Burden of Pneumococcal Disease Due to Serotypes Covered by the 13-Valent and New Higher-Valent Pneumococcal Conjugate Vaccines in Children with and without Underlying Medical Conditions in the United States

Liping Huang,[1] Alejandro Cane,[2] Johnna Perdrizet,[1] Adriano Arguedas[3]

[1]*Global Health Economics and Outcomes Research, Pfizer Inc, Collegeville, PA, USA;* [2]*Pfizer Vaccines, Pfizer Inc, Collegeville, PA, USA;* [3]*Vaccines US Medical Affairs, Pfizer Inc, Collegeville, PA, USA*

For more information please contact:
Liping Huang, MD, MA, MS
Economics and Outcomes Research
Pfizer Inc
liping.huang@pfizer.com

INTRODUCTION

- Children with underlying medical conditions, including at-risk conditions (asthma, chronic heart, liver, or lung disease, chronic use of oral steroids, diabetes, trisomy 21, neuromuscular/seizure disorders, prematurity/low birthweight) and at-high-risk conditions (chronic renal failure, cochlear implant, congenital immunodeficiency, disease of white blood cells, functional/anatomic asplenia, HIV, immunosuppressive drugs/conditions) have a higher likelihood of contracting pneumococcal disease caused by *Streptococcus pneumoniae*.[1]
- Routine vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) in infants along with a catch-up option with PCV13/PPSV23 in children with underlying medical conditions (UMC), has demonstrated a great impact on the reduction of invasive pneumococcal disease (IPD) in the United State (US).[2]
- However, the pneumococcal disease (PD) burden associated with non-PCV13 serotypes persists.
- A 15-valent PCV (PCV15) containing the same serotypes in PCV13 plus two additional serotypes (22F, 33F) was recently approved by FDA, and ACIP voted to recommend the use of PCV15 as an option to PCV13 (13-valent pneumococcal conjugate vaccine) for children aged <19 years according to currently recommended PCV13 dosing and schedules.
- A 20-valent PCV (PCV20), containing additional 7 serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) to PCV13 is approved for adults in the US and is anticipated for pediatric use soon.[3]

OBJECTIVE

- To estimate the annual cases, deaths, and economic burden of PD attributable to PCV13, PCV15, and PCV20 serotypes in all children and children with UMC in the US.

METHODS

- An Excel model was developed. The estimated annual cases, deaths and costs in all children (with and without UMC) were extrapolated based on population size, incidence rates, case fatality rates and direct medical cost of IPD, inpatient and outpatient community acquired pneumonia (CAP), and acute otitis media (AOM) **(Table 1)**.
- The estimates in children with underlying medical conditions were extrapolated based on proportions of children with UMCs and incidence rate ratio of children with and without medical conditions **(Table 1)**.

METHODS (continued)

Table 1. Source Data for the Calculation

Parameter	Value Used for 0–4 Years of Age	Value Used for 5–17 Years of Age	Source
Population	20,438,539	53,528,080	US population projection 2020[o]
Incidence rate per 100,000			
Total IPD	7.2	1.7	ABCs 2018 report[b]
Meningitis, %	7.8		ABCs 2018 report[c]
Bacteremia, %	92.2		
Inpatient CAP	379.5	63.8	Jain et al 2015[d]
Outpatient CAP	4880.0	1231.0	Kronman et al 2011[e]
CAP caused by *Streptococcus pneumoniae*, %	25.0		Huang et al 2011[f]
Total AOM	37,811.7	9050.0	Tong et al 2018[g]
AOM caused by *S pneumoniae*, %	20.0		Kaur et al 2017[h]
Case fatality rate, %			
Meningitis	4.8	1.0	ABCs 2018
Bacteremia	4.8	1.0	
Pneumococcal pneumonia	0.4	0.3	Rubin et al 2010[i]
Medical cost per event, USD			
Inflation factor	1.325		US Healthcare Inflation calculator
Bacteremia	42,848.0		Weycker et al 2016[j]
Meningitis	42,848.0		
Inpatient CAP	18,696.0		Weycker et al 2016
Outpatient CAP	629.0		Weycker et al 2016
AOM	284.7	186.1	Tong et al 2018[k]
Serotype distribution, %			
PCV13[l]	18.8	37.4	Data on file (2018 CDC data)
PCV15	35.3	55.4	
PCV20[l]	51.8	62.7	
Proportion of children with underlying medical condition (UMC), %	10.1	8.3	Pelton et al 2014
UMC: At-risk[m]	9.7	7.8	
UMC: High-risk[n]	0.4	0.5	
IPD Incidence rat ratio			Pelton et al 2014
UMC: At-risk vs. healthy	1.8	3.3	
UMC: High-risk vs. healthy	11.2	10.1	
All-cause pneumonia rate ratio			Pelton et al 2014
UMC: At-risk vs. healthy	2.4	3.4	
UMC: High-risk vs. healthy	6.8	10	

