of available post PCV incidence of AOM in Korea.

Incidence of pneumococcal pneumonia was also derived from KCDC reporting from 2005 through 2014 for all age groups.[26] In Korea the majority of pneumonia cases are treated in the inpatient setting, and given there is limited evidence on the number of outpatient cases, we assumed all pneumococcal pneumonias to be inpatient cases based on clinical practice in Korea.[30] Rates of all-cause AOM were derived from a recent cost-effectiveness study and were only considered for 0-<2 and 2–4 year olds.[12] However, because these AOM rates were assumed pre-PCV, these were adjusted from 2010 to 2015 to reflect a small decline year on year to reflect increasing PCV use. This was based on data from the United States where a 3 + 1 PCV13 schedule was used.[31] However, because our model only considers pneumococcal AOM, we only considered relative rates of change for those 39.7% of AOM cases are assumed to be caused by the *S. pneumoniae* bacteria.[9] No consideration was made for AOM cases caused by other pathogens for either vaccine.

Both IPD and pneumococcal pneumonia cases were assumed to carry an age-specific risk of mortality based on published case fatality rates.[32–36] No risk of mortality was considered for AOM cases.

Economic parameters

Costs included vaccine acquisition and direct medical costs associated with disease outcomes. Costs associated with each outcome were derived from the 2018 Health Insurance Review and Assessment (HIRA) database based on Korean Standard Classification of Diseases (KCD) code: pneumococcal bacteremia (A403), pneumococcal meningitis (G001), pneumococcal pneumonia (J13), and otitis media (H66).[37] For otitis media and pneumonia, outpatient cost was used for mild cases and inpatient cost for moderate and severe cases. Additional costs related to sequelae from meningitis were not included to avoid double counting. Costs are reported in US Dollars in Table 2.

Both PCV13 and PCV10 were assumed to be given in a 3 + 1 schedule at a price of 56 USD and 48 USD per dose in 2018, respectively, based on the Korean NIP program implemented by KCDC. In addition, vaccine administration fee of 17 USD was considered.[38]

Utility decrements were applied for each disease outcome. Annual decrements of 0.0079 and 0.0232 were assumed for bacteremia and meningitis, respectively.[39] Meningitis-related sequelae utility decrements were considered for neurological impairment (0.40) and hearing loss (0.20).[40,41] AOM, and pneumococcal pneumonia carried decrements of 0.005 and 0.006, respectively.[42] Both costs and outcomes were discounted at a rate of 5%.

Base case assumptions

In the base case analysis, incidence of pneumococcal disease is forecasted based on circulating disease with either a PCV13 only or PCV10 only immunization program. In the base case, impact of PCV13 is estimated based on the trends observed from 2010 through 2015 in Korea while PCV10 trends are assumed based on historic trends observed in Finland and applied to the baseline Korean epidemiology.[17]

The base case also assumes that any change in serotype epidemiology between the two vaccines would take at least one year given a sizable portion of the infant population would need to be vaccinated with one vaccine or another. Indirect effects for pneumococcal pneumonia were also included in the base case analysis and results were estimated over a 5 year time horizon as serotype trends become less reliable over longer time periods given changes in vaccination rates and antibiotic resistance.

Sensitivity analysis

Given South Korea has not used a single vaccine in its NIP, sensitivity analyses were undertaken leveraging serotype behavior trends from several different countries to test uncertainties around future serotype behavior. For

Table 2. Cost, utility and case fatality parameters used in cost-effectiveness analysis.

