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The annual impact of seasonal influenza in the US: Measuring disease burden and costs☆

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Abstract

Background: Despite preventive efforts, influenza epidemics are responsible for substantial morbidity and mortality every year in the United States (US). Vaccination strategies to reduce disease burden have been implemented. However, no previous studies have systematically estimated the annual economic burden of influenza epidemics, an estimate necessary to guide policy makers effectively.
Objective: We estimate age- and risk-specific disease burden, and medical and indirect costs attributable to annual influenza epidemics in the United States.
Methods: Using a probabilistic model and publicly available epidemiological data we estimated the number of influenza-attributable cases leading to outpatient visits, hospitalization, and mortality, as well as time lost from work absenteeism or premature death. With data from health insurance claims and projections of either earnings or statistical life values, we then estimated healthcare resource utilization associated with influenza cases as were their medical and productivity (indirect) costs in $2003.
Results: Based on 2003 US population, we estimated that annual influenza epidemics resulted in an average of 610,660 life-years lost (undiscounted), 3.1 million hospitalized days, and 31.4 million outpatient visits. Direct medical costs averaged $10.4 billion (95% confidence interval [C.I.], $4.1, $22.2) annually. Projected lost earnings due to illness and loss of life amounted to $16.3 billion (C.I., $8.7, $31.0) annually. The total economic burden of annual influenza epidemics using projected statistical life values amounted to $87.1 billion (C.I., $47.2, $149.5).
Conclusions: These results highlight the enormous annual burden of influenza in the US. While hospitalization costs are important contributors, lost productivity from missed work days and lost lives comprise the bulk of the economic burden of influenza.

Keywords: Influenza; Disease burden; Health-care cost; Productivity losses

1. Introduction

Influenza has attained an unprecedented degree of attention in recent years as a result of disruptions in vaccine supply and distribution, and concerns about the nation's ability to respond to an influenza pandemic. Influenza has a long history, however, of causing substantial morbidity and mortality nearly every year. Despite vaccination recommendations targeted to high-risk groups and their contacts, an annual average of 36,000 deaths and over 200,000 hospitalizations occurred during the 1990s [1]. Illness severity and mortality are greatest in high-risk groups, and so are the associated healthcare costs and productivity losses [1].

☆ *Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

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In addition, costs and lost productivity among non-high-risk groups are not trivial [1,2]. In order to reduce the burden of influenza, various vaccination strategies have been proposed; most recently the Advisory Committee on Immunization Practices extended the recommendation to include children 24–59 months [1].

Economic considerations are an essential ingredient to effectively guide policy-making for influenza vaccination. Numerous studies have considered the cost effectiveness of influenza vaccination [3–5]. However, only one previous study systematically estimated the economic impact of influenza in the United States and that study focused on the impact of pandemic influenza [2]. This study estimates the annual impact of seasonal influenza in the US by measuring disease burden and associated medical and indirect costs. Projected costs were estimated by age and risk strata. We examined direct medical expenses to treat the disease and its sequelae as well as indirect costs from lost productivity and lives lost due to premature death. Our estimate of the average cost of an influenza season is based on 2003 US population demographics.

2. Methods

We used both payer and societal perspectives to estimate the economic burden of influenza in the US. The economic burden of influenza at the population level is a function of the cost per case of influenza and the number of cases. In order to account for variation in costs by age and risk of severe complications from influenza, we estimated costs for five age groups: <5 years, 5–17, 18–49, 50–64, and ≥65. In addition, we distinguished the cost for high-risk and low-risk groups. Finally, we estimated numbers for four categories based on final outcomes: (1) ill but not medically attended; (2) ill with outpatient visit(s) only; (3) ill with hospitalization; (4) ill followed by death [2].

2.1. Estimating cases of influenza and their outcomes

The number of influenza cases in any year depends on the influenza infection rate, mortality and morbidity rates given influenza infection, as well as the size of the population. Incidence of influenza illness, hospitalizations, and deaths must be estimated since infection is not typically confirmed by laboratory tests nor are hospitalizations and deaths from influenza necessarily specified as such on hospital discharge forms or death certificates. To estimate health outcome rates in each of the four categories, we used the following sources.

Age-specific influenza attack rates were based on surveillance studies and published literature [5,6–8]. Attack rates ranged from 6.6% (range: 2.6%–15.5%) for working-age adults to 20.3% (range: 7.5%–25.8%) for children under 5 years old.

