Health and Economic Burden Associated With 15-Valent Pneumococcal Conjugate Vaccine Serotypes in Children in Australia

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Background and Objectives

- *Streptococcus pneumoniae* is a bacterium that causes invasive and noninvasive pneumococcal disease. Invasive pneumococcal disease (IPD) syndromes include bacteremia without focus, bacteremic pneumonia, and meningitis. The most common noninvasive syndromes are non-bacteremic pneumococcal pneumonia (NBPP) and acute otitis media (AOM)
- The introduction of pneumococcal conjugate vaccines (PCV) in infant immunization schedules has led to substantial disease reduction. However, unmet needs remain due to the emergence of nonvaccine serotypes and select vaccine serotypes that continue to persist, such as serotype 3[2]
- Future pediatric PCVs must therefore include serotypes contained in currently licensed PCVs to maintain disease reduction and expand serotype coverage to key nonvaccine serotypes that have emerged
- MSD is developing V114, an investigational 15-valent PCV that contains the PCV7 and PCV13 serotypes as well as 2 additional serotypes, 22F and 33F
- This study quantifies the health and economic burden of IPD attributable to all 15 serotypes in V114 in a hypothetical unvaccinated birth cohort in Australia. To demonstrate the value of continued disease protection while also expanding serotype coverage, IPD cases and costs attributable to V114 serotypes are estimated at several time points prior to and following PCV7 and PCV13 introduction

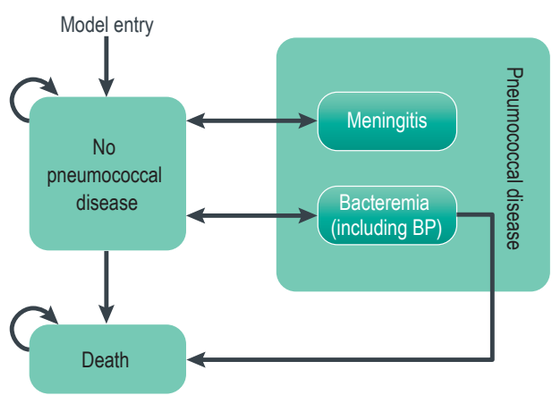
Methods

Target population: A cohort of unvaccinated newborns in 2018 in Australia.

Modeling approach:

- A Markov model with 3 health states – no pneumococcal disease, IPD (meningitis and bacteremia including bacteremic pneumonia), and death (**Figure 1**) – was adapted.[3] The model assumes that infants could experience only one IPD event during each year. Post-meningitis sequelae and NBPP were not considered in the current analysis. Herd impact of vaccination from children to adults was not considered because the model included an unvaccinated birth cohort

Figure 1. Model Structure



- A cohort of unvaccinated newborns in 2018 in Australia was followed for 20 years to estimate cases, deaths, direct medical costs, and indirect costs for IPD. The total cohort consisted of 315,147 newborns[4]
- Health and economic outputs were estimated under 2 scenarios:
  1. **Value of V114 serotypes prior to PCV7 introduction ("Pre-PCV"):** Pre-PCV7 disease incidence and serotype distribution in 2002 were applied to all 15 serotypes in V114[5]
  2. **Value of V114 serotypes post-PCV7 and post-PCV13 introduction ("Post-PCV"):**
     a) Pre-PCV7-era epidemiological inputs in 2002 were applied to the common PCV7 serotypes in V114.[5] Prior to the introduction of PCV7, the majority of all IPD cases were caused by the 7 vaccine serotypes in children. This is the potential burden that any currently licensed or future vaccines should continue to protect against
     b) Pre-PCV13 epidemiological inputs in 2010 were applied to the additional 6 PCV13 serotypes not in PCV7 (PCV13-PCV7) circulating in the post-PCV7 era.[5] Following the introduction of PCV7, there was a significant increase in IPD incidence associated with several non-PCV7 serotypes due to serotype replacement
     c) Disease related to the unique V114 serotypes (22F and 33F) was estimated using recent epidemiological data from the post-PCV13 era in 2017.[5] The epidemiological inputs were used to highlight the serotypes that will be included in the investigational 15-valent PCV
- Epidemiologic and economic parameters were retrieved from the literature and are summarized in **Table 1**
- The most recent case fatality rates were retrieved from the literature to reflect current access to care and medical treatment for IPD
- Direct medical costs were estimated from the healthcare perspective. A limited societal perspective considered all direct medical costs, productivity losses due to premature death among children, and productivity losses among adult caregivers. Costs were updated to 2018 Australian dollars (AUD) and discounted at 5% annually
- Deterministic sensitivity analysis (DSA) was utilized to assess the impact of uncertainties around key parameters and assumptions in the pre-PCV scenario only. The following assumptions were explored: incidence rate of IPD is 0.8-1.2 times the base case value, case fatality rate of IPD is 0.8-1.2 times the base case value, direct medical costs and indirect costs associated with treating meningitis and bacteremia are 0.8-1.2 times the base case value, discount rate is either 3% or 7%

