Healthcare utilization and cost of pneumococcal disease in the United States

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ABSTRACT

Background: Streptococcus pneumoniae continues to cause a variety of common clinical syndromes, despite vaccination programs for both adults and children. The total U.S. burden of pneumococcal disease is unknown.
Methods: We constructed a decision tree-based model to estimate U.S. healthcare utilization and costs of pneumococcal disease in 2004. Data were obtained from the 2004–2005 National (Hospital) Ambulatory Medical Care Surveys (outpatient visits, antibiotics) and the National Hospital Discharge Survey (hospitalization rates), and CDC surveillance data. Other assumptions regarding the incidence of each syndrome due to pneumococcus, expected health outcomes, and healthcare utilization were derived from literature and expert opinion. Healthcare and time costs used 2007 dollars.
Results: We estimate that, in 2004, pneumococcal disease caused 4.0 million illness episodes, 22,000 deaths, 445,000 hospitalizations, 774,000 emergency department visits, 5.0 million outpatient visits, and 4.1 million outpatient antibiotic prescriptions. Direct medical costs totaled $3.5 billion. Pneumonia (866,000 cases) accounted for 22% of all cases and 72% of pneumococcal costs. In contrast, acute otitis media and sinusitis (1.5 million cases each) comprised 75% of cases but only 16% of direct medical costs. Patients ≥65 years old, accounted for most serious cases and the majority of direct medical costs ($1.8 billion in healthcare costs annually). In this age group, pneumonia caused 242,000 hospitalizations, 1.4 million hospital days, 194,000 emergency department visits, 374,000 outpatient visits, and 16,000 deaths. However, if work loss and productivity are considered, the cost of pneumococcal disease among younger working adults (18–<50) nearly equaled those ≥65.
Conclusions: Pneumococcal disease remains a substantial cause of morbidity and mortality even in the era of routine pediatric and adult vaccination. Continued efforts are warranted to reduce serious pneumococcal disease, especially adult pneumonia.

1. Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of bacterial disease in children and adults. Its clinical spectrum includes localized disease such as acute otitis media (AOM) and sinusitis, and more serious infections such as pneumonia and meningitis, which cause substantial morbidity and mortality. Because of this, pneumococcal vaccines have been long recommended for widespread use.

The 23-valent pneumococcal polysaccharide vaccine was licensed in 1983 and is 50–85% effective in preventing invasive pneumococcal disease (IPD) among healthy adults [1,2]. The U.S. licensure of a pediatric 7-valent pediatric conjugate vaccine (PCV7) in 2000, led to a 4-fold decrease in the IPD rate among children <5 years old [3], and a decrease in the IPD rate among adults >50 years old of nearly one-third [4,5]. Uptake of PCV7 vaccine has been high (>90%) given the addition of this vaccine to the routine pediatric vaccine schedule [6,7].

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Nevertheless, despite extensive vaccination programs, pneumococcus remains a common human pathogen. Surveillance from the Centers for Disease Control and Prevention (CDC) suggests that post-PCV7 reductions in invasive disease plateaued by 2004, with non-vaccine serotypes causing the remaining IPD [4,8–11]. Other pneumococcal diseases such as AOM and non-invasive pneumonia have declined modestly [12,13], but are more common than IPD and are important drivers of healthcare utilization and related costs. Thus, the burden of pneumococcal disease may still be considerable in the current vaccine era [14]. Robust estimates of this burden may help drive further prevention strategies. Currently, only 64% of adults ≥65 and 37% of adults with diabetes aged 18–64 are vaccinated [15,16].

Pneumococcal disease burden has been estimated in other countries [17,18]. We sought to estimate U.S. healthcare utilization and costs for IPD and non-invasive pneumococcal infections to identify population targets to reduce pneumococcal disease, and quantify the potential savings of further prevention efforts, such as future vaccines covering non-PCV7 serotypes.

2. Methods

We developed a decision tree-based model to estimate U.S. healthcare utilization, outcomes, and costs attributable to pneumococcal disease in 2004. We used the most recently available national healthcare utilization and cost data, data from the CDC's Active Bacterial Core Surveillance (ABCs) system, existing literature, and expert panel opinion to inform parameter values (Appendices A–E). This study was exempted from human research oversight by the Harvard Pilgrim Health Care Institutional Review Board.

We assessed annual incidence and outcomes for seven clinical syndromes using ICD9 codes (Appendix A) for the following diagnoses and applying the fraction due to pneumococcus based upon literature and expert opinion: AOM, sinusitis, acute exacerbation of chronic bronchitis (AECB), pneumonia, meningitis, bone and joint infections, and bacteremia/sepsis (not associated with other syndromes). Pneumococcal syndromes were assessed across six age groups (<2, 2–<5, 5–<18, 18–<50, 50–<65, and ≥65 years old) with three exclusions due to rare events: (1) sinusitis <2 years old, (2) AECB <18 years old, and (3) bone and joint infections ≥18 years old. Results are shown for collapsed age groups (see Appendices A–E for full details).

Major model parameters and their sources are provided in Appendices A–E. An expert panel provided estimates when literature estimates were inadequate or conflicting. AOM and sinusitis were considered exclusively outpatient diseases. Meningitis, bone/joint infections, and bacteremia/sepsis were considered inpatient conditions with post-discharge outpatient follow-up. Pneumonia and AECB were considered both outpatient and inpatient conditions with three possible treatment pathways: outpatient treatment alone, initial outpatient treatment with hospitalization after outpatient treatment failure, and initial inpatient treatment with post-discharge outpatient follow-up. Initial inpatient treatments arose from emergency department (ED) or outpatient visits resulting in same-day admission.

The expert panel was convened for a one-day, in-person meeting in which we asked authorities in pneumococcal disease epidemiology to derive quantitative estimates for selected assumptions in the model in response to a series of structured questions. The experts formed these estimates based on evidence that was provided from a comprehensive literature review, as well as their own knowledge of published data and experience. We used a modified Delphi approach in which the initial estimates were reviewed a second time by the expert panel and revised where appropriate based on their input. The final estimates were also circulated to the expert panelists for review and comment.

2.1. Model outcomes

Model outcomes included the number of pneumococcal cases and healthcare utilization by syndrome and age group. Healthcare utilization included outpatient and ED visits, hospital and nursing home admissions, sinus surgery, and tympanostomy. Health outcomes included hospitalization for selected outpatient syndromes (AECB, pneumonia) and long term disability or death from inpatient syndromes. We assessed costs incurred for medical care and work loss associated with disease episodes, as well as productivity and other future costs associated with long-term disability and death.

2.2. Model parameters and assumptions – outpatient syndromes

The number of annual outpatient incident cases of AOM, sinusitis, AECB, and pneumonia from all pathogens were derived from the 2004–2005 National Ambulatory Medical Care Survey (NAMCS) and 2004–2005 National Hospital Ambulatory Medical Care Survey (NHAMCS) using ICD-9 codes (all diagnosis locations) by age. Patients could contribute to >1 syndrome. For most conditions, incident cases were restricted to visits during which an antibiotic was prescribed. In addition, since physician diagnosis and antibiotic prescribing may overestimate actual disease [19–22], we corrected for age-specific over-diagnosis using expert panel consensus. Estimates of over-diagnosis (weighted-averages across age groups) were 14% for AOM (23% in children <5), 52% for sinusitis, 20% for AECB, and 16% for pneumonia. The fraction attributable to pneumococcus (Table 1) was applied to the adjusted all-pathogen incidence.

