Room for improvement in current influenza vaccines? 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 [?]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. Objective: This systemic literature review aimed to explore the economic and humanistic burden of influenza in adults aged [?]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 [?]65 years. Studies were to be published in English and conducted in Germany, France, Spain, and Italy, United Kingdom, United States, Canada, China, Japan, Brazil, Saudi Arabia, and South Africa. Results: Twenty-five studies reported on the economic and humanistic burden of influenza in adults aged [?]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. Despite the limited data identified for, 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.

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 due to 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 oedema, 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 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, has been shown to further lower the HRQoL in both outpatients and inpatients (8).

HRQoL instruments and patient reported outcome (PRO) 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 that are traditionally used for the assessment of chronic diseases, such as disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs), can be used (12). Several studies utilizing these measures have been conducted in patients with respiratory disease such as influenza and chronic obstructive pulmonary disease (COPD) (10, 11, 13-15). Influenza-specific evidence suggests that infection reduces HRQoL, which has a significant impact on healthcare systems and populations (12, 16).

Due to their risk status, the World Health Organization (WHO) recommends annual influenza vaccination in adults aged [?]65 years (17). Over the past centuries, vaccination has become the mainstay of prevention of infectious diseases, such as influenza (18, 19). 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 (18, 19). 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-dose) (18-20). Despite the ongoing evolution of vaccines, influenza continues to exert a significant economic and humanistic burden worldwide (6, 7, 12, 13, 16).

Currently, egg-derived influenza vaccines are the most frequently distributed type of influenza vaccine worldwide and considered to be the safest and most effective. Nevertheless, these types of vaccines come with limitations (21). Challenges may occur during production and selection of seasonal and regional influenza vaccine strains, due to genetic changes, referred to as "egg-adapted" changes (22, 23). These mutations impact the accuracy of the annual vaccine strain selection, which promotes antigen mismatch and reduces vaccine effectiveness (22, 23). In addition, manufacturing can take up to six 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 (22, 23).

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, 21). Manufactured synthetically, mRNA vaccines allow for a more precise match between the selected antigens and the virus strain targeted (1, 21). 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, 21). 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.

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 (24). Here, we report the humanistic and economic findings.

Materials and 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 (25, 26). 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 to February 9, 2022 (Supplementary Table S1). Studies were contained to a ten-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(c)* , *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.

Many countries have substantial differences in disease surveillance infrastructure, testing practices and reporting, healthcare services and administration. As such, we carefully selected countries in disparate regions in efforts to capture a global overview. These target countries were as followed: France, Germany, Italy, and Spain (EU4), United Kingdom (UK), US, Canada, China, Japan, Brazil, Saudi Arabia, and South Africa.

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 were also searched. The conference proceedings deemed most relevant were: 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 a 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 due to the novel nature of COVID-19 and unknown effects of co-infection.

Study selection and data extraction

Study selection

Two independent reviewers conducted abstract and full-text screening based on the pre-specified 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 were assessed independently by two reviewers, in accordance with the Critical Appraisal Tools developed by JBI Systematic Reviews (27). Reviewers selected the relevant checklist, based on the study type (Supplementary Table S2-S7).

Results

Summary of results

A comprehensive search of electronic databases and gray literature searches identified 6,298 influenza burden publications. Through abstract and full-text screening, 5,916 publications were excluded, leaving 109 publications eligible for extraction. Sixteen additional studies were identified through manual bibliography checks of relevant SLRs and CEMs (Supplementary Figure S1). Of the 125 studies identified that reported data on the burden of influenza, 40 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 14 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. The remaining studies reported on clinical burden and results have been reported elsewhere (24).

Of all included studies, four were assessed to have a high risk of bias due to uncertainty in measurement validity and reliability,(5) lack of required analyses,(28) lack of generalizability,(29) and inadequate participant allocation methods.(30) Full risk of bias assessments are reported in Supplementary Tables S9–S14.

