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Economic burden of seasonal influenza in the United States

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ABSTRACT

Background: Seasonal influenza is responsible for a large disease and economic burden. Despite the expanding recommendation of influenza vaccination, influenza has continued to be a major public health concern in the United States (U.S.). To evaluate influenza prevention strategies it is important that policy makers have current estimates of the economic burden of influenza.

Objective: To provide an updated estimate of the average annual economic burden of seasonal influenza in the U.S. population in the presence of vaccination efforts.

Methods: We evaluated estimates of age-specific influenza-attributable outcomes (ill-non medically attended, office-based outpatient visit, emergency department visits, hospitalizations and death) and associated productivity loss. Health outcome rates were applied to the 2015 U.S. population and multiplied by the relevant estimated unit costs for each outcome. We evaluated both direct healthcare costs and indirect costs (absenteeism from paid employment) reporting results from both a healthcare system and societal perspective. Results were presented in five age groups (<5 years, 5–17 years, 18–49 years, 50–64 years and ≥65 years of age).

Results: The estimated average annual total economic burden of influenza to the healthcare system and society was $11.2 billion ($6.3–$25.3 billion). Direct medical costs were estimated to be $3.2 billion ($1.5–$11.7 billion) and indirect costs $8.0 billion ($4.8–$13.6 billion). These total costs were based on the estimated average numbers of (1) ill-non medically attended patients (21.6 million), (2) office-based outpatient visits (3.7 million), (3) emergency department visit (0.65 million) (4) hospitalizations (247.0 thousand), (5) deaths (36.3 thousand) and (6) days of productivity lost (20.1 million).

Conclusions: This study provides an updated estimate of the total economic burden of influenza in the U.S. Although we found a lower total cost than previously estimated, our results confirm that influenza is responsible for a substantial economic burden in the U.S.

1. Introduction

Seasonal influenza is a highly pathogenic viral infection. It occurs annually in the United States (U.S.) typically from late fall through early-mid spring [1,2]. Influenza infection is common in all age groups, with children infected most frequently. In most cases, influenza infection is a self-limiting disease from which individuals will recover without serious complications; however, it can result in severe illness and death [3,4]. Influenza also results in a substantial economic burden, due to both medical care costs and productivity loss [5].

While the U.S. Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination to all person aged ≥6 months, less than half the population are vaccinated for influenza each year [6]. Populations at high-risk of severe illness from infection include children, pregnant women, adults aged over 50 years, and patients with comorbidities (e.g. cardiovascular disease, asthma, metabolic disorders) [3]. Some high-risk groups have higher uptake in the U.S., for instance, in 2015 coverage was 59.3% in children aged 6 months to 17 years and 63.4% in adults aged ≥65 years [6].

Molinari et al. estimated that, in the U.S., seasonal influenza is associated with approximately 10 million individuals seeking outpatient care, 300,000 hospitalizations, and 41,000 deaths annually based on the 2003 demographic profile [5]. The associated direct medical costs in $US2003 were estimated to be $10.4 billion, with lost productivity due to illness and death estimated to be

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$16.3 billion. These past estimates of the economic burden of influenza have been critical in understanding the importance of influenza in the U.S. but are now over a decade old and new influenza outcome estimates have emerged.

To be able to evaluate intervention programs around influenza prevention, it is important for policy makers to understand the current influenza burden including the economic burden. This study aims to provide an updated estimate of the average annual economic burden of seasonal influenza in the U.S. population (using the 2015 demographic profile, reporting in 2015 US$), including both direct medical and productivity costs. These estimates are calculated in the presence of vaccination and other preventive efforts within the U.S. setting.

2. Methods

This study adopted a societal perspective (including direct healthcare costs and indirect productivity costs related to absenteeism from paid employment) but also reported results for direct healthcare costs only. The direct medical costs were calculated from the estimated age-specific average annual number of events (e.g. influenza hospitalizations) multiplied by the unit cost for a given outcome (e.g. cost of influenza hospitalization). In line with best practice, where possible, we avoided the use of charges and rather used the cost (e.g. estimated to the hospital) or the amount paid for the event (e.g. reimbursement and patient co-pay) [7,8]. Indirect costs were calculated by the estimated total days/hours of lost (paid) work due to influenza multiplied by value of a lost time (i.e. the human capital approach) [9].

