

RESEARCH PAPER



Health and economic burden associated with 15-valent pneumococcal conjugate vaccine serotypes in Korea and Hong Kong

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ABSTRACT

Use of pneumococcal conjugate vaccines (PCVs) has greatly reduced the incidence of invasive pneumococcal disease (IPD). V114 (VAXNEUVANCE™, Merck Sharp & Dohme Corp. a subsidiary of Merck & Co. Inc. Kenilworth, NJ, USA) is a 15-valent PCV currently approved in adults in the United States, containing the 13 serotypes in licensed PCV13 and 2 additional serotypes (22F and 33F) which are important contributors to residual pneumococcal disease. This study quantified the health and economic burden of IPD attributable to V114 serotypes in hypothetical birth cohorts from Korea and Hong Kong. A Markov model was used to estimate the case numbers and costs of IPD in unvaccinated birth cohorts over 20 years. The model was applied to 3 scenarios in Korea (pre-PCV7, pre-PCV13, and post-PCV13) and to 2 scenarios in Hong Kong (pre-PCV7 and post-PCV13). For Korea, the model predicted 62, 26, and 8 IPD cases attributable to V114 serotypes in the pre-PCV7, pre-PCV13, and post-PCV13 scenarios, respectively. Costs of V114-type IPD fell from \$1.691 million pre-PCV7 to \$2.212 million post-PCV13. For Hong Kong, the model estimated 62 V114-associated IPD cases in the pre-PCV7 scenario and 46 in the post-PCV13 scenario. Costs attributed to all V114 serotypes were \$2.322 million and \$1.726 million in the pre-PCV7 and post-PCV13 periods, respectively. Vaccine-type serotypes are predicted to cause continuing morbidity and cost in Korea (19A) and Hong Kong (3 and 19A). New pediatric pneumococcal vaccines must continue to protect against serotypes in licensed vaccines to maintain disease reduction, while extending coverage to non-vaccine serotypes.

ARTICLE HISTORY

Received 20 September 2021
Revised 16 February 2022
Accepted 22 February 2022

KEYWORDS

Pneumococcal infections; vaccines, conjugate; Asia; streptococcus pneumoniae; cost of illness

Introduction

Streptococcus pneumoniae is a gram-positive bacterium that causes both invasive and noninvasive pneumococcal disease. Noninvasive manifestations include otitis media and non-bacteremic pneumococcal pneumonia (NBPP), while invasive pneumococcal disease (IPD) syndromes include bacteremic pneumonia, bacteremia without focus, and meningitis.^{1,2} Despite a substantial epidemiologic decline at the beginning of the 21st century, pneumococcal disease remains a significant source of morbidity and mortality in infants and children worldwide, causing an estimated 318,000 deaths in children <5 years in 2015.³ In East Asia, incidence data for IPD are somewhat sparse, but reported incidence values in children <5 years range from 13/100,000 in Japan from 2003–2005⁴ to 422/100,000 in Taiwan in 2006.⁵ Case fatality rates in this region range from 1.6% in Japan to 8.1% in Taiwan.⁴ In Hong Kong, the incidence of IPD in children ≤5 years was reported to be 15.6/100,000,⁶ and the risk of death was found to be significantly increased (odds ratio 3.26) among children admitted to a pediatric intensive care unit (PICU) with pneumococcal disease compared to those without pneumococcal disease.⁷ A 10-year analysis of data from this PICU showed a mortality rate of 20% among patients with IPD.⁸

Global surveillance has shown that, among the more than 90 known pneumococcal serotypes, only a small number cause a majority of IPD.^{9,10} These are the serotypes contained in past

pediatric pneumococcal conjugate vaccines (PCVs), which were introduced to the market in the early 2000s. The first PCV was heptavalent (PCV7) and contained serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F.² Since then, PCV13, a 13-valent vaccine, which contains all the PCV7 serotypes plus an additional 6 serotypes: 1, 3, 5, 6A, 7F, and 19A (“PCV13-specific” serotypes) has been introduced.² The introduction of PCVs via infant immunization schedules has led to substantial decreases in IPD associated with vaccine-targeted *S. pneumoniae* serotypes in children, and has indirectly benefited adult populations.¹¹ However, the emergence of non-PCV serotypes has been observed,^{12–16} and select vaccine-targeted serotypes, such as 3^{8,17} and 19A,^{12,13} continue to persist in East Asian populations.

