ORIGINAL RESEARCH

Estimates of the Health and Economic Burden of Pneumococcal Infections Attributable to the 15-Valent Pneumococcal Conjugate Vaccine Serotypes in the USA

Kwame Owusu-Edusei · Arijita Deb · Kelly D. Johnson

ABSTRACT

Introduction: Despite the availability of vaccines, pneumococcal disease (PD) is associated with high clinical and economic burden, mainly caused by non-vaccine serotypes and certain vaccine-type serotypes. V114 is a 15-valent pneumococcal conjugate vaccine (PCV) that contains two epidemiologically important serotypes, 22F and 33F, in addition to the 13 serotypes in 13-valent PCV (PCV13). This study quantified the epidemiologic and economic burden of PD attributable to V114 serotypes among adults in the USA.

Methods: A Markov model was used to estimate the burden of V114 serotypes in a hypothetical, non-vaccinated cohort of US adults ≥ 19 years of age who were tracked from 2019 until death. The model calculated all the invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) cases, deaths, and costs. Economic burden was estimated from a healthcare payer perspective (2019 US dollars) and discounted at 3%.

Results: The model estimated 415,229 and 10.3 million lifetime cases of V114-type IPD and NBPP, respectively. Serotypes 22F and 33F caused approximately 33% of IPD cases and 20% of NBPP cases, while serotype 3 accounted for approximately 36% of IPD cases and 13% of NBPP cases. V114 serotypes caused 472,063 total lifetime deaths. Total discounted lifetime costs attributable to V114 serotypes were $44.8 billion US dollars.

Conclusions: In this hypothetical model of a non-vaccinated cohort of US adults, V114 serotypes were associated with a substantial health and economic burden, the majority of which was attributable to serotypes 3, 22F, and 33F. The addition of V114 to the national vaccination recommendations may help to reduce the epidemiologic and economic burden associated with PD in adults ≥ 19 years of age in the USA by providing increased coverage of these serotypes.

Keywords: Invasive pneumococcal disease; Non-bacteremic pneumococcal pneumonia; Pneumococcal conjugate vaccine; Markov model; Health and economic burden

K. Owusu-Edusei (✉) · A. Deb · K. D. Johnson
Center for Observational and Real-World Evidence (CORE), Merck & Co., Inc., 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA
e-mail: kwame.owusu-edusei@merck.com

Key Summary Points

Why carry out this study?

Pneumococcal disease (PD) is associated with significant morbidity, mortality, and costs among adults in the USA.

V114 is a 15-valent pneumococcal conjugate vaccine that contains two epidemiologically important serotypes, 22F and 33F, in addition to the 13 serotypes in the 13-valent pneumococcal conjugate vaccine.

In this study, we aimed to estimate the epidemiologic and economic burden of PD attributable to V114 serotypes among adults in the USA.

What was learned from the study?

Our results suggest a substantial burden of PD caused by V114 serotypes, especially serotypes 3, 22F, and 33F.

The introduction of V114 into the national immunization schedule may help reduce the burden caused by V114 serotypes in US adults.

INTRODUCTION

Streptococcus pneumoniae is a Gram-positive bacterium that commonly colonizes the respiratory tract, potentially causing invasive and non-invasive pneumococcal disease (PD) [1]. Pneumococcal pneumonia is the most common clinical presentation of PD among adults in the USA [1]. The common types of invasive pneumococcal disease (IPD) include bacteremic pneumonia, meningitis, and septicemia, whereas non-invasive disease comprises pneumonia without bacteremia, otitis media, and sinusitis [1]. The annual incidence of IPD in US adults 19–64 years of age and adults ≥ 65 years of age was eight cases per 100,000 and 24 cases per 100,000 in 2018, respectively [2].

Non-bacteremic pneumococcal pneumonia (NBPP) continues to be a major concern, accounting for approximately 75% of cases of pneumococcal pneumonia [3]. Moreover, the presence of comorbid conditions is associated with a higher risk of PD [4, 5].

PD continues to cause significant morbidity and mortality in the USA. In 2004, PD was estimated to be responsible for 4 million episodes of illness, 445,000 hospitalizations, and 22,000 deaths in the USA [6]. The Active Bacterial Core surveillance (ABCs) report for *S. pneumoniae* from 2018 estimated 3297 cases and 361 deaths per 100,000 population in the USA; a high mortality rate was observed among adults > 35 years of age in the USA, with higher rates seen in individuals ≥ 65 years of age [7]. PD is also associated with high healthcare costs [6, 8]. In 2015, the total US costs of PD were estimated at $1.86 billion in adults ≥ 19 years of age, of which $1.8 billion was attributable to direct medical costs [8].