Rates of influenza-attributable hospitalizations and deaths were based on excess seasonal rates of hospitalizations and deaths estimated using influenza surveillance data together with data from the National Center for Health Statistics and the National Hospitalization Discharge Survey from 1980 to 2001 [9–18]. Methods previously developed for estimating influenza-attributable morbidity and mortality were used to estimate excess hospitalizations and deaths [15,19]. Two influenza associated diagnostic categories were modeled: (1) underlying pneumonia and influenza (ICD-9 codes 480–487; ICD-10 codes J10-J18) and (2) underlying respiratory and circulatory conditions (ICD-9 codes 390–519: ICD-10 codes I00–I99, J00–J99) for the five study age groups [10,14]. For the excess hospitalization and death estimates, we fit simple peri-season risk-difference models. These rates are usually slightly higher than rates obtained from a Serfling regression model. For the primary analyses using the influenza-attributable hospitalization and mortality rates, we used estimates based on underlying respiratory and circulatory conditions. These estimates offered greater sensitivity than the pneumonia and influenza rates [5,15,16]. For the sensitivity analyses, we used the more specific excess pneumonia and influenza hospitalization and mortality rates. Because risk-specific rates were not available, the same rates were applied to the proportions of persons at high and low risk [20–24]. For purposes of this analysis, a person was defined as high risk if one or more medical conditions consistent with ACIP-identified high-risk conditions were present that placed the individual at increased risk; for persons ≥65 years age alone was not sufficient to be considered high risk [1].

Rates of outpatient visits attributable to influenza were based on published studies that account for age-specific variation in health care utilization [1,4,8,22,23]. We assumed that the probability of a high-risk patient visiting the doctor given influenza infection was twice that of a non-high-risk patient [25,26].

Finally, the probability that an individual with influenza would not seek medical attention, i.e. a case not medically attended (CNMA), was assumed to equal one minus the sum of the probabilities of the other outcomes: outpatient treatment only (OPvisit), hospitalization (Hosp), and death given influenza infection (Death). This is represented by the following expression:

$$\Pr(\text{CNMA}|\text{flu}) = 1 - \Pr(\text{OPvisit}|\text{flu}) - \Pr(\text{Hosp}|\text{flu}) - \Pr(\text{Death}|\text{flu})$$

Here $\Pr(\cdot|\text{flu})$ stands for probability of a particular final outcome given influenza illness.

We combined health outcome rates with US Census population estimates by age group in 2003 to estimate the number of influenza cases in a year by final health outcome. We used estimates of the proportion of persons with comorbid conditions from the National Health Interview Survey 2002 to calculate the proportion of the population at high risk of serious complications from influenza in each age group [20]. We calculated the number of influenza cases in each age/risk category by applying age-specific attack rates to US Cen-

Table 1
Health outcome probabilities[a]

Variable	Age Group	Mean	S.D.
Gross attack rate [2,5–7][b]			
All risk	0–4	0.203	0.062
	5–17	0.102	0.032
	18–49	0.066	0.017
	50–64	0.066	0.017
	65+	0.090	0.024
Proportion high risk of serious complications [2]			
	0–4	0.052	0.890
	5–17	0.106	0.360
	18–49	0.149	0.340
	50–64	0.330	0.700
	65+	0.512	0.730
Pr(outpatient visit/flu infection)[c] [2,4,5,8,21–23,25]			
Non-high-risk	0–4	0.455	0.098
	5–17	0.318	0.061
	18–49	0.313	0.014
	50–64	0.313	0.014
	65+	0.620	0.027
High risk	0–4	0.910	0.250
	5–17	0.635	0.167
	18–49	0.625	0.118
	50–64	0.625	0.118
	65+	0.820	0.093
Pr(hospitalization/flu infection)			
All risk	0–4	0.0141	0.0047
	5–17	0.0006	0.0002
	18–49	0.0042	0.0014
	50–64	0.0193	0.0064
	65+	0.0421	0.0140
Pr(death/flu infection)			
All risk	0–4	0.00004	0.00001
	5–17	0.00001	0.00000
	18–49	0.00009	0.00003
	50–64	0.00134	0.00045
	65+	0.01170	0.00390

[a] For sensitivity analyses, log normal probability distributions were fitted for variables in the table based on their mean and S.D. values.
[b] Bibliographic references in parentheses.
[c] Pr(*x*/flu infection): probability of *x* given influenza infection. Probabilities are bounded between 0 and 1.

sus population estimates for 2003. Estimated health outcome rates were then applied to cases in each age/risk category to determine the numbers of influenza cases that were ill but not medically attended, ill with outpatient visit(s) only, ill with hospitalization, and ill followed by death.

The total number of outpatient visits in each age group was calculated by multiplying the estimated number of outpatient visits resulting from outpatient and hospitalized cases and deaths per case of influenza by the total number of cases estimated in that age group. Hospitalized days and total days of productivity lost were similarly calculated. We calculated the number of life years lost in each age group by multiplying the estimated number of deaths in that age group by expected remaining life years based on life expectancy at the mean age in that age group in the absence of influenza-related illness using standard life tables [24].

Table 1 presents epidemiologic baseline values and distributional assumptions used in the model.