For outpatient syndromes, we assumed antibiotics may have differential treatment outcomes depending on antibiotic susceptibility profiles. Using literature and expert opinion, we estimated the distribution of prescribed antibiotics by syndrome, the probability of susceptibility to received antibiotics, and the resulting likelihood of typical vs. prolonged illness, generally characterized by additional outpatient visits and a second antibiotic course. Follow-up visits and average illness duration were also estimated. When outpatient outcomes resulted in hospitalization (AECB, pneumonia), the entire episode and associated costs were included in inpatient utilization.

2.3. Model parameters and assumptions – inpatient syndromes

Inpatient syndromes included AECB, pneumonia, meningitis, bone/joint infections, and bacteremia/sepsis due to syndromes not otherwise modeled. Annual incidence and duration of hospitalizations were obtained from the 2004 National Hospital Discharge Survey (NHDS) and 2004 National Inpatient Sample (NIS, meningitis only) using ICD-9 codes (primary diagnosis only) by age (Appendix A). Hospitalizations arising from outpatient and ED episodes (same day admissions (direct admissions) and admissions following outpatient failure) were assumed to be included in NHDS estimates. No corrections for over-diagnosis were made for inpatient diseases. In addition, inpatient antibiotics were assumed to be sufficiently broad-spectrum to overcome antibiotic resistance, with the exception of meningitis and AECB. For meningitis, the distribution of prescribed antibiotics and the likelihood of high-level antibiotic resistance to penicillin or 3rd generation cephalosporins were obtained from the literature and ABCs data. For AECB, estimates for narrow-spectrum treatment with penicillins or macrolides alone and the risk of clinical failure due to antibiotic resistance were obtained from the literature and expert opinion. We estimated the fractions of inpatient syndromes due to pneumococcus (Table 1), likelihood of follow-up outpatient vis-

Table 1
Estimated proportion of clinical syndromes due to pneumococcus in 2004.

Disease	% Cases due to pneumococcus	Sensitivity analysis	
		% Pneumococcus – low	% Pneumococcus – high
1. Acute otitis media			
All ages	12%	5%	20%
2. Sinusitis			
2–<18 y	24%	16%	28%
18–65 y+	20%	13%	23%
3. Outpatient AECB			
18–65 y+	15%	10%	18%
4. Outpatient pneumonia			
All ages	20%	10%	25%
5. Inpatient AECB			
18–65 y+	6%	3%	10%
6. Inpatient pneumonia			
All ages	30%	20%	40%
7. Meningitis			
0–<5 y	10%	8%	13%
5–<18 y	17%	13%	21%
18–<50 y	42%	32%	53%
50–<65 y	60%	45%	75%
65 y+	51%	38%	64%
8. Bone/joint infection			
0–<18 y	2%	0%	4%
9. Bacteremia/sepsis[a]			
All ages	100%[b]	–	–

[a] Due to syndromes not otherwise categorized.
[b] Pneumococcal bacteremia was restricted to the primary inpatient diagnosis code that designated bacteremia/sepsis due to *S. pneumoniae.*

its, nursing home stays (pneumonia, AECB), permanent disability (meningitis), and death from expert opinion and literature review (Appendices D and E).

2.4. Model parameters and assumptions – costs

Four categories of costs were assessed: (1) direct costs, which included medical care costs, and patient out-of-pocket costs (e.g. parking); (2) costs due to adverse outcomes (e.g. long term direct medical costs of hearing loss and neurologic sequelae due to meningitis, as well as lifetime special education, developmental services, and custodial care costs related to disability); (3) work-loss costs for patients (or parents) associated with illness; and (4) other costs from lost wages due to disability or death (Appendices D and E).

Work loss and family medical expenses were calculated for each outpatient encounter and hospitalization. Length of time missed from work and daily market compensation estimates were taken from Grosse et al. [23], and were adjusted for the percentage of adults in the work force for each age group. For pediatric patients, work loss was calculated for the caregiver based upon the expected disease-specific duration of symptoms and published estimates of hours of missed work [24]. For inpatient healthcare utilization costs, private-to-public insurer ratios were obtained from the literature and a 0.38 cost-to-charge ratio was applied. Disability costs due to hearing loss or neurologic disability following meningitis were estimated from the literature. Future costs related to disability or death were taken from Grosse et al. [23], and were based on the expected future lifetime earnings for each age group with 3% discounting Costs are reported in 2007 dollars. Cost inputs and data sources are found in Appendix C.

2.5. Sensitivity analysis

We performed one-way sensitivity analyses for the incidences of clinical syndromes due to all pathogens, and the proportions of those syndromes due to pneumococcus in each age group. We evaluated the impact of incidence estimates based upon designation as the primary diagnosis compared to these diagnoses being present in any coding location. We explored assumptions about hospitalization costs by obtaining state-by-state reimbursement rates and using average rates from the top and bottom decile. Finally, we assessed differences in cost using a 0% or 5% discount rate.

3. Results

In 2004, pneumococcus caused an estimated 4.0 million disease episodes (Table 2). Over 3.5 million were seen in outpatient settings only, with AOM and sinusitis responsible for 85% of outpatient cases (1.5 million cases each). Of the 445,000 pneumococcal-related hospitalizations, >90% were for pneumonia. All results are rounded to the nearest thousand, or first significant digit if less than a thousand. Slight differences may occur in reported numbers due to rounding.

3.1. Pneumococcal disease by age groups

Overall, an equal number of pneumococcal cases were estimated in children (<18 years old) and adults (2.0 million episodes each). Over half of outpatient disease episodes occurred in children. In contrast, 87% (386,000) of pneumococcal hospitalizations occurred in adults, with 60% of hospitalizations and 65% of hospital days among those ≥65 years old. Among all cases, the proportion of pneumococcal cases represented by specific syndromes was as follows: sinusitis (37%), AOM (38%), pneumonia (22%), AECB (3%), bacteremia/sepsis (<1%), and meningitis (<1%).

The proportion of pneumococcal disease syndromes showed large differences by age (Table 2). AOM was more than twice as common as sinusitis in children (<18 years old), but the opposite was true for adults. Among children <5 years old, AOM composed the vast majority (74%) of pneumococcal cases. In children 5–<18 years old, AOM and sinusitis jointly composed 89% of cases and contributed almost equally (47% and 42%, respectively). In contrast, among adults ≥65 years, pneumonia accounted for the majority of cases (58%), with 80% of pneumonias requiring hospitalization. Sinusitis was a distant second (20%). Among adults 50–<65 years old, sinusitis composed 49% of cases, and pneumonia accounted for 29%, with less than half requiring hospitalization.

Table 2
Estimated annual healthcare burden attributable to *Streptococcus pneumoniae* (SP), 2004.