The introduction of a 7-valent pneumococcal conjugate vaccine (PCV7 or Prevnar®, Wyeth Pharmaceuticals Inc. Philadelphia, PA, USA) in 2000 to pediatric immunization programs in the USA, and its replacement in 2010 with a 13-valent pneumococcal conjugate vaccine (PCV13 or Prevnar 13®, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Philadelphia, PA, USA), has been associated with reduced carriage and transmission of *S. pneumoniae* among non-vaccinated infants and a substantial decline in the incidence of vaccine-type IPD among adults ≥ 65 years of age through indirect effects of PCV13 use [9]. The use of PCV13 was recommended for all adults ≥ 65 years of age in 2014; however, the reduction in cases has since plateaued [2, 9] and IPD has continued to cause significant morbidity and mortality in this age group [7]. Pneumococcal vaccine coverage in the USA in 2018 was 23.3% and 69% among adults 19–64 years of age and ≥ 65 years of age, respectively [10]. In 2019, the US Advisory Committee on Immunization Practices recommendation for routine PCV13 vaccination was updated to shared clinical decision-making for PCV13 use in adults ≥ 65 years of age without an immunocompromising condition [9].

The sustained prevalence of NBPP and IPD may be related to strains not covered by PCV13. A considerable proportion of cases of IPD in the USA are caused by the non-PCV13 serotypes 22F and 33F, which are among the most common causes of IPD in adults ≥ 18 years of age [11, 12]. In addition, certain PCV13 vaccine serotypes, such as serotype 3, continue to impose a considerable burden [12, 13].

The US Food and Drug Administration recently approved a 15-valent pneumococcal conjugate vaccine, V114 (VAXNEUVANCE™, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA), for active immunization to prevent/reduce invasive disease caused by *S. pneumoniae* in adults ≥ 18 years of age in the USA. V114 contains antigens for serotypes 22F and 33F, along with the 13 serotypes included in PCV13 [14, 15].

The objective of this study was to quantify the epidemiologic and economic burden of PD attributable to the 15 serotypes targeted by V114 in a hypothetical, non-vaccinated cohort in the USA.

METHODS

Analytical Approach

A probabilistic Markov state transition model was used to conduct this analysis from a healthcare payer perspective.

Model Overview

A state-transition global Markov model was developed to track adults until death or 100 years of age. The adult population was divided into cohorts of low-risk, at-risk (high-risk but immunocompetent), and high-risk immunosuppressed adults.

Model Structure

As illustrated in Fig. 1, the model contains six health states: no PD, inpatient NBPP, outpatient
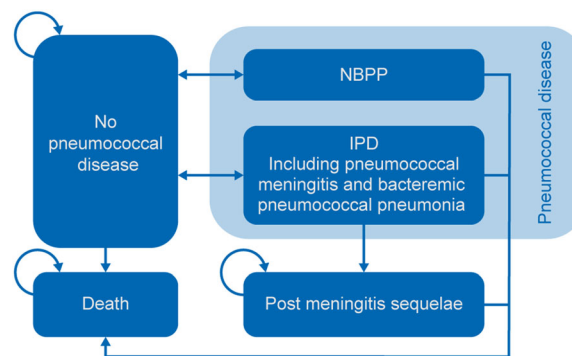

Fig. 1 Markov model structure. IPD invasive pneumococcal disease, NBPP non-bacteremic pneumococcal pneumonia. Background mortality is applied to all health states in the model

NBPP, IPD, post meningitis sequelae (PMS), and death. All individuals enter the model in the "no PD" health state and are subsequently at risk of developing IPD or NBPP. Vaccinated individuals without PD have a lower chance of developing IPD or NBPP. Individuals who develop IPD or NBPP are faced with a higher risk of death than those without PD. After IPD or NBPP, surviving individuals either recover and return to the "no PD" health state or may develop PMS after IPD meningitis. It is assumed that, after PMS, the patients cannot develop another episode of IPD or NBPP, because such a situation is considered rare. Hence, the PMS health state is an absorbing health state, and they may subsequently die. However, the background mortality still applies to the individuals with PMS. The model tracks the cohort over the specified time horizon and calculates all the IPD and NBPP cases, deaths, costs, and quality-adjusted life years (QALYs); not all of these data are included in this report. In addition, half-cycle correction is applied to account for events that occur at any point (week/month) during the year.

Model Inputs

The model has the following input categories:

1. General model inputs (currency, perspective, time horizon, uncertainty assumptions, and discount rate).

2. Population inputs (population size, life table, proportion of patients in different risk groups, age of vaccine administrations, choice of intervention and comparators, and vaccine coverage rate).

3. Efficacy inputs (serotype distribution together with serotype-specific vaccine efficacy for intervention and comparators, vaccine waning function, childhood herd immunity, and childhood serotype replacement).

