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REVIEW

The Cost of Seasonal Influenza: A Systematic Literature Review on the Humanistic and Economic Burden of Influenza in Older (≥ 65 Years Old) Adults

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ABSTRACT

Introduction: Adults aged $\geq$ 65 years contribute a large proportion of influenza-related hospitalizations and deaths due to increased risk of complications, which result in high medical costs and reduced health-related quality of life (HRQoL). Although seasonal influenza vaccines are recommended for older adults, the effectiveness of current vaccines is dependent on several factors including strain matching and recipient demographic factors. This systemic literature review aimed to explore the economic and humanistic burden of influenza in adults aged $\geq$ 65 years.
Methods: An electronic database search was conducted to identify studies assessing the economic and humanistic burden of influenza, including influenza symptoms that impact the HRQoL and patient-related outcomes in adults aged $\geq$ 65 years. Studies were to be published in English and conducted in Germany, France, Spain, and Italy, the UK, USA, Canada, China, Japan, Brazil, Saudi Arabia, and South Africa.
Results: Thirty-eight studies reported on the economic and humanistic burden of influenza in adults aged $\geq$ 65 years. Higher direct costs were reported for people at increased risk of influenza-related complications compared to those at low risk. Lower influenza-related total costs were found in those vaccinated with adjuvanted inactivated trivalent influenza vaccine (aTIV) compared to high-dose trivalent influenza vaccine (TIV-HD). Older age was associated with an increased occurrence and longer duration of certain influenza symptoms.
Conclusion: Despite the limited data identified, results show that influenza exerts a high humanistic and economic burden in older adults. Further research is required to confirm findings and to identify the unmet needs of current vaccines.

Keywords: Burden of disease; Health-related quality of life; Older adults; Economic burden; Costs; Influenza; Humanistic burden

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Key Summary Points

- Fewer humanistic burden studies were identified in this systematic literature review (SLR), making it apparent that further research is needed to confirm findings.
- Limited focus by the National Immunization Technical Advisory Groups (NITAGs), health technology assessments (HTAs), and internationally recognized organizations, including the World Health Organization (WHO), on patient perspectives might explain the lack of humanistic evidence identified in this SLR.
- Results from two studies showed that influenza-related direct costs were greater in high-risk groups, particularly those with comorbidities.
- Influenza-related direct costs appeared to be unrelated to an increasing age in older adults, which may be due to a state-covered care for this age group.
- The limited body of literature identified showed that the burden of influenza in older adults persists, despite available vaccination.

INTRODUCTION

Influenza is a respiratory infection associated with a significant clinical, humanistic, and economic burden worldwide [1]. Approximately five million cases of severe illness and up to 640,000 deaths are caused by influenza each year [2, 3]. Adults aged ≥ 65 years are at an increased risk of severe influenza symptoms and development of serious complications as a result of chronic comorbidity and immunosenescence, a deterioration of the immune system due to aging [2]. The most common secondary infection is pneumonia, with possible complications including edema, hyperemia, hemorrhaging, consolidation, and formation of pus in the lung [4]. Secondary infections associated with influenza A viruses can be particularly harmful [4]. As such, older adults account for a large proportion of influenza-related healthcare resource utilization (HCRU) including hospitalization, which is associated with high medical costs [2, 5]. Studies have shown that overall hospital admissions of older adults can have a major impact on their health-related quality of life (HRQoL) and cause psychological distress such as anxiety [6, 7]. In addition, the presence of an underlying medical condition further lowers the HRQoL in both outpatients and inpatients [8].

HRQoL instruments and patient reported outcome (PRO) questionnaires including the EuroQoL 5D (EQ-5D), or disease-specific questionnaires such as the inFLUenza Patient Reported Outcome (FLU-PRO©) diary and the influenza intensity and impact questionnaire™ (FluiiQ™), measure limitations in daily life, impact on daily activities and emotions, symptom intensity, signs/symptoms across body systems, and emotional implications [9–11]. In order to assess combined morbidity/HRQoL and mortality outcomes, measures such as disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs) can be used [12]. Influenza-specific evidence suggests that infection reduces HRQoL, which has a significant impact on healthcare systems and populations [12, 13].

As a result of their risk status, the World Health Organization (WHO) recommends annual influenza vaccination in adults aged ≥ 65 years [14]. Over the past decades, vaccination has become the mainstay of prevention of infectious diseases such as influenza [15, 16]. Seasonal influenza vaccination helps to prevent infection-related decline in HRQoL, while relieving healthcare and social systems by reducing HCRU caused by high infection rates and severe infections [15, 16]. Influenza vaccines have evolved with advancements in scientific understanding and technology, from the first inactivated influenza vaccine to egg-derived vaccines (targeting up to four strains), through to adjuvant and recombinant vaccines which use different dose formulations (standard and high doses) [15–17]. Despite the ongoing evolution of vaccines, influenza continues to exert a significant economic and humanistic burden worldwide [1–6].

A systematic literature review (SLR) was conducted to characterize the clinical, humanistic, and economic burden of influenza in adults ≥ 65 years. The findings of the clinical burden SLR have been previously reported [18]. Here, we report the humanistic, considering the impact of influenza on a patient's HRQoL, daily activities, and caregiver health and/or QoL, and economic findings, including direct and indirect costs associated with influenza.

