

Incidence of Acute Otitis Media in Children in the United States Before and After the Introduction of Pneumococcal Conjugate Vaccines (PCV7 and PCV13) During 1998-2018

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Introduction

- Acute otitis media (AOM) is a common infectious disease affecting infants and young children, leading to considerable healthcare resource utilization¹
- Streptococcus pneumoniae* is a leading cause of bacterial AOM.^{2,3} Pneumococcal conjugate vaccines were introduced in the US in 2000 (7-valent, PCV7) and 2010 (13-valent, PCV13)
- Merck is currently developing V114, a 15-valent pneumococcal conjugate vaccine (PCV15) for the prevention of invasive and noninvasive 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 calculate annual AOM incidence rates (IRs) before and after the introduction of PCV7 and PCV13 in children <18 years in the US during 1998-2018
- To assess time trends in AOM incidence after the introduction of PCV7 and PCV13 in children <18 years in the US during 1998-2018

Methods

Data Source

A retrospective observational study was conducted using two IBM MarketScan® claims databases

- 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
- Multi-State Medicaid databases (2001-2018)
 - Contains enrollment, medical, surgical, and prescription drug data for more than 44 million Medicaid enrollees across 12 states

Sample Selection

- The population at risk included all children <18 years old with any health plan enrollment over the time frame of the study
- AOM claims were identified by the presence of at least one of the following diagnosis codes
 - ICD-9 code 382.x
 - ICD-10 codes H66.x, H67.x
- Claims with pneumonia or 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

Statistical Analyses

- AOM episodes were identified as sequences of one or more AOM-related outpatient or inpatient claims; a gap of ≥14 days between two consecutive AOM-related claims defined the start of a new episode
- Annual IRs were calculated as the number of episodes per 1,000 person-years (PY) and reported separately for the CCAE and Medicaid populations, overall and stratified by age groups (<2, 2-4, and 5-17 years)
- Interrupted time series (ITS) analysis was performed to assess any immediate change (change in level) or gradual change (change in trend) in monthly AOM IRs before and after the introduction of PCVs. The ITS analysis was conducted using generalized linear models with a negative binomial distribution and log link for the following study periods
 - CCAE:** pre-PCV7 (1998-1999), early PCV7 (2001-2005), late PCV7 (2006-2009), early PCV13 (2011-2013), late PCV13 (2014-2018)
 - Medicaid:** pre-PCV13 (2006-2009), early PCV13 (2011-2013), late PCV13 (2014-2018)
- For each period, incidence rate ratios (IRRs) and 95% confidence intervals (95% CIs) were estimated
- ITS models were adjusted for seasonality by including monthly indicators and additionally for age, sex, geographic region, urbanicity, and type of health plan (CCAE) or age, sex, and type of health plan (Medicaid)

Results

Sample Characteristics

- On average, children in commercial plans contributed 5.8 million PY at risk each year, and children in Medicaid plans contributed 3.5 million PY at risk each year
- The proportion of patients <2 years ranged from 28.6% to 31.5% across the study periods among children enrolled in commercial plans, versus 36.8% to 44.7% among children enrolled in Medicaid plans (**Table 1**)

Incidence Rates

- AOM IRs declined overall from 251 episodes per 1,000 PY in 1998 to 195 in 2018 in children <18 years enrolled in commercial plans and from 300 in 2001 to 199/1,000 PY in children <18 years enrolled in Medicaid plans (**Figure 1A**)
 - In children <2 years enrolled in commercial plans, AOM IRs declined from 1,111 in 1998 to 738/1,000 PY in 2018 and from 895 in 2001 to 656/1,000 PY in 2018 in children enrolled in Medicaid plans (**Figure 1B**)
 - In children 2-4 years enrolled in commercial plans, AOM IRs declined from 517 in 1998 to 408/1,000 PY in 2018 and from 385 in 2001 to 329/1,000 PY in 2018 in children enrolled in Medicaid plans (**Figure 1C**)
 - In children 5-17 years enrolled in commercial plans, AOM IRs declined from 112 in 1998 to 89/1,000 PY in 2018 and from 98 in 2001 to 87/1,000 in 2018 in children enrolled in Medicaid plans (**Figure 1D**)

ITS Results

Results from the ITS analysis in children enrolled in commercial plans are presented in **Table 2**