	Age range (years)						
Parameter	<2	2 to 4	5 to 17	18–34	35–49	50–64	≥ 65
Population							
Percentage of IPD presenting as meningitis[5,32]	47.8%	27.1%	48.0%	16.3%	16.3%	6.6%	6.4%
Direct costs (USD$)[37]							
Bacteremia	$3515.00	$3515.00	$3515.00	$3515.00	$3515.00	$3515.00	$3515.00
Meningitis	$3681.00	$3681.00	$3681.00	$3681.00	$3681.00	$3681.00	$3681.00
Hospitalized pneumonia	$1730.00	$1730.00	$1730.00	$1730.00	$1730.00	$1730.00	$1730.00
Acute otitis media	$60.00	$60.00					
Case-fatality rates[26,32,35]							
Bacteremia	5.6%	5.6%	5.6%	18.4%	18.4%	26.9%	40.7%
Meningitis	15.6%	11.6%	6.4%	18.4%	18.4%	26.9%	40.7%
Hospitalized pneumonia	0.1%	0.1%	0.1%	7.0%	7.0%	7.0%	7.0%

PCV13, trends from the United States were used given that it also uses a 3 + 1 schedule similar to South Korea[43] and the United Kingdom was used given its higher level of serotype placement observed compared to other PCV13 countries.[44] No country currently uses a 3 + 1 PCV10 schedule in a full NIP with robust surveillance, so we also leveraged data from the Netherlands to determine an alternative trajectory of disease with PCV10.[45,46]

Additional sensitivity analyses were undertaken varying the time horizon (10 and 20 years) and the percent of AOM that is assumed to be caused by *S. pneumoniae* (25%, 50%). Additionally, because South Korea does not use a single NIP, we varied the time before the serotype incidence trends would diverge in sensitivity analysis. This was varied by assuming the vaccines would produce the same benefit for 1- or 2-years post implementation given that previous cohorts of infants would have been largely protected by PCV13 given its widespread use.

One-way sensitivity analyses were also undertaken by varying the remainder of model variables by 95% Confidence intervals where available, or by ± 10% around the base case value. Probabilistic sensitivity analysis was also undertaken using a second-order Monte Carlo simulation with 1,000 iterations in which all parameters were varied. Maximum disease incidence reemergence limits, time to disease reemergence, costs, and all-cause mortality were drawn from a gamma distribution. All other parameters were drawn from a beta distribution.

Results

Base case

At the year of modeled vaccine introduction, 11% of all IPD cases in 0-<2 year olds (1.64 per 100,000) and 38% of IPD cases in 65+ year olds (2.33 per 100,000) were estimated to be caused by PCV13 serotypes, with the remaining disease caused by non-PCV13 serotypes (Figure 1). Because vaccine-type disease and overall incidence of IPD are low in South Korea the model assumes that disease has reached somewhat of an equilibrium, allowing minimal additional reductions in vaccine-type disease. Therefore, both PCV13 and PCV10 were predicted to cause serotype replacement and have a marginal net increase of 0.51 cases and 1.06 cases of IPD per 100,000 in 0-<2 year olds 5-years following NIP implementation, respectively. These rates, however, are still lower than pre-PCV incidence, highlighting an overall reduction in disease since introduction of PCVs. The higher level of replacement with PCV10, however, was driven by serotypes 3 and 19A, which were estimated to form most of the disease burden in the PCV10 arm. Non-PCV13 type disease increased in the PCV13 arm in all age groups but net changes were less significant than in the PCV10 arm due to broader protection against serotype 3 and 19A. This was consistent in the 65+ age group where the incidence of IPD increased by 0.29 cases per 100,000 in the PCV13 arm, and by 0.87 cases per 100,000 in the PCV10 arm. In contrast to 0–2 year olds, there was a steady increase in serotype 3 in both the PCV13 and PCV10 groups.