METHODS

Search Strategy

A search was conducted via the OVID platform using unique search terms specific to each of the five electronic databases searched (Embase, Medline, Econlit, PsycINFO, and Evidence-Based Medicine Reviews). The search was conducted in line with the Cochrane handbook for SLRs, following the 2020 PRISMA statement [19, 20]. Identified studies were included if they met the eligibility criteria, reporting data which describes the humanistic or economic burden of influenza in the population aged ≥ 65 years, and were published in English, between January 1, 2012 and February 9, 2022 (Supplementary Table S1). Studies were contained to a 10-year period to capture the most relevant and timely cost data.

The search used terms specifying disease, direct/indirect costs of disease, societal costs, HCRU, impact and duration of long-term symptoms/complications, and HRQoL including measures such as FLU-PRO© and FluiiQ™. The search strategy used key terms in a combination of free-text searching (multipurpose terms) and "subject headings" (common descriptive terms assigned to publications as part of the database indexing, which negated the need for multiple synonyms for each search term and ensured the most relevant literature was identified and reviewed). Search strings used appropriate Boolean operators so relevant primary literature was identified.

Although influenza is considered a significant public health challenge, many countries have substantial differences in disease surveillance infrastructure, testing practices and reporting, healthcare services and administration. As the aim of this review was to assess the global burden of influenza, the authors carefully considered specific countries of interest to represent a variation in geographic, cultural, and economic settings. Recognizing that there are substantial differences in global influenza surveillance infrastructure, testing practices and reporting, healthcare services, and administration, we carefully selected countries in disparate regions to achieve a considered global overview including the following target countries: France, Germany, Italy, and Spain (EU4), the UK, USA, Canada, China, Japan, Brazil, Saudi Arabia, and South Africa, with appropriate representation from all WHO regions.

This review was based on previously conducted studies and did not consider any new studies with human participants or animals performed by any of the authors.

Supplementary Searches

Database searches were supplemented by conducting a manual bibliography check of relevant SLRs and cost-effectiveness models (CEMs) that were identified in the search.

To capture a comprehensive evidence base, conference proceedings from January 1, 2020 that have not been indexed in OVID were also searched. The following conference proceedings were selected on the basis of the likelihood and relevance of topic area and subject matter: The International Society for Pharmacoeconomic and Outcomes Research (ISPOR), European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), American Thoracic Society (ATS), and IDWeek (joint annual meeting of the Infectious Diseases Society of America [IDSA], Society for Healthcare Epidemiology of America (SHEA), the HIV Medical Association [HIVMA], the Pediatric Infectious Diseases Society [PIDS], and the Society of Infectious Diseases Pharmacists [SIDP]).

Study Eligibility Criteria

Studies were screened against the patient, intervention, comparison, outcome, time, and study design (PICOTS) criteria outlined in Table 1. To accurately report the burden in adults ≥ 65 years, studies were strictly limited to those reporting age ranges above the 65-year cutoff. Studies reporting exclusively on pandemic influenza data were excluded to ensure only the burden of seasonal influenza was identified. The search time spanned the outbreak and height of the COVID-19 pandemic. Data reporting influenza and COVID-19 co-infection were excluded because of the novel nature of COVID-19 and unknown effects of co-infection. The objective of this SLR was not to quantify overall vaccine effectiveness and therefore results of studies reporting on vaccine effectiveness have not been reported within this manuscript.

Study Selection and Data Extraction

Study Selection

Two independent reviewers conducted abstract and full-text screening based on the prespecified eligibility criteria. Any discrepancies were resolved by discussion or involvement of a third senior reviewer.

Data Extraction

Data were extracted by one reviewer and quality checked by a second reviewer, with discrepancies resolved by discussion or involvement of a third senior reviewer. Data were extracted into a bespoke data extraction form in Microsoft Excel, which was designed to capture all relevant aspects and outcomes of the studies outlined in Table 1. For each of the included studies, the following information was collated: publication information, study characteristics, population characteristics, and outcomes of interest.

Quality Assessments for Study Bias

All studies were subject to a risk of bias assessment to understand the strength of study findings. The risk of study bias was assessed independently by two reviewers, in accordance with the Critical Appraisal Tools developed by JBI Systematic Reviews [21]. Reviewers selected the relevant checklist on the basis of the study type (Supplementary Tables S2–S7).

RESULTS

Summary of Results

A comprehensive search of electronic databases and gray literature searches identified 6025 influenza burden publications after deduplication. Through abstract and full-text screening, 5889 publications were excluded, leaving 136 publications eligible for extraction. Sixteen additional studies were identified through manual bibliography checks of relevant SLRs and CEMs (Supplementary Fig. S1). Of the 152 studies identified that reported data on the burden of influenza, 38 reported data on the humanistic and economic burden of influenza, as well as influenza symptoms. The focus of this manuscript was the economic cost burden and therefore the 11 studies reporting on HCRU have not been reported here (studies detailed in Supplementary Table S8). Influenza symptom studies were included to identify those that assess the impact of influenza on the HRQoL. Studies reporting on clinical burden have been reported elsewhere [18].

Of all included studies, four were assessed to have a high risk of bias due to uncertainty in measurement of validity and reliability [5], lack of required analyses [22], lack of generalizability [23], and inadequate participant allocation methods [24]. Full risk of bias assessments are reported in Supplementary Tables S9–S14.