We considered five categories of outcomes due to influenza: (1) ill but not medically attended; (2) office-based outpatient visit; (3) emergency department (ED) visit (4) hospitalization; and (5) death. We analyzed the data by each single year of age from 0 to 100 years, which were then aggregated for illustration purposes into the age groups: <5 years, 5–17 years, 18–49 years, 50–64 years, and ≥65 years. All analyses were conducted in Excel Version 15.19.1.

2.1. Estimation of number of outcomes

In each age group, we estimated the number of health outcomes by multiplying estimated average age-specific population rates of each outcome by the age-specific size of the 2015 U.S. population [10]. We obtained the rates for each health outcomes from published U.S. sources which were estimated in the presence of influenza vaccination (see Table 1). The exception to this was the estimation of ill but not medically attended rates, which were derived by subtracting rates of all other outcomes (combined) from the estimated age-specific symptomatic influenza rate in unvaccinated individuals. Where sources provided estimates over more than 6 years we used the average estimate over the 6 most years in base case Table 2.

Age-specific symptomatic attack rates for seasonal influenza were estimated from a recent U.S. study [11]. Estimates of influenza office-based outpatient and ED visits (in children ≤7 years) were derived from studies that included laboratory confirmation of influenza infection (in at least a subset) individuals presenting with either influenza-like illness [12] or acute respiratory symptom/s [13], respectively. Estimated rates of hospitalization [14], death [15] and ED visits (in adults [16]) were derived from studies that applied time series statistical modelling methods to population level data. The types of methods applied in these studies have been widely used to quantify the disease burden from influenza where laboratory testing is not routine [17,18]. These models examine the relationship over time between available influenza surveillance time series and broad population outcome categories such as hospitalizations for respiratory and/or circulatory illness [19]. Detail on the age-specific disease rates are provided in Table 1 and Appendix.

The number of days or hours loss associated with each health outcome was obtained from published sources (see Appendix Table A1) [5,20–24]. In cases where estimates were of the total

Table 1
Estimated annual average attack rates and health outcome rates per 1000 people* for base case and sensitivity analysis.

Variable	Age group (years)	Mean	Range		Source
			Lower limit	Upper limit	
Overall attack rates	0–17	93.000	82.000	111.000	[11]
	18–64	89.000	82.000	99.000	
	≥65	39.000	34.000	42.000	
Office-based outpatient visit rates	0–1	14.330	11.730	17.000	[12]
	2–4	31.130	27.200	35.200	
	5–17	31.600	29.530	33.600	
	18–24	8.530	7.730	9.400	
	25–49	7.600	6.930	8.470	
	50–64	5.000	4.200	6.070	
	≥65	3.330	2.800	4.200	
Emergency department visit rates	0–7	10.200	4.000	26.400	[13]
	8–49	0.410	0.270	0.550	[16]
	50–64	2.110	1.690	2.520	
	≥65	2.450	2.030	2.880	
Hospitalization rates	<1	1.988	1.053	6.596	[14]
	1–4	0.537	0.241	2.132	
	5–49	0.184	0.098	0.584	
	50–64	0.654	0.350	2.700	
	≥65	3.226	1.860	11.037	
Death rates	0–17	0.004	0.002	0.006	[15]
	18–49	0.011	0.006	0.015	
	50–64	0.061	0.059	0.084	
	65–74	0.219	0.221	0.305	
	≥75	1.221	1.183	1.638	

* Note that all values presented are estimates in the presence of vaccination in the U.S.

Table 2
Cost per health outcome by age for base case and sensitivity analysis ($US, 2015).

Variable[a]	Age group (years)	Mean	Range[b]		Source
			Lower limit	Upper limit	
Ill but not medically attended	All ages	$7.00	$5.25	$8.75	[33]
Office-based outpatient visit[c]	0–17	$114.28	$85.71	$142.85	[27]
	18–64	$74.41	$55.81	$93.02	[28]
	≥65	$102.12	$76.59	$127.65	[29,30],
Emergency department visit	0–4	$864.25	$648.19	$1080.31	[22]
	5–49	$583.98	$581.93	$586.03	[16]
	50–64	$582.96	$580.90	$585.01	
	≥65	$605.53	$604.51	$607.59	
Hospitalization	<1	$5211.68	$3908.76	$6514.61	[21]
	1–17	$7346.58	$5509.94	$9183.23	
	18–44	$11,908.00	$8931.00	$14,885.00	
	45–64	$12,102.27	$9076.70	$15,127.83	
	65–84	$8329.79	$6247.34	$10,412.24	
	≥85	$7848.50	$5886.38	$9810.63	