In a recent global systematic review including results from 27 countries published between 2010–2015, serotypes 22F and 33F were two of the most commonly observed non-PCV13 serotypes in children with IPD,¹⁶ and a new 15-valent PCV, V114 (VAXNEUVANCE™, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA), includes serotypes 22F and 33F as well as the PCV7- and PCV13-specific serotypes. V114 has been approved by the United States Food & Drug Administration for use in adults aged ≥18 years and is undergoing clinical trials in pediatric populations. To demonstrate the need for continued protection against established serotypes while also expanding serotype coverage, this study quantified the health and

economic burden of IPD attributable to all 15 serotypes in V114 using two hypothetical birth cohorts from Korea and Hong Kong. IPD cases and costs attributable to all 15 V114 serotypes were estimated prior to and following PCV7 and PCV13 introduction.

Methods

Model design

A Markov model with three health states—no pneumococcal disease, IPD (meningitis and bacteremia including bacteremic pneumonia [BP]), and death (Figure 1)—was adapted from a previous analysis.¹⁸ At the start of the model, an unvaccinated birth cohort enters into the “no pneumococcal disease” state and is at risk of developing IPD. The probability of an infant developing pneumococcal disease varies by age over the time horizon of the model. During each cycle, some individuals move into the IPD state based on the annual incidence. Those who are in the bacteremia (including BP) state may die due to their infection, with rates based on case fatality rates. Background mortality is applied to all states in the model. The model assumed that infants could experience only one IPD event during each year and that IPD could lead to either recovery (return to the no pneumococcal disease health state) or death. Post-meningitis sequelae, NBPP, and acute otitis media were not considered in the model. Indirect protection of adults via pediatric vaccination was not considered because the model included an unvaccinated birth cohort.

Model inputs

Cohorts of unvaccinated infants born in 2018 in Korea and Hong Kong were modeled over 20 years to estimate cases, deaths, direct medical costs, and indirect costs for IPD. Based on local census data, the total cohort consisted of 336,309 newborns in Korea¹⁹ and 56,890 newborns in Hong Kong.²⁰ The model tracked each infant up to 20 years of age or death, whichever occurred first.

Epidemiologic and economic parameters were retrieved from the literature. PCVs were introduced intermittently in Korea—PCV7 in 2003, the 10-valent PCV (PCV10, which contains the PCV7 serotypes plus serotypes 1, 5, and 7F) in 2010, and PCV13 in 2010—so incidence and serotype distribution data were available for three eras: pre-PCV7, pre-PCV13, and post-PCV13.^{21–23} Epidemiological inputs for Korea are shown in Table 1. In all three eras, the case fatality rates were 9.5% for meningitis and 5.6% for bacteremia.²⁴ In Hong Kong, PCVs were incorporated consecutively into the childhood immunization program (PCV7 in 2009, PCV10 in 2010, and PCV13 in 2011), so outcomes were only estimated for two eras, pre-PCV7 and post-PCV13, and incidence and serotype distribution data were retrieved for those two eras.^{6,25,26} Epidemiological inputs for Hong Kong are shown in Table 1. In both eras, the case fatality rates were 9.0% for meningitis and 4.6% for bacteremia.^{27,28} For both analyses, the case fatality rates retrieved from the literature reflected current access to care and medical treatment for IPD.

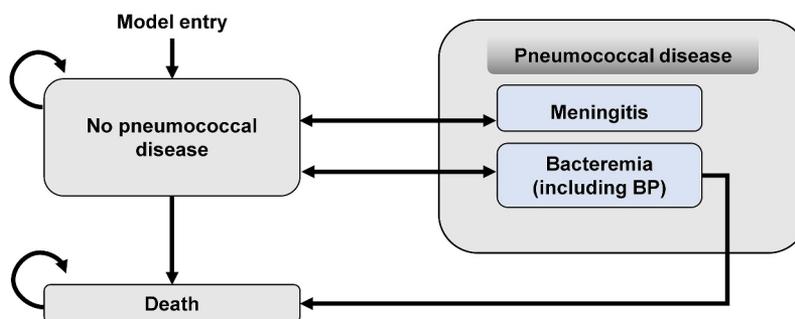


Figure 1. Structure of the Markov model. BP, bacteremic pneumonia

Table 1. Epidemiological inputs for Korea and Hong Kong.