ABCs=Active Bacterial Core surveillance; AOM=acute otitis media; CAP=community-acquired pneumonia; CDC=US Centers for Disease Control and Prevention; IPD=invasive pneumococcal disease; PCV13=13-valent pneumococcal conjugate vaccine; PCV15=15-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine; UMC=underlying conditions; USD=United States dollars.
[o]2017 National Population Projections Datasets (census.gov).
[b]The incidence rate in the ABC report was based on <1, 1, 2–4, and 5–17 years of age. The cases for each age group were determined using the population size per age group. The overall incidence rate for pediatrics 0–4 years of age and 5–17 years of age was based on the total number of cases of the 0–4 and the 5–17 age groups, respectively.
[c]The distribution was adjusted based on known cases.
[d]The incidence rate of inpatient CAP rate for the 0– to 4–year age group was based on the weighted average between <2 and 2–4 years of age. For the 5– to 17–year age group, it was based on the weighted average between 5–9 and 10–17 years of age.
[e]The incidence rate of outpatient CAP was based on Table 2, 2006–2007 data.
[f]All-ages average between outpatient and inpatient pneumonia percentage.
[g]Data from 2014 only. Weighted average incidence per 100,000 for age groups <1, 1, and 2–4 years of age (for 0– to 4–year age group).
[h]Data from 2016 only.
[i]Weighted average of <1, 1–2, 2–3, 3–4, and 4–5 years old.
[j]Weighted average for all risk groups <18 years of age, inflated to 2020 USD.
[k]Weighted average cost per episode for age groups <1, 1, and 2–4 years of age, inflated to 2020 USD. Average cost for ages 5–17, inflated to 2020 USD.
[l]At-risk conditions include asthma, chronic heart, liver, or lung disease, chronic use of oral steroids, diabetes, trisomy 21, neuromuscular/seizure disorders, prematurity/low birthweight.
[m]High-risk conditions include chronic renal failure, cochlear implant, congenital immunodeficiency, disease of white blood cells, functional/anatomic asplenia, HIV, immunosuppressive drugs/conditions.

RESULTS

- Of the total children aged 0–4 years old and 5–17 years old, 9.7% and 7.8% had at-risk conditions and 0.4% and 0.5% had high-risk conditions, respectively **(Table 1)**.
- The estimated annual PD cases attributable to PCV13, PCV15, and PCV20 in all children 0-17 years old were 768,301, 1,275,187, and 1,656,716 and in children 0–17 years old with UMC were 23,209, 43,579, 63,949 **(Table 2.1)**, respectively.
- Of the total IPD cases attributed to serotypes covered by PCV20 in children 0–17 years old, 23.6% (313/1328) of IPD cases, 25.7% (63,636/247,760) of CAP, 8.7% (122,399/1,407,628) of AOM, and 25.5% (24/94) deaths could occur in children 0–17 years old with UMC **(Table 2.1)**.
- The proportions of cases in children with UMC vs. all children were higher in children 0–4 years old than in children 5–17 years old **(Table 2.2** and **2.3)**.

Table 2. Estimated Cases and Death in all Children and At-risk/High-risk Children

2.1 Age 0–17 years

	All Children 0–17 years			Children 0–17 years with UMC[o]		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
Cases						
IPD, n	615	1021	1328	114	213	313
Meningitis	47	79	103	9	17	24
Bacteremia	567	942	1225	105	197	289
CAP, n	115,239	190,998	247,760	23,096	43,366	63,636
Inpatient CAP	6835	11,585	15,395	1412	2650	3889
Outpatient CAP	108,404	179,412	232,365	21,684	40,715	59,747
AOM, n	652,448	1,083,168	1,407,628	44,423	83411	122,399
Total, n	768,301	1,275,187	1,656,716	23,209	43,579	63,949
Deaths	39	68	94	9	16	24

