Incidence of Non-Invasive Pneumococcal Pneumonia in Children in the United States Before and After Introduction of 7- and 13-Valent Pneumococcal Conjugate Vaccines From 1998-2018

Tianyan Hu[1]; Eric Sarpong[1]; Yan Song[2]; Nicolae Done[2]; Qing Liu[2]; James Signorovitch[2]; Tanaz Petigara[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA;
[2]Analysis Group, Inc., Boston, MA, USA

Background

- Pneumonia causes significant pediatric morbidity, mortality, and healthcare resource utilization worldwide.[1,2] *Streptococcus pneumoniae* is a leading cause of bacterial pneumonia in children[3]
- The introduction of pneumococcal vaccines (PCV7 and PCV13) has decreased the burden of invasive and non-invasive disease in children, including pneumococcal pneumonia (PP)[4-6]; however, residual disease caused by persistent vaccine-type serotypes and non-vaccine serotypes remains[7]
- Merck is currently developing V114, a 15-valent pneumococcal conjugate vaccine (PCV15) for the prevention of invasive and non-invasive pneumococcal disease in children
- It is important to quantify the residual burden of pneumococcal disease prior to the introduction of higher-valent PCVs

Objectives

- To estimate incidence rates (IR) of non-invasive PP before and after introduction of PCV7 and PCV13 in children aged <18 years in the United States from 1998-2018
- To conduct interrupted time series (ITS) analyses to assess time trends in PP incidence after the introduction of PCV7 in 2000 and PCV13 in 2010 in children aged <18 years in the United States from 1998-2018

Methods

Data Source

- A retrospective observational study was conducted using IBM MarketScan® Commercial Claims and Encounters (CCAE) database (1998-2018)
  - Contains enrollment, medical, surgical, and prescription drug data for ~90 million unique individual employees, their spouses, and dependents covered by employer-sponsored private health insurance

Sample Selection

- PP claims were identified using the following ICD-9/10 codes
  - **ICD-9:** Either 482.9, 485, or 486 in combination with 041.2; or 481
  - **ICD-10:** Either J15, J18.0, or J18.9 in combination with B95.3; or J13
- Claims with any invasive pneumococcal disease (ie, bacteremia, meningitis, bacteremic pneumonia, and other invasive conditions including arthritis, peritonitis, pericarditis, endocarditis, and osteomyelitis) ICD-9/10 codes were excluded[8]
- A non-invasive PP episode was defined as a sequence of one or more PP inpatient or outpatient claims. A gap of 90 days with no PP-related diagnoses defined the start of a new episode
- Children aged <18 years with at least one episode of non-invasive PP were identified in each calendar year
- Episodes with any inpatient stays were categorized as inpatient and as outpatient otherwise

Statistical Analyses

- Annual IRs for non-invasive PP episodes were defined as the numbers of episodes per 100,000 person-years (P-Y)
- Age-stratified (<2, 2-4, and 5-17 years) IRs were reported during the pre-PCV7 (1998-1999), early PCV7 (2001-2005), late PCV7 (2006-2009), early PCV13 (2011-2013), and late PCV13 (2014-2018) periods. The years 2000 and 2010 were considered transitional years, when the PCV7 and PCV13 vaccines were introduced, respectively
- Annual IRs were also calculated separately for inpatient and outpatient PP episodes
- The ITS analysis was performed to assess any immediate change (change in level) or gradual change (change in trend) in monthly IRs before and after the introduction of PCVs. The ITS analysis was conducted using generalized linear models with negative binomial distribution and log link, adjusting for age, sex, geographic region, urbanicity, type of health plan, and monthly indicators. For each period, incidence rate ratios (IRR) and 95% confidence intervals (95% CI) were estimated

Results

Sample Characteristics

- On average, 12.5 million privately insured children contributed 5.8 million P-Y at risk each year
- The sample had slightly more male patients (~53%); patients were more likely to reside in the South and in an urban area (**Table 1**)
- On average, about 20% of children with non-invasive PP were aged <2 years old, ~25% were aged 2-4, and more than half were aged 5-17 years

Incidence of Non-Invasive Pneumococcal Pneumonia

- Non-invasive PP IRs in children aged <18 years increased slightly from 45.6 to 47.1 per 100,000 P-Ys from the pre-PCV7 to early PCV7 period, then declined to 43.7, 33.7, and 15.3 per 100,000 P-Ys in the late PCV7, early PCV13, and late PCV13 periods, respectively (**Figure 1A**)
  - In children aged <2 years, non-invasive PP IRs decreased steadily from 130.4 to 30.1 per 100,000 P-Yrs from the pre-PCV7 to late PCV13 period (**Figure 1B**)
  - In children aged 2-4 years, non-invasive PP IRs increased slightly from 76.6 to 84.2 per 100,000 P-Yrs from the pre-PCV7 to early PCV7 period, and then declined to 75.6, 56.8, and 28.4 per 100,000 P-Yrs in the late PCV7, early PCV13, and late PCV13 periods (**Figure 1C**)
  - In children aged 5-17 years, non-invasive PP IRs increased slightly from 31.0 to 32.8 per 100,000 P-Yrs from the pre-PCV7 to early PCV7 period, and then declined to 31.7, 25.9, and 11.1 per 100,000 P-Yrs in the late PCV7, early PCV13, and late PCV13 periods (**Figure 1D**)
- Over 80% of non-invasive PP episodes were outpatient episodes only. Outpatient IRs decreased from 96.8 to 24.5 per 100,000 P-Yrs in children aged <2 years, 60.4 to 25.1 per 100,000 P-Yrs in children aged 2-4 years, and 25.3 to 10.0 per 100,000 P-Yrs in children aged 5-17 years