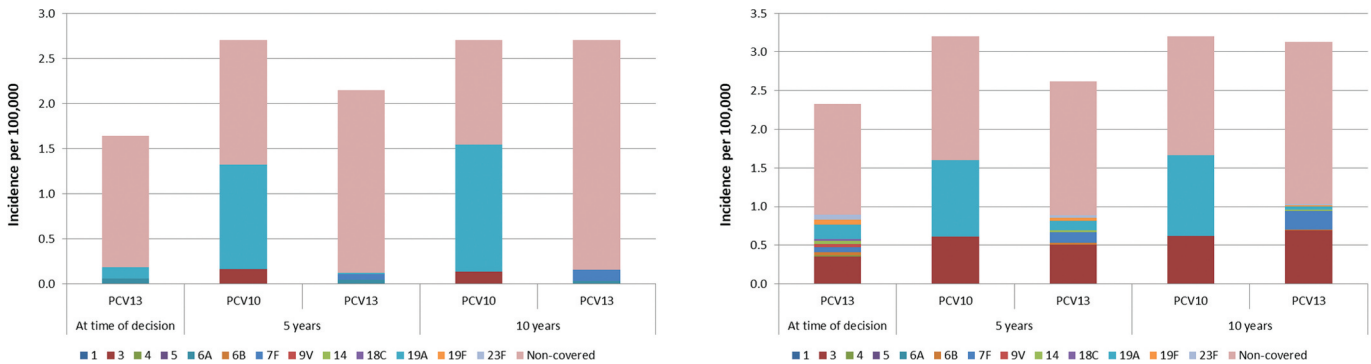

Figure 1. Incidence of IPD today and in 5 and 10 years from now given a PCV10 and PCV13 vaccination policy in individuals aged 0 to 2 years and ≥65 years. Figure 1 presents the impact of an infant vaccination program with PCV10 and PCV13 in individuals aged 0 to 2 years (Figure 1a) and those 65+ (Figure 1b) in Korea at the time of switch and over the next 5 and 10 years. PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Table 3. Prospective impact of a PCV13 or PCV10 NIP over 5 years.

Parameter	PCV13 Program	PCV10 Program	Incremental
Outcome			
Number of cases of:			
IPD	2370	2956	−586
Pneumococcal AOM	2,602,436	3,107,409	−504,973
Hospitalized pneumococcal pneumonia	56,365	107,186	−50,821
Total cases	**2,661,171**	**3,217,551**	**−556,379**
Deaths	3183	5309	−2126
QALYs	184,212,041	184,205,503	6537
Costs			
Vaccine-related	$396,227,238	$339,622,828	$56,604,411
IPD direct medical	$7,210,119	$9,013,219	−$1,803,099
Pneumonia direct medical	$83,973,075	$159,232,950	−$75,259,875
AOM direct medical	$134,625,456	$161,586,490	−$26,961,034
Total costs	**$622,035,889**	**$669,455,487**	**−$47,419,598**
Incremental cost-effectiveness			PCV13 Cost-Saving

AOM, acute otitis media; IPD, invasive pneumococcal disease; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life-year.

Table 3 presents the cumulative number of cases of pneumococcal disease, costs, and deaths associated with implementing either a PCV10 3 + 1 or PCV13 3 + 1 NIP over 5 years in South Korea. Based on forecasted serotype trends, model estimates determined that a PCV13 only NIP in South Korea would result in 556,379 fewer cases of pneumococcal disease compared to a PCV10 only NIP. Based on these cases, there would also be a reduction in over 2,000 pneumococcal deaths with PCV13 compared to PCV10. Despite an additional 56 USD million USD investment cost in a PCV13 only NIP, overall use of PCV13 would result in a net-savings of 47 USD million USD due to less disease cases. This resulted in a PCV13 only NIP being a cost-saving strategy compared to a PCV10 only NIP over a 5-year time horizon.

Sensitivity analysis

In scenario analysis varying trend line assumptions (Table 4), PCV13 remained cost-saving except when Netherlands trends were used for PCV10 and United Kingdom trends were used for PCV13; however, PCV13 remained highly cost-effective at 15,210 USD per quality-adjusted life year (QALY) (<1xGDP per capita). When lengthening the model time horizon and varying the percent of AOM cases that are caused by *S. pneumoniae*, PCV13 remained cost-saving across all scenarios. When assuming the two vaccines would produce an equivalent effect for 2 years, the ICER increased to 7,373 USD per QALY.