- In the early PCV7 period, there were no significant immediate or gradual changes in monthly IRs in children of all ages compared with the pre-PCV period
- No significant immediate or gradual changes were detected in children <2 years in the late PCV7 period. There was a significant gradual increase in monthly IRs in the late PCV7 period compared with the early PCV7 period for both children 2-4 (IRR 1.009, 95% CI [1.002-1.016], $P = 0.012$) and 5-17 years (IRR 1.013, 95% CI [1.004-1.022], $P = 0.005$)
- In the early PCV13 period, the monthly IRs gradually decreased by 0.8% each month for children 5-17 years (IRR 0.992, 95% CI [0.985-1.000], $P = 0.048$) compared with the late PCV7 period. No significant immediate or gradual changes were detected in younger children
- In the late PCV13 period, monthly IRs gradually increased by 1.3% and 1.4%, respectively, each month for children 2-4 (IRR 1.013, 95% CI [1.004-1.022], $P = 0.003$) and 5-17 years (IRR 1.014, 95% CI [1.005-1.024], $P = 0.003$) compared with the early PCV13 period. No significant immediate or gradual changes were detected in children <2 years

Results from the ITS analysis in children enrolled in Medicaid plans are presented in **Table 3**

- There were no significant immediate or gradual changes in monthly IRs in the early PCV13 period in children of all ages
- There was an immediate reduction in monthly IRs from the early PCV13 period to the late PCV13 period in children <2 years (IRR 0.817, 95% CI [0.727-0.918], $P = 0.001$), 2-4 years (IRR 0.868, 95% CI [0.768-0.981], $P = 0.024$), and 5-17 years (IRR 0.836, 95% CI [0.727-0.961], $P = 0.012$)

Limitations

- This study is subject to several limitations that are common in claims studies
 - Miscoded diagnoses may lead to outcome misclassification
 - Study results may not be generalizable to all children in the US
- The shift from the ICD-9 to ICD-10 diagnosis code system in 2015 may have particularly led to outcome misclassification, as the codes do not map perfectly between the two systems
- The study identified AOM episodes due to all causes. Pathogen-specific incidence could not be calculated. Changes in clinical practice guidelines or prevalence of risk factors for AOM over time may have impacted study results

Table 1. Demographic Characteristics of Children With AOM Episodes

	Commercially Insured					Medicaid				
	Pre-PCV7	Early PCV7	Late PCV7	Early PCV13	Late PCV13	Early PCV7	Late PCV7	Early PCV13	Late PCV13	
	(1998-1999)	(2001-2005)	(2006-2009)	(2011-2013)	(2014-2018)	(2001-2005)	(2006-2009)	(2011-2013)	(2014-2018)	
Total number of children with AOM, N	N = 237,100	N = 2,388,239	N = 4,226,586	N = 4,320,277	N = 4,157,822	N = 1,999,282	N = 1,863,802	N = 1,947,259	N = 3,758,547	
Age, mean (SD)	4.82 (4.56)	4.63 (4.44)	4.65 (4.43)	4.89 (4.49)	4.93 (4.58)	3.42 (3.98)	3.47 (3.98)	3.84 (4.04)	4.09 (4.21)	
<2 years, %	31.1%	31.5%	30.9%	28.6%	29.2%	44.7%	43.8%	38.2%	36.8%	
2-4 years, %	26.7%	28.3%	28.7%	28.6%	28.2%	27.1%	27.3%	28.8%	27.7%	
5-17 years, %	42.2%	40.2%	40.4%	42.8%	42.6%	28.2%	29.0%	33.0%	35.5%	
Male, %	51.8%	52.0%	52.1%	52.1%	52.1%	51.6%	52.0%	51.6%	51.7%	
Region										
Northeast, %	17.7%	10.5%	10.7%	17.4%	17.5%	-	-	-	-	
North Central, %	26.3%	23.9%	27.2%	25.9%	22.1%	-	-	-	-	
South, %	40.4%	43.1%	48.7%	36.7%	44.4%	-	-	-	-	
West, %	6.0%	21.1%	12.8%	17.1%	14.8%	-	-	-	-	
Missing/unknown, %	9.6%	1.5%	0.6%	2.9%	1.2%	-	-	-	-	
Urbanicity										
Urban, %	70.3%	80.8%	83.2%	82.7%	83.1%	-	-	-	-	
Rural, %	20.0%	17.8%	16.2%	14.3%	11.9%	-	-	-	-	
Missing, %	9.6%	1.4%	0.6%	2.9%	4.9%	-	-	-	-	
Health plan types										
HMO/EPO, %	10.6%	23.2%	16.2%	14.3%	10.2%	22.3%	57.0%	61.9%	71.5%	
PPO/POS, %	57.1%	66.4%	76.0%	69.4%	64.5%	34.0%	8.4%	3.1%	0.1%	
CDHP/HDHP, %	0.0%	1.2%	2.8%	9.0%	20.5%	0.0%	0.0%	0.0%	0.0%	
FFS, %	31.9%	6.6%	1.6%	0.9%	1.3%	43.7%	32.5%	34.9%	28.3%	
Missing, %	0.4%	2.6%	3.3%	6.3%	3.5%	0.0%	2.0%	0.0%	0.1%	