Study Characteristics

A breakdown by study type and region in which the 28 included studies were conducted is presented in Supplementary Table S15. The majority of studies identified reported on the economic burden of influenza (n = 18) and were conducted in Europe (n = 13), followed by the

Table 1 PICOTS criteria

Study characteristics	Inclusion criteria	Exclusion criteria
Patient population	People aged ≥ 65 years with laboratory confirmed seasonal influenza or symptomatic ILI	Studies reporting data from people aged < 65 years
		Studies reporting data from people without influenza or symptomatic ILI
		Studies reporting data from people with pandemic influenza
		Studies reporting data from people co-infected with influenza and COVID-19
Interventions	Any/none	N/A
Comparisons	All	N/A
Outcomes	Humanistic	N/A
	QALYs/QALDs and HRQoL	
	Patient satisfaction and preference	
	Influenza-specific PROs	
	Impact on daily living	
	Functional decline	
	Transition to assisted care	
	Impact of long-term symptoms/complications	
	Time to return to baseline	
	Caregiver reported symptoms, QoL, and HRQoL	
	Economic	N/A
	Office/outpatient/ER visits	
	Incidence and duration of hospital/ICU stays	
	Pharmacy costs	
	Diagnosis/laboratory testing	
	Short- and long-term care	
	Progression to secondary infection	
	Absenteeism for patients and caregivers	
	Transition to assisted care	
	Societal costs of strain mismatch	
	Differences between influenza vaccinated and non-vaccinated individuals	
Time frame	Studies published from January 2012 to February 2022	N/A

Table 1 continued

Study characteristics	Inclusion criteria	Exclusion criteria
Study design	Study types to be included are:	Study types to be excluded are:
	RCTs	Editorials
	Non-randomized interventional studies	Case studies
	Observational studies	Letters to journals
	SLRs and meta-analyses	Non-systematic literature reviews
		Conference minutes
Countries	France, Germany, Italy, Spain, UK, USA, Canada, China, Japan, Brazil, Saudi Arabia, South Africa	All other countries
Other	Human studies	Animal studies
	English language	Non-English language

ER emergency room, *HRQoL* health-related quality of life, *ICU* intensive care unit, *ILI* influenza-like illness, *N/A* not applicable, *PRO* patient reported outcome, *QALD* quality-adjusted life day, *QALY* quality-adjusted life year, *QoL* quality of life, *RCT* randomized controlled trial, *SLR* systematic literature review, *UK* United Kingdom, *USA* United States

Americas (n = 12). Study periods ranged from 2003 to 2020.

Humanistic Burden

Limited data on the humanistic burden of influenza in people aged ≥ 65 years were identified through this SLR (n = 10). As a result of the heterogeneity across studies in reporting humanistic burden outcomes, outcomes were categorized according to symptoms, QALYs and/or LYs lost, or PROs. Although seven studies reported on influenza symptoms, only one study focused on the impact of long-term symptoms on HRQoL in adults aged ≥ 65 years [25].

Patient Reported Outcomes and Measures

Two studies were identified reporting influenza-related PROs [26, 27]. One of these studies, conducted across several countries worldwide, used the FluiiQ™ in adults aged ≥ 65 years [26]. The FluiiQ™ was used to compare the impact of AS03-adjuvanted inactivated trivalent influenza vaccine (AS03-TIV) or trivalent influenza vaccine (TIV) seasonal vaccination on influenza symptoms [26]. The FluiiQ™ is scored from 0 (none) to 3 (severe) across symptom intensity and impact (including daily activities, impact on others, and impact on emotions). Results indicate that older adults who received the AS03-TIV vaccination had lower overall mean scores (1.50 [standard error [SE] 0.04] vs 1.64 [SE 0.04]), which suggests improved HRQoL [26]. Similar results were observed for the impact on daily activities rates, with lower mean rates for the AS03-TIV cohort than for the TIV cohort (1.27 [SE 0.1] vs 1.54 [SE 0.1]) [26]. In contrast, mean respiratory symptoms, impact on emotions (0.89 [SE 0.05] vs 1.02 [SE 0.06]), and impact on relationships scores (0.67 [SE 0.05] vs 0.74 [SE 0.47]) were similar with AS03-TIV vs TIV [26]. Additionally, influenza tended to be less severe in those who received AS03-TIV [26]. However, the minimal important difference (MID) (threshold set at > 7.0% difference) was achieved only for impact on activities (mean 9.0%) [26].

In addition, an Italian study assessed the proportion of people reporting change in their daily routine during an ILI episode (e.g., staying off work) [27]. The study showed that across the influenza seasons from 2012 to 2015, approximately 27.7% of patients aged ≥ 65 years experienced a change in their daily routine [27].

QALYs and Life Years Lost Measures

QALYs were used to measure differences in populations based on their risk of influenza-related complications [28] and antiviral drug use [24] in two studies, one conducted across 15 European countries [24] and one in the USA [28].

Total QALYs lost were assessed in a US Veterans Affairs population aged ≥ 65 years with unconfirmed influenza at low or high risk of influenza-related complications [28]. The high-risk group was defined as people with chronic cardiac, pulmonary, renal, metabolic, liver, or neurological diseases; diabetes mellitus; hemoglobinopathies; and/or immunosuppressive conditions and malignancy [28]. Results showed that people at high risk of influenza-related complications had greater a QALYs loss compared to those at low risk of complications (N = 38.2 [95% CI 33.8–42.6] vs N = 3.1 [95% CI 2.4–3.7]) [28].