	Pre-PCV7			Pre-PCV13			Post-PCV13		
	PCV7-specific	PCV13-specific	V114-specific	PCV7-specific	PCV13-specific	V114-specific	PCV7-specific	PCV13-specific	V114-specific
Korea									
Incidence of IPD (per 100,000 persons per year) ^a									
0–1 years	2.93	0.97	0.0	0.27	1.06	0.04	0.04	0.15	0.04
2–3 years	1.36	0.45	0.0	0.08	0.33	0.01	0.04	0.16	0.04
4–12 years	0.33	0.11	0.0	0.05	0.20	0.01	0.01	0.05	0.01
13–18 years	0.27	0.09	0.0	0.05	0.19	0.01	0.02	0.07	0.02
Hong Kong									
Incidence of IPD (per 100,000 persons per year) ^b									
0–2 years	16.84	0.66	0.0	-	-	-	0.17	2.51	0.0
3–5 years	13.98	0.55	0.0	-	-	-	0.72	10.47	0.0
6–14 years	0.81	0.06	0.0	-	-	-	0.17	2.44	0.0

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

^aSources: Lee et al., Cho et al., and Korea Disease Control and Prevention Agency.^{21,22,23} The incidence for the 13–18 year age group was used for individuals up to 20 years of age.

^bSources: Ho et al., Ho et al., and Hong Kong Center for Health Protection.^{6,25,26} The incidence for the 6–14 year age group was used for individuals up to 20 years of age.

Table 2. Cost inputs for Korea and Hong Kong.

	Korea	Hong Kong
Direct medical cost per episode ^a		
Meningitis	\$13,033	\$18,425
Bacteremia	\$6,078	\$12,230
Indirect medical cost per episode ^b		
Meningitis	\$1,024	\$473
Bacteremia	\$651	\$528

Costs are reported in 2020 USD.

^aSource: Korea: Zhang et al.²⁴ Hong Kong: Wu et al.²⁸

^bSources: Korea: Myers et al. and Olarte et al.^{29,30} and <https://tradingeconomics.com/south-korea/wages>. Hong Kong: Wu et al.²⁸

Direct medical costs were obtained from the literature^{24,28} and estimated from the healthcare perspective. Cost inputs for Korea and Hong Kong are shown in Table 2. A societal perspective considered direct medical costs and indirect costs, including productivity losses linked to premature death among children, and productivity losses among adult caregivers. However, due to lack of data on out-of-pocket costs, they were not included. For Korea, costs were updated to 2020 US dollars (USD) and discounted at 4.5% annually.³¹ For Hong Kong, costs were updated to 2020 USD and discounted at 3% annually.^{32,33} Cost updates were performed using the medical component of the consumer price index^{34,35} and publicly available currency conversion ratios.^{36,37}

Model outputs

Health and economic outputs were estimated for Korea under three scenarios (pre-PCV7, pre-PCV13, and post-PCV13), and for Hong Kong under two scenarios (pre-PCV7 and post-PCV13). Disease incidence and serotype distributions corresponding to each vaccination era were applied to all 15 serotypes in V114. Outcomes included cases of IPD, mortality, and costs of IPD by serotype.

Sensitivity analysis

Deterministic sensitivity analysis was utilized to assess the impact of uncertainties around key parameters and assumptions in the pre-PCV7 scenario only. The following assumptions were explored: incidence rate of IPD $\pm 20\%$ (.8-1.2 the base case value), case fatality rate of IPD $\pm 20\%$ the base case value, direct medical costs and indirect costs associated with treating meningitis and bacteremia $\pm 20\%$ the base case value, and discount rates of 0% or 5%.