The remainder of one-way sensitivity analyses remained cost-saving when varying upper and lower bound values by 10% in one-way sensitivity analysis (Figure 2). In 1,000 simulations in probabilistic sensitivity analysis around the base case, 97.6% of simulations remained cost-saving, with 2.4% of simulations remaining cost-effective under 5,000 USD per QALY (Figure 3).

Discussion

The objective of this modeling exercise was to add to the existing literature on PCVs in South Korea by estimating the national impact of using either a 3 + 1 PCV13 or 3 + 1 PCV10 NIP rather than the current NIP where both vaccines are used. Our model estimated that a single source NIP with PCV13 would be cost-saving compared to a program with PCV10, preventing over 550,000 cases of pneumococcal disease and 2,000 associated deaths. Despite the higher investment cost, PCV13 was determined to be a cost-saving strategy in the base case analysis and was robust to numerous different sensitivity analyses. In one scenario where the two vaccines were assumed to produce short-term comparable effects based on the routine use of both vaccines in clinical practice in South Korea, the ICER was highest in this study at 7,373 USD per QALY. However, recent evidence from Belgium where routine practice changed from PCV13 to PCV10 found that serotype dynamics have rapidly changed, resulting in a 10 fold increase in 19A cases in 0–2 year olds; therefore, our base-case results are likely justified and may even be considered conservative.[47,48] Results of this exercise highlight the importance of providing broad PCV coverage, which will be important to reconsider as higher valency PCVs become available.[49] Higher-valent PCVs may add even more clinical and economic benefit by preventing more disease burden due to additional serotypes in their formulations. Thus, increased serotype protection by the highest-valent PCV available can drive direct health-care cost-savings and improve cost-effectiveness results, which was demonstrated in this analysis. The impact of switching from PCV13 to a higher valency PCV in the NIP will need to be considered to maintain the broadest coverage considering local epidemiology both in terms of direct protection, as well as overall population impact through indirect effects. For example, local assessment of the most prevalent serotypes and a PCV's potential to reduce the total pneumococcal disease burden which might increase without the broadest coverage due to serotype replacement.

Our findings are consistent with numerous previously published models looking at the cost-effectiveness of PCV13 versus PCV10.[13,14,18,50-52] While there is a body of evidence, including a recent study in South Korea, found PCV10 to be cost-saving compared to PCV13,[12,53-55] these analyses are driven primarily by a supposed impact of PCV10 on AOM including AOM-

Table 4. Scenario analyses of a PCV13 NIP compared with a PCV10 NIP in South Korea.

Parameter	Incremental cost	Incremental QALYs	ICER
Base Case	−$47,419,598	6537	PCV13 Cost-Saving
Trend Line Analysis			
PCV13 South Korea/PCV10 Netherlands	−$14,901,478	4660	PCV13 Cost-Saving
PCV13 US/PCV10 Finland	−$78,809,117	9174	PCV13 Cost-Saving
PCV13 US/PCV10 Netherlands	−$46,290,996	7296	PCV13 Cost-Saving
PCV13 UK/PCV10 Finland	−$6,433,955	3593	PCV13 Cost-Saving
PCV13 UK/PCV10 Netherlands	$26,084,165	1715	$15,210/QALY
Time Horizon			
10 Years	−$25,277,949	13,713	PCV13 Cost-Saving
20 Years	−$14,086,452	26,352	PCV13 Cost-Saving
Lag in serotype divergence			
1 Years	−$1,570,895	4249	PCV13 Cost-Saving
2 Years	$18,366,678	7374	$7,373 USD/QALY
Varying Percent AOM cases caused by *S. pneumoniae*			
25%	−$245,964	4459	PCV13 Cost-Saving
50%	−$63,584,114	9918	PCV13 Cost-Saving

IPD, invasive pneumococcal disease; AOM, acute otitis media; QALY, quality-adjusted life-years.