ITS Results

- In the early PCV7 period, no immediate or gradual changes in monthly IRs were detected in children aged <2 and 2-4 years. There was a gradual increase in monthly IRs by 7.4% compared to the pre-PCV7 period in children aged 5-17 years (IRR 1.074, 95% CI [1.026, 1.123], $P = 0.002$) (**Table 2**)
- No immediate or gradual changes in monthly IRs were detected in children aged <2 and 2-4 years in the late PCV7 period compared to the early PCV7 period. In children aged 5-17 years, there was an immediate reduction in monthly incidence between early and late PCV7 periods (IRR 0.634, 95% CI [0.449-0.893], $P = 0.009$) (**Table 2**). However, monthly IRs gradually increased by 2.6% each month in the late PCV7 period (IRR 1.026, 95% CI [1.001, 1.052], $P = 0.042$)
- In the early PCV13 period, there were no immediate or gradual changes in monthly IRs detected in children aged <2 and 5-17 years. There was an immediate increase in monthly incidence in children aged 2-4 years compared to the late PCV7 period (IRR 1.982, 95% CI [1.064-3.690], $P = 0.031$)
- No immediate or gradual changes in monthly IRs were detected in children of any age in the late PCV13 period compared to the early PCV13 period

Limitations

- This study is also subject to limitations that are common in claims studies
  - Miscoded diagnoses may lead to outcome misclassification
  - Study results may not be generalizable to children outside the CCAE database
- The transition from ICD-9 to ICD-10 codes in 2015 may have particularly led to outcome misclassification over time, as the codes do not map perfectly between the two systems
- Due to the diagnostic limitations associated with pediatric non-invasive PP, the incidence estimated using pneumococcal-specific ICD codes might underestimate the total burden

Table 1. Demographic Characteristics of Children With Non-Invasive Pneumococcal Pneumonia Episodes

	Pre-PCV7 (1998-1999)	Early PCV7 (2001-2005)	Late PCV7 (2006-2009)	Early PCV13 (2011-2013)	Late PCV13 (2014-2018)
Total number of children with non-invasive PP, N	N = 690	N = 8,210	N = 13,071	N = 10,300	N = 4,739
Age, mean (SD)	6.05 (5.04)	6.03 (4.89)	6.24 (4.88)	6.51 (4.85)	6.24 (4.76)
<2 years, %	23.9%	20.7%	18.9%	16.6%	17.7%
2-4 years, %	22.9%	25.9%	25.6%	24.7%	26.7%
5-17 years, %	53.2%	53.4%	55.5%	58.7%	55.6%
Male, %	53.2%	53.4%	54.5%	53.8%	52.7%
Region					
Northeast, %	15.9%	11.7%	11.1%	16.5%	18.8%
North Central, %	24.9%	24.1%	25.5%	23.5%	20.7%
South, %	44.2%	38.6%	49.0%	38.6%	39.7%
West, %	5.4%	24.0%	13.7%	18.5%	19.6%
Missing/unknown, %	9.6%	1.6%	0.7%	2.9%	1.2%
Urbanicity					
Urban, %	58.6%	81.1%	81.2%	82.7%	84.1%
Rural, %	31.9%	17.3%	18.1%	14.4%	13.1%
Missing, %	9.6%	1.6%	0.7%	2.9%	2.8%
Health plan types					
HMO/EPO, %	11.2%	26.8%	15.0%	14.6%	10.8%
PPO/POS, %	49.0%	63.0%	77.3%	69.9%	64.9%
HDHP/CDHP, %	0.0%	1.0%	2.8%	8.7%	19.2%
FFS, %	39.0%	6.5%	1.5%	0.6%	1.2%
Missing, %	0.9%	2.8%	3.5%	6.1%	3.9%

CDHP, consumer directed health plan; EPO, exclusive provider organization; FFS, fee-for-service; HDHP, high deductible health plan; HMO, health maintenance organization; PCV, pneumococcal conjugate vaccine; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

Figure 1. Non-Invasive Pneumococcal Pneumonia Incidence (episodes per 100,000 person-years) Among Children Aged <18 Years (1998-2018)