Results

Health and economic burden of V114-targeted pneumococcal serotypes in Korea

Cases of IPD by serotype

In the model for Korea, V114 serotypes caused 62, 26, and 8 IPD cases in the pre-PCV7, pre-PCV13 and post-PCV13 scenarios, respectively (Table 3). In the pre-PCV7 scenario, the majority of cases (46 cases, 75%) were attributable to the PCV7 serotypes. Most cases were attributable to serotype 19A in the pre-PCV13 scenario (18 cases, 67%) and the post-PCV13 scenario (4 cases, 44%). PCV13-specific serotypes increased from 15 cases in the

Table 3. IPD cases attributable to V114 serotypes in the pre-PCV7, pre-PCV13, and post-PCV13 periods in Korea and Hong Kong^a

	Korea			Hong Kong	
	Pre-PCV7	Pre-PCV13	Post-PCV13	Pre-PCV7	Post-PCV13
PCV7-specific serotypes	46 (75)	5 (19)	1 (17)	59 (96)	3 (6)
PCV13-specific serotypes	15 (25)	21 (78)	5 (67)	3 (4)	43 (94)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)	1 (2)	38 (83)
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6A	8 (12)	3 (11)	1 (11)	1 (2)	0 (0)
7F	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)
19A	8 (12)	18 (67)	4 (44)	0 (0)	5 (10)
V114-specific serotypes	0 (0)	1 (3)	1 (17)	0 (0)	0 (0)
All V114 serotypes	62	26	8	62	46

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine

^aData are presented as n (%). Some totals sum to more or less than 100% due to rounding.

pre-PCV7 scenario to 21 cases in the pre-PCV13 scenario. The increase was primarily due to an increase in serotype 19A from 8 cases in the pre-PCV7 scenario to 18 cases in the pre-PCV13 scenario. V114-specific serotypes 22F and 33F accounted for 0 (0%), 1 (3%), and 1 (17%) IPD cases in the pre-PCV7, pre-PCV13, and post-PCV13 scenarios, respectively.

Mortality by serotype

The number of estimated deaths in Korea associated with V114 serotypes was 4 in the pre-PCV7 scenario, 2 in the pre-PCV13 scenario, and 1 in the post-PCV13 scenario (data not shown). Most of these deaths (75%) were attributable to PCV7-specific serotypes in the pre-PCV7 scenario. In the pre-PCV13 and post-PCV13 scenarios, deaths were attributable to the six additional serotypes in PCV13.

Costs of IPD by serotype

Total discounted costs (direct and indirect) in Korea due to V114 serotypes were estimated to be \$1.691 million in the pre-PCV7 scenario, \$743 million in the pre-PCV13 scenario, and \$212 million in the post-PCV13 scenario (Table 4). PCV7-specific serotypes accounted for the majority of costs in the pre-PCV7 scenario (\$1.269 million, 75%). Costs due to PCV13-specific serotypes increased from \$442 million (25%) in the pre-PCV7 scenario to \$578 million (78%) in the pre-PCV13 scenario. This was primarily due to increases in costs attributable to serotype 19A from \$211 million (12%) to \$496 million (67%). Total costs associated with V114-specific serotypes 22F and 33F were \$0 in the pre-PCV7 scenario, \$0.020 million (3%) in the pre-PCV13 scenario, and \$0.035 million (17%) in the post-PCV13 scenario.

Sensitivity analysis

The discounted total cost was sensitive to uncertainties around all key parameters, especially the discount rate (Table 5). When the discount rate was 0% or 5%, total costs for IPD attributable to V114 serotypes increased by 290% or decreased by 11%, respectively.