Disease	Total pneumococcal cases	Antibiotic courses	Outpatient visits		ED visits	Hospitalizations	Hospital days
			Initial	Follow-up			
1. Acute otitis media							
0–<5 y	780,000	854,000	655,000	195,000	125,000	–	–
5–<18 y	442,000	468,000	394,000	133,000	49,000	–	–
18–<50 y	202,000	231,000	173,000	53,000	28,000	–	–
50–<65 y	54,000	62,000	51,000	14,000	3000	–	–
65 y+	47,000	54,000	44,000	13,000	2000	–	–
Total[a]	1,524,000	1,669,000	1,318,000	407,000	207,000		
2. Sinusitis							
2–<5 y	108,000	131,000	104,000	36,000	4000	–	–
5–<18 y	396,000	486,000	380,000	139,000	16,000	–	–
18–<50 y	626,000	772,000	595,000	223,000	31,000	–	–
50–<65 y	228,000	280,000	219,000	80,000	9000	–	–
65 y+	106,000	128,000	102,000	35,000	3000	–	–
Total[a]	1,465,000	1,798,000	1,401,000	513,000	64,000		
3. Outpatient AECB							
18–<50 y	2000	2000	100	1000	2000	–	–
50–<65 y	36,000	41,000	33,000	27,000	3000	–	–
65 y+	40,000	48,000	34,000	56,000	6000	–	–
Total[a]	78,000	90,000	67,000	84,000	11,000		
4. Outpatient pneumonia							
0–<5 y	120,000	147,000	81,000	157,000	39,000	–	–
5–<18 y	89,000	100,000	70,000	62,000	19,000	–	–
18–<50 y	116,000	132,000	65,000	79,000	51,000	–	–
50–<65 y	78,000	89,000	51,000	52,000	27,000	–	–
65 y+	62,000	76,000	37,000	81,000	24,000	–	–
Total[a]	465,000	544,000	305,000	432,000	160,000		
5. Inpatient AECB							
18–<50 y	2000	–	0	2000	2000	2000	7000
50–<65 y	8000	–	90	7000	4000	8000	36,000
65 y+	19,000	–	300	17,000	10,000	19,000	99,000
Total[a]	29,000		400	26,000	16,000	29,000	142,000
6. Inpatient pneumonia							
0–<5 y	40,000	–	1000	40,000	25,000	40,000	121,000
5–<18 y	17,000	–	7000	17,000	9000	17,000	57,000
18–<50 y	43,000	–	400	42,000	46,000	43,000	197,000
50–<65 y	60,000	–	10,000	55,000	53,000	60,000	303,000
65 y+	242,000	–	50,000	206,000	170,000	242,000	1,354,000
Total[a]	401,000		68,000	361,000	302,000	401,000	2,031,000
7. Meningitis							
0–<5 y	200	–	–	100	200	200	2000
5–<18 y	100	–	–	70	100	100	1000
18–<50 y	1000	–	–	700	1000	1000	9000
50–<65 y	1000	–	–	600	1000	1000	11,000
65 y+	700	–	–	400	700	700	8000
Total[a]	3000			2000	3000	3000	31,000
8. Bone/joint infection							
0–<5 y	70	70	–	70	70	70	700
5–<18 y	100	100	–	100	100	100	1000
Total[a]	200	200		200	200	200	2000
9. Bacteremia/sepsis[b]							
0–<5 y	1000	–	–	1000	1000	1000	8000
5–<18 y	300	–	–	300	300	300	2000
18–<50 y	4000	–	–	3000	4000	4000	34,000
50–<65 y	2000	–	–	1000	2000	2000	17,000
65 y+	5000	–	–	4000	5000	5000	44,000
Total[a]	12,000			10,000	12,000	12,000	106,000
10. All SP diseases							
0–<5 y	1,050,000	1,132,000	841,000	429,000	194,000	42,000	132,000
5–<18 y	945,000	1,054,000	851,000	351,000	92,000	17,000	61,000
18–<50 y	995,000	1,138,000	834,000	404,000	165,000	49,000	246,000
50–<65 y	467,000	471,000	365,000	238,000	102,000	70,000	368,000
65 y+	520,000	306,000	268,000	412,000	221,000	267,000	1,504,000
Total[a]	3,977,000	4,101,000	3,159,000	1,834,000	774,000	445,000	2,312,000

[a] Slight differences in totals may occur due to rounding.
[b] Due to diseases not otherwise categorized.

3.2. Death and disability

Pneumococcal disease caused an estimated 22,000 annual deaths, including 19,000 deaths from pneumonia, 600 deaths from AECB, 2000 deaths from bacteremia/sepsis and 300 deaths from meningitis. In addition, meningitis resulted in 700 cases of permanent neurologic disability and nearly 200 cases of moderate-to-severe hearing loss annually. There were approximately 200 pediatric deaths (40% due to pneumococcal bacteremia/sepsis), and 18,000 deaths in adults ≥65 years (91% due to pneumococcal pneumonia).