When the impact of antiviral treatment was assessed, using oseltamivir in usual care among patients with ILI aged ≥ 65 years, the use of oseltamivir positively impacted patients QALYs [24]. After 14- and 28-day follow-up, patients treated with oseltamivir gained a total of 0.0006 QALYs (range 0.0002–0.0010) and 0.0008 QALYs (range 0.0003–0.0014), respectively [24]. These gains in QALYs were deemed statistically significant, although a p value was not reported [24].

Additionally, a South African study assessed the life years (LY) lost in older adults aged ≥ 65 years at risk of influenza-associated illness due to their age [29]. Across influenza seasons 2013 to 2015, a total of 35,601 (95% CI 23,853–47,349) LY were lost in adults aged ≥ 65 years, due to influenza-associated disease [29].

Influenza Symptoms and Associated Impact on QoL

Studies reporting on influenza-associated symptoms were also captured in this SLR. Overall, influenza and influenza-like illness (ILI) associated symptoms in people aged ≥ 65 years were reported in seven studies [5, 25, 30–34]. However, only one of the studies identified assessed the impact of influenza symptoms on the HRQoL in adults aged ≥ 65 years [25]. Influenza-related symptoms captured in this review are reported in Table 2.

An increase in age appeared to have an impact on symptom manifestation. One study reported that older age appeared to be attributed to longer duration of symptoms in people with influenza B infections [25]. An additional study reported that the occurrence of altered mental status/confusion in people aged ≥ 65 years with influenza increased with age [31]. In people aged 65–74 years, 75–-84 years, and ≥ 85 years with influenza infection, 14.3%, 20.7%, and 23.0% of people presented an altered mental status/confusion, respectively [31]. A final study stated that headaches were significantly reduced in vaccinated people aged ≥ 65 years when compared to those unvaccinated [32]. No statistically significant decrease was observed for other symptoms assessed (adenopathy, asthenia, bronchitis/bronchiolitis, conjunctivitis, cough, dyspnea, expectoration, fever, gastrointestinal symptoms, myalgia, otitis/earache, pharyngitis, rhinitis, and shivering) [32].

Economic Burden

Eighteen studies reported the economic burden of seasonal influenza in adults aged ≥ 65 years [22, 28, 29, 35–49]. The majority of studies (n = 10) were conducted in the USA (Supplementary Table S16) [28, 35–40, 47–49]. Very few studies were conducted in other countries of interest, including Spain (n = 2) [44, 45], China (n = 1) [41], France (n = 1) [42], Germany (n = 1) [43], the UK (n = 1) [22], Japan (n = 1) [46], and South Africa (n = 1) [29]. No studies were identified for Canada, Brazil, or Saudi Arabia.

Table 2 Influenza symptoms contributing to overall humanistic burden

Country	Author	Key outcomes
USA	van Wormer, 2014 [34]	The symptom severity scores (higher scores indicate greater perceived severity) for individuals vaccinated against influenza vs unvaccinated individuals for the following symptoms were: Cough 2.41 vs 2.80 Fatigue 2.25 and 2.50 Fever 1.70 vs 2.63 Headache 1.58 vs 2.13 Muscle ache 1.93 vs 2.43 Nasal congestion 1.89 vs 2.13 Sore throat 1.67 vs 2.57 Wheezing 1.85 vs 1.78
Europe: Belgium, England, France, Germany, Italy, Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, Wales	Bruyndonckx, 2020 [25]	*Duration of symptoms after initial consultation in influenza-positive adult patients with acute cough:* Reported symptoms in patients with influenza A and B included cough, shortness of breath, wheeze, runny nose, disturbed sleep, interference with normal activities or work, chest pain, fever The mean duration of symptoms in people with influenza B ranged from 4 to 12 days, with the longest-lasting symptoms being cough and runny nose, and the shortest being chest pain • Interference with normal activities and work lasted for a mean value of 5 days (IQR 4–6 days) The mean duration of symptoms in people with influenza A ranged between 2 and 15 days, with the longest-lasting symptom being cough and the shortest being fever • Interference with normal activities and work lasted for a mean value of 8 days (IQR 7–9 days)

Table 2 continued

Country	Author	Key outcomes
Spain	Casado, 2016 [30]	The proportions of hospitalized patients who had received the influenza vaccination presenting with certain symptoms were: • Cough 82.1% • Sore throat 14.1% • Shortness of breath 82.6% • Fever 75.7% • Headache 20.8% • Myalgia 26.6% • Malaise 70.9%
	Gonzalez, 2016 [5]	The proportion of non-specific symptoms such as agitation or disorientation was 16%. The proportion of dyspnea was 84%
	Czaja, 2019 [31]	Symptoms at the time of hospital admissions included cough, fever, shortness of breath/respiratory distress, congested/runny nose, myalgia/muscle aches, nausea/vomiting, wheezing, chest pain, altered mental status/confusion, diarrhea, sore throat, headache, rash, conjunctivitis/pink eyes, and seizures In patients aged 65–74 years, 75–84 years, and $\geq$ 85 years, the three most frequently reported symptoms were cough (2234–3041 cases), fever (1754–2202 cases), shortness of breath/respiratory distress (1662–2011 cases) Altered mental status/confusion was detected in: • 401 (14.3%) patients aged 65–74 years • 773 (20.7%) patients aged 75–84 years • 921 (23.0%) patients aged $\geq$ 85 years Occurrence increased with age ($P < 0.01$)