Table 4. Discounted direct and indirect costs associated with IPD in Korea^a

\$ in millions (%)	Pre-PCV7			Pre-PCV13			Post-PCV13		
	Direct costs	Indirect costs	Total costs	Direct costs	Indirect costs	Total costs	Direct costs	Indirect costs	Total costs
Korea									
PCV7-specific serotypes	0.296 (75)	0.973 (75)	1.269 (75)	0.033 (19)	0.111 (19)	0.144 (19)	0.008 (17)	0.028 (17)	0.035 (17)
PCV13-specific serotypes	0.098 (25)	0.323 (25)	0.442 (25)	0.134 (78)	0.444 (78)	0.578 (78)	0.031 (67)	0.111 (67)	0.141 (67)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6A	0.049 (12)	0.162 (12)	0.211 (12)	0.019 (11)	0.063 (11)	0.082 (11)	0.005 (11)	0.018 (11)	0.024 (11)
7F	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.005 (11)	0.018 (11)	0.024 (11)
19A	0.049 (12)	0.162 (12)	0.211 (12)	0.115 (67)	0.381 (67)	0.496 (67)	0.020 (44)	0.074 (44)	0.094 (44)
V114-specific serotypes	0 (0)	0 (0)	0 (0)	0.005 (3)	0.015 (3)	0.020 (3)	0.008 (17)	0.028 (17)	0.035 (17)
All V114 serotypes	0.394	1.297	1.691	0.172	0.570	0.743	0.046	0.166	0.212
Hong Kong									
PCV7-specific serotypes	0.719 (96)	1.508 (96)	2.227 (96)	-	-	-	0.033 (6)	0.078 (6)	0.110 (6)
PCV13-specific serotypes	0.030 (4)	0.065 (4)	0.096 (4)	-	-	-	0.479 (94)	1.137 (94)	1.616 (94)
1	0 (0)	0 (0)	0 (0)	-	-	-	0 (0)	0 (0)	0 (0)
3	0.014 (2)	0.031 (2)	0.044 (2)	-	-	-	0.419 (82)	1.000 (82)	1.419 (82)
5	0 (0)	0 (0)	0 (0)	-	-	-	0.003 (1)	0.007 (1)	0.010 (1)
6A	0.017 (2)	0.035 (2)	0.051 (2)	-	-	-	0 (0)	0 (0)	0 (0)
7F	0 (0)	0 (0)	0 (0)	-	-	-	0 (0)	0 (0)	0 (0)
19A	0 (0)	0 (0)	0 (0)	-	-	-	0.056 (11)	0.130 (11)	0.187 (11)
V114-specific serotypes	0 (0)	0 (0)	0 (0)	-	-	-	0 (0)	0 (0)	0 (0)
All V114 serotypes	0.749	1.573	2.322	-	-	-	0.512	1.215	1.726

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine

^aData are presented as cost (%). Costs are reported in millions of 2020 USD. Some totals sum to more or less than 100% due to rounding.

Health and economic burden of V114-targeted pneumococcal serotypes in Hong Kong

Cases of IPD by serotype

In Hong Kong, V114 serotypes caused an estimated 62 and 46 IPD cases in the pre-PCV7 and post-PCV13 scenarios, respectively (Table 3). In the pre-PCV7 scenario, a majority of cases (59 cases, 96%) were attributable to PCV7 serotypes. PCV13-specific serotypes increased from 3 cases (4%) in the pre-PCV7 scenario to 43 cases (94%) in the post-PCV13 scenario. This increase was primarily due to an increase in serotype 3 from 1 case (2%) in the pre-PCV7 scenario to 38 cases (83%) in the post-PCV13 scenario. Cases due to serotype 19A increased from 0 (0%) to 5 (10%) across these time periods.

Mortality

Three deaths from IPD due to V114 serotypes were predicted in Hong Kong for the pre-PCV7 scenario, all of which were attributable to PCV7-specific serotypes (data not shown). Three deaths were predicted for the post-PCV13 scenario, 2 of which (67%) were attributable to serotype 3.

Table 5. Results of sensitivity analysis for Korea and Hong Kong.

	Korea discounted total costs ^a	Hong Kong discounted total costs ^a
Base case	\$1.69	\$2.3
Incidence -20%	1.28 (-24%)	1.86 (-20%)
Incidence +20%	2.13 (+26%)	2.79 (+20%)
Case fatality rate -20%	1.44 (-15%)	2.01 (-13%)
Case fatality rate +20%	1.94 (+15%)	2.63 (+13%)
Cost -20%	1.61 (-5%)	2.17 (-7%)
Cost +20%	1.78 (+5%)	2.48 (+7%)
Discount rate 0%	6.60 (+290%)	6.62 (+185%)
Discount rate 5%	1.50 (-11%)	1.48 (-36%)

^aNumbers in parentheses indicate the percentage change from the base case value. Costs are reported as millions of 2020 USD.