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

Figure 1. Annual AOM Incidence Rates in Commercially and Medicaid-Insured Children by Age Group, Episodes per 1,000 Person-Years (1998-2018)

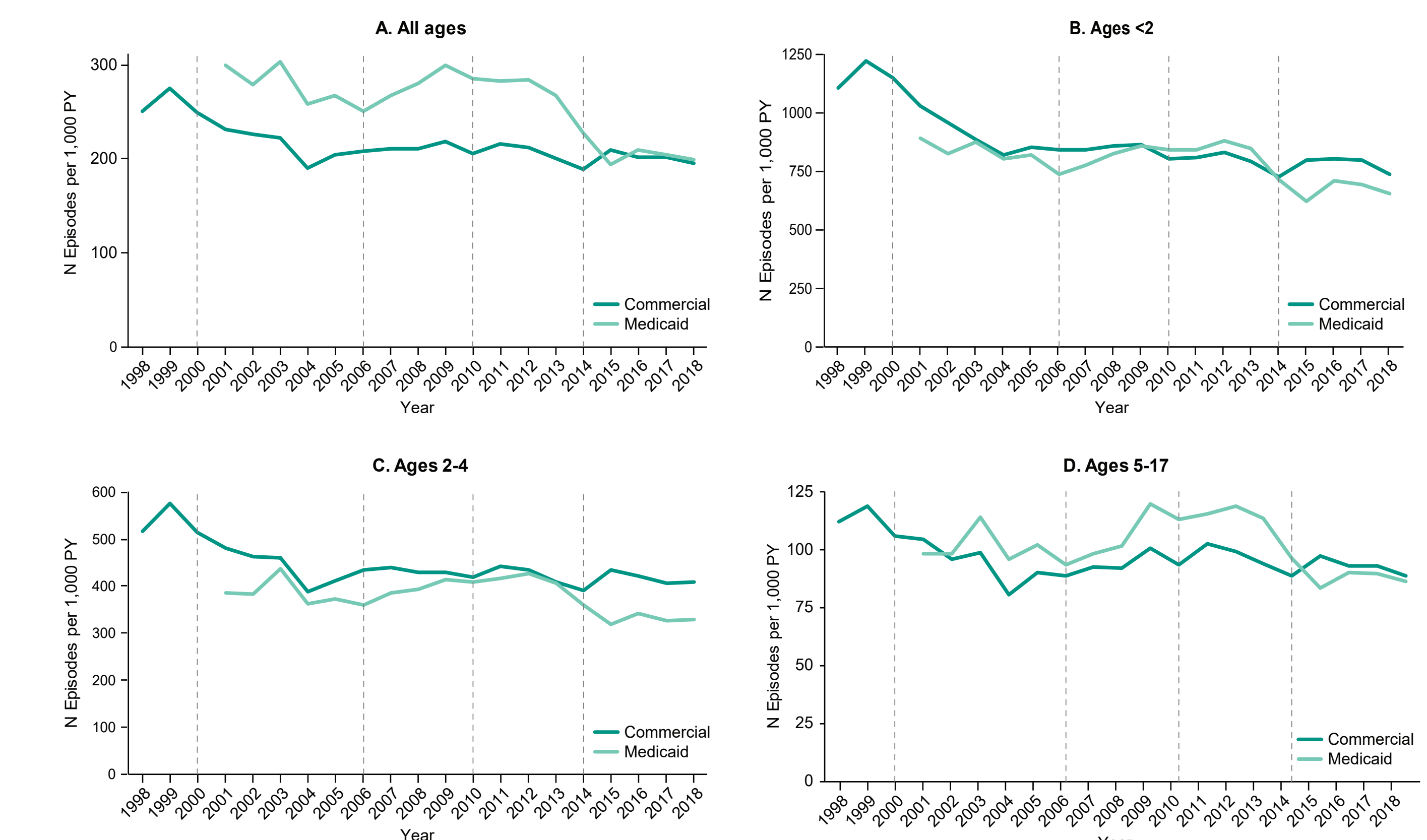


Table 2. Estimates From Interrupted Time Series Analyses of Monthly AOM Episode Incidence Rates in Children <18 Years Enrolled in Commercial Plans (1998-2018)