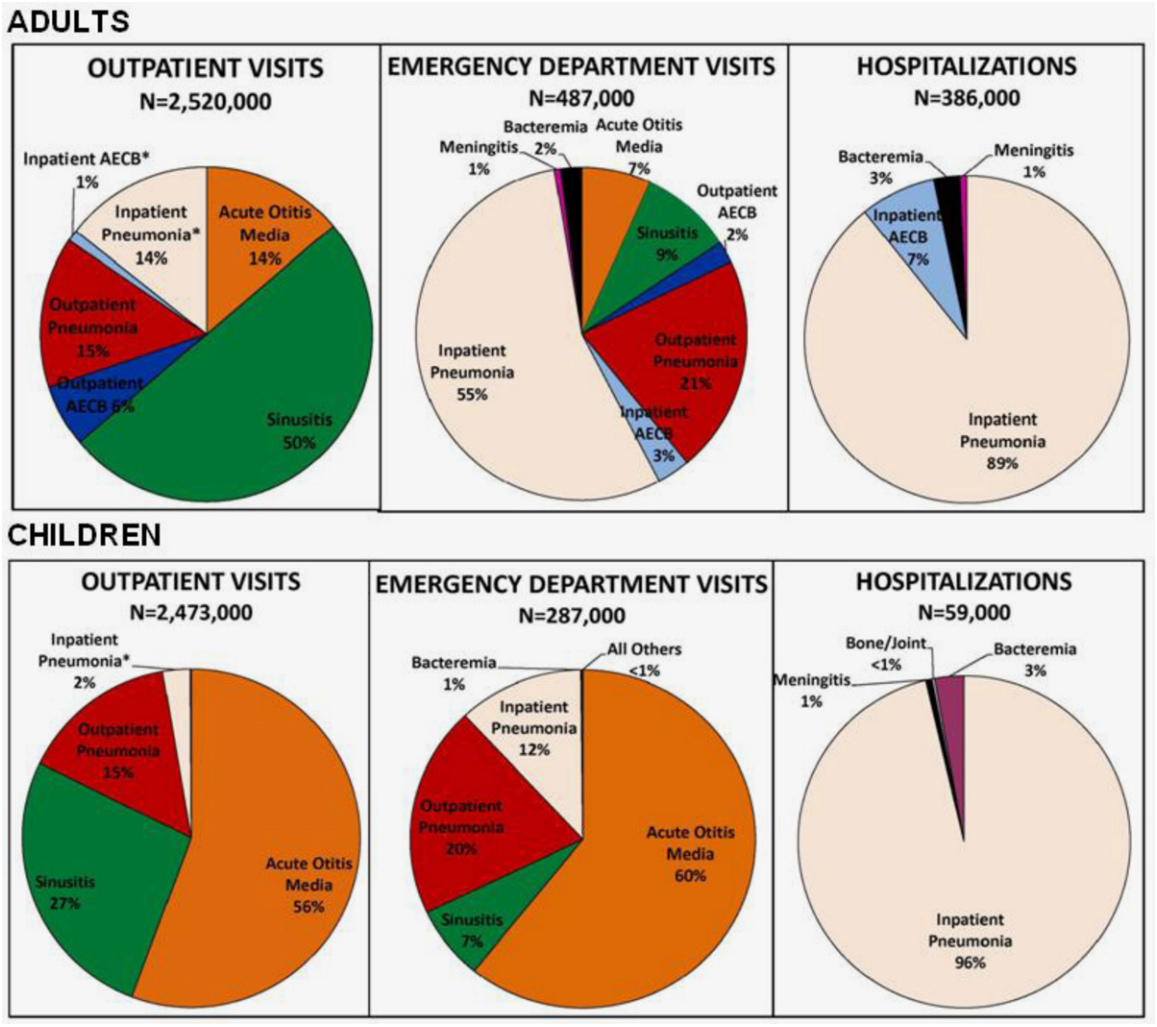

Fig. 1. Healthcare utilization by pneumococcal syndrome in outpatient, inpatient, and emergency departments, stratified by adults and children.

3.3. Healthcare utilization

Pneumococcal disease caused an estimated 5.0 million outpatient visits, 4.1 million outpatient antibiotic prescriptions, 774,000 ED visits, 445,000 hospitalizations, and 24,000 nursing home stays (Table 2). Pneumonia caused 89% of pneumococcal hospitalizations in adults and 96% of those in children (Fig. 1). Overall, pneumococcal hospitalizations were responsible for 2.3 million hospital days.

AOM accounted for 56% of outpatient visits in children; and, sinusitis accounted for 50% in adults. Reasons for ED visits paralleled reasons for office visits in children, with only 12% of pneumococcal ED visits requiring hospitalization. In contrast, 55% of pneumococcal ED visits in adults were due to pneumonia requiring hospitalization.

Adults ≥65 years old were responsible for 374,000 outpatient visits, 194,000 ED visits and 1.4 million hospital days due to pneumonia, and 107,000 outpatient visits, 16,000 emergency department visits, and 99,000 hospital days due to AECB.

3.4. Costs of pneumococcal disease

Pneumococcal disease in 2004 was estimated to result in direct medical costs of $3.5 billion (Table 3). Work loss costs added $914 million, and productivity costs due to death and disability produced an additional $3.1 billion. Inpatient conditions led to 76% ($2.6 billion) of direct medical costs, and 82% ($6.3 billion) of total costs.

Costs by clinical syndrome and age are shown in Fig. 2. Together AOM and sinusitis represented 75% of 2004 pneumococcal cases, but only 16% of direct medical costs. In contrast, inpatient and outpatient pneumonia together accounted for only 22% of cases (866,000), but 72% of direct medical costs. Inclusion of work loss and productivity costs had the largest effect on costs associated with bacteremia/sepsis, increasing from 4% of direct medical costs to 14% of total costs.

Adults accounted for 83% ($3 billion) of direct healthcare costs and 84% ($6.5 billion) of total costs when work loss and productivity costs were included. Costs in younger adults (18–<50 years old) increased from 17% of direct medical costs to 31% of total costs because of the fraction of employed patients in that age group. In fact, total costs were similar for patients 18–<50 years and those 65+ years old (Fig. 2).

3.5. Sensitivity analysis

One-way sensitivity analyses (Table 4) showed a broad range of burden estimates due to uncertainty in key model parameters. Pneumococcal disease episodes ranged from 2.4 to 6.0 million depending on the pneumococcal fraction of all-cause disease incidence, resulting in a range of direct medical costs of $2.4–4.9 billion. Similarly, ranges in disease incidence from national datasets based

Table 3
Costs in millions attributable to *Streptococcus pneumoniae* in 2004 (provided in 2007 dollars).

	Outpatient and ED costs[a]	Inpatient costs[b]	Direct medical costs	Hearing loss and neurologic sequelae costs[c]	Work loss costs	Future productivity losses[d]	Total costs: medical, sequelae, work loss, productivity
Acute otitis media	272	–	272		168	–	440
Sinusitis	297	–	297		191	–	487
Outpatient AECB	25	–	25		30	–	56
Outpatient pneumonia	150	–	150		271	–	421
Inpatient AECB	4	163	168		15	49	232
Inpatient pneumonia	84	2275	2359		220	1863	4442
Meningitis	0.7	56	56	220	5	278	559
Bone/joint infection	0.6	2	3		0.4	–	3
Bacteremia	3	150	152		14	916	1083
TOTAL	836	2645	3481	220	914	3107	7722

[a] Includes visits, antibiotics, tube insertions, sinus surgeries, and other family costs.
[b] Includes hospital days, physician fees, nursing home costs.
[c] Includes long term direct medical costs of hearing loss and neurologic sequelae due to meningitis, lifetime special education, developmental services, and custodial care costs.
[d] Includes costs due to long-term employment loss from death or disability.