Table 2 continued

Country	Author	Key outcomes
France	Mosnier, 2017 [32]	Symptoms reported included adenopathy, asthenia, bronchitis/bronchiolitis, conjunctivitis, cough, dyspnea, expectoration, fever, gastrointestinal symptoms, headache, myalgia, otitis/earache, pharyngitis, rhinitis, and shivering
		Headaches were significantly reduced in vaccinated people compared to non-vaccinated people (OR 0.69 [95% CI 0.48–0.98, $P < 0.05$]). The proportion of people with headache was 61.7% in vaccinated and 70.9% in non-vaccinated people. No other symptoms were reduced significantly
	Regis, 2014 [33]	Among people with community-acquired ILI, 85.2%, 73.7%, and 12.3% had cough, fever (> 37.88 °C), and sore throat
		Among people with hospital-acquired ILI, 88.2%, 67.6%, and 14.7% had cough, fever (> 37.88 °C), and sore throat

C Celsius, *CI* confidence interval, *ILI* influenza-like illness, *IQR* interquartile range, *OR* odds ratio, *USA* United States

All studies reported on direct costs [22, 28, 29, 35–49]; however, only four studies presented indirect cost results [23, 28, 46, 47]. Economic study characteristics are presented in Supplementary Table S17.

Direct Costs of Influenza

All 18 studies reported on influenza-related direct costs in adults aged ≥ 65 years in eight different countries from 2010 to 2020 (Table 3) [22, 28, 29, 35–49].

Results from two studies showed that influenza-related direct costs were higher in patients aged ≥ 65 years that were considered at high risk of severe influenza or influenza-related complications due to comorbidities compared to those at low risk [28, 41]. Moreover, studies that focused on different age groups within the "older age" category did not show a clear correlation between higher direct costs and increasing age [36, 43, 44].

Focusing on vaccination results from several studies, we note that people aged ≥ 65 years who received an inactivated trivalent influenza vaccine (aTIV) had lower influenza-related total costs than those who received a high-dose trivalent influenza vaccine (TIV-HD) [37–39]. This was driven by the relative vaccine effectiveness against HCRU. An additional study reported slightly higher total influenza-related costs for those who received aTIV than for those who received TIV-HD [40]. Comparing hospitalization costs between vaccinated and unvaccinated people aged ≥ 65 years showed that costs for unvaccinated people were slightly higher (vaccinated €1,152,333 vs unvaccinated €1,184,808 [2015]) [45].

Only one study reported on patient out-of-pocket costs/co-payments. Results of this US-based study showed that in 2018 mean out-of-pocket costs/co-payments were the highest in people aged 65–74 years ($1065 [SD 807]) and decreased in higher age groups (75–84 years = $1000 [SD 790]; ≥ 85 years = $896 [SD 813]) [35]. In addition, mean patient out-of-pocket/co-pay costs were slightly higher for

Table 3 Direct costs of influenza results

Country	Author	Key outcomes
Inpatient costs		
USA	Belk, 2022 [49]	Median costs of inpatient treatment: $31,237 (IQR 40,260, $P < 0.0001$)
	Lee, 2020 [36]	Median total cost of first hospital stay by age group: • 64–79 years = $5789.50 (IQR 5454.50, $P < 0.0001$) • $\geq$ 80 years = $6220.30 (IQR 5556.60, $P < 0.0001$) Median total cost per day by age group: • 64–79 years = $1776.70 (IQR 1084.2, $P < 0.0001$) • $\geq$ 80 years = $1627.60 (IQR 930.2, $P < 0.0001$)
	Putri, 2018 [47]	Estimated direct cost (in million) for: • Ill but not medically attended = $9.81 • Office-based outpatient visits = $16.24 • Emergency department = $70.86 • Hospitalization = $1273.73 • Deaths = NR • Total = $1370.64
	Near, 2020 [48]	Mean influenza-related hospitalization cost $18,770
France	Lemaitre, 2022 [42]	Total cost (€ million [M]) of excess influenza-attributable hospitalizations was reported across eight influenza seasons: • 2010–11: 13.5M • 2011–12: 120.9M • 2012–13: 105.2M • 2013–14: 34.8M • 2014–15: 155.5M • 2015–16: 74.8M • 2016–17: 186.4M • 2017–18: 173.6M

Table 3 continued

Country	Author	Key outcomes
Germany	Goettler, 2022 [43]	Mean (SD) hospitalization costs per person from 2010 to 2019 were reported by age group: • 70–79 years: €4275 (9912) • 80–89 years: €3489 (5952) • ≥ 90 years: €2903 (2230) Median (IQR) hospitalization costs per person from 2010 to 2019 were reported by age group: • 70–79 years: €2408 (1578–2741) • 80–89 years: €2613 (1629–2771) • ≥ 90 years: €2688 (1722–2858)
Spain	de Miguel, 2022 [44]	Median and total costs (€) for hospitalizations were reported by age group: • 65–74 years: €4373.48; €4,872,057.10 • > 74 years: €3951.18; €12,149,892.20
	Torner, 2017 [45]	Hospitalization costs (€ 2015) for unvaccinated patients per annum were €1,184,808 and €1,152,333 for vaccinated patients
UK	Moss, 2020 [22]	Cost per influenza admission between September 2017 and March 2018 were: • £3023.70 in those aged 65–74 years (n = 7320) • £3506.06 in those aged ≥ 75 years (n = 16,060) Cost per influenza admission between September 2018 and March 2019 were: • £3103.75 in those aged 65–74 years (n = 4975) • £3675.91 in those aged ≥ 75 years (n = 8495) Cost per admission LOS (12.55 days) between September 2017 and March 2018 were: • £3100 in those aged 65–74 years (n = 7320) • £3500 in those aged ≥ 75 years (n = 16,060)