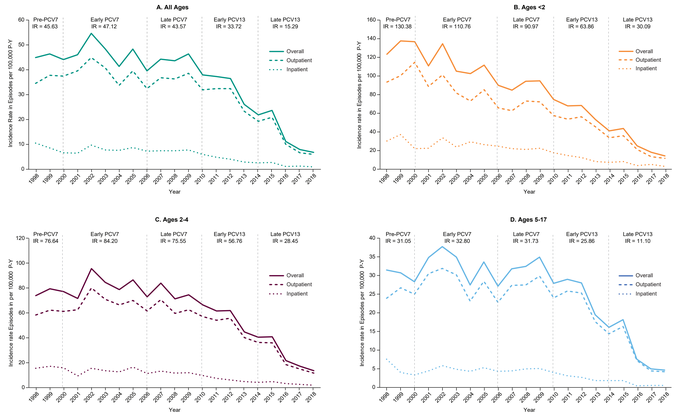

Table 2. Estimates From Interrupted Time Series Analyses of Monthly Pneumococcal Pneumonia Episode Incidence Rates in Children Aged <18 Years (1998-2018)

		All Ages		Ages <2		Ages 2-4		Ages 5-17	
Period	**IRR**	**IRR (95% CI)**	***P*-value**	**IRR (95% CI)**	***P*-value**	**IRR (95% CI)**	***P*-value**	**IRR (95% CI)**	***P*-value**
Pre-PCV7	Base trend	0.927 (0.892-0.963)	<0.001[a]	0.965 (0.914-1.019)	0.204	1.009 (0.962-1.059)	0.708	0.902 (0.861-0.946)	<0.001[a]
Early PCV7	Change in level	0.125 (0.003-5.831)	0.288	0.186 (0.007-4.896)	0.314	3.438 (0.160-73.838)	0.430	0.153 (0.002-14.115)	0.416
	Change in trend	1.040 (1.006-1.076)	0.021[a]	1.018 (0.982-1.054)	0.328	0.993 (0.963-1.024)	0.640	1.074 (1.026-1.123)	0.002[a]
Late PCV7	Change in level	0.674 (0.461-0.987)	0.043[a]	0.628 (0.349-1.131)	0.121	0.925 (0.583-1.467)	0.741	0.634 (0.449-0.893)	0.009[a]
	Change in trend	1.030 (1.011-1.049)	0.002[a]	1.015 (0.994-1.036)	0.162	1.011 (0.995-1.028)	0.163	1.026 (1.001-1.052)	0.042[a]
Early PCV13	Change in level	0.971 (0.463-2.038)	0.938	1.226 (0.571-2.632)	0.600	1.982 (1.064-3.690)	0.031[a]	1.062 (0.462-2.438)	0.887
	Change in trend	1.000 (0.986-1.014)	0.973	0.989 (0.972-1.005)	0.182	0.999 (0.984-1.015)	0.949	1.005 (0.988-1.023)	0.557
Late PCV13	Change in level	0.457 (0.203-1.030)	0.059	0.790 (0.332-1.877)	0.593	1.413 (0.665-3.002)	0.369	0.488 (0.183-1.299)	0.151
	Change in trend	0.988 (0.969-1.008)	0.252	0.995 (0.971-1.020)	0.701	0.986 (0.967-1.006)	0.171	0.978 (0.954-1.003)	0.079

[a]$P < 0.05$.
All coefficients were obtained through a negative binomial model with a log link. IRRs represent the exponentiated regression coefficients and indicate a multiplicative change. Model intercepts are not shown.

Conclusions

- In children of all ages, non-invasive PP IRs decreased from 1998-2018 after vaccine introduction
- ITS was used to investigate changes in monthly IRs across several time periods before and after vaccine introduction. No significant immediate or gradual changes were detected in children aged <2 years; IRs trended downwards across all time periods
- In older children, although there was an immediate reduction in incidence between early and late PCV7 periods, IRs gradually increased in the early and late PCV7 periods
- Despite declines in IRs, there remains a residual burden of non-invasive PP in children in the United States
- The impact of future PCVs on pneumonia incidence rates will depend on the proportion of pneumonia caused by *Streptococcus pneumoniae* and the prevalence of vaccine-type serotypes

References

1. Sulley S, Ndanga M. *Int J Pediatr Adolesc Med.* 2019;6(3):79–86.
2. Wiese AD, Griffin MR, Grijalva CG. *Expert Rev Vaccines.* 2019;18(4):327-341.
3. Wahl B, et al. *Lancet Glob Health.* 2018;6(7):e744–e757.
4. Tong S, et al. *BMC Health Serv Res.* 2018;18(1):1-8.
5. Hayes BH, et al. *Chest.* 2018;153(2):427-437.
6. Simonsen L, et al. *Lancet Respir Med.* 2014;2(5):387-394.
7. Beall B, et al. *Front Microbiol.* 2018;9:2670.

https://bit.ly/34mEOgH

Presented at IDWeek 2020; October 21-25, 2020