[a]Alternate trend lines apply trends from each country to serotype distribution in the year of switch in Mexico to estimate sensitivity of potential serotype replacement

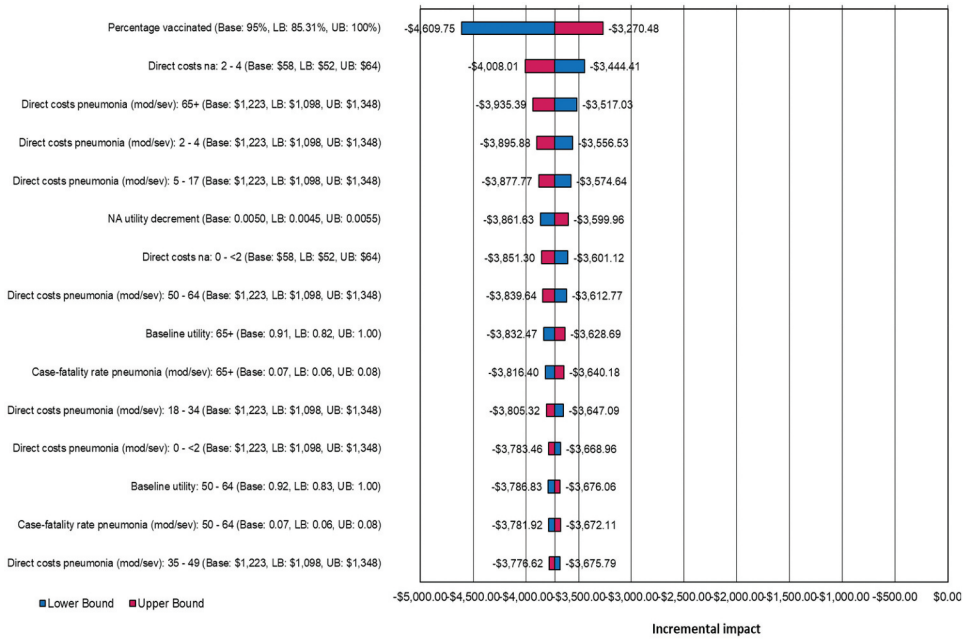

Figure 2. One-way sensitivity analysis: PCV13 versus PCV10 incremental cost per quality-adjusted life-year. Figure 2 presents the results of the one-way sensitivity analysis for PCV13 versus PCV10. Red-shaded bars represent the incremental cost-effectiveness ratio at the upper bound of the input parameter estimate, and blue-shaded bars represent the incremental cost-effectiveness ratio at the lower bound of the parameter estimate.

associated tube replacement caused by *non-typeable haemophilus influenzae* (NTHi). However, this benefit was based on evidence from an investigational 11-valent vaccine rather than from the PCV10 vaccine,[56] and there have not been any real-world population-based studies to demonstrate any statistically significant effect of PCV10 on AOM caused by NTHi. In contrast, there are several studies that have suggested PCV13 prevents AOM cases caused by NTHi given the likelihood for PCV13 to avert more severe early onset vaccine-type pneumococcal otitis that then reducing late-stage non-pneumococcal pathogens.[57–59] However, considering this contrasting evidence, our model conservatively did not include any benefits for non-pneumococcal pathogens.