Table 3 continued

Country	Author	Key outcomes
Outpatient costs		
USA	Young-Xu, 2017 [28]	Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, ED visit: • Low-risk group = $176 (thousand) (95% CI 101–251) • High-risk group = $3968 (thousand) (95% CI 3314–4623) Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, hospitalization only: • Low-risk group = $57 (thousand) (95% CI 0–175) • High-risk group = $28,909 (thousand) (95% CI 24,112–33,765) Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, hospitalization with extended care: • Low-risk group = $6 (thousand) (95% CI 0–20) • High-risk group = $5168 (thousand) (95% CI 4167–6232)
	Putri, 2018 [47]	Estimated direct/indirect/total cost (in million) for: • Ill but not medically attended = $9.81/$266.67/$276.48 • Office-based outpatient visits = $16.24/$15.60/$31.85 • Emergency department = $70.86/$11.42/$82.28 • Hospitalization = $1273.73/$40.45/$1314.18 • Deaths = NR/$710.1/$710.1 • Total = $1370.64/$1044.24/$2414.88
Spain	de Miguel, 2022 [44]	Total costs (€) for referrals were reported by age group: • 64–74 years: €2,308,881.60 • > 74 years: €1,502,578.08 Total costs (€) for visits were reported by age group: • 64–74 years: €2,956,829.17 • 74 years: €1,817,988.08

Table 3 continued

Country	Author	Key outcomes
Out-of-pocket costs		
USA	Chua 2021 [35]	Mean patient out-of-pocket/co-pay by age group in 2018: • 65–74 years = $1065 (SD 807) • 75–84 years = $1000 (SD 790) • ≥ 85 years = $896 (SD 813) Mean patient out-of-pocket/co-pay by sex (2018 USD): • Male = $971 (SD 790) • Female = $999 (SD 806)
Total costs		
USA	Levin, 2021 [37]	Predicted mean annualized cost per patient by vaccine type: • aIIV3 (*n* = 798,987) = $22.98 (95% CI 19.3–27.2) • HD-IIV3e (*n* = 1,655,979) = $22.04 (95% CI 19.7–24.5)
	Pelton, 2021 [38]	Mean annual influenza-related total costs per person by vaccine type: • TIV-HD (*n* = 561,243) = $18.74 (95% CI 17.4–20.6) • aTIV (*n* = 561,243) = $17.28 (95% CI 15.9–18.9)
	Pelton, 2020 [39]	Mean annual influenza-related total cost per person by vaccine type: • aTIV = $28.21 (95% CI 24.6–32.4) • TIV-HD = $31.77 (95% CI 27.7–36.3)
	Postma, 2020 [40]	Mean annualized influenza-related costs per patient by vaccine type: • aTIV = $23.75 • TIV-HD = $21.79
China	Zhou, 2013 [41]	The median overall costs (USD 2010) for patients at high risk of severe influenza were $2340 (*n* = 23,080) vs low-risk patients median cost of $1295 (*n* = 2553)
Japan	Sruamsiri, 2017 [46]	Mean overall costs (USD) were reported for procedures (6546 [SD 5793]) and DPC (5526 [SD 5296])
South Africa	Tempia, 2020 [29]	Mean cost per illness episode was reported as $31 (95% CI 11–64) USD in 2013–2015 in South Africa
		Mean overall costs was reported as $15,723,585 USD (95% CI 5,788,357–32,915,907) in patients aged ≥ 65 years

aTIV *adjuvanted trivalent influenza vaccine, CI* confidence interval, *DPC* diagnosis procedure combination, *ED* emergency department, *IQR* interquartile range, *LOS* length of stay, *M* million, *NR* not reported, SD standard deviation, *TIV-HD* high dose trivalent influenza vaccine, *UK* United Kingdom, *USD* United States dollar women ($999 [SD 806]) than for men ($971 [SD 790]) [35].

Indirect Costs of Influenza

The indirect economic cost burden of influenza was reported by four separate studies [23, 28, 46, 47]. A retrospective cross-sectional study conducted in Japan presented the indirect factors contributing to total healthcare cost in patients with influenza from March 2014 to April 2015 [46]. For individuals aged ≥ 65 years authors calculated an annual indirect cost of $854 US dollars (USD) (95% CI $580–1127). A structural equation modeling framework was used to assess the relationship between direct effects (total hospitalization cost) and indirect effects (length of stay). Length of stay was considered an intermediate effect and used to derive an indirect cost from total hospitalization costs [46].

A South African study conducted between 2013 and 2015 estimated the mean annual direct and indirect costs of absenteeism due to influenza-associated illness [29]. For individuals aged ≥ 65 years, the mean absenteeism rate for patients and caregivers (aged 20–64 years) per illness episode was 0.5 days (95% CI 0.2–1.6), resulting in a total of 601,592 (95% CI 294,085–1,016,692) days between 2013 and 2015 [29]. When compared to other risk groups within the study, individuals aged ≥ 65 years were the eighth largest contributor to annual influenza-associated absenteeism, between 2013 and 2015; individuals aged ≥ 6 months with HIV and/or tuberculosis and/or underlying medical conditions, including pregnant women, accounted for greatest absenteeism rate [29].