4. Epidemiological inputs (proportion of antimicrobial resistance per serotype, IPD and NBPP incidence, case fatality rate [CFR] for IPD and NBPP, proportion of meningitis in IPD cases, proportion of PMS in meningitis cases and proportion of NBPP cases hospitalized).

5. Cost inputs (vaccine and vaccine administration costs, costs of IPD, inpatient and outpatient NBPP, meningitis, PMS, and antimicrobial resistance cases, loss of productivity costs, and travel costs).

6. Utility inputs (baseline utility value per risk group and age group, utility decrement values of PD, utility value of individuals with PMS, and days of decrement per PD). All input values are modifiable and can be updated with data for the population under study.

The outputs generated by the model can include the number of cases of IPD, inpatient and outpatient NBPP, PMS, and antimicrobial resistance cases in IPD and NBPP for each vaccination strategy, by subgroup and by serotype within each subgroup. Other outcomes that can be determined by the model include IPD and NBPP deaths, serotype-specific costs, incremental costs, life years and QALYs, incremental cost-effectiveness ratios, sensitivity analyses, and threshold analyses. The lifetime horizon is chosen to capture all benefits provided by the vaccinations throughout the study population's lifetime. The cost and outcomes can be discounted at separate adaptable rates in the model. The model uses a 1-year cycle length to circumvent the seasonality of PD [16].

Model Validation

The model implementation has been verified through a series of tests to ensure that the model is performing as expected and is in line with the design objective, and that the outputs of the model are acceptable with respect to the real data-generating process. The technical aspects were checked against a checklist, stress testing was applied to the model, and tests were built into the model for verification and to ensure internal validity [17]. Finally, the model results were checked with the systematic literature review outcomes of the study by Shiri and colleagues [18].

The Current Analysis

Given the research question and objective of the current analysis (quantifying the epidemiologic and economic burden of PD attributable to the 15 serotypes targeted by V114 in a hypothetical, non-vaccinated cohort in the USA), the model was used to predict the number of cases and associated costs for the 15 serotypes over the lifetime of all adults ($\geq$ 19 years of age) in the USA.

This article does not contain any new studies with human participants or animals performed by any of the authors. The data used are presented below.

Target Population

The target population of the study was a 2019 cohort of non-vaccinated adults in the USA $\geq$ 19 years of age who were tracked from 2019 until death. The cohort size of approximately 250 million adults was based on annual estimates of the adult population in the USA in 2019 according to the US Census Bureau [19]. The study population was stratified into three mutually exclusive risk groups: low-risk (LR), at-risk (AR), and high-risk (HR) adults, based on proportions per age group (Table S1 in the supplementary material) from Pelton et al. [4].

- LR refers to healthy individuals.
- AR refers to immunocompetent individuals having one or more of the following

conditions: chronic heart disease, diabetes mellitus, pulmonary disease, liver disease, alcoholism, cerebrospinal fluid leaks, cochlear implants, or cigarette smoking/smokers.

- HR refers to immunosuppressed individuals who have one of the following conditions: anatomic asplenia, human immunodeficiency virus infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation).

Having more than one of these conditions is not considered in the model. The model combines all conditions related to high-risk immunosuppression into one high-risk immunosuppressed subgroup. The model assumes that changes between different risk groups (e.g., from LR to AR following the incidence of a medical condition, such as diabetes mellitus) are not possible.

Life Table

A life table presenting the age-specific annual probabilities of death based on the general population was included to cover background mortality for the cohort (Table S2 in supplementary material). These probabilities were applied to the model population to ensure that the natural survival seen in the general population is reflected. The life table was obtained from the US National Vital Statistics Report [20].

Epidemiological Inputs

Epidemiological data obtained from published literature and publicly available reports were used as model parameters (Table 1). IPD incidence was obtained from Ahmed et al. [21] and serotype distribution was obtained from unpublished 2017 CDC serotype data shared with the authors. The CFRs for IPD were taken from the ABCs report for *S. pneumoniae* from 2017 [22].

Age-specific hospitalization rates of all-cause community-acquired pneumonia (CAP) were taken from a population-based cohort study of hospitalized adults with CAP conducted by Ramirez et al. [23]. Rates of outpatient all-cause CAP were obtained from a retrospective analysis of pneumonia-related healthcare utilization in the USA conducted by Tong et al. [24]. The proportion of all-cause CAP attributable to NBPP was estimated at 11% [3]. Rates of inpatient and outpatient NBPP were then split into LR, AR, and HR using the relative risk estimates and weighted by the prevalence of the healthy (LR), AR, and HR populations obtained from Weycker et al. [25].

The CFR of NBPP for outpatients was assumed to be zero, and the hospitalization rates among patients were assumed to be the same across the three risk groups. The CFR of NBPP for inpatients was obtained from a retrospective cohort study conducted by Wuerth et al. [26]. Serotype distribution and proportions were estimated from Isturiz et al. [27].