2.2. Estimating cost per case

We estimated cost per case of influenza using the Medstat Marketscan database covering the years 2001–2003. Cases of influenza in the three medically attended categories were identified using the influenza associated diagnostic categories: underlying pneumonia and influenza (ICD-9 codes 480–487; ICD-10 codes J10–J18). We used pneumonia and influenza codes because they offered greater specificity than the respiratory and circulatory codes and for purposes of cost calculations we were less concerned with sensitivity [5,25,26]. The Medstat Marketscan health insurance claims database is compiled from health insurance claims of 40 self-insured employers. All 50 states are represented in the database, which captured 17.9 million covered life years over the 2001–2003 time period. This time period allowed inclusion of cases from four influenza seasons, October–March, for the 2000–2001, 2001–2002, 2002–2003, and 2003–2004 seasons.

The finalized cost database included 179,718 medically attended cases from four influenza seasons involving outpatient treatment, hospitalization, or death. When necessary and for consistency, we inflated costs to reflect 2003 prices using the medical care component of the consumer price index (CPI). Cases included in the cost database were categorized within the extracted data according to the risk of severe complications from influenza as indicated by ICD-9 codes [1,19].

Table 2 presents cost inputs for this analysis.

2.2.1. Medical costs

For cases that did not seek medical attention, we assumed that direct costs amounted to over-the-counter (OTC) medication costing $3 per case of influenza based on the average cost of OTC medication and doses of medication per case. For outpatient cases without subsequent hospitalization, all pharmaceutical claims for the 3 days after an influenza-attributable visit were extracted. Direct medical expenses for each outpatient case were the sum of outpatient and pharmaceutical claims. Outpatient claims included office visits, laboratory tests, imaging tests, professional consult fees, outpatient procedures, and prescription medications. The cost per outpatient case ranged from a mean of $95 for non-high-risk 5–17-year-olds to $733 for high risk 50–64-year-olds.

For each hospitalized case identified, all inpatient, outpatient, and pharmaceutical claims bearing pneumonia and influenza diagnoses for that person were extracted from the database for 2 weeks before the date of admission through 30 days post-discharge [2]. Direct medical costs, including inpatient, outpatient, and pharmaceutical claims, were summed for each person, and average medical costs estimated for each age, risk, and health outcome group. Deaths were identified by discharge status. The direct medical cost for a death included inpatient, outpatient, and pharmaceutical claims because for this analysis we assumed all persons who died received some hospital care before death. Out-of-hospital deaths were not captured. The cost per hospitalized case ranged from a mean of $10,880 for non-high-risk children <5 years of age to $267,954 for high-risk children <18 years of age who died and was not sensitive to the time window. We identified few children who died from influenza in the cost database. Therefore, costs were calculated for the combined age group 0–17 years.

2.2.2. Indirect costs

For cases that did not seek medical attention, we assumed that indirect costs amounted to one-half day of lost productivity for those 5–64 years of age and 1 day of lost productivity for those <5 years of age or ≥65 years of age, who were assumed to convalesce longer due to relatively greater likelihood of severe illness symptoms [2]. For outpatient cases, indirect costs were based on days of productivity lost. Because actual days per case were not available, the number of outpatient visits per case was used to represent the number of days of productivity lost per outpatient case. For hospitalized cases, indirect costs were based on days of productivity lost calculated as the sum of length of stay (LOS) plus outpatient visits, similar to Meltzer et al. [2,27]. While children and the elderly may not be involved in the labor force per se, their average potential productivity is not zero. Furthermore, family members of children and elders that are in the labor force are likely to experience work interruptions due to visitation and care giving. It is therefore reasonable to value lost productivity based on the number of days the ill individual is incapacitated as an estimate of the productivity lost to society. Days of productivity for all age groups were valued at the average daily wage in 2003 of $145 [27].

Indirect costs of death were measured using published estimates based on two separate methods: (1) the value of a statistical life (VSL) and (2) the present value of lost earnings (PVLE) [28,29]. VSL includes the value of lost productivity as well as the intrinsic, or social, value placed on human life [28,30,31]. Aldy and Viscusi estimate VSL for working age adults from age 18 to 62 years. We applied Aldy's and Viscusi's parameter estimates to both working and non-working age individuals in order to extrapolate VSL for all five age groups used in our analysis [28]. The second method, PVLE, measures only lost earnings due to loss of life. We used estimates from Haddix et al., who calculated the discounted sum of future earnings given remaining life expectancy and expected productivity growth over a range of ages [29].

Given medical and indirect cost estimates and the population-based case estimates, we estimated total costs attributable to influenza illness. The total medical costs of influenza (Medical) included only direct medical costs. Total medical costs plus lost earnings from illness and death used the PVLE method of valuation (Medical + Lost Earnings [PVLE]). The total economic burden of influenza included direct medical costs, lost earnings from illness, and the VSL method of valuation (Medical + Lost Earnings + Lost Life [VSL]).