A USA-specific study reported losses in productivity for a US Veterans Affairs population aged ≥ 65 years [28]. The estimated annual cost for lost productivity due to influenza-attributed ED visits, hospitalization (only), and hospitalization with extended care was $229,000, $350,000, and $105,000 over five influenza seasons, respectively [28]. The cost for lost productivity due to influenza-attributable mortality was $14 million over the same time period (2010–2014) [28]. Additionally, the study found that in those aged ≥ 65 years, the majority of productivity losses due to influenza-attributed work absenteeism were the result of hospitalizations (only), hospitalizations with extended care, and mortality (56%, 53%, and 52%, respectively) [28].

An additional US study estimated the indirect cost of influenza infection in older adults aged ≥ 65 years based on the total days/hours of lost (paid) work due to influenza (Supplementary Table S17) [47]. The total indirect cost for influenza infection in 2015 was reported at $1044.24 million [47]. The biggest contributors to the total cost were death and infection classified as "illness not medically attended" with $710.1 million and $266.67 million, respectively [47]. Moreover, the base case analysis of this study resulted in an estimated 1,756,517 days of productivity loss (excludes from death) due to influenza [47].

DISCUSSION

The aim of this SLR was to characterize the humanistic and economic burden of influenza in older adults aged ≥ 65 years to reveal potential unmet needs in this population. Despite the global impact of influenza, only 38 studies were captured in this review that reported the economic or humanistic burden, or the impact of influenza-associated symptoms on patients' HRQoL in adults ≥ 65 years. This may suggest that the humanistic and economic burden of influenza is underrecognized or underreported and warrants further investigation. The majority of economic studies reported direct medical costs, whereas limited information was available on indirect costs. Most humanistic burden studies identified reported on influenza symptoms; however, only one assessed the direct impact of symptoms on HRQoL. In addition, one PRO study utilized an influenza-specific PRO measure (FluiiQ™) to assess the impact of vaccination on influenza symptoms and HRQoL [26]. As per the inclusion criteria, this SLR was designed to capture data on long-term influenza symptoms/complications and their impact on HRQoL. While we identified data on symptom occurrence, severity, and duration, very minimal data were identified in relation to long-term symptoms.

As a result of heterogeneity in study design, outcomes, and population characteristics presented, it was not possible to make direct comparisons between study results. Of the 10 humanistic burden studies that were identified, one study reported that an increased occurrence and longer duration of certain influenza symptoms was associated with older age [31]. These findings may be a result of independent factors such as frailty or functional status [31]. A separate study found that influenza-related headaches were significantly reduced in vaccinated people [32]. However, a similar reduction was not seen in other symptoms [32]. This could be explained through the study design, focusing only on patients who consulted their general practitioner (GP), not considering the proportion of patients who went directly to hospital with more severe symptoms [32]. It is apparent from these results that further research is needed to confirm findings.

Assessment of vaccine efficacy and comparison of vaccinated vs non-vaccinated populations using specific humanistic burden measures like PROs and QALYs may help to direct future vaccine recommendations and support health technology assessments (HTAs). National Immunization Technical Advisory Groups (NITAGs), such as the US CDC Advisory Committee on Immunization Practices (ACIP), utilize randomized controlled trial (RCT) data to evaluate the benefit of vaccines to inform their seasonal influenza vaccination recommendations [50, 51]. However, limited evidence is available to suggest that humanistic data are used to inform recommendations. In addition, the WHO 2021/22 position paper stated that countries should base their decision about switching influenza vaccines on national disease and economic burden data as well as the availability of different products [52]. The assessment of humanistic burden, in terms of people-focused perspectives and elements, was not mentioned [52]. Moreover, vaccine HTAs are largely driven by efficacy, safety, and cost-effectiveness analyses. The limited focus by NITAGs, HTAs, and internationally recognized organizations on people and patient perspectives might explain the lack humanistic evidence identified in this SLR [53]. Nevertheless, these findings highlight the importance of economic data in the evaluation of and recommendations for influenza vaccines.

While this SLR was intended to capture the economic burden of influenza across several countries, most studies were conducted in the USA, with limited evidence reported in other countries. No economic burden studies were identified for Canada, Brazil, or Saudi Arabia. This was an unexpected finding considering the WHO stated in 2021 that economic evaluations, particularly in high-income countries, had increased in the past 20 years [52]. The definition of “older adults” as those aged $\geq$ 65 years used in the eligibility criteria of this SLR may be a plausible explanation for the limited number of studies identified. Although annual influenza vaccination is recommended specifically for older adults $\geq$ 65 years old by official bodies in countries like the UK or USA [54, 55], other countries might expand their recommendations including ages below 65 years, leading to a broader age classification in this research field. Results show that despite ongoing research there is a need to further investigate the global economic burden of influenza in older adults, particularly in non-US countries.

Results from two studies captured in this SLR showed that influenza-related direct costs were greater in high-risk groups, particularly in those with comorbidities [28, 41]. Nevertheless, study limitations such as selection bias due to small sample sizes should be considered when extrapolating results to the general population [28, 41]. Findings suggest that further studies are needed that include data from larger population sample sizes, including provincial as well as local hospitals in order to reduce the selection bias towards more severe cases which may attend provincial rather than local hospitals. In addition, increasing age in older adults did not appear to be associated with higher influenza-related direct costs, which was observed across several studies [36, 43, 44]. However, state-covered care for the oldest adult age group may be a confounding factor to this finding. As these results are from different countries, including the USA, Germany, and Spain, a comparison of populations with similar healthcare systems is needed.