Costs of IPD by serotype

Total discounted medical costs and indirect costs in Hong Kong were estimated to be approximately \$2.322 million over 20 years in the pre-PCV7 scenario and decreased to \$1.726 million in the post-PCV13 scenario (Table 4). PCV7 serotypes accounted for the majority of total costs in the pre-PCV7 scenario (96%), whereas PCV13-specific serotypes accounted for the majority of the total costs in the post-PCV13 scenario (94%). The increase in PCV13-specific costs from the pre-PCV7 scenario to the post-PCV13 scenario was primarily due to increases in costs attributable to serotype 3 from \$0.044 million (2%) to \$1.419 million (82%).

Sensitivity analysis

The discounted total cost was sensitive to uncertainties around all key parameters, especially the discount rate (Table 5). When the discount rate was 0% and 5%, total costs for IPD attributable to various serotypes increased by 185% and decreased by 36%, respectively.

Discussion

This study showed that PCV-targeted serotypes of *S. pneumoniae* are predicted to cause ongoing morbidity and cost in both Korea and Hong Kong. The models predicted that PCV13-specific serotypes of *S. pneumoniae* persisted to various degrees after implementation of routine PCV13 vaccination. Specifically, serotype 19A in Korea and serotype 3 in Hong Kong still caused a majority of IPD cases in the most recent period. Serotypes specific to the V114 vaccine, 22F and 33F, were predicted to impart additional morbidity and costs in Korea.

Our findings are consistent with the literature. Prior to the introduction of PCVs, the majority of IPD was caused by serotypes in PCV7.³⁸ In Korea, approximately 60% of IPD cases were due to PCV7 serotypes prior to PCV7 introduction,³⁹ and in Hong Kong, 89.6% of IPD cases were caused by PCV7 serotypes before PCV7

introduction.¹⁷ Our results showed that IPD cases associated with PCV7 serotypes still persist. Thus, it is important to retain protection against PCV7 serotypes in current and future vaccine formulations.

Our findings indicated that *S. pneumoniae* serotype 19A is dominant in Korea, and serotype 3 is currently dominant in Hong Kong, despite these serotypes being included in PCV13. These results are in agreement with recent epidemiological studies from both Hong Kong^{8,17,18} and Korea.¹³ A survey of incidence rates in Hong Kong from 1995 to 2017 found that IPD cases due to serotype 3 were steadily increasing across all vaccine eras.¹⁷ Consistent with this, several studies have demonstrated a lack of PCV13 effectiveness against IPD caused by serotype 3,⁴⁰ and studies from the United States and the United Kingdom have highlighted the persistence of serotype 3 after PCV13 introduction.^{41,42} Regarding serotype 19A, data from 2010–2015 in Korea showed that, although serotype 19A prevalence decreased steadily, it remained as prevalent as many non-PCV serotypes in 2015 and was the most prevalent serotype overall during this time period.¹³ Elsewhere, the prevalence of IPD caused by serotype 19A has plateaued in recent years,^{41,42,43} and this serotype remains a persistent cause of IPD in Europe.¹⁶

Regarding serotype 3, a survey of incidence rates in Hong Kong from 1995 to 2017 found that IPD cases due to serotype 3 were steadily increasing across all vaccine eras.¹⁷ Consistent with this, several studies have demonstrated a lack of PCV13 effectiveness against IPD caused by serotype 3,^{18,40} and studies from the United States and the United Kingdom have highlighted the persistence of serotype 3 after PCV13 introduction.^{40,44,45,46} Together, these findings highlight the importance of retaining the protection against the vaccine-type serotypes as new PCVs are developed. Moreover, higher-valency PCVs have been found to elicit lower immune responses relative to first-generation PCVs for the shared serotypes,⁴⁷ and this phenomenon, known as ‘geometric mean concentration creep’, becomes more pronounced as more serotypes are added.⁴⁸ New PCVs will need to incorporate strategies for better targeting of persistent serotypes.