[a] All costs are reported in 2015 US$ with those sourced from previous years inflated to year 2015 using the medical care component of the U.S. Consumer Price Index (CPI) [26].
[b] A range of ±25% of the base case value was used to establish lower and upper limits. The exception to this was ED costs for those aged over 5 years where confidence intervals could be located.
[c] The estimated costs here include potential repeat visits for the same incident influenza case (see Method for further details).

time lost (i.e. irrespective of if paid or leisure time etc.) we adjusted by the U.S. age specific labor participation [25]. For those ≤15 years, we applied estimates for different healthcare seeking outcomes from a single study, which collected data on the number of caregiver workdays lost [22]. For office-based outpatient and ED visit cases in adult (≥16 years), we used an estimate of productivity loss for medically attended laboratory-confirmed influenza cases [23]. For hospitalizations in adults, we assumed that the number of days lost was equivalent to the hospital length of stay [21] plus an additional 3 days of recovery post-hospitalization.

2.2. Estimation of cost for each outcome

The unit costs for each outcome were based on data from public databases and the literature (Table 3). All costs are reported in 2015 US$ with those sourced from previous years inflated to year 2015 using the medical care component of the U.S. Consumer Price Index (CPI) [26]. There were four sources of direct medical costs: (1) over the counter medicine costs for non-medically attended cases; (2) office-based outpatient visits costs; (3) ED visit costs; and (4) hospitalization costs.

Office-based outpatient visit costs were estimated from three separate sources dependent on the age group. For those ≤17 years and 18–64 years estimated office-based healthcare costs for influenza cases were identified from studies that used MarketScan databases, [27,28], respectively. The cost of office visits for those aged ≥65 was approximated by the Medicare Physician Fee Schedule reimbursement for an established patient with low to moderate severity problem (within 15 min; code 99213) [29,30],. We multiplied this cost by 1.4 based on the assumption that 40% of new cases would have (at least) two encounters [31]. The costs for over the counter medicine were based on a study that used data from the RED BOOK Drug References [32,33].

Hospitalizations costs were estimated from Healthcare Cost and Utilization Project (HCUPnet), a nationally representative database of hospital discharge data using the National Inpatient Sample. We estimated the hospitalization costs using the diagnostic categories of underlying influenza (ICD-9-CM coded 487–488) [21]. This dataset includes all patients irrespective of insurance status and we used the "cost" category for hospitalization, which is calculated from a cost-to-charge ratio. The cost of ED visits for influenza in children aged ≤4 years and adults were estimated from [22] and [16] respectively.

The cost of productivity loss from paid employment for each outcome was calculated by multiplying the number of days/hours loss by estimates of the hourly or daily wage (see Appendix Table A1). Daily earnings were estimated by multiplying wages per hour ($25.03) by average work hours per day [34]. The value of lost productivity from premature mortality was estimated based on the present value of lifetime market productivity. The age-specific market production estimates (discounted at 3% per annum [35]) were sourced from a previous study [36] and inflated to 2015 dollars using the employment cost index for all civilian workers [37].

2.3. Sensitivity analysis

One-way sensitivity analysis was conducted using the 95% confidence limits provided by the various input sources. Where confidence limits were not available, we used the base case ±25% to establish a range. We also conducted extreme analyses, for example, changing all inputs within a given category to their upper or lower value (e.g. all rates, all direct costs, all indirect costs). We calculated the most influential variables from the difference between the total costs when using the upper value and the lower value (see Appendix Table A3).

2.4. Scenario analysis

Scenario analyses were also conducted by applying alternative inputs for key variables from other published sources to assess how these impacted on results (See Appendix 1, Tables A2 and A4). We also explored the use of a friction-cost method to estimate productivity loss from influenza mortality using the same basic approach outlined in a previous analysis (40 days with 0.8 elasticity adjustment factor [38]). The friction-cost method values only the period of interruption when a worker is replaced not the lost life-time earnings [39]. Using age-specific labor participation rates [25] we used adjusted daily wages (described above).