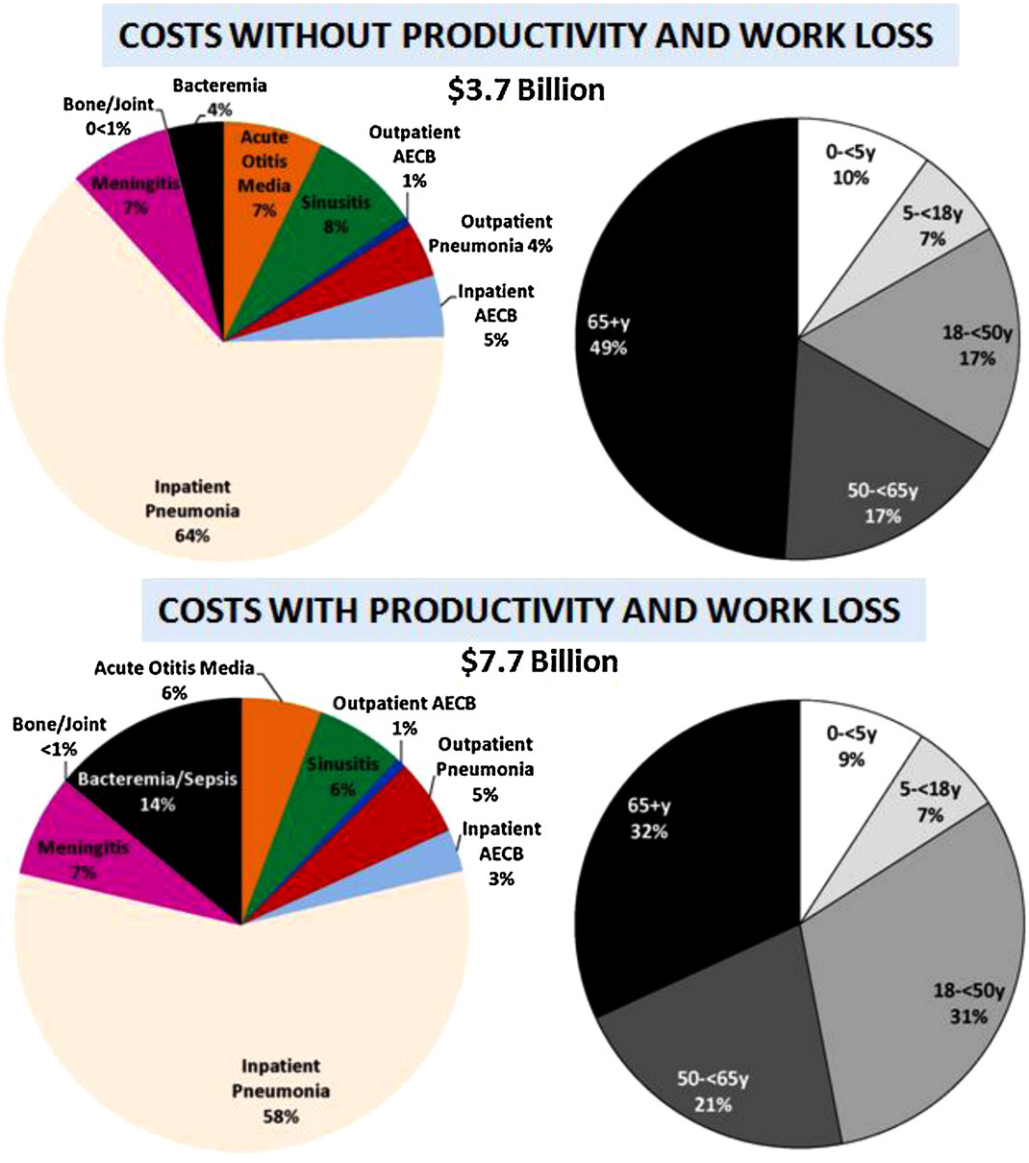

Fig. 2. Pneumococcal disease costs by age and syndrome categories comparing direct medical costs to total costs including work loss and productivity costs.

Table 4
Range of pneumococcal outcomes in millions based on one-way sensitivity analyses.

	Impact of varying % *S. pneumoniae*[a]		Impact of varying disease incidence[b]		Impact of varying discount rate[c]		Impact of varying hospital cost (day rate)[d]	
	Lower bound	Higher bound	Lower bound	Higher bound	Lower bound	Higher bound	Lower bound	Higher bound
Disease episodes	2.4	6.0	3.2	5.7				
Outpatient office visits	2.8	6.8	3.5	6.6				
Ed visits	0.4	1.1	0.6	0.9				
Antibiotic prescriptions	2.2	5.6	3.0	5.2				
Hospital days	1.6	3.1	1.2	4.1				
Deaths	0.02	0.03	0.01	0.04				
Direct medical costs	2418	4943	2195	6455	3867	3651	3104	4418
Work loss costs	523	1214	595	1318	914	914	914	914
Productivity costs	2395	3833	1864	5423	4896	2481	3107	3107
Total costs	5336	9990	4654	13,196	9677	7046	7125	8439

[a] Based upon using the lowest and highest estimate for the fraction of each disease type that is due to pneumococcus.
[b] Based upon using the lowest and highest estimate of pneumococcal disease when using primary diagnosis only vs. all diagnostic code locations for all disease types.
[c] Based upon using 0 vs. 5% discount rates, instead of 3% (base model).
[d] Based upon using the lowest and highest estimates for hospitalization costs based upon state ranges after removing outlier deciles.

upon disease-specific codes in the primary vs. all code locations led to a nearly 2-fold change in pneumococcal disease episodes and a 3-fold change in direct medical costs from $2.2 to 6.5 billion.

For inpatient disease episodes, use of all diagnoses would have produced a substantial increase in disease episodes compared to results reported here, which are limited to primary diagnoses. Had the model included diagnoses in any position, pneumococcal cases due to inpatient pneumonia would have increased 1.7-fold; inpatient AECB, 2.2-fold; meningitis, 2.8-fold; and, bone/joint disease, 1.4-fold. Bacteremia/sepsis episodes would have remained unchanged since it was the only inpatient syndrome where all diagnosis locations were used since ICD9 codes were limited to those specifying "pneumococcal" bacteremia or sepsis in the absence of codes for diseases already under consideration.

4. Comment

S. pneumoniae continues to be responsible for a large disease burden in the U.S. despite introduction of routine childhood pneumococcal vaccination in 2000 and availability of polysaccharide vaccine since 1983. The estimated 4 million cases and $3.5 billion in direct medical costs in 2004 has likely remained stable through 2008 since overall rates of disease have not increased despite modest increases in non-PCV7 serotypes [25]. Introduction of a 13-valent pneumococcal conjugate vaccine (PCV13) for children, which began in March 2010, is likely to reduce disease rates further. This study's results provide an important benchmark for monitoring pneumococcal disease burden in the conjugate vaccination era.

These results highlight adult pneumococcal disease as the major driver of healthcare utilization. Although the number of pneumococcal disease episodes was similar in adults and children, adult disease was responsible for 83% ($3 billion) of direct medical costs. This emphasizes the need to reduce the many missed opportunities for vaccination with the 23-valent pneumococcal polysaccharide vaccine [2,26] and to assess the benefits of direct use of conjugate vaccines among adults beyond the indirect effects that occur following vaccination of children [26–30]. Over one-third of adults >65 remain unvaccinated, along with nearly two-thirds of high risk adults aged 18–64 for whom vaccination is recommended [15,16].

Prevention of pneumococcal pneumonia would produce the greatest cost savings from a single clinical syndrome. Direct medical costs of pneumococcal disease are largely driven by hospitalization costs among those ≥65 years old. However, if work loss and productivity are considered, the cost of pneumococcal disease among younger working adults (18–<50) nearly equals those ≥65.

This study has several limitations. First, it may underestimate pneumococcal disease and costs by excluding Veteran Administration and Indian Health Service hospitals and clinics, and restricting inpatient cases to those with a primary diagnosis of interest. We also applied corrections for over-diagnosis among outpatients, but did not account for pneumococcal episodes misdiagnosed, but treated (e.g. pneumonia treated as acute bronchitis). Both limitations result in lower estimates of disease burden than may actually be the case. Finally, there is substantial uncertainty in several model parameters, including disease incidence and the fraction due to pneumococcus, which influence overall burden and cost estimates. This uncertainty arises from sampling methods in the national datasets used, as well as expert panel opinion, which may change as more data become available.

In 2004, we estimated that four million episodes of pneumococcal disease occurred in the U.S., amounting to $3.5 billion dollars in healthcare costs. Additional prevention efforts are needed, including improved vaccination efficacy and uptake to particularly prevent adult pneumococcal pneumonia.