Cost Inputs

Economic burden was estimated from a publicly funded healthcare payer perspective [28, 29]. Total direct medical costs per episode of IPD or NBPP were obtained by multiplying the number of hospitalizations by the cost per hospitalization for IPD or NBPP (Table 2). Costs were adjusted to 2019 US dollars and discounted at an annual rate of 3%.

Model Assumptions

The model makes a few assumptions: (1) The movement between risk categories as the person ages is not possible; (2) a patient may develop IPD or NBPP in 1 year; and (3) after PMS, patients would not develop another episode of IPD or NBPP, because such a situation was considered rare. Therefore, PMS is an absorbing state.

Model Outputs

Modeled outcomes included the number of IPD cases and deaths, the number of NBPP cases and deaths, and the overall total direct costs attributable to IPD and NBPP combined, and that were attributable to all V114 serotypes, serotypes 22F and 33F combined, and serotype 3 individually.

Table 1 Epidemiologic model parameters

Model parameters	18–64 years			65+ years		
	LR	AR	HR	LR	AR	HR
IPD incidence (per 100,000) [21]	3.90	14.00	26.60	15.40	35.40	38.70
Proportion of ST3 IPD (%)[†]	12.10	12.10	12.10	15.5	15.5	15.5
Proportion of 22F + 33F IPD (%)[†]	11.20	11.20	11.20	13.20	13.20	13.20
Proportion of V114 serotypes (%)[†]	35.10	35.10	35.10	36.60	36.60	36.60
Case fatality rate of IPD (%) [22]	8.30	8.30	8.30	16.40	16.40	16.40
NBPP inpatient incidence (per 100,000) [3, 23, 25]	16	84	261	131	403	632
NBPP outpatient incidence (per 100,000) [3, 24, 25]	29	160	512	142	423	638
Proportion of ST3 NBPP (%) [27]	9.61	9.61	9.61	7.89	7.89	7.89
Proportion of 22F + 33F NBPP (%) [27]	10.92	10.92	10.92	11.50	11.50	11.50
Proportion of V114 serotypes (%) [27]	54.87	54.87	54.87	51.90	51.90	51.90
Case fatality rate for inpatient NBPP (%) [26]	3.81	3.81	3.81	9.77	9.77	9.77

[†]Data obtained from unpublished CDC ABCs serotype data (2017) shared with the authors

ABCs Active Bacterial Core surveillance, *AR* at risk, *CDC* Centers for Disease Control and Prevention, *HR* high risk, *IPD* invasive pneumococcal disease, *LR* low risk, *NBPP* non-bacteremic pneumococcal pneumonia, *ST* serotype, *V114* 15-valent pneumococcal conjugate vaccine

Table 2 Economic model parameters [25]

Age category, years	Costs of IPD per episode (in 2019 USD)	Cost of NBPP per episode (in 2019 USD)	
		Inpatient	Outpatient
18–64	$55,622	$23,384	$760
65–69	$31,298	$11,423	$574
70–74	$33,775	$11,055	$633
75–79	$30,009	$11,215	$695
80–84	$26,445	$10,419	$889
85–89	$20,790	$7681	$882
90–100	$20,368	$8746	$1342

IPD invasive pneumococcal disease, *NBPP* non-bacteremic pneumococcal pneumonia, *USD* US dollars
Source of cost data: Weycker et al. and MSD internal analysis using Humana claims data

Scenario Analyses

Scenario analyses were conducted by varying the incidence and cost data by ± 20% and varying the discount rate to 0% and 5% to assess the lifetime total direct medical costs attributable to V114 serotypes in adults ≥ 19 years of age.

RESULTS

IPD and NBPP Lifetime Cases by Serotype

For the approximately 250 million adults ≥ 19 years of age, the model estimated 415,229 cases of IPD that were attributable to V114 serotypes. Among these, 135,838 (32.7%) and 149,476 (36%) cases were caused by serotypes 22F + 33F and serotype 3, respectively (Table 3).

The number of cases of NBPP attributable to V114 serotypes was 10,317,709; 2,106,878 (20.4%) cases were associated with serotypes 22F + 33F and 1,290,011 (12.5%) cases were caused by serotype 3, respectively. The numbers of IPD and NBPP cases by age groups are provided in Table 3.

In older patients ≥ 65 years of age, the majority of IPD and NBPP cases attributable to V114 serotypes occurred in AR and HR patients.

IPD and NBPP Lifetime Mortality by Serotype

Of the estimated 57,192 deaths associated with V114 serotypes among patients with IPD, 18,811 (32.9%) and 20,780 (36.3%) deaths were due to serotypes 22F + 33F and serotype 3, respectively (Table 4).