Period	Change	All Ages		Ages <2		Ages 2-4		Ages 5-17	
		IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Pre-PCV7	Base trend	0.987 (0.975-1.000)	0.046 ^a	1.011 (0.995-1.028)	0.189	0.988 (0.974-1.003)	0.110	0.981 (0.966-0.996)	0.015 ^a
Early PCV7	Change in level	0.272 (0.070-1.062)	0.061	1.219 (0.376-3.946)	0.742	0.405 (0.130-1.256)	0.118	0.270 (0.040-1.828)	0.180
	Change in trend	0.999 (0.992-1.006)	0.749	0.991 (0.981-1.000)	0.056	1.000 (0.991-1.009)	0.962	1.002 (0.993-1.011)	0.671
Late PCV7	Change in level	0.961 (0.795-1.163)	0.684	1.012 (0.836-1.225)	0.905	1.070 (0.896-1.278)	0.453	0.953 (0.748-1.213)	0.693
	Change in trend	1.009 (1.002-1.016)	0.012 ^a	1.001 (0.994-1.007)	0.808	1.009 (1.002-1.016)	0.008 ^a	1.013 (1.004-1.022)	0.005 ^a
Early PCV13	Change in level	1.017 (0.813-1.273)	0.882	1.283 (0.969-1.700)	0.082	1.070 (0.987-1.477)	0.066	0.956 (0.730-1.251)	0.741
	Change in trend	0.994 (0.988-0.999)	0.025 ^a	0.994 (0.988-1.000)	0.056	0.995 (0.988-1.001)	0.088	0.992 (0.985-1.000)	0.048 ^a
Late PCV13	Change in level	0.791 (0.586-1.067)	0.125	1.095 (0.830-1.445)	0.520	0.879 (0.687-1.124)	0.305	0.717 (0.485-1.059)	0.095
	Change in trend	1.013 (1.005-1.020)	<0.001 ^a	1.006 (0.996-1.016)	0.252	1.013 (1.004-1.022)	0.003 ^a	1.014 (1.005-1.024)	0.003 ^a

^a $P < 0.05$.

All coefficients were obtained through a negative binomial model with a log link. Incidence rate ratios (IRRs) represent the exponentiated regression coefficients and indicate a multiplicative change. Model intercept is not shown.

Table 3. Estimates From Interrupted Time Series Analyses of Monthly AOM Episode Incidence Rates in Children <18 Years Enrolled in Medicaid Plans (1998-2018)

Period	Change	All Ages		Ages <2		Ages 2-4		Ages 5-17	
		IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
Pre-PCV13	Base trend	1.004 (0.999-1.009)	0.083	1.006 (1.002-1.011)	0.007 ^a	1.004 (1.000-1.009)	0.078	1.003 (0.997-1.008)	0.359
Early PCV13	Change in level	1.007 (0.871-1.165)	0.926	0.943 (0.823-1.081)	0.401	1.036 (0.880-1.220)	0.671	1.132 (0.944-1.358)	0.181
	Change in trend	0.994 (0.986-1.003)	0.179	0.993 (0.986-1.001)	0.080	0.994 (0.987-1.001)	0.095	0.996 (0.987-1.005)	0.334
Late PCV13	Change in level	0.846 (0.735-0.973)	0.019 ^a	0.817 (0.727-0.918)	<0.00 ^a	0.868 (0.768-0.981)	0.024 ^a	0.836 (0.727-0.961)	0.012 ^a
	Change in trend	1.001 (0.996-1.006)	0.694	1.000 (0.996-1.005)	0.983	1.001 (0.996-1.006)	0.827	1.001 (0.995-1.007)	0.693

^a $P < 0.05$.

All coefficients were obtained through a negative binomial model with a log link. Incidence rate ratios (IRRs) represent the exponentiated regression coefficients and indicate a multiplicative change. Model intercept is not shown.

Conclusions

- In children of all ages enrolled in commercial and Medicaid plans, AOM IRs decreased after vaccine introduction
- ITS was used to investigate changes in monthly IRs across several time periods before and after vaccine introduction. For children enrolled in commercial plans, no significant immediate or gradual changes were detected in children <2 years; IRs trended downward across all time periods. In older children, IRs gradually decreased in the early PCV13 period but gradually increased in the late PCV7 and PCV13 periods
- For children of all ages enrolled in Medicaid plans, no significant immediate or gradual changes in IRs were detected in the early PCV13 period. There was an immediate reduction in AOM IRs in the late PCV13 period.
- AOM disease burden remains substantial in children enrolled in both commercial and Medicaid plans, with IRs of ~70% of those in the pre-PCV7 era, including in younger children
- The impact of future PCVs on AOM IRs will depend on the proportion of AOM caused by *S pneumoniae* and vaccine-type serotypes

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