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Appendix A. Model parameters and sources

Model parameter	Data source
Outpatient syndromes and utilization parameters	
Annual incidence	
Visits with antibiotics prescribed, all pathogens	NAMCS/NHAMCS[a]
Exclusions for over-diagnosis and follow-up visits	Expert panel, primary literature
% Pneumococcus among incident cases	Expert panel, primary literature
Distribution of prescribed antibiotics	Prospective™ Data (Premier Inc)
Antibiotic susceptibility	CDC ABCs data
% Experiencing typical resolution of disease	
With antibiotic to which organism is susceptible[b]	Expert panel
Without antibiotic to which organism is susceptible[b]	Expert panel
Healthcare utilization – visits[c]	
Outpatient physician visits per episode	NAMCS/NHAMCS, expert panel, primary literature
ED visits per episode	NAMCS/NHAMCS, expert panel, primary literature
% Admitted to hospital[d]	NAMCS/NHAMCS, primary literature
Inpatient syndromes and utilization parameters	
Cases, all pathogens	NHDS, NIS[e]
% Pneumococcus among all cases	Expert panel, primary literature
% Experiencing typical resolution of disease	
With antibiotic to which organism is susceptible[a]	Expert panel, primary literature
Without antibiotic to which organism is susceptible (meningitis only)[a]	Expert panel, primary literature
Healthcare utilization – visits[a]	
Average length of stay	Expert panel, primary literature, NIS, Premier
% with resulting disability (meningitis only)	Primary literature
% Discharged to nursing home	Primary literature
% Death	Primary literature, CDC ABCs Data
Cost parameters	
Direct costs	
Initial and follow up outpatient physician visits	Federal register[f]
ED visits	Federal register[g]
Outpatient antibiotics	Drug Topics Red Book
Hospitalization[a]	Federal register, premier, NIS, primary literature
Tympanostomy tube placement	Federal register[g]
Sinus surgery	Federal register[g]
Physician fees	Federal register, CMS Physician Fee Schedule
Skilled nursing facility stay (10 days, including physician fees)	Federal register[g]
Hearing loss (lifetime medical costs)	Primary literature
Neurologic disability (lifetime medical/special services costs)	Primary literature
Additional cost to family	Primary literature
Proportion public payer (vs. private)	Primary literature
Cost to charge ratio	Federal register, US Census Bureau
Workloss costs	
Missed work per visit or per day[h]	Primary literature
Productivity costs	
Lost wages due to long-term disability (3% discount rate)	Primary literature
Lost wages due to death (3% discount rate)	Primary literature

[a] ICD9 codes: acute otitis media (381.0–381.4, 382), sinusitis (461, 473), outpatient AECB (491), outpatient pneumonia (480–486, 487.0).

[b] Example of penicillin-susceptibility and non-susceptibility provided.

[c] Stratified by typical vs. delayed disease resolution.

[d] Only includes outpatient diagnoses that subsequently result in hospitalization at a later date. Outpatient visits that result in direct admission are included in inpatient estimates.

[e] ICD9 codes: inpatient AECB (491), inpatient pneumonia (480–486, 487.0), meningitis (036.0, 036.1, 053.0, 320), bone and joint disease (711.0, 730 (except 730.1)), bacteremia (041.2, 038.2, 790.7, excluding where codes were jointly listed with other modeled inpatient diseases).

[f] CMS Physician Fee Schedule, 2007.

[g] Hospital Outpatient Prospective Payment System and CMS Physician Fee Schedule, 2007.

[h] Cost of missed work per outpatient visit or per day of hospitalization.

Appendix B. Outpatient model parameters: incidence and healthcare utilization

Outpatient syndromes	Visits with prescribed antibiotics, All pathogens[a,b,c]	Adjustment factors[d]		% Pneumococcus[e,k,l,m]	% Initial visit in ED[c]	% Experiencing typical resolution of disease	
		% Reduction, Over-diagnosis[e,f,g]	% Reduction, Follow-up visits with antibiotics[e,h,i,j]			With antibiotic to which organism is susceptible[e,m]	Without antibiotic to which organism is susceptible[e,n]
AOM							
0–<2 y	5,350,000	23%	10%	12%	16%	95%	74%
2–<5 y	4,180,000	23%	15%	12%	16%	95%	74%
5–<18 y	4,468,000	3%	15%	12%	11%	95%	74%
18–<50 y	1,975,000	3%	13%	12%	14%	95%	48%
50–<65 y	528,000	3%	13%	12%	5%	95%	48%
65 y+	461,000	3%	13%	12%	5%	95%	48%
Sinusitis							
2–<5 y	1,003,000	46%	17%	24%	4%	85%	60%
5–<18 y	3,749,000	46%	19%	24%	4%	85%	60%
18–<50 y	8,365,000	54%	19%	20%	5%	85%	40%
50–<65 y	3,026,000	54%	19%	20%	4%	85%	40%
65 y+	1,390,000	54%	18%	20%	3%	85%	40%
AECB							
18–<50 y	15,000	20%	11%	15%	42%	74%	71%
50–<65 y	338,000	20%	11%	15%	22%	74%	71%
65y+	400,000	20%	17%	15%	23%	65%	62%
Pneumonia							
0–<2 y	409,000	16%	19%	20%	46%	71%	68%
2–<5 y	478,000	18%	19%	20%	22%	71%	68%
5–<18 y	613,000	18%	12%	20%	20%	81%	77%
18–<50 y	768,000	14%	12%	20%	39%	81%	75%
50–<65 y	525,000	15%	12%	20%	33%	81%	75%
65 y+	452,000	16%	19%	20%	50%	71%	66%

Outpatient syndromes	Outpatient clinic visits per episode[c,e,h,i,j]		ED visits per episode[c]		% Tympanostomy tubes[n,o,p,q,r,s]	% Sinus surgery[e,t]
	Typical resolution of disease	Delayed resolution	Typical resolution of disease	Delayed resolution		
AOM						
0–<2 y	0.9	2	0.2	0.2	2%	
2–<5 y	0.9	2	0.2	0.2	2%	
5–<18 y	1	2	0.1	0.1		
18–<50 y	1	2	0.1	0.1		
50–<65 y	1	2	0.1	0.1		
65 y+	1	2	0.1	0.1		
Sinusitis						
2–<5 y	1	2	<0.1	<0.1		2%
5–<18 y	1	2	<0.1	<0.1		2%
18–<50 y	1	2	0.1	0.1		2%
50–<65 y	1	2	<0.1	<0.1		2%
65 y+	1	2	<0.1	<0.1		2%
AECB						
18–<50 y	1	2	0.4	0.4		
50–<65 y	1	2	0.2	0.2		
65 y+	2	3	0.2	0.2		
Pneumonia						
0–<2 y	2	3	0.5	0.5		
2–<5 y	2	3	0.2	0.2		
5–<18 y	1	2	0.2	0.2		
18–<50 y	1	2	0.4	0.4		
50–<65 y	1	2	0.3	0.3		
65 y+	2	3	0.5	0.5		

[a] Reported numbers are rounded to nearest thousand.
[b] Excluding those directly admitted to the hospital.
[c] NAMCS/NHAMCS 2004–2005. http://www.cdc.gov/nchs/ahcd.htm.
[d] Represents weighted average of different estimates for episodes in outpatient vs. ED settings.
[e] Expert panel opinion.
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[m] Expert opinion, personal communication, Dr. Anzueto (1/23/2008).
[n] Percents provided represent penicillin-resistant strains treated with penicillin.
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[t] Among those with delayed resolution of disease.