2.3. Sensitivity analyses

To gauge the relative importance of the assumptions in this analysis, multivariate probabilistic sensitivity analysis was performed using Monte Carlo simulation analysis. In this Monte Carlo analysis, we introduced variability to some of the economic and epidemiologic parameters by fitting probability distributions. We then conducted simulation analyses and estimated most likely results and cost ranges by heath outcome.

For the probability distributions of the epidemiologic variables (Table 1), we used our point estimates and risk assessment analysis to compare the performance of a number

Table 2
Costs per health outcome and distributions for sensitivity analysis[a]

Cost per health outcome by age and risk group	Medical cost ($2003)			Lost productivity (days)	
	Mean	S.D.	Distribution	Mean	Distribution
Case not medically attended					
All risk					
0–4	3	2	log normal	1.0	Poisson
5–17	3	2	log normal	0.5	Poisson
18–49	3	2	log normal	0.5	Poisson
50–64	3	2	log normal	0.5	Poisson
65+	3	2	log normal	1.0	Poisson
Outpatient visit					
Non-high-risk					
0–4	167	307	log normal	1	Poisson
5–17	95	258	log normal	1	Poisson
18–49	125	438	log normal	1	Poisson
50–64	150	766	log normal	2	Poisson
65+	242	1,544	log normal	3	Poisson
High risk					
0–4	574	1,266	log normal	6	Poisson
5–17	649	1,492	log normal	4	Poisson
18–49	725	1,717	log normal	2	Poisson
50–64	733	1,307	log normal	4	Poisson
65+	476	1,131	log normal	7	Poisson
Hospitalization					
Non-high-risk					
0–4	10,880	36,189	log normal	8	Poisson
5–17	15,014	86,804	log normal	9	Poisson
18–49	19,012	44,636	log normal	12	Poisson
50–64	22,304	95,727	log normal	13	Poisson
65+	11,451	23,128	log normal	13	Poisson
High risk					
0–4	81,596	123,626	log normal	31	Poisson
5–17	41,918	50,393	log normal	23	Poisson
18–49	47,722	85,644	log normal	21	Poisson
50–64	41,309	74,798	log normal	24	Poisson
65+	16,750	32,091	log normal	18	Poisson
	Non-high-risk		High risk		
	Mean	S.D.	Mean	S.D.	Distribution
Medical cost per death by age and risk group					
0–17	28,818	24,483	267,954	221,130	log normal
18–49	76,336	91,654	75,890	65,267	log normal
50–64	118,575	333,879	118,842	345,973	log normal
65+	41,948	96,467	33,011	61,904	log normal
Value of lost productive day [30][b]					
All risk/age	145	13			log normal
Value of lost life estimates by age group [31–33,39]	VSL[c] [31]		Present value of future earnings [32]		
All risk					
0–4	1,520,471	1,297,669	1,074,866	222,803	log normal
5–17	3,077,881	2,176,947	1,276,012	900,934	log normal
18–49	6,882,779	4,128,447	1,374,115	2,754,332	log normal
50–64	3,698,753	2,109,918	521,083	1,588,835	log normal
65+	1,381,123	783,484	185,846	597,639	log normal

[a] Unless otherwise indicated, the data reported here were estimated by the authors using the Medstat Marketscan Database for the years 2001–2003.
[b] Bibliographic references in parentheses.
[c] VSL: value of a statistical life.

Table 3
Annual population based estimates of influenza attributable cases by final health outcomes

	<5 years			5–17 years			18–49 years			50–64 years			65+ years			Total Ill		
	Cases	95% CI[a]		Cases	95% CI		Cases	95% CI		Cases	95% CI		Cases	95% CI		Cases	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Ill[b]																		
NonHigh	2,030,349	1,345,729	2,588,919	3,295,838	2,784,877	3,722,339	5,191,816	4,993,101	5,378,591	1,375,732	1,301,259	1,441,278	520,756	399,171	625,696	12,414,492	8,978,039	16,164,125
High risk	14,229	0	60,408	214,140	58,158	343,581	483,672	329,424	663,305	367,070	234,042	517,495	207,801	0	470,862	1,286,912	519,775	2,757,455
Outpatient only																		
NonHigh	1,740,536	1,205,794	2,391,867	1,534,552	1,109,311	2,043,745	2,374,753	2,202,191	2,553,786	644,607	597,713	693,109	988,035	920,128	1,059,270	7,282,483	5,306,133	9,402,384
High risk	170,915	125,905	208,182	373,141	243,853	528,908	815,420	638,227	966,288	647,232	506,172	767,222	1,344,159	1,119,190	1,575,914	3,350,867	1,688,720	6,093,910
Hospitalized																		
NonHigh	54,353	30,588	87,557	2,805	1,564	4,546	31,836	17,924	51,105	39,711	22,193	64,281	67,070	37,430	108,611	195,776	110,887	295,607
High risk	2,669	1,502	4,299	341	190	553	5,466	3,077	8,774	19,937	11,142	32,272	68,989	38,501	111,718	97,401	42,126	193,540
Death																		
NonHigh	142	79	227	43	24	69	684	384	1,097	2,660	1,524	4,060	17,754	10,362	26,564	21,282	3,375	41,732
High risk	7	4	11	5	3	8	117	66	188	1,335	765	2,038	18,262	10,659	27,325	19,726	7,341	42,563
Total Ill	4,013,200	1,363,872	5,341,470	5,420,865	1,354,945	6,643,749	8,903,764	2,861,869	9,623,134	3,098,284	1,139,509	3,521,755	3,232,826	2,535,441	4,005,960	24,668,939	19,915,014	30,151,934