Interestingly, although serotypes 22F and 33F are two of the most commonly observed non-PCV13 serotypes in children with IPD,¹⁶ we observed only a minimal burden from these serotypes in the current analysis. This is likely because these serotypes were rarely or never observed in most serotyping studies from Korea and Hong Kong,^{8,12,13,17,49,50} suggesting a geographically tailored approach to surveillance, vaccination policy, and vaccine development will be needed. However, even in locations where serotypes 22F and 33F are rare, their invasiveness, which is comparable to that of serotype 19A,⁵¹ may prioritize them for targeting by new PCVs. In some locations, the antibiotic resistance of both persistent and emergent serotypes may be the greater immediate concern. For example, in a prospective study at Seoul National University Children’s Hospital from 2010 to 2015, 91% of nasopharyngeal *S. pneumoniae* isolates from children exhibited multi-drug resistance.¹³ Isolates from Korean children attending daycare centers in 2014 showed an 82% multi-drug resistance rate.¹⁵ In a multi-center study of *S. pneumoniae* isolates collected from Korean hospitals between 2014 and 2016, serotype 19A had one of the highest rates of multi-drug resistance.⁵²

Our results show that PCV-targeted serotypes of *S. pneumoniae* will cause ongoing costs in both Korea and Hong Kong. Similar to the prevalence trends, total costs were expected to decrease from

the pre-PCV7 scenario to the post-PCV13 scenario with costs decreasing by 87% in Korea and 26% in Hong Kong. Of interest, in Korea total costs associated with V114-specific serotypes 22F and 33F increased by 17% from the pre-PCV7 scenario to the post-PCV13 scenario. The costs associated with emerging serotypes 22F and 33F will likely vary by location, with these serotypes persisting in Korea.

There are several limitations of this study. First, the use of an unvaccinated cohort in combination with post-PCV13 incidence data provides an estimate of what will happen in the current era in the absence of external influences. The actual outcomes will, of course, be affected by local vaccination rates and other factors. In Korea, reported PCV coverage has ranged from 74% as of 2010⁵³ to 98% as of 2015.⁵⁴ Although a survey of Hong Kong parents of primary school children found that only 42% reported having had their children vaccinated with PCVs,⁵⁵ most studies from Hong Kong claim nearly universal infant vaccination with PCVs.^{17,27,28,56,57} The high vaccination rates in both locations would be expected to affect the serotype replacement patterns over time, especially if new PCVs are introduced.

Secondly, although we assumed constant IPD incidence over 20-year time horizon, the incidence of IPD may shift over time in response to the invasiveness of emergent pneumococcal serotypes and to widespread health events such as the COVID-19 pandemic. In Korea, IPD cases decreased by 22% in the first half of 2020 compared to the previous 5 years.⁵⁸ In Hong Kong, cases of IPD decreased by 75% in 2020 compared to the previous five years, likely due to mask wearing adopted during the pandemic (similar results were observed in Singapore and Taiwan).⁵⁹

Other limitations of our analysis include the fact that non-invasive syndromes such as NBPP and acute otitis media were not considered in the model. Similarly, sequelae of meningitis, such as deafness or other long-term disability, were not included. The cost calculations also did not include direct non-medical costs accrued by families and caregivers, such as transportation and lodging. Indirect costs associated with productivity loss were estimated using conservative values for earnings, and for caregivers, only absenteeism was included in the productivity loss calculation. Furthermore, the average income for individuals under 20 years of age was assumed to be zero. As a result, the cost calculations presented here are likely an underestimation. Our Markov model did not account for transmission dynamics, outcomes such as nasopharyngeal carriage, and the indirect protective effect of PCVs on unvaccinated groups. Finally, the many IPD cases attributed to non-vaccine-type serotypes in all three time periods likely caused our model to underestimate the health and economic burden of IPD attributable V114 serotypes.⁶⁰

In conclusion, our health and economic model showed that PCV-targeted serotypes, particularly serotypes 3 and 19A, continue to be associated with substantial IPD-related morbidity and costs after the introduction of PCVs. The persistence of PCV-targeted serotypes, and the morbidity and costs associated with emerging serotypes 22F and 33F, will likely vary by location. Thus, future pediatric PCVs must include serotypes contained in currently licensed PCVs to maintain disease reduction as well as expand serotype coverage to key non-vaccine serotypes that have emerged. Furthermore,

surveillance of serotype prevalence should guide vaccine design and vaccination policy.

Acknowledgments

The authors thank Melissa Stauffer, PhD, in collaboration with ScribCo, for medical writing assistance.

Disclosure statement

Salini Mohanty, Tianyan Hu, GyongSeon Yang, Tsz K Khan, Kwame Owusu-Eduese, and Isaya Sukarom are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

Funding

The study was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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