The number of deaths attributable to V114 serotypes in patients diagnosed with NBPP was 414,871. In total, 85,132 (20.5%) and 70,018 (16.9%) deaths were attributable to serotypes 22F + 33F and serotype 3, respectively (Table 4).

Table 3 Lifetime IPD and NBPP cases attributable to all V114 serotypes, serotypes 22F + 33F, and serotype 3

Age group	Risk cohorts	V114 serotypes			Serotypes 22F + 33F			Serotype 3		
		IPD	NBPP	Total	IPD	NBPP	Total	IPD	NBPP	Total
19–49	HR	30,974	702,334	733,308	9883	139,792	149,675	10,677	122,949	133,627
	AR	54,803	1,409,522	1,464,325	17,487	280,550	298,037	18,892	246,748	265,641
	LR	142,751	3,081,986	3,224,737	45,550	613,435	658,985	49,210	539,527	588,738
50–64	HR	26,443	654,787	681,230	8438	130,328	138,766	9116	4613	13,729
	AR	40,941	1,123,466	1,164,408	13,064	223,613	236,677	14,114	8319	22,433
	LR	38,896	976,445	1,015,341	12,411	194,351	206,762	13,409	7442	20,851
65–74	HR	16,896	443,924	460,820	6094	98,337	104,430	7155	67,532	74,688
	AR	24,231	698,435	722,666	8739	154,715	163,454	10,262	106,250	116,512
	LR	10,760	307,890	318,649	3881	68,203	72,083	4557	46,838	51,395
75+	HR	10,984	339,779	350,762	3961	75,267	79,228	4652	51,689	56,341
	AR	13,738	449,944	463,681	4955	99,670	104,624	5818	68,448	74,266
	LR	3813	129,197	133,010	1375	28,619	29,994	1615	19,654	21,269
	Total	415,229	10,317,709	10,732,938	135,838	2,106,878	2,242,716	149,476	1,290,011	1,439,487

Note: Numbers may not add up due to rounding

AR at risk, *HR* high risk, *IPD* invasive pneumococcal disease, *LR* low risk, *NBPP* non-bacteremic pneumococcal pneumonia, *V114* 15-valent pneumococcal conjugate vaccine

Table 4 Lifetime IPD and NBPP deaths attributable to all V114 serotypes, serotypes 22F + 33F, and serotype 3

Age group	Risk cohorts	V114 serotypes			Serotypes 22F + 33F			Serotype 3		
		IPD	NBPP	Total	IPD	NBPP	Total	IPD	NBPP	Total
19–49	HR	3540	20,660	24,199	1129	4112	5242	1220	3617	4837
	AR	6892	48,142	55,034	2199	9582	11,781	2376	8428	10,804
	LR	18,285	115,923	134,209	5835	23,073	28,908	6304	20,293	26,597
50–64	HR	3570	26,352	29,922	1139	5245	6384	1231	4613	5844
	AR	5815	47,522	53,336	1855	9459	11,314	2004	8319	10,324
	LR	5571	42,513	48,084	1778	8462	10,239	1920	7442	9363
65–74	HR	2584	20,381	22,965	932	4515	5447	1094	3100	4195
	AR	3821	32,155	35,976	1378	7123	8501	1618	4892	6510
	LR	1707	14,211	15,918	616	3148	3764	723	2162	2885
75+	HR	2081	17,380	19,461	751	3850	4601	881	2644	3525
	AR	2603	23,021	25,624	939	5099	6038	1102	3502	4604
	LR	723	6612	7335	261	1465	1725	306	1006	1312
	Total	57,192	414,871	472,063	18,811	85,132	103,944	20,780	70,018	90,798

Note: Numbers may not add up due to rounding

AR at risk, *HR* high risk, *IPD* invasive pneumococcal disease, *LR* low risk, *NBPP* non-bacteremic pneumococcal pneumonia, *V114* 15-valent pneumococcal conjugate vaccine

In the 19–49 years of age and 50–64 years of age groups, more deaths were observed in the LR and AR groups. In older adults (≥ 65 years of age), higher numbers of deaths were observed in the AR and HR populations.

Economic Impact by Serotype

Total discounted lifetime costs (direct medical costs; US dollars) of IPD and NBPP attributable to all V114 serotypes were estimated to be $44.8 billion; serotypes 22F + 33F and serotype 3 accounted for $10.3 billion (22.9%) and $9.3 billion (20.7%) of total direct medical costs, respectively (Table 5). Generally, AR and HR patients in the ≥ 65 years of age groups were associated with a higher economic burden. In the 19–49 years of age and 50–64 years of age groups, the economic burden was higher for the LR and AR subgroups.