[a] CI: confidence interval.
[b] In this group are individuals with clinical influenza infection who were sick but did not seek medical attention. The probability that an individual with influenza would not seek medical attention was assumed to equal one minus the sum of the probabilities of the other three final outcomes, namely outpatient only, hospitalized and death (see text).

Table 4
The annual burden of influenza in the United States by age group and health outcome in thousands

Age (year)	Outpatient visits			Hospitalized days			Days of productivity lost			Life years lost (undiscounted)		
	Mean	95% CI[a]		Mean	95% CI		Mean	95% CI		Mean	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
<5	3,728	2,154	6,020	280	137	493	5,328	1,173	12,665	11	6	19
5–17	3,718	1,709	7,428	22	9	42	6,666	644	13,421	3	1	6
18–49	5,270	2,988	9,124	305	144	550	10,178	1,018	19,506	36	17	65
50–64	4,329	2,232	8,157	717	345	1,291	6,616	2,024	11,776	92	44	160
65+	14,309	7,879	24,252	1,807	958	3,027	15,215	7,072	30,045	468	226	803
Total	31,354	22,636	43,507	3,131	2,108	4,511	44,003	25,694	62,484	611	360	953

[a] CI: confidence interval.

of possible distributions in terms of minimizing error. Such an approach is a standard risk analysis procedure in the face of limited data [31–35]. This method indicated most epidemiologic variables were best represented by a log normal distribution. Therefore, we assumed a log normal distribution for the epidemiologic variables with range falling between 0 and 1.

For the cost variables (Table 2), our cost database included 478 hospitalized cases that end in death, 11,459 hospitalized cases not ending in death, and 167,781 outpatient cases. Distributions for costs and days lost were fitted based on these observations and on χ^2 criterion. For the indirect cost variables shown in Table 2, the mean and range values and distributions for wages, present value of lost earnings, and values of statistical lives were based on published studies [28–30,36–40]. We also chose the distributions that minimized the squared difference between the estimate and the mean value of the potential probability distribution.

Monte Carlo simulation analysis sampled from the distributions of each of the input variables using the Latin hypercube sampling method and then evaluated the outcome variable: the total cost of influenza. Sampling iterations continued until values for the outcome variable converged to within one-half percent, yielding the most likely value for the total cost of influenza. Sensitivity analyses also provided information on the sensitivity of total cost to changes in input variables.

3. Results

Consistent with earlier studies, results indicated 24.7 million cases of influenza annually with about 31.4 million attributed outpatient visits based on 2003 population demographics. Case-patients accounted for 334,185 hospitalizations and about 3.1 million hospitalized days (Tables 3 and 4). Days of productivity lost due to illness amounted to 44.0 million (Table 4). We estimated 41,008 deaths in case-patients amounting to 610,656 life years lost; the majority of deaths occurred in the older population (Tables 3 and 4). A lower bound of these annual estimates of hospitalizations and deaths was obtained by applying hospitalization and mortality rates based on underlying pneumonia and influenza diagnoses to the analysis. This method yielded approximately 128,710 hospitalizations leading to 1.2 million hospitalized days and 9,187 deaths or 141,783 life years lost to annual influenza epidemics (not shown).

3.1. Economic burden of influenza

Medical costs, medical costs plus lost earnings (PVLE method), and the total economic burden (VSL method) were $10.4 billion, $26.8 billion, and $87.1 billion, respectively (Table 5). Estimates were $5.8 billion, $14.7 billion, and $28.0 billion, respectively, when applying underlying pneumonia and influenza diagnoses to the analysis (not shown). Of the total economic burden of influenza, 64% was borne by those ≥65 years. Those aged 50–64 years bore 21% of the burden, while those aged 18–49 years bore 10% of the burden. About 5% of the total burden of this illness was borne by children.

When considering the share of total economic burden by health outcome, $72.2 billion (83%) of the cost of influenza was attributed to the estimated 41,008 annual deaths. The estimated 334,185 hospitalizations comprised $6.0 billion (7% of the burden). The 10.6 million outpatient cases accounted for $6.8 billion (8%) of the burden. In contrast, the 13.7 million cases not medically attended accounted for $2.0 billion, about 2% of the burden of influenza.