3. Results

In the base case analysis, there was an estimated 26.2 million influenza cases annually (based on the 2015 population), with approximately 82.2% of cases ill but not medically attended and 14.2%, 2.5%, 0.9%, 0.1%, resulting in office-based outpatient visits,

Table 3
Annual average population based estimates of influenza-attributable outcomes and days of productivity lost due to influenza.

Age group (years)		Ill but not medically attended	Office-based outpatient visit	Emergency department	Hospitalizations	Deaths	Total number of events	Total days of productivity loss (excludes from death)
<5	Base	1,145,563	486,211	203,054	16,466	82	1,851,377	2,515,167
	Lower	1,126,150	418,544	79,629	8028	46	1,632,397	1,440,205
	Upper	1,067,728	556,108	525,552	60,200	119	2,209,708	4,929,874
5–17	Base	2,741,258	1,698,115	141,331	9897	222	4,590,823	4,121,245
	Lower	2,599,283	1,586,878	65,779	5266	124	4,257,330	2,566,512
	Upper	2,708,924	1,805,591	338,740	31,383	322	4,884,960	6,500,515
18–49	Base	11,023,809	1,068,720	56,088	25,195	1452	12,175,264	7,972,040
	Lower	10,193,511	973,005	36,936	13,406	800	11,217,659	5,127,878
	Upper	12,198,378	1,187,737	75,240	79,892	2025	13,543,271	12,450,221
50–64	Base	5,238,676	316,061	133,378	41,362	3864	5,733,341	3,714,956
	Lower	4,875,015	265,491	106,829	22,124	3698	5,273,156	2,387,630
	Upper	5,663,555	383,698	159,295	170,673	5310	6,382,529	6,810,891
≥65	Base	1,401,823	159,044	117,014	154,085	30,708	1,862,673	1,756,517
	Lower	1,274,362	133,730	96,955	88,835	29,986	1,623,869	1,167,114
	Upper	1,099,157	200,596	137,551	527,137	41,516	2,005,956	2,830,190
Total	Base	21,551,129	3,728,150	650,865	247,004	36,329	26,213,478	20,079,925
	Lower	20,068,321	3,377,648	386,128	137,660	34,654	24,004,412	12,689,338
	Upper	22,737,741	4,133,729	1,236,378	869,284	49,292	29,026,425	33,521,691

ED visits, hospitalizations and death respectively (Table 3). Influenza was estimated to result in 20.1 million days of lost productivity (Table 3).

The total annual economic burden of influenza was $11.2 billion, with direct medical costs of $3.2 billion (28.7%) and indirect costs of $8.0 billion (71.3%) (Table 4). Lost lifetime earnings from deaths represented the largest overall share of the total costs of influenza (37.2%, $4.2 billion), however all categories involving medical attendance resulted in a substantial share of the total costs. The age groups contributing most to the total costs were those aged 18–49 years and those 50–64 years (32.9% and 24.9% of the total respectively), with the population in the age group 18–49 years representing the largest (43%) share of the total population.

3.1. Direct medical costs

The age group with the largest share of the total direct medical costs was those aged ≥65 years (42.7% of the total), which was driven primarily by hospitalization costs ($1.3 billion). The other groups aged <5 years, 5–17 years, 18–49 years and 50–64 years contributed 10.7%, 11.5%, 15.3% and 19.9% of the total direct healthcare burden, respectively. In those aged ≤17 years, total direct medical costs were more evenly spread across different healthcare seeking outcomes. The direct healthcare costs associated with non-medically attended cases was higher as a proportion of total costs in adults aged 18–49 years, who were less likely seek other forms of healthcare.

3.2. Indirect costs

The age group with the largest share of the total indirect medical costs was those aged 18–49 years (39.9% of the total, $3.2 billion). The other groups aged <5 years, 5–17 years, 50–64 years and ≥65 years contributed 7.0%, 13.1%, 27.0% and 13.1% of the total indirect burden respectively. Over half of the total indirect cost resulted from the value of lost earnings due to death

Table 4
Estimated annual average economic burden of influenza in the United States by age group and health outcome (millions US$, 2015).