Appendix C. Inpatient model parameters: incidence and healthcare utilization

Inpatient syndromes	Hospitalized cases, All pathogens[a,b,c]	% Pneumococcus among hospitalized cases[d,e,f,g,h,i]	% Experiencing typical resolution of disease[b,c,e,j]	
			With antibiotic to which organism is susceptible	Without antibiotic to which organism is susceptible[k]
AECB				
18–<50 y	29,000	6%	79%	76%
50–<65 y	132,000	6%	80%	77%
65 y+	323,000	6%	74%	71%
Pneumonia				
0–<2 y	87,000	30%	74%	n/a
2–<5 y	47,000	30%	77%	n/a
5–<18 y	56,000	30%	70%	n/a
18–<50 y	143,000	30%	72%	n/a
50–<65 y	198,000	30%	73%	n/a
65 y+	806,000	30%	74%	n/a
Bone/joint infection				
0–<2 y	1000	2%	90%	n/a
2–<5 y	2000	2%	90%	n/a
5–<18 y	5000	2%	90%	n/a
Meningitis				
0–<2 y	2000	10%	66%	33%
2–<5 y	300	10%	49%	24%
5–<18 y	900	17%	49%	25%
18–<50 y	2000	42%	66%	33%
50–<65 y	2000	60%	64%	32%
65 y+	1000	51%	56%	28%
Bacteremia				
0–<2 y	1000	100%	90%	n/a
2–<5 y	200	100%	90%	n/a
5–<18 y	300	100%	90%	n/a
18–<50 y	4000	100%	60%	n/a
50–<65 y	2000	100%	60%	n/a
65 y+	5000	100%	60%	n/a

Inpatient syndromes	Inpatient outcomes					
	Length of stay (typical resolution)[c,g,j]	Length of stay (delayed resolution)[c,g,j,l]	% With resulting hearing loss (meningitis only)[m,n,o,p,q]	% With resulting disability (meningitis only)[r,m,n,o,p,q]	% Requiring nursing home care[s,t,u]	% Death[c]
AECB						
18–<50 y	2.8	8.5	n/a	n/a	n/a	0.4%
50–<65 y	3.3	9.7	n/a	n/a	8%	1.1%
65 y+	3.5	9.9	n/a	n/a	8%	2.6%

Inpatient syndromes	Inpatient outcomes					
	Length of stay (typical resolution)[c,g,j]	Length of stay (delayed resolution)[c,g,j,l]	% With resulting hearing loss (meningitis only)[m,n,o,p,q]	% With resulting disability (meningitis only)[r,m,n,o,p,q]	% Requiring nursing home care[s,t,u]	% Death[c]
Pneumonia						
0–<2 y	2.0	6.0	n/a	n/a	n/a	0.2%
2–<5 y	2.0	5.9	n/a	n/a	n/a	0.1%
5–<18 y	2.0	6.6	n/a	n/a	n/a	0.3%
18–<50 y	2.9	9.3	n/a	n/a	n/a	1.6%
50–<65 y	3.4	10.4	n/a	n/a	4%	3.2%
65 y+	4.1	11.2	n/a	n/a	8%	6.7%
Bone/joint infection						
0–<2 y	9.8	16.5	n/a	n/a	n/a	n/a
2–<5 y	9.8	16.5	n/a	n/a	n/a	n/a
5–<18 y	9.8	16.5	n/a	n/a	n/a	n/a
Meningitis						
0–<2 y	8.1	11.9	10%	24%	n/a	2.0%
2–<5 y	4.0	8.9	10%	37%	n/a	4.5%
5–<18 y	4.0	8.7	10%	37%	n/a	3.9%
18–<50 y	5.0	8.8	10%	22%	n/a	7.5%
50–<65 y	6.7	11.8	10%	22%	n/a	9.7%
65 y+	6.3	12.1	10%	22%	n/a	17.4%
Bacteremia						
0–<2 y	5.7	10.9	n/a	n/a	n/a	5.0%
2–<5 y	5.7	10.9	n/a	n/a	n/a	5.0%
5–<18 y	5.7	10.9	n/a	n/a	n/a	5.0%
18–<50 y	7.4	14.1	n/a	n/a	n/a	20.0%
50–<65 y	7.4	14.1	n/a	n/a	n/a	20.0%
65 y+	7.4	14.1	n/a	n/a	n/a	20.0%

[a] Reported numbers are rounded to nearest thousand, or first significant digit if less than a thousand.
[b] National Hospital Discharge Survey 2004–2005. http://www.cdc.gov/nchs/nhds.htm.
[c] National Inpatient Survey 2004. http://www.hcup-us.ahrq.gov/nisoverview.jsp.
[d] Includes adjustment for culture negativity (meningitis only).
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[k] Applicable only to meningitis (ceftriaxone-resistant strain treated with ceftriaxone) and AECB (penicillin-resistant strain treated with penicillin).
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[u] Nursing home costs only include the excess costs attributable to pneumococcal disease.

Appendix D. Cost estimates – outpatients, 2007 dollars

Outpatient syndromes	Direct costs per visit				Work loss	Other	
	Cost of outpatient visit[a]	Cost of ED visit[a,b]	Cost of initial antibiotics[c]	Out-of-pocket costs to patient[d]	Total cost of missed work per episode (typical resolution)[e,f,g]	Cost of tympanostomy[a,b]	Cost of sinus surgery[a,b]
Acute otitis media							
0–<2 y	42	191	44	18	92	1167	
2–<5 y	42	191	48	18	92	1167	
5–<18 y	42	191	58	18	92		
18–<50 y	42	191	89	18	125		
50–<65 y	42	191	81	18	119		
65 y+	42	191	87	18	27		
Sinusitis							
2–<5 y	42	191	55	18	92		1548
5–<18 y	42	191	62	18	92		1548
18–<50 y	42	191	89	18	125		1548
50–<65 y	42	191	90	18	119		1548
65 y+	42	191	99	18	27		1548
AECB							
18–<50 y	67	191	80	18	569		
50–<65 y	67	191	105	18	542		
65 y+	67	191	115	18	123		
Pneumonia							
0–<2 y	42	191	61	18	569		
2–<5 y	42	191	76	18	569		
5–<18 y	42	191	60	18	569		
18–<50 y	67	191	129	18	569		
50–<65 y	67	191	151	18	542		
65 y+	67	191	128	18	123		

[a] CMS Physician Fee Schedule 2007. https://www.cms.gov/apps/physician-fee-schedule/.

[b] Federal register. Vol. 71, No. 226, November 24, 2006.

[c] Drug Topics Red Book, 2007.

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[g] Fine MJ, Stone RA, Singer DE, Coley CM, Marrie TJ, Lave JR, et al. Arch Intern Med 1999;159(9):970–80 (duration of symptoms as source of missed time from work).