Our study differs from the recent publication by Zhang et al. (2018) for other important reasons aside from excluding NTHi.[12] First, we leveraged real-world population-level surveillance data to model serotype dynamics and vaccine impact across all ages. This methodology captures nuances of vaccine introduction such as uptake, indirect effects, and serotype replacement, and by including sensitivity analyses using different experiences with both vaccines, various potential serotype trajectories could be explored. This is specifically important given the assumption made by Zhang et al. that PCV10 provides cross-protection against serotype 19A based on case-control studies undertaken in Finland and Brazil.[15,16] However, in both countries surveillance data have since

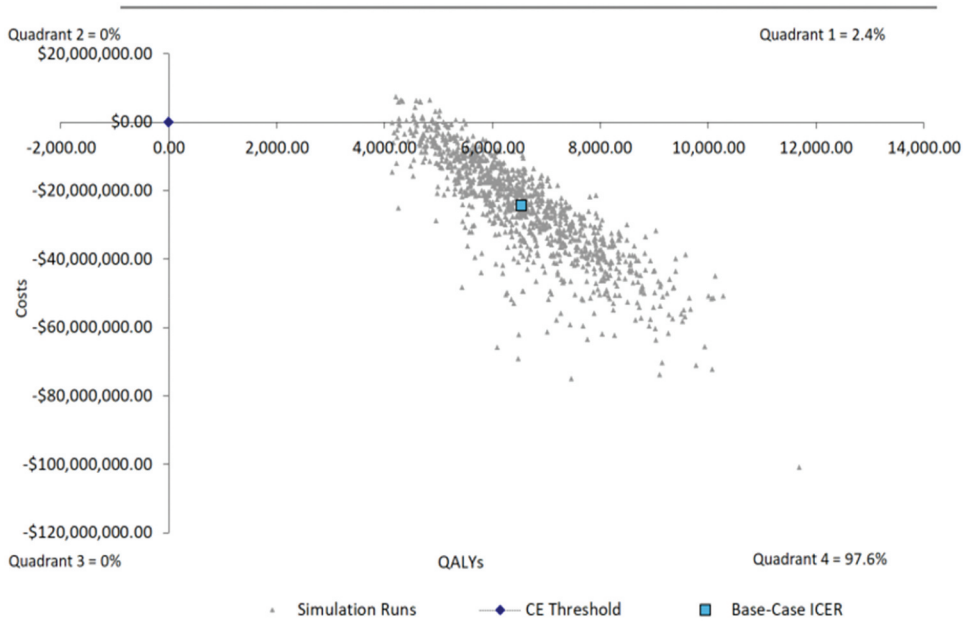

Figure 3. Probabilistic sensitivity analysis for Base Case Analysis. Figure 3 presents the results of a first-order Monte Carlo simulation with 1000 simulations. Gray dots represent the incremental cost and QALY results for each of 10,000 iterations of the simulation. The blue square represents the base case incremental cost and QALY estimate. ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

shown increases in 19A disease, which now represents a significant proportion of pneumococcal disease in both countries[60,61] and there have been several recent studies pointing to limited cross-protection from PCV10 against 19A.[62,63] Furthermore, recent real-world evidence has emerged from Belgium where 18 months following a change from PCV13 to PCV10 there was a 10 fold increase in cases of 19A in children 0-<2 years olds [47]. Second, our model includes the indirect effects afforded by both vaccines reducing vaccine-type disease in unvaccinated age groups as well as the impact on serotype replacement. There is a significant body of evidence demonstrating the effect of PCVs on unvaccinated age groups for both PCV10 and PCV13,[4,64] demonstrating that the broader serotype coverage afforded by PCV13 results in less serotype replacement in older ages. Therefore, by ignoring this important impact, much of the value of pneumococcal vaccination is excluded. Finally, Zhang et al. (2018) assume that PCV13 provides 0.0% vaccine efficacy (VE) for PCV13 against disease caused by serotype 3. Like serotype 19A, our model estimates impact of PCV13 on serotype 3 based on real-world surveillance changes. In children, our model estimated that serotype 3 remained at low levels given limited observed cases in South Korea. This is consistent with a recent meta-analysis that found PCV13 to have a positive statistically significant direct effect against serotype 3.[65] In contrast, our model found serotype 3 disease in adults to increase in both the PCV13 and PCV10 arm, highlighting potentially limited indirect effect of PCV13 against serotype 3. This is consistent with a clinical trial comparing PCV7 and PCV13 which found no efficacy against serotype 3 carriage.[66]