Scenario Analysis

The scenario analysis indicated that lifetime total direct medical costs were sensitive to changes around all key parameters. Total costs were most affected by the discount rate, whereby total IPD and NBPP costs attributable to V114 serotypes increased by 46% and decreased by 18% for 0% and 5% discount rates, respectively (Table 6). When the incidence and total disease cost for IPD and NBPP were varied by ± 20%, total costs increased and decreased by 20% accordingly. Similar trends were observed for IPD and NBPP cases attributable to serotypes 22F + 33F and serotype 3.

DISCUSSION

Our study used a modeling approach to estimate the lifetime burden of PD among adults in the USA. This modeling analysis demonstrated

Table 5 Lifetime discounted direct 2019 medical costs (USD, millions) for IPD and NBPP attributable to all V114 serotypes, serotypes 22F + 33F, and serotype 3

Age group	Risk cohorts	V114 serotypes			Serotypes 22F + 33F			Serotype 3		
		IPD	NBPP	Total	IPD	NBPP	Total	IPD	NBPP	Total
19–49	HR	$787.0	$2783.3	$3570.3	$251.1	$554.0	$805.1	$271.3	$487.2	$758.5
	AR	$1138.1	$4565.3	$5703.4	$363.1	$908.7	$1271.8	$392.3	$799.2	$1191.5
	LR	$2846.4	$8229.2	$11,075.7	$908.3	$1637.9	$2546.2	$981.3	$1440.6	$2421.8
50–64	HR	$706.1	$3203.2	$3909.3	$225.3	$637.6	$862.9	$243.4	$560.7	$804.2
	AR	$951.9	$4600.1	$5552.1	$303.8	$915.6	$1219.4	$328.2	$805.3	$1133.5
	LR	$889.0	$3452.1	$4341.2	$283.7	$687.1	$970.8	$306.5	$604.3	$910.8
65–74	HR	$350.7	$1782.4	$2133.1	$126.5	$394.8	$521.3	$148.5	$271.2	$419.7
	AR	$476.1	$2633.9	$3110.0	$171.7	$583.4	$755.2	$201.6	$400.7	$602.3
	LR	$209.0	$1098.2	$1307.2	$75.4	$243.3	$318.6	$88.5	$167.1	$255.6
75+	HR	$207.7	$1312.9	$1520.6	$74.9	$290.8	$365.7	$87.9	$199.7	$287.7
	AR	$259.6	$1738.2	$1997.8	$93.6	$385.0	$478.7	$110.0	$264.4	$374.4
	LR	$72.0	$498.9	$570.9	$26.0	$110.5	$136.5	$30.5	$75.9	$106.4
	Total	$8893.7	$35,897.8	$44,791.6	$2903.4	$7348.8	$10,252.2	$3190.0	$6076.3	$9266.3

Note: Numbers may not add up due to rounding

AR at risk, *HR* high risk, *IPD* invasive pneumococcal disease, *LR* low risk, *NBPP* non-bacteremic pneumococcal pneumonia, *USD* US dollars, *V114* 15-valent pneumococcal conjugate vaccine

Table 6 Scenario analyses: lifetime total direct medical costs (in 2019 USD, millions) of IPD and NBPP attributable to V114 serotypes in adults

Scenario	V114	22F + 33F	Serotype 3
Base case	$44,791.6	$10,252.2	$9266.3
Incidence + 20%	$53,728.6	$12,297.7	$11,115.2
Incidence − 20%	$35,847.5	$8205.0	$7416.0
Disease cost + 20%	$53,749.9	$12,302.6	$11,119.6
Disease cost − 20%	$35,833.3	$8201.7	$7413.1
Discount rate 0%	$65,539.3	$15,001.1	$13,558.6
Discount rate 5%	$36,537.1	$8362.8	$7558.7

IPD invasive pneumococcal disease, *NBPP* non-bacteremic pneumococcal pneumonia, *USD* US dollars, *V114* 15-valent pneumococcal conjugate vaccine

PD attributable to V114 serotypes as a major driver of healthcare utilization and costs in a hypothetical non-vaccinated cohort of US adults ≥ 19 years of age, followed until death. We estimated approximately 11 million lifetime cases of PD and 0.5 million deaths. A substantial

proportion of these cases were caused by serotypes 3, 22F, and 33F. PCV13 serotype 3 and non-PCV13 serotypes 22F and 33F were responsible for 13.4% and 20.9% of PD cases, respectively. The number of cases associated with these three serotypes was disproportionate when compared with overall incidence due to all V114 serotypes. In another retrospective observational study conducted in the USA in 2017, 12.4–13.6% of IPD cases in adults were attributed to serotypes 22F and 33F; serotype 3 accounted for 11.6–15.5% of IPD cases [30]. A similar increase in cases attributed to serotype 22F after PCV13 introduction to the vaccination program was reported in Canada [31], Australia, and some European countries [32]. Several other studies have highlighted the persistence of some vaccine serotypes in adults after the introduction of PCVs, especially serotype 3 [11, 32, 33]. This evidence suggests a need for vaccines with greater effectiveness against vaccine serotypes that are persistent and continue to contribute significantly to disease burden, such as serotype 3, and that also extend coverage to include highly prevalent non-PCV13 serotypes causing substantial disease burden.