Appendix E. Cost estimates – inpatients, 2007 dollars

Inpatient syndromes	General cost parameters				Direct costs		
	Proportion public vs. private payer[a]	Cost to charge ratio (private payer)[b,c]	Hospital day (no MD fees)[b]	Hospital stay[b,d,e,f]	Hospital stay w/MD fees[f,g]	Post-discharge IV antibiotics[f,h,i]	Follow-up outpatient visit[g]
AECB							
18–<50 y	0.34	0.377	1141	3196	3433	n/a	42
50–<65 y	0.34	0.377	1141	3766	4036	n/a	42
65 y+	1.0	n/a	970	3395	3678	n/a	42
Pneumonia							
0–<2 y	0.34	0.377	1016	2031	2218	n/a	42
2–<5 y	0.34	0.377	1016	2031	2218	n/a	42
5–<18 y	0.34	0.377	1016	2031	2218	n/a	42
18–<50 y	0.34	0.377	1116	3236	3480	n/a	42
50–<65 y	0.34	0.377	1116	3793	4070	n/a	42
65 y+	1.0	n/a	967	3966	4287	n/a	42
Bone/Joint Infection							
0–<2 y	0.34	0.377	1035	10,145	10,833	3481	42
2–<5 y	0.34	0.377	1035	10,145	10,833	3677	42
5–<18 y	0.34	0.377	1035	10,145	10,833	3874	42
Meningitis							
0–<2 y	0.34	0.377	1805	14,624	15,202	n/a	42
2–<5 y	0.34	0.377	1805	7222	7536	n/a	42
5–<18 y	0.34	0.377	1805	7222	7536	n/a	42
18–<50 y	0.34	0.377	1805	9027	9406	n/a	42
50–< 65y	0.34	0.377	1805	12,096	12,585	n/a	42
65 y+	1.0	n/a	1508	9502	9965	n/a	42
Bacteremia							
0–<2 y	0.34	0.377	1582	9020	9444	n/a	42
2–<5 y	0.34	0.377	1582	9020	9444	n/a	42
5–<18 y	0.34	0.377	1582	9020	9444	n/a	42
18–<50 y	0.34	0.377	1422	10,522	11,055	n/a	42
50–<65 y	0.34	0.377	1422	10,522	11,055	n/a	42
65 y+	1.0	n/a	1191	8810	9344	n/a	42

Inpatient syndromes	Direct costs from adverse outcomes			Workloss costs		Productivity costs[s]	
	Skilled nursing facility (10 days, w/MD fees)[g,j]	Hearing loss (lifetime)[k,l,m]	Neurologic sequelae (lifetime)[m,n,o,p]	Day of missed work[q]	Missed work per event[f,q,r]	Disability[q]	Death[q]
AECB							
18–<50 y	n/a	n/a	n/a	114	683	n/a	963,296
50–<65 y	3378	n/a	n/a	108	650	n/a	309,851
65 y+	3378	n/a	n/a	25	173	n/a	31,400

Inpatient syndromes	Direct costs from adverse outcomes			Workloss costs		Productivity costs[s]	
	Skilled nursing facility (10 days, w/MD fees)[g,j]	Hearing loss (lifetime)[k,l,m]	Neurologic sequelae (lifetime)[m,n,o,p]	Day of missed work[q]	Missed work per event[f,q,r]	Disability[q]	Death[q]
Pneumonia							
0–<2 y	n/a	n/a	n/a	114	455	n/a	820,892
2–<5 y	n/a	n/a	n/a	114	455	n/a	820,892
5–<18 y	n/a	n/a	n/a	114	455	n/a	1,001,625
18–<50 y	n/a	n/a	n/a	114	683	n/a	963,296
50–<65 y	3378	n/a	n/a	108	758	n/a	309,851
65 y+	3378	n/a	n/a	25	197	n/a	31,400
Bone/Joint Infection							
0–<2 y	n/a	n/a	n/a	114	2162	n/a	820,892
2–<5 y	n/a	n/a	n/a	114	2162	n/a	820,892
5–<18 y	n/a	n/a	n/a	114	2162	n/a	1,001,625
Meningitis							
0–<2 y	n/a	99,345	366,622	114	1821	342,038	820,892
2–<5 y	n/a	98,998	533,465	114	910	488,098	820,892
5–<18 y	n/a	97,606	527,835	114	910	595,561	1,001,625
18–<50 y	n/a	89,917	318,737	114	1138	350,290	963,296
50–<65 y	n/a	77,719	293,329	108	1408	112,673	309,851
65 y+	n/a	63,474	90,942	25	296	11,418	31,400
Bacteremia							
0–<2 y	n/a	n/a	n/a	114	1252	n/a	820,892
2–<5 y	n/a	n/a	n/a	114	1252	n/a	820,892
5–<18 y	n/a	n/a	n/a	114	1252	n/a	1,001,625
18–<50 y	n/a	n/a	n/a	114	1707	n/a	963,296
50–<65 y	n/a	n/a	n/a	108	1625	n/a	309,851
65 y+	n/a	n/a	n/a	25	370	n/a	31,400

[a] Kaiser Family Foundation, Kaiser Commission on Medicaid and the Uninsured/Urban Institute analysis of March 2007 CPS. http://facts.kff.org/chartbook.aspx?cb=50&CFID=36161100&CFTOKEN=81276349 (percent of non-elderly population with private insurance vs. no insurance or public insurance).

[b] Federal register. Vol. 71, No. 160, August 18, 2006 (2006 state-by-state cost to charge ratios; hospital cost per day).

[c] US Census Bureau (State population used to calculate national average cost to charge ratio).

[d] Prospective™ Data (Premier Inc) (length of stay distribution for AECB and pneumonia).

[e] Tan TQ, Mason EO Jr, Barson WJ, Wald ER, Schutze GE, Bradley JS, et al. Pediatrics 1998;102(6):1376–82 (length of stay for bone/joint infection).

[f] Cost provided for typical resolution.

[g] CMS Physician Fee Schedule, 2007. https://www.cms.gov/apps/physician-fee-schedule/.

[h] Drug Topics Red Book, 2007.

[i] Tice AD, Hoaglund PA, Nolet B, McKinnon PS, Mozaffari E. Pharmacotherapy 2002;22(2 Pt 2):63S–70S (daily administrative cost of outpatient IV antibiotics for bone/joint infection, provided in 2000 dollars and inflated to 2007).

[j] Federal register. Vol. 72, No. 230, November 30, 2007 (cost of skilled nursing facilities, 2007 dollars).

[k] Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, et al. J Am Med Assoc 2000;283(11):1460–8 (cost of hearing loss due to meningitis estimated by the cost of cochlear implant).

[l] Cheng AK, Rubin HR, Powe NR, Mellon NK, Francis HW, Niparko JK. J Am Med Assoc 2000;284(7):850–6 (direct and indirect cost of cochlear implant, provided in 1999 dollars, inflated to 2007 dollars).

[m] National Vital Statistics Report, US Life Tables, 2006. http://www.cdc.gov/nchs/products/nvsr.htm (age-specific expected years of life left, used to determine duration and cost of long-term sequelae).

[n] Weighted average of mild and moderate-severe neurologic sequelae costs; estimated using cerebral palsy in children (see footnote 'o'), and stroke in adults (see footnote 'p') (2007 dollars).

[o] Waitzman NJ, Scheffler RM, Romano PS. The Cost of Birth Defects. Lanham, MD: University Press of America Inc; 1996 (age-specific cost of cerebral palsy, provided in 1988 dollars, inflated to 2007 dollars).

[p] Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Stroke 1996;27(9):1459–66 (age-specific cost of stroke, provided in 1990 dollars, inflated to 2007 dollars).

[q] Grosse SD, Krueger KV, Mvundura M. Med Care 2009;47(7(Suppl 1)):S94–103 (age-specific present value of lifetime market production, 2007 dollars).

[r] Fine MJ, Stone RA, Singer DE, Coley CM, Marrie TJ, Lave JR, et al. Arch Intern Med 1999;159(9):970–80 (duration of symptoms; assumed equivalent to missed time from work).

[s] Future costs discounted at 3%.

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