Despite the strengths of our modeling exercise, there are several important limitations. First, our model assumes that serotypes move in a constant direction based on historical behaviors. While these trend lines are based on up to 8 years of vaccine history in most cases, changes in population dynamics and antibiotic use could possibly alter the trajectories of specific serotypes. We attempted to mitigate for these uncertainties by varying trend lines from several different countries to try to capture different serotype behaviors, under which scenarios our results remained consistent; however, these results should be updated as more years of surveillance become available to reflect changes in both vaccine and non-vaccine serotypes.

A second limitation in our study is the lack of nationwide surveillance system for pneumococcal disease in South Korea. Our study relied on time-specific, hospital-based reports for serotype-specific incidence data; most of which were based on confirmed cultured cases. Therefore, our study and the incidence reports used to generate model estimates, likely underestimate the true burden of pneumococcal disease in South Korea. Further research is necessary to fully evaluate the burden of invasive and noninvasive pneumococcal disease outcomes.

Finally, our model assumes a constant proportion of AOM cases are caused by *S. pneumoniae* and does not make any consideration for AOM cases caused by other pathogens such as NTHi. As already discussed, evidence has suggested PCVs may reduce noninvasive disease caused by other pathogens, but this was deemed outside the scope of our study. As these vaccines are used however, the proportion of disease caused by each pathogen would change and therefore the total proportion of disease impacted by PCVs would alter over time. The model presented is limited in that it assumes the proportion of AOM and pneumonia caused by *S. pneumoniae* is static, which may over or underestimate the impact of PCVs. However, data have demonstrated that there is a strong correlation between changes in IPD and noninvasive pneumococcal disease outcomes,[67] and that there is a multiplicative relationship between these outcomes.[21,23,24] So, while the overall proportion of disease may change, our model captures the relative

transmission dynamics between serotypes, so the overall conclusions should remain robust when choosing PCV13 versus PCV10. In addition, one-way sensitivity analysis found that the proportion of noninvasive disease caused by *S. pneumoniae* was not a variable that significantly impacted the results of our analysis (Table 4).

Some parts of the benefit of vaccination program are difficult to capture and evaluate due to lack of reliable information. One of the vaccination benefits is reduction of antibiotic-resistant pneumococcus and change of antibiotic-resistant serotypes. The vaccine efficacy change and the potential herd effect from decreased antibiotic resistance is difficult to be assessed; however, a recent systematic review found consistent reductions in antimicrobial resistance of *S. pneumoniae* isolates following the introduction of PCVs in NIPs.[68] As resistance is considered as a risk factor for infections, antibiotic-resistance reduction could have additional benefits not measured in the current analysis and this should be considered in future research on the impact of PCVs in South Korea.

Conclusion

This model represents the first population-based analysis to estimate the population-level impact of implementing either a PCV10 or PCV13 program in South Korea, taking into consideration all serotype dynamics and indirect effects. While net vaccine acquisition cost may be lower with PCV10 compared to PCV13, when implementing NIPs it is integral to consider the impact of vaccines on total vaccine-preventable disease and their value for money.

Contributors

HYK, ESK, SML, SBP, HJK, and MW conceived and designed the analysis; HYK, ESK, SML, SBP, HJK, and MW collected the data; HYK, ESK, SML, SBP, HJK, and MW analyzed and/or interpreted the results; HYK, ESK, SML, MW wrote the first draft; HYK, ESK, SML, SBP, HJK, and MW critically reviewed the content and approved the final version.

Data sharing

Data used for the analyses are available on request.

Disclosure of potential conflicts of interest

HY Kim and ES Kang are employees of Pfizer Ltd. and M Wasserman is an employee of Pfizer Inc. SB Park, SM Lee, and HJ Kim are no longer an employee of Pfizer Ltd. but were when this study was conducted.

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Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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