Lost earnings due to lost productivity from illness and loss of life amounted to $16.3 billion annually, about 20% of the total burden of influenza. About $6.2 billion was due to lost productivity from illness. Indirect costs of illness comprised about $76.7 billion (88%) of the total economic burden of influenza. Direct costs of medical treatment for influenza amounted to $10.4 billion annually, or 12% of the total economic burden.

About $4.2 billion, or 40% of direct medical costs, was spent on treatment of those ≥65 years of age. Treatment of those aged 50–64 years accounted for 27% of expenditures and 18% was spent treating those aged 18–49 years. The remaining $1.7 billion (15%) in medical expenditures on this illness were spent treating children.

When considering the share of direct medical expenditures by health outcome, 52% of expenditures on influenza were attributable to hospitalizations. Outpatient visits accounted for 30% of expenditures and 18% of expenditures were attributed to treatment of persons who died from the disease. Non-medically attended cases accounted for $41.1 million, less than 1% of medical expenditures for treatment of influenza.

3.2. Sensitivity analysis

Sensitivity analyses generated confidence intervals around our estimates and provided information on the sensitivity of our results to changes in the values of epidemiologic and economic variables used in the model. The sensitivity analyses identified the variables to which our estimates were most sensitive, or most highly correlated (Fig. 1). For direct medical costs, the three most highly correlated variables were: (1) the cost of high-risk cases ≥65 years of age that were hospitalized ($\rho = 0.224$); (2) the attack rate in those aged ≥65 years ($\rho = 0.20$) and (3) the cost of hospitalized cases aged 50–64 years not at high risk ($\rho = 0.20$). For direct medical costs plus lost earnings (PVLE), the three most highly correlated variables were: (1) the PVLE for those ≥65 years ($\rho = 0.50$); (2) the attack rate in those ≥65 years ($\rho = 0.25$) and (3) the PVLE for those aged 50–64 years ($\rho = 0.22$). For the total economic burden of influenza (VSL), the three most highly correlated variables were: (1) the VSL for those ≥65 years ($\rho = 0.62$); (2) the mortality rate for individuals ≥65 years ($\rho = 0.43$) and (3) the attack rate in those ≥65 years ($\rho = 0.42$) (Fig. 1).

Table 5
Projected economic burden of influenza in the United States by age group, health outcome and type of cost—millions of $2003

	<5 years			5–17 years			18–49 years			50–64 years			65+ years			Total cost by outcome		
	Mean	95% CI[a]		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Ill (not medically attended)																		
Medical[b]	6.1	2.4	9.2	10.5	3.7	19.4	17.0	5.5	36.3	5.2	1.8	10.5	2.2	0.8	4.3	41.1	30.3	54.4
Medical + Lost Earnings[c]	296.5	77.2	225.5	508.9	0.9	27.8	822.9	0.0	26.7	252.7	0.0	7.7	105.6	0.0	3.1	1986.7	1468.5	2600.2
Outpatient only																		
Medical	388.5	63.3	1348.3	388.2	38.0	471.0	887.6	80.8	7766.2	571.1	27.8	2312.9	879.3	79.3	2778.4	3114.6	854.8	7690.6
Medical + Lost Earnings	781.2	63.6	1360.2	831.6	38.3	479.8	1456.4	81.5	7779.7	1121.8	28.1	2326.5	2636.3	79.6	2848.2	6827.3	3802.9	13014.1
Hospitalized																		
Medical	809.1	47.4	4296.6	56.4	2.8	283.7	866.1	40.8	5688.9	1709.3	82.6	9654.7	1923.6	116.4	10736.6	5364.5	1321.5	14011.2
Medical + Lost Earnings	882.6	47.4	4298.8	61.1	2.8	283.9	936.7	40.8	5691.2	1850.5	82.6	9659.4	2223.8	116.5	10745.7	5954.7	1818.2	14634.6
Death																		
Medical	6.0	0.2	20.2	2.6	0.1	8.4	61.1	1.8	376.6	474.0	4.2	2485.1	1347.6	38.2	6292.4	1891.3	323.7	5704.1
Medical + Lost Earnings (PVLE)[d]	165.8	53.4	616.2	63.7	20.4	121.9	1162.5	166.1	4196.6	2555.6	178.4	32421.4	8040.8	319.2	113665.0	11988.5	2021.0	33354.7
Medical + Lost Earnings + Lost Life (VSL)[e]	232.1	0.2	20.2	149.8	32.1	155.7	5577.9	831.1	6455.4	15249.7	7774.0	75930.9	51089.0	36332.3	367643.4	72298.6	34308.7	130230.0
Total medical cost	1209.7	170.8	3643.7	457.7	97.2	1349.4	1831.9	272.0	5546.6	2759.6	433.4	8169.2	4152.6	851.0	11526.2	10411.6	4083.3	22197.1
Total Medical + Lost Earnings	2126.1	846.9	5042.2	1465.3	654.6	3073.5	4378.5	1584.6	10321.7	5780.7	1438.4	15615.8	13006.5	3290.7	33448.5	26757.2	12813.0	53155.9
Total economic burden	2192.4	898.8	5124.6	1551.5	706.6	3195.0	8793.9	3865.6	17305.2	18474.7	6990.5	37752.9	56054.7	20982.7	113680.7	87067.3	47215.3	149508.6

[a] CI: confidence interval.