Age group (years)	Category	Ill but not medically attended	Office-based outpatient visit	Emergency department	Hospitalization	Deaths	Total	Total (per 100,000 persons)
<5	Direct	8.02	55.56	175.49	104.09	-	343.16	1.72
	Indirect	217.92	133.87	96.57	30.10	79.56	558.02	2.80
	Direct + Indirect	225.94	189.43	272.06	134.19	79.56	901.18	4.53
5–17	Direct	19.19	194.06	82.53	72.71	-	368.49	0.69
	Indirect	260.73	440.84	66.18	16.23	258.47	1042.45	1.94
	Direct + Indirect	279.92	634.90	148.71	88.94	258.47	1410.94	2.63
18–49	Direct	77.17	79.53	32.75	300.76	-	490.21	0.36
	Indirect	1048.52	417.69	22.04	28.25	1672.49	3188.99	2.33
	Direct + Indirect	1125.69	497.22	54.80	329.01	1672.49	3679.20	2.69
50–64	Direct	36.67	23.52	77.75	500.57	-	638.51	1.01
	Indirect	498.27	112.86	47.63	47.94	1447.06	2153.75	3.41
	Direct + Indirect	534.94	136.38	125.38	548.50	1447.06	2792.26	4.42
≥65	Direct	9.81	16.24	70.86	1273.73	-	1370.64	2.87
	Indirect	266.67	15.60	11.42	40.45	710.10	1044.24	2.19
	Direct + Indirect	276.48	31.85	82.28	1314.18	710.10	2414.88	5.06
Total	Direct	150.86	368.91	439.39	2251.86	-	3211.02	1.00
	Indirect	2292.11	1120.86	243.84	162.96	4167.68	7987.44	2.49
	Economic burden (Direct + Indirect)	2442.96	1489.77	683.22	2414.82	4167.68	11198.46	3.48

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($4.2 billion), which was particularly high in those aged over 18 years (Fig. 1). Indirect costs due to short-term absence from paid employment were primarily associated with non-medically attended cases (60.0%) and office-based outpatient visits (29.3%), with the less common ED and hospitalizations events representing only a small share of indirect costs.

3.3. Sensitivity analysis

When varying individual inputs across their range, hospitalization rates resulted in the most substantial difference in the total cost of influenza (upper limit resulted in a total of $17.4 billion or an increase of 55.1%). Variation in other parameter inputs resulted in less than 10% differences in total costs (Appendix Table A3). Extreme analyses where we set all parameter inputs from the same category (outcome rates, healthcare unit cost, or productivity losses) to their upper or lower value, resulted in substantial changes particularly when setting all to upper values, which increased the total (direct and indirect) cost to $19.9 billion, $11.9 billion and $13.5 billion respectively (Appendix Table A3). When applying the lower or upper value for all parameter inputs, the total costs of influenza varied from $6.3 billion to $25.3 billion. The total direct healthcare costs ranged from $1.5 billion to $11.7 billion, while total indirect costs ranged from $4.8 billion to $13.6 billion (Appendix Table A3).

3.4. Scenario analysis

Scenario analysis using alternative sources from the literature to inform inputs often resulted in substantial differences in results (Appendix Table A4). The largest difference occurred when we applied either an alternative higher office-based visit rates, higher hospitalization costs, higher days lost for non-medically attended cases, or when we applied a more conservative estimate of influenza deaths (See Appendix Tables A2 and A4 for details). The use of the cost-friction method to estimate the lost productivity from influenza deaths also substantially reduced productivity costs with total influenza-related mortality productivity loss reduced from $4167.68 million to $46.88 million.

4. Discussion

We estimated that the average annual total economic burden of influenza using the 2015 demographic profile (in 2015 US$) was $3.2 billion (range from $1.5–$11.7 billion) to the healthcare system and $11.2 billion (range from $6.3–$25.3 billion) when lost productivity was included. This updated estimate suggests that substantial costs from influenza remain despite the vaccination efforts in the U.S. setting. The total direct and indirect costs of influenza were equal to $34.8 per capita annually (direct $10.0 and indirect $24.9) with the total costs equal to approximately 0.35% of U.S. per capita health expenditure [40]. Persons aged ≥65 years had the largest share of total direct costs, resulting primarily from hospitalization. The majority of indirect costs occurring in working aged adults, with most productivity costs resulting from lost income due to influenza-related mortality (Fig. 1).