Zhang et al. previously reported a higher rate of IPD in US adults with HR or AR conditions than in healthy adults [34]. Moreover, costs of PD are substantially higher among persons with certain chronic and immunocompromising conditions [25]. Our findings continue to indicate that PD rates are substantially higher among older adults ≥ 65 years of age with AR or HR conditions when compared with healthy adults of the same age, with a similar trend seen for PD-related mortality and costs.

Our study also estimated a substantial economic burden of PD, accounting for approximately $45 billion in lifetime direct medical costs, with notable and disproportionate costs attributable to serotypes 3, 22F, and 33F. Huang et al. estimated $3.5 billion in direct medical costs associated with PD in the USA in 2004 [6]. Prevention of pneumococcal pneumonia with vaccines extending coverage to include serotypes 22F + 33F and increased effectiveness against serotype 3 might result in significant cost savings and reduce the burden of PD.

Limitations

Our study had a few limitations. First, our results were based on a modeling analysis that may not provide an accurate representation of the real future situation. Second, the analysis did not include direct non-medical costs borne by families or caregivers, such as transportation and lodging, or any indirect costs associated with productivity loss. Consequently, overall estimates of health and economic burden of IPD and NBPP associated with V114 serotypes were conservative. Although individuals aged through the model over their lifetime and their health risk changed substantially, the current model assumed the same risk for each age throughout their lifetime. This underestimated the PD-related cases, mortality, and costs associated with the risk groups over time.

Given that the treatment and management of IPD and NBPP depends on antibiotics, there is the potential for the development of resistance to specific antibiotics due to mutation over time. Currently, many bacteria, including some *S. pneumoniae*, have become resistant to one or more antibiotics [35], leading to treatment failure and extra treatment-associated costs. The current analysis did not include the associated health and economic impact of antimicrobial resistance. Finally, the current model did not include the cost of death attributable to PD, thereby underestimating the total cost presented in this study.

Strengths

Despite the limitations outlined above, the current analysis has several strengths. First, to our knowledge, this is the first study that focused on estimating the health and economic outcomes attributable to the 15 serotypes contained in V114. Second, given the importance of serotype-specific information for PDs, the model provided the relevant serotype-specific outcome information. The current analysis included all adults ≥ 19 years of age by risk category.

The value of next-generation adult pneumococcal vaccines should, therefore, not be

limited to prevention of disease caused by serotypes not currently covered. This analysis demonstrates that to achieve full value in addressing the ongoing burden of PD, next-generation vaccines should account for both currently licensed vaccine serotypes as well as non-vaccine serotypes.

CONCLUSIONS

Using our Markov model, we estimated that, in the USA, V114 serotypes were associated with a substantial health and economic burden of PD among adults $\geq$ 19 years of age, the majority of which was attributable to serotypes 3, 22F, and 33F. The addition of V114 to the national vaccination program could reduce hospitalizations, costs, and deaths associated with PD in non-vaccinated adults $\geq$ 19 years of age in the USA.

ACKNOWLEDGEMENTS

REFERENCES

1. Centers for Disease Control and Prevention. The Pink Book: epidemiology and prevention of vaccine-preventable diseases. 14th ed. Chapter 17: pneumococcal disease. 2021. https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html. Accessed 23 Aug 2021.

2. Centers for Disease Control and Prevention. Surveillance and reporting. 2017. https://www.cdc.gov/pneumococcal/surveillance.html. Accessed 3 Apr 2019.

3. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS ONE. 2013;8(4): e60273.

4. Pelton SI, Bornheimer R, Doroff R, Shea KM, Sato R, Weycker D. Decline in pneumococcal disease attenuated in older adults and those with comorbidities following universal childhood PCV13 immunization. Clin Infect Dis. 2019;68(11):1831–8.

5. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70(10):984–9.

6. Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. Vaccine. 2011;29(18):3398–412.

7. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) report: *Streptococcus pneumoniae*, 2018. 2018. https://www.cdc.gov/abcs/reports-findings/survreports/spneu18.html. Accessed 21 Jul 2021.

8. Ozawa S, Portnoy A, Getaneh H, et al. Modeling the economic burden of adult vaccine-preventable diseases in the United States. Health Aff (Millwood). 2016;35(11):2124–32.

9. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68(46):1069–75.

10. Lu PJ, Hung MC, Srivastav A, et al. Surveillance of vaccination coverage among adult populations—United States, 2018. MMWR Surveill Summ. 2021;70(3):1–26.

11. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015;15(3):301–9.

12. Varghese J, Chochua S, Tran T, et al. Multistate population and whole genome sequence-based strain surveillance of invasive pneumococci recovered in the USA during 2017. Clin Microbiol Infect. 2020;26(4):512e1-e10.

13. Adam HJ, Golden AR, Karlowsky JA, et al. Analysis of multidrug resistance in the predominant *Streptococcus pneumoniae* serotypes in Canada: the SAVE study, 2011–15. J Antimicrob Chemother. 2018;73(suppl_7):vii12–9.

14. Food and Drug Administration. VAXNEUVANCE[TM] (Pneumococcal 15-valent Conjugate Vaccine) Prescribing Information. 2021. https://www.fda.gov/media/150819/download. Accessed 21 Jul 2021.

15. Ermlich SJ, Andrews CP, Folkerth S, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naive adults >/=50 years of age. Vaccine. 2018;36(45): 6875–82.

16. Dowell SF, Whitney CG, Wright C, Rose CE Jr, Schuchat A. Seasonal patterns of invasive pneumococcal disease. Emerg Infect Dis. 2003;9(5): 573–9.

17. Dasbach EJ, Elbasha EH. Verification of decision-analytic models for health economic evaluations: an overview. Pharmacoeconomics. 2017;35(7): 673–83.

18. Shiri T, Khan K, Keaney K, Mukherjee G, McCarthy ND, Petrou S. Pneumococcal disease: a systematic review of health utilities, resource use, costs, and economic evaluations of interventions. Value Health. 2019;22(11):1329–44.

19. United States Census Bureau. Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2019 2020. https://www.census.gov/newsroom/press-kits/2020/population-estimates-detailed.html. Accessed 15 Apr 2021.

20. Arias E, Xu JQ. United States life tables, 2018. National Vital Statistics Reports. 2020. https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr69-12-508.pdf. Accessed 12 Jul 2021.

21. Ahmed SS, Pondo T, Xing W, et al. Early impact of 13-valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions—United States. Clin Infect Dis. 2020;70(12):2484–92.

22. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) report: *Streptococcus pneumoniae*, 2017. 2017. https://www.cdc.gov/abcs/reports-findings/survreports/spneu17.html. Accessed 15 Apr 2020.

23. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017;65(11):1806–12.

24. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008–2014. BMC Health Serv Res. 2018;18(1):715.

25. Weycker D, Farkouh RA, Strutton DR, Edelsberg J, Shea KM, Pelton SI. Rates and costs of invasive pneumococcal disease and pneumonia in persons with underlying medical conditions. BMC Health Serv Res. 2016;16:182.

26. Wuerth BA, Bonnewell JP, Wiemken TL, Arnold FW. Trends in pneumonia mortality rates and hospitalizations by organism, United States, 2002–2011(1). Emerg Infect Dis. 2016;22(9):1624–7.

27. Isturiz RE, Ramirez J, Self WH, et al. Pneumococcal epidemiology among us adults hospitalized for community-acquired pneumonia. Vaccine. 2019;37(25):3352–61.

28. Stoecker C, Kobayashi M, Matanock A, Cho BH, Pilishvili T. Cost-effectiveness of continuing pneumococcal conjugate vaccination at age 65 in the context of indirect effects from the childhood immunization program. Vaccine. 2020;38(7):1770–7.

29. MSD. Internal analysis from 65+ BOD study. 2020. Data on File.

30. Grant LR, Suaya JA, Pugh S, Chilson E. Coverage of the 20-valent conjugate vaccine against invasive pneumococcal disease by age group in the United States, 2017. In: 12th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD); 2020 June 20–24. Toronto, Canada (abstract number ID 237).

31. Demczuk WH, Martin I, Griffith A, et al. Serotype distribution of invasive *Streptococcus pneumoniae* in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010–2012. Can J Microbiol. 2013;59(12):778–88.

32. Lochen A, Croucher NJ, Anderson RM. Divergent serotype replacement trends and increasing diversity in pneumococcal disease in high income settings reduce the benefit of expanding vaccine valency. Sci Rep. 2020;10(1):18977.

33. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–43.

34. Zhang D, Petigara T, Yang X. Clinical and economic burden of pneumococcal disease in US adults aged 19–64 years with chronic or immunocompromising diseases: an observational database study. BMC Infect Dis. 2018;18(1):436.

35. Center for Disease Control and Prevention. Drug-resistant *Streptococcus pneumoniae*. 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/strep-pneumoniae-508.pdf. Accessed 5 Aug 2021.