[b] Medical costs of individuals with clinical influenza infection who were sick but did not seek medical attention were expenses on over-the-counter medications.

[c] For cases not medically attended, indirect costs were assumed to involve one half day of lost productivity for those 5–64 years of age and 1 day of lost productivity for those less than 5 years of age or ≥65 years of age, who were assumed to convalesce longer due to relatively greater likelihood of severe illness symptoms [1].

[d] Indirect costs of death were measured using the present value of lost earnings due to loss of life (PVLE). Haddix et al. calculated the PVLE as the discounted sum of future earnings given remaining life expectancy and expected productivity growth over a range of ages [29]. Here, total cost of illness is the sum of all medical costs, lost of earnings due to lost productivity from illness (for recovered cases), and lost of earnings due to lost productivity from premature death (see Table 1 for PVLE estimates).

[e] Indirect costs of death are measured using the value of a statistical life (VSL). The VSL is the market value of a life, including the value of lost productivity as well as the intrinsic, or social, value placed on human life [28,30]. Here, total cost of illness is the sum of all medical costs, lost of earnings due to lost productivity from illness (for recovered cases), and the value of lost life, using VSL estimates (see Table 1).

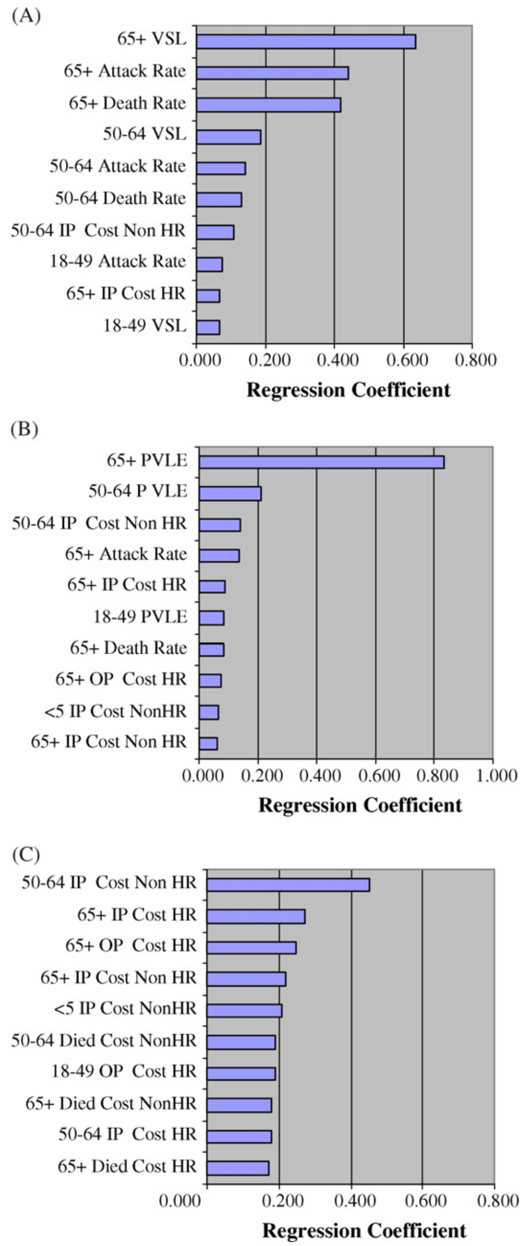

Fig. 1. Sensitivity analyses of total economic burden, Total Medical + Lost Earnings, and Total Medical Cost. The sensitivity of the total economic burden, total medical + lost earnings, and total medical costs of influenza illness to input parameters was measured using standard regression coefficients. Here, the base-case scenario is described at the zero value of the vertical axis. The size of the bars indicates the proportional response in total economic burden (A), total medical + lost earnings (B), and total medical costs (C) to incremental increases in the particular input parameter given all other inputs. Abbreviations: VSL, value of statistical life; PVLE, present value of lost earnings; IP, impatient; OP, outpatient; HR, high-risk condition; NonHR, non-high-risk condition.