The total economic burden we estimated was substantially lower (approximately half) than that estimated by Molinari et al. for 2003 [5], with our base case results just outside of the range

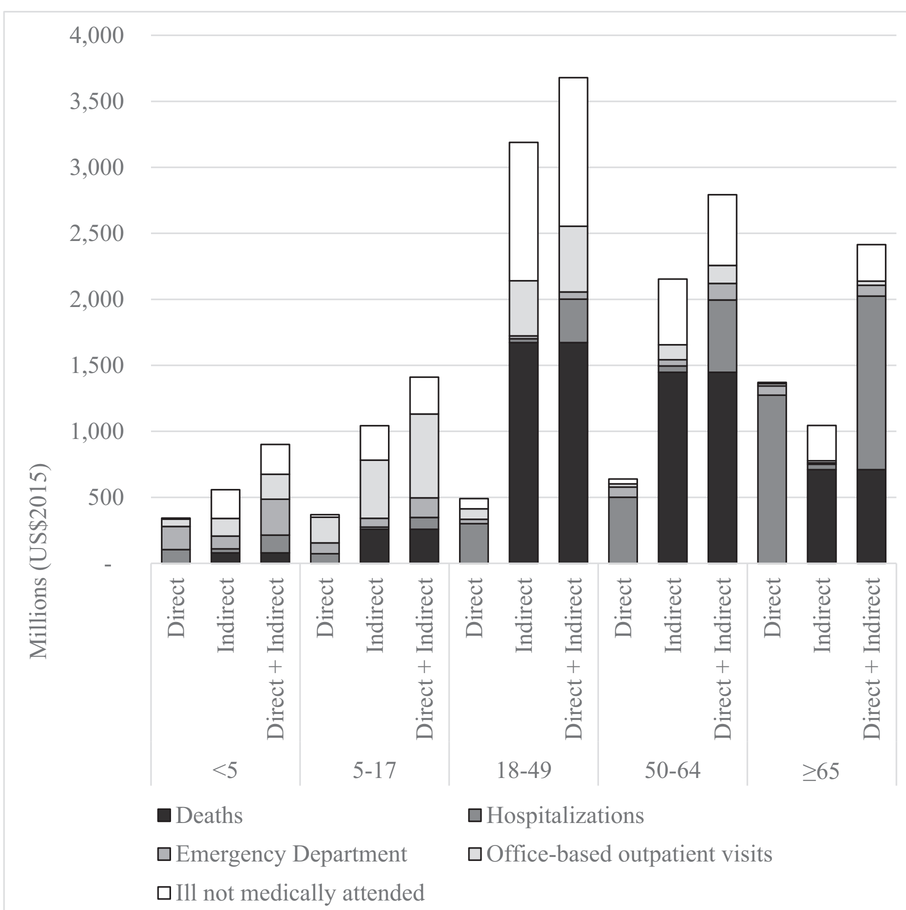

Fig. 1. Breakdown of estimated annual average cost of influenza using base case parameter inputs (millions, US$, 2015).

estimated in that study of $12.8–$53.2 billion (base case $26.8 bil lion). We found that the working-aged adult (18–64 years old) account for the largest share of the total (direct and indirect) cost of influenza (57.8% or $6.5 billion) (see Fig. 1). This result was different from Molinari et al. which estimated that approximately 48.5% of the total economic burden of influenza was in the older adults group (≥65 years old) and the working aged adults shared only 37.3% of the total. There are several explanations for the various differences between the previous study by Molinari et al. and our current results (discussed in detail below), these include variation in: (1) the estimates of the number of events attributable to influenza; (2) the unit costs attached to these events; and (3) alternative methodological decisions.

There is relatively poor data to inform symptomatic influenza attack rates (due to the lack of routine testing), however the annual symptomatic influenza attack rates assumed by Molinari et al. were relatively high and may have overestimate influenza cases. For example, they assumed that on average 20% of children under 5 years have symptomatic influenza infection, which is approximately double estimates of the historically observed average rate [41]. We applied estimates from a recent study which applied statistical methods to estimate the incidence of symptomatic influenza cases in the U.S. population [11].