Two of the four indirect cost studies identified in this SLR utilized absenteeism to characterize the indirect cost of influenza in older adults [28, 29]. One of these studies reported absenteeism in patients aged ≥ 65 years, not including absenteeism in their caregivers [28]. As a significant proportion of individuals aged ≥ 65 are likely be retired, this might have led to an overestimation of the economic burden in this age group [28]. In contrast, not including the indirect cost burden of absenteeism in caregivers might have led to an underestimation of the economic burden [28].

Results show that absenteeism data may not be reflective of the indirect economic burden in older adults with influenza. These findings highlight the importance of considering more appropriate measures to characterize the indirect economic burden in this population, such as the need for home care or premature mortality.

This SLR highlighted the paucity of information on the economic and humanistic burden of influenza in adults aged ≥ 65 years, underlining the importance for further research in these areas to quantify the burden of disease. Economic and humanistic data are needed to identify unmet needs of current vaccinations, to guide vaccine recommendations, and to assess the benefit of new treatments, in order to support funding of new vaccines in the older population.

Although limited data were identified in this SLR, results show that influenza is associated with a reduced HRQoL and increased economic burden in older adults. Vaccines are an effective strategy in the prevention of influenza and the associated burden of disease. Currently, egg-derived influenza vaccines are the most frequently distributed type of influenza vaccine worldwide [17]. Nevertheless, these types of vaccines come with limitations [56]. Challenges may occur during production and selection of seasonal and regional influenza vaccine strains, due to genetic changes, referred to as “egg-adapted” changes [57, 58]. These mutations impact the accuracy of the annual vaccine strain selection, which promotes antigen mismatch and reduces vaccine effectiveness [57, 58]. In addition, manufacturing can take up to 6 months, which further challenges the selection of the most predominant circulating strain at the time, promoting antigen mismatch and contributing to an increased burden of disease for patients and healthcare systems [57, 58]. New vaccine technologies may further alleviate this burden. Messenger ribonucleic acid (mRNA) vaccines, a novel vaccine technology that was used during the COVID-19 pandemic, are the latest step in vaccine evolution [1, 56]. mRNA vaccines may provide an effective solution to some limitations of current influenza vaccines. Vaccines with mRNA technology have efficient, fast production processes, without the need for chicken egg or mammalian cells [59]. In addition, mRNA vaccine manufacturing can be held on a larger scale, is more flexible, and rapid, which enables production to start closer to the influenza season when predictions of the most predominant circulating strain are most accurate [1, 56]. This ability of mRNA vaccines to be manufactured more rapidly could allow a rapid and effective response to seasonal and regional variation in circulating influenza strains and could help to address existing issues around influenza strain mismatch. In addition, this technology may allow for the targeting of multiple strains and the identification of potential novel viral epitopes [1, 52]. As such, this latest advancement in vaccine technology may help to provide better protection against influenza infection and further reduce the economic and humanistic burden of influenza. Currently the strains are selected twice annually, once per hemisphere, 6 months in advance by the WHO to allow for sufficient manufacturing time particularly of egg-based vaccines which requires approximately 6 months. Approximately, 100 days is needed to manufacture mRNA-based influenza vaccines allowing for strain selection closed to the start of the influenza season and thus may reduce the likelihood of strain mismatch by a delayed development time and therefore, as such, mRNA technology could potentially have a positive impact on the influenza vaccine effectiveness [60].

Several limitations were associated with this SLR. Besides the geographical limitation, the age restriction applied to the study population potentially resulted in the exclusion of studies in older populations. The PICOTS criteria were designed to include studies with age stratifications reported in the study title or abstract. At full-text stage, only studies reporting data that were explicitly for adults aged ≥ 65 years were included. This may have led to the exclusion of data for older adults with ages ranging below 65 years. However, this age group has the highest burden of disease due to influenza virus and is hence representative to evaluate the humanistic and economic burden of disease. Additionally, the search was refined at full-text screening stage by excluding studies that did not define the population age or used terms such as "older" or "elderly" to describe the population without stating the age. Further, as this review focused on the general population aged ≥ 65 years, more in-depth research is needed to explore health equity between different minority groups within this age group.

Studies were further excluded if they were not conducted in one of the prespecified target countries. Although the countries included were carefully considered for the appropriateness and representativeness of global burden, this may have limited the data identified by this review.

Although the search was designed to capture publications such as RCTs reporting PRO and QALY outcomes, relevant RCTs may have been excluded at the abstract screening phase if humanistic outcomes were not reported in the abstract. Humanistic outcomes are often considered as a secondary outcome and therefore may not be presented in the abstract. Nevertheless, limited evidence identified does indicate a data gap and highlights the need for improvement within this research area, to gain a better insight into people and patient perspectives.

Lastly, this SLR did not identify any studies reporting data regarding post-acute sequalae of influenza. Although, studies assessed the duration of influenza symptoms, there was no particular focus on long-term outcomes in the studies reviewed. Given the increased occurrence and research on this particular outcome as a result of COVID-19, this area might become more important in the future and requires further investigation into the economic and humanistic burden of influenza in adults aged ≥ 65 years.

CONCLUSION

This SLR found that a limited body of published literature available to characterize the humanistic and economic burden of influenza in adults aged ≥ 65 years. However, studies that were identified showed that the burden of influenza persists, despite vaccination. Additional research is needed to further investigate the economic and humanistic burden of influenza in older adults. Doing so could support the development of improved influenza interventions such as mRNA vaccines, which may help to further reduce the significant burden of influenza in older adults.

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Declarations

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