Table 1. Epidemiology and Economic Model Parameters

Input	Manifestation	Age Groups	PCV7 Serotypes (pre-PCV era)	PCV13 not PCV7 Serotypes (pre-PCV era)	V114 not PCV13 Serotypes (pre-PCV era)	PCV13 not PCV7 Serotypes (post-PCV era)	V114 not PCV13 Serotypes (post-PCV era)
Serotype-specific incidence rate by age group and by vaccine-type serotypes in various periods (per 100,000 person-years)[1]	IPD[5,6]	0-4	51.0	6.1	0.5	12.3	1.3
		5-9	6.0	0.7	0.1	2.6	0.3
		10-14	2.1	0.3	0	0.4	0
		15-19	2.6	0.3	0	0.9	0
Case fatality rate	Meningitis[7]	12.5%					
	Bacteremia[8]	0.5%					
Direct medical cost (per episode)	Meningitis[9]	$11,699					
	Bacteremia[9]	$10,006					
Indirect cost (per episode)	Meningitis[10]	$1,905					
	Bacteremia[10]	$1,120					

Results

Figures 2 and **3** present IPD cases attributable to V114 serotypes in the pre- and post-PCV scenarios over the 20-year time horizon in Australia.

- V114 serotypes cause nearly 1,104 and 1,259 IPD cases in the pre- and post-PCV scenarios, respectively. In both scenarios, a majority of cases, 89% (pre-PCV) and 78% (post-PCV), are attributable to PCV7 serotypes
- PCV13 not PCV7 serotypes cause an additional 143 IPD cases in the post-PCV scenario, primarily due to increases in ST 7F (12 cases, which account for 8% of the increase), ST 1 (19 cases, 13% of the increase), and ST 19A (139 cases, 97% of the increase)
- The numbers of cases caused by 22F and 33F account for 1% and 2% of all IPD cases attributable to V114 serotypes in the pre- and post-PCV scenarios, respectively

Figure 2. IPD Cases Attributable to PCV15 Serotypes in the Pre-PCV Scenario (proportion of cases among total cases attributable to V114 serotypes in parentheses)

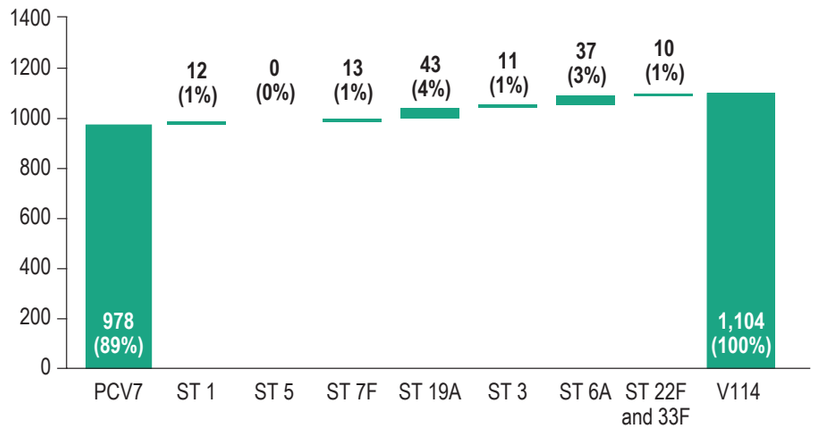


Figure 3. IPD Cases Attributable to PCV15 Serotypes in the Post-PCV Scenario (proportion of cases among total cases attributable to V114 serotypes in parentheses)

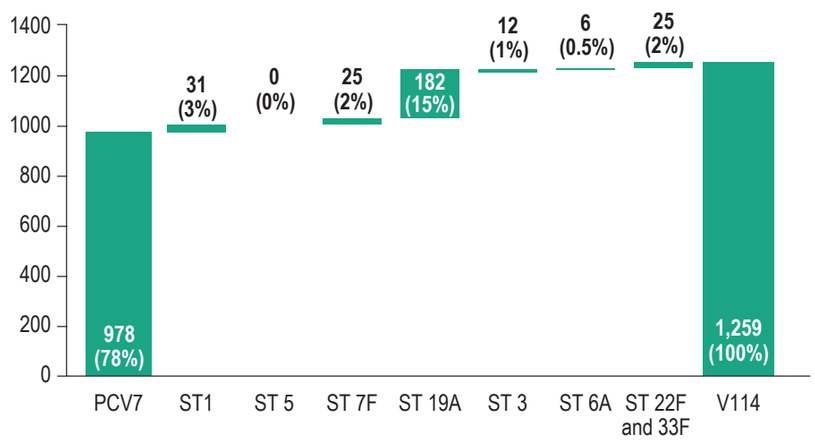


Table 2 presents discounted direct medical costs and indirect costs for IPD cases attributable to V114 serotypes.