2.2 Age 0–4 years

	All Children 0–4 years			Children 0–4 years with UMC		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
Cases						
IPD, n	275	517	758	61	114	167
Meningitis	21	40	59	5	9	13
Bacteremia	254	477	699	56	105	154
CAP, n	50,524	94,974	139,209	14,009	26,304	38,600
Inpatient CAP	3646	6853	10,045	918	1724	2529
Outpatient CAP	46,878	88,120	129,163	13,091	24,581	36,070
AOM, n	290,579	546,227	800,638	29,317	55,047	80,777
Total, n	341,378	641,717	940,605	14,070	26,418	38,767
Deaths	26	49	72	7	12	18

2.3 Age 5–17 years

	All Children 5–17 years			Children 5–17 years with UMC		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
Cases						
IPD, n	340	504	570	53	99	146
Meningitis	26	39	44	4	8	11
Bacteremia	313	465	526	49	92	134
CAP, n	64,715	96,024	108,551	9086	17,061	25,036
Inpatient CAP	3189	4732	5350	494	927	1360
Outpatient CAP	61,526	91,292	103,202	8593	16,135	23,676
AOM, n	361,869	536,941	606,990	15,106	28,364	41,622
Total, n	426,923	633,470	716,111	9139	17,161	25,182
Deaths	13	19	22	2	4	6

AOM=acute otitis media; CAP=community-acquired pneumonia; IPD=invasive pneumococcal disease; PCV13=13-valent pneumococcal conjugate vaccine; PCV15=15-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
[o]Defined by children with underlying at-risk or high-risk medical conditions (see Table 1, notes m and n).

RESULTS (continued)

- The total annual costs due to PD cases attributed to serotypes covered by PCV20 in children with UMC was $186 million vs. $1.103 million in all children **(Table 3)**.

Table 3. Direct Medical Costs

3.1 Age 0–17 years

	All Children 0–17 years			Children 0–17 Years with UMC		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
IPD, million USD	35	58	75	6	12	17
CAP, million USD	259	436	576	61	115	168
Inpatient CAP	169	287	382	45	85	125
Outpatient CAP	90	150	194	16	30	43
AOM, million USD	199	338	452	11	21	31
Total, million USD	494	833	1,103	76	127	186

3.2 Age 0–4 years

	All Children 0–4 years			Children 0–4 Years with UMC		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
IPD, million USD	16.0	29.0	43.0	3.3	6.3	9.2
CAP, million USD	129.0	243.0	357.0	38.4	72.2	105.9
Inpatient CAP	90.0	170.0	249.0	29.0	54.4	79.8
Outpatient CAP	39.0	74.0	108.0	9.5	17.8	26.1
AOM, million USD	110.0	206.0	302.0	8.3	15.7	23.0
Total, million USD	255.0	479.0	702.0	50.1	78.4	115.1

3.3 Age 5–17 Years

	All Children 5–17 years			Children 5–17 Years with UMC		
	PCV13	PCV15	PCV20	PCV13	PCV15	PCV20
IPD, million USD	19.0	29.0	32.0	3.0	5.6	8.2
CAP, million USD	130.0	193.0	219.0	22.6	42.5	62.4
Inpatient CAP	79.0	117.0	133.0	16.4	30.7	45.1
Outpatient CAP	51.0	76.0	86.0	6.3	11.8	17.3
AOM, million USD	89.0	132.0	150.0	2.8	5.3	7.7
Total, million USD	239.0	354.0	401.0	25.6	48.1	70.6

AOM=acute otitis media; CAP=community-acquired pneumonia; IPD=invasive pneumococcal disease; USD=United States dollars.

LIMITATIONS

- Current IPD surveillance in the United States may have potential sources of bias due to inadequate diagnostic techniques or changes in reporting rates/diagnostic criteria over time.
- The serotype epidemiology of CAP and otitis media is largely unknown and make it challenging to estimate incidence of pneumococcal pneumonia and AOM accurately.
- The analysis did not consider the burden of the 4 serotypes unique to PPSV23 in line with the ACIP sequential use recommendation for PCV13.
- The analysis did not consider the humanistic burdens and the long-term burden.
- All indirect costs borne by families or caregivers were not included.

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CONCLUSIONS

- **This study demonstrates that additional serotypes included in higher valent vaccines are substantial contributors to the pneumococcal clinical and economic burden in children with UMCs.**
- **Despite the success of the PCV13 program, broader PCV serotype coverage is needed to further reduce pneumococcal disease burden caused by remaining non-PCV13 serotypes.**
- **The results shows that PCV20 may offer broader vaccine coverage in the prevention of PD in all children and specifically in children with UMC.**

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DISCLOSURES

All authors are employees of Pfizer Inc and may hold stock or stock options.

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