In contrast to our approach, which used independent (separate) estimates of the rate/s of influenza outpatient visits, Molinari et al. established outpatient cases based on age-specific estimates of the proportion of influenza cases seeking outpatient care. This means in their assumptions around the overall attack rate for symptomatic influenza were very influential in estimating the number of outpatient visits. This was not the case in our model, where overall attack rates were only used to estimate non-healthcare seeking cases. While Molinari et al. [5] did not explicitly mention ED visits their total estimate of all outpatient visits was substantially higher than our estimate of office-based and ED visit combined. In other cases, our disease burden estimates were more consistent, for example, although we applied newer sources, our estimates of influenza hospitalizations and deaths were similar to Molinari et al.

In terms of costs, our study used hospitalization costs data from HCUP, which is a representative database of hospital discharge data for all patients obtained from the National Inpatient Sample [21,42],. Molinari et al. used cost data from the MarketScan database. Each source has its own advantages and disadvantages [43] but one reason for their higher hospitalization costs was that it included the cost of all healthcare (including outpatient etc.) around a hospitalization episode (e.g. "for 2 weeks before the date of admission through 30 days post-discharge" [5]). However, as our estimate of the total number of events (e.g. office-based visits) were established from independent sources and costed separately, we wanted to avoid double counting outpatient visit costs for hospitalized cases.

We also made several methodological choices that differed from Molinari et al. [5]. One important choice was how to value of lost time. Molinari et al. valued lost time from unusual activities (e.g. both paid work and unpaid work), where as we applied a more conservative method counting only the value of lost time from paid employment. This choice contributes to our finding that the working aged adult shared largest burden of indirect costs. There is no definitively correct approach to valuing lost time in economic analyses, with different decision makers and health economists preferring different approaches [39]. The very high estimates of the total economic burden of influenza (i.e. $87 billion) from Molinari et al. came from the use of the statistical value of life, a method that attempts to capture the broader value of a life [44]. This is a valid approach but it is less frequently used within the healthcare setting than a human capital approach which only values lost time [39]. There are also more conservative methods, such as the cost-friction method [39], which we applied as a form of scenario analysis.

Results from our sensitivity and scenario analysis indicated that the total cost of influenza was sensitive to several key variables. For example, applying the upper value for hospitalization rates resulted in a large change to total costs, due to the large uncertainty range from the input source [14]. In other cases, the largest changes from single inputs came from the application of alternative sources, rather than the upper or lower ranges from selected sources. For instance, there was a substantial increase in costs when we applied office-visit outpatient rates from an alternative source [45], which provided a less conservative estimate derived from statistical modelling methods. This highlights the uncertainty in estimates of influenza disease burden and the need to establish a more robust and consistent method in estimating influenza-associated outcomes. For example, although regression models have been widely used to estimate influenza-attributable disease, results can vary substantially depending on the methodological choices made within these analyses (e.g. analysis of all-cause or only respiratory deaths) [46]. In the case of ED visits due to influenza in the U.S., our estimates are particular uncertain as they are estimated from populations that are not fully representative of the U.S. population [13,16].

Alongside, this uncertainty in the accuracy of the sources used, our study had several other limitations. For example, while we applied rates of disease from more recent studies, in some cases they included data from before recent changes to vaccination in the U.S setting. We did not attempted to adjust the disease rates applied for any differences between vaccination rates observed in these studies and the most current estimates for the U.S., which could potentially overestimate the disease burden. Likewise, since 2009 high dose influenza vaccine has been licensed in the U.S. for those aged ≥65 years, which may have reduced influenza disease in this age group [47,48],. In several cases no reliable age-specific representative data could be located to inform parameter estimation, for example, on co-payments, direct non-medical cost (e.g. out of pocket costs for travel expenses) and on the costs associated with presenteeism for influenza in the U.S. We also chose not to stratify our results into high/low risk individuals as data was not always available to inform input parameters for risk groups separately. Finally, although we projected our results using the 2015 population, our results should be viewed as an estimate of the average influenza economic burden, as in any given season results will vary substantially dependent on the circulating strains and vaccine match.

This study provides an updated estimate of the total economic burden of influenza in the U.S. using new sources that have become available since the previous estimate [5]. Although we found a lower total cost than previously estimated, our results confirm that influenza is responsible for a substantial economic burden to the healthcare system and to society. The high cost of influenza illness suggests that further efforts are required to increase influenza vaccination uptake in the U.S. to help reduce this burden.

Potential conflict of interests

M.S. Stockwell was a co-investigator but received no financial support for an unrelated, investigator-initiated grant from the Pfizer Medical Education Group.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.05.057.

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