- Total discounted medical costs and indirect costs are estimated to be approximately $17.3 million over 20 years in the pre-PCV scenario and increased to $20.1 million in the post-PCV scenario
- PCV7 serotypes account for the majority of costs – 89% and 76% of the total costs in the pre- and post-PCV scenarios, respectively
- PCV13 not PCV7 serotypes cause an additional $2.5 million in the post-PCV scenario, primarily due to increases in ST 7F ($0.2 million, 9% of the increase), ST 1 ($0.3 million, 12% of the increase), and ST 19A ($2.5 million, 98% of the increase)
- Total costs associated with 22F and 33F account for 1% and 2% of total costs attributable to V114 serotypes in the pre-PCV and post-PCV scenarios, respectively

Table 2. Discounted Direct and Indirect Costs Associated With IPD in Australia (in millions, 2018 AUD, proportion of each vaccine type serotype among total V114 in parentheses)

	Pre-PCV Scenario			Post-PCV Scenario		
	Total Costs	Direct Costs	Indirect Costs	Total Costs	Direct Costs	Indirect Costs
PCV7 serotypes	$15.3 (89%)	$8.5 (89%)	$6.9 (89%)	$15.3 (76%)	$8.5 (78%)	$6.9 (74%)
PCV13 not PCV7 serotypes	$1.8 (11%)	$1.0 (11%)	$0.8 (11%)	$4.4 (22%)	$2.2 (20%)	$2.2 (24%)
ST 5	$0 (0%)	$0 (0%)	$0 (0%)	$0 (0%)	$0 (0%)	$0 (0%)
ST 3	$0.2 (1%)	$0.1 (1%)	$0.08 (1%)	$0.2 (1%)	$0.09 (1%)	$0.1 (1%)
ST 6A	$0.6 (3%)	$0.3 (3%)	$0.3 (3%)	$0.1 (1%)	$0.05 (0%)	$0.5 (1%)
ST 7F	$0.2 (1%)	$0.1 (1%)	$0.09 (1%)	$0.4 (2%)	$0.2 (2%)	$0.2 (2%)
ST 19A	$0.7 (4%)	$0.4 (4%)	$0.3 (4%)	$3.2 (16%)	$1.6 (15%)	$1.6 (17%)
ST 1	$0.2 (1%)	$0.1 (1%)	$0.09 (1%)	$0.5 (2%)	$0.2 (2%)	$0.3 (3%)
V114 not PCV13 serotypes	$0.2 (1%)	$0.09 (1%)	$0.07 (1%)	$0.4 (2%)	$0.2 (2%)	$0.2 (2%)
Total V114 serotypes	$17.3 (100%)	$9.5 (100%)	$7.8 (100%)	$20.1 (100%)	$10.9 (100%)	$9.3 (100%)

Table 3 presents results from DSA to assess the impact of uncertainties on key parameters in the pre-PCV scenario only. The discounted total cost is sensitive to uncertainties around all key parameters, especially the discount rate. When the discount rate is 3%, discounted total costs for IPD attributable to various serotypes increase by 43%.

Table 3. DSA Results (costs in millions, 2018 AUD)

	Discounted Total Costs (percentage change from base case in parentheses)		
	PCV7 Serotypes	PCV13 not PCV7 Serotypes	PCV15 not PCV13 Serotypes
Base case	$15.3	$1.8	$0.2
Incidence -20%	$12.3 (-20%)	$1.5 (-20%)	$0.1 (-20%)
Incidence +20%	$18.4 (20%)	$2.2 (20%)	$0.2 (20%)
CFR -20%	$14.1 (-8%)	$1.7 (-8%)	$0.1 (-8%)
CFR +20%	$16.5 (8%)	$2.0 (8%)	$0.2 (8%)
Cost -20%	$13.4 (-12%)	$1.6 (-12%)	$0.1 (-12%)
Cost +20%	$17.2 (12%)	$2.0 (12%)	$0.2 (12%)
Discount factor 3%	$22.0 (43%)	$2.6 (43%)	$0.2 (43%)
Discount factor 7%	$12.0 (-22%)	$1.5 (-22%)	$0.1 (-22%)

Limitations

- Post-meningitis sequelae, AOM, and pneumonia were not considered in the current analysis
- The analysis did not include direct nonmedical costs
- The analysis did not account for the higher burden of serotype 3 in the current data due to the model only using recent epidemiological data (2017) for unique V114 serotypes (22F and 33F)

Conclusions

- PCV7 serotypes caused the most pneumococcal disease-related morbidity and costs in both the pre-PCV and post-PCV scenarios
- Three additional serotypes in PCV13, ST 7F, 1, and 19A, were associated with substantial morbidity and costs after the introduction of PCV7
- Emerging serotypes, such as ST 22F and 33F, are associated with additional morbidity and costs
- Investigational PCVs for infants must continue to retain serotypes in currently licensed vaccines to maintain disease reduction, while expanding coverage to emerging disease-causing serotypes

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