4. Discussion

Our results indicate that the annual economic burden of influenza remains very high. The total annual economic burden of influenza epidemics in the United States across all age groups was $87.1 billion (C.I., $47.2 billion, $149.5 billion) using the VSL method to value lost lives including direct medical costs of $10.4 billion (C.I., $4.1 billion, $22.2 billion). The annual burden per capita ranged between $92 (considering only lost earnings) and $299 (including lost lives). When considered from the perspective of the 2003 United States' Gross Domestic Product (GDP) of $11 trillion, the annual influenza burden amounts to between 0.24% (PVLE) and 0.79% (VSL) of GDP [44]. While this represents less than 1% of GDP, because influenza epidemics occur annually, this burden amounts to an annual reduction in the rate of economic growth, a reduction that is at least in part preventable through prophylaxis. Programs to further reduce the impact of influenza on older Americans would likely have the greatest economic benefit since 64% of the total economic burden falls on the elderly, including 36,000 deaths.

We used two methods to value lost lives in this analysis. We calculated the total economic burden of influenza (Medical + Lost Earnings + Lost Life [VSL]) using estimates of VSL based on the hedonic wage method of valuation, a standard economic method for estimating the labor market value of a life. We also calculated the economic burden of influenza based on total medical costs plus lost earnings (Medical + Lost Earnings [PVLE]) using the PVLE method. Results indicated that, when only considering the lost earnings resulting from lost lives and lost days of productivity, the mean economic burden of influenza was still $26.8 billion (C.I., $12.8 billion, $53.2 billion) annually. However, this figure does not include the total loss to society due to lost lives, but merely lost potential earnings. It also tends to discount most heavily the value of lives lost in the oldest age categories, since remaining potential lifetime earnings decline with age [28]. Independent of the approach used, the economic burden was highly sensitive to the value of lost lives, particularly those in the oldest age categories.

The study has several limitations. First, because influenza cases are not directly counted, overall influenza disease burden is estimated using historical data from clinical studies and estimates of excess influenza-attributed hospitalizations and deaths. Therefore, any limitations in influenza case estimation are also reflected in our estimate of the economic burden [15,16,18]. Second, the number of observations used to estimate direct medical costs per death in children was small ($N = 36$). However, given that influenza deaths in children are rare, any uncertainty around this estimate has a small effect on overall costs. Third, our primary analyses included estimates of excess hospitalizations and deaths using peri-season risk-difference models which are less conservative than estimates from Serfling regression models [14–16,18,19]. However, we also calculated costs using a more conservative outcome of only pneumonia and influenza in addition to R&C hospitalizations and deaths to present a range of cost outcomes. Finally, costs are estimated from a national database of privately insured individuals, including Medicare-eligible individuals who have supplemental insurance. These costs may not represent the uninsured or non-elderly publicly insured population. Private reimbursement rates tend to be higher than public reimbursement rates [41–44]. This might lead to overestimation of the cost per case of influenza. However, the privately insured population may be healthier than the publicly insured population, which conversely would tend to underestimate the cost per case of influenza. One important advantage of the database that supports the accuracy of our estimated cost per case is its use of actual paid claims rather than charges, eliminating any need for cost to charge ratio adjustments. The limitations listed here have been addressed with sensitivity analyses. The resulting variance in the estimate represents the degree of uncertainty introduced by these limitations.

There are few economic analyses of the burden of influenza in the literature. One previous study estimated a total economic burden of pandemic influenza that ranged between $89.7 billion and $209.4 billion, assuming attack rates of 15% and 35%, respectively, and $2003 [2]. If we applied our methodology to similar attack rates, estimated costs would be substantially higher. There are a number of differences in approach that may account for this discrepancy. The authors used net payments for hospital costs and net payments plus co-payments for outpatient and drug costs, which lowered their estimate of the economic burden [2]. This approach excluded patient and secondary insurer payments from costs. In 2003, these payments amounted to 37% of total hospital payments, 50% of outpatient payments, and 1% of pharmaceutical payments [42]. A cost to charge ratio of 53% was also applied to the cost per case estimate. See Orsini et al. for more on application of the cost to charge ratio to health insurance claims data [45]. In addition, the previous study valued deaths based only on lost earnings (PVLE) rather than the value of a statistical life. Note that the confidence interval surrounding our estimate of the total economic burden is slightly wider than that of Meltzer et al. This is due in part to the greater complexity of our model compared to that of Meltzer et al., which includes more strata by age as well as risk.

Immunization against influenza can effectively reduce the annual economic burden of influenza in the United States [7,46–48]. Nevertheless, despite efforts to vaccinate those at highest risk of severe influenza-related complications, many still go unvaccinated. Even among those that are vaccinated, some may not be adequately protected by the vaccine [49–51]. Consequently, new strategies such as vaccination of school-aged children or universal vaccination are being discussed as a means to decrease the burden in all ages and complications among the elderly [52–54]. Further research is necessary to identify the most efficient and effective methods of minimizing influenza disease in the elderly and its contribution to the annual economic burden of influenza epidemics in the United States. For additional methodologic details contact corresponding author.

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