Study characteristics

A breakdown by study type and region in which the 26 included studies were conducted is presented in Supplementary Table S15. The majority of studies identified reported on the economic burden of influenza (n=20) and were conducted in Europe (n=12), followed by the Americas (n=8). Study periods ranged from 2003–2020.

Humanistic burden

Limited data on the humanistic burden of influenza in people aged [?]65 years were identified through this SLR (n=10). Due to 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 (31).

Patient reported outcomes and measures

Two studies were identified reporting influenza-related PROs (32, 33). One of these studies, conducted across several countries worldwide, used the *FluiiQ* in adults aged [?]65 years (32). 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 (32). 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 (32). 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]) (32). 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 (32). Additionally, influenza tended to be less severe in those who received AS03-TIV

(32). However, the minimal important difference (MID) (threshold set at >7.0% difference) was achieved only for impact on activities (mean 9.0%) (32).

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) (33). 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 (33).

QALYs and life years lost measures

QALYs were used to measure differences in populations based on their risk of influenza-related complications (34) and antiviral drug use (30) in two studies; one conducted across 15 European countries (30) and one in the US (34).

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 (34). 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 (34). 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]) (34).

When assessing the impact of antiviral treatment, using oseltamivir in usual care among patients with ILI aged [?]65 years, the use of oseltamivir positively impacted patients QALYs (30). After 14- and 28-days 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 (30). These gains in QALYs were deemed statistically significant, although a p-value was not reported (30).

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 (35). 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 (35).

Influenza symptoms and associated impact on quality of life

Studies reporting on influenza-associated symptoms were also captured in this SLR. Overall, influenza and ILI-associated symptoms in people aged [?]65 years were reported in seven studies (5, 31, 36-40). However, only one of the studies identified assessed the impact of influenza symptoms on the HRQoL in adults aged [?]65 years (31). 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 (31). An additional study reported that the occurrence of altered mental status/confusion in people aged [?]65 years with influenza increased with age (37). 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 (37). A final study stated that headaches were significantly reduced in vaccinated people aged [?]65 years when compared to those unvaccinated (38). 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) (38).

Economic burden

Fifteen studies reported the economic burden of seasonal influenza in adults aged [?]65 years (28, 34, 35, 41-52). The majority of studies (n=7) were conducted in the US (34, 41-46). Very few studies were conducted in other countries of interest, including Spain (n=2) (50, 51), China (n=1) (47), France (n=1) (48), Germany (n=1) (49), the UK (n=1) (28), Japan (n=1) (52), and South Africa (n=1) (35). No studies were identified for Canada, Brazil, or Saudi Arabia.

All studies reported on direct costs (28, 34, 35, 41-52), however, only three studies presented indirect cost results (29, 34, 52). Economic study characteristics are presented in Supplementary Table S15.

Direct costs of influenza

Overall, 15 studies reported on influenza-related direct costs in adults aged [?]65 years in eight different countries (Table 3) (28, 34, 35, 41-52).

Results across several studies showed that there was no clear correlation between higher direct costs and older age groups (41, 42, 49, 50). Results from two additional 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 (34, 47).

Focusing on vaccination results from several studies, 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) (43-45). 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 (46). Comparing hospitalization costs between vaccinated and unvaccinated people aged [?]65 years showed that costs for unvaccinated people were slightly higher (vaccinated: \euro1,152,333 vs unvaccinated: \euro1,184,808 [2015]) (51).

Out-of-pocket expenses associated with influenza

One study showed that mean patient out-of-pocket costs/co-payments in 2018 were the highest in people aged 65–74 years and decreased in higher age groups (41). In addition, mean patient out-of-pocket/co-pay costs were higher for females than for males (41), presented in Table 4.

Indirect costs of influenza

The indirect economic cost burden of influenza was reported by three separate studies (34, 35, 52). 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 (52). For individuals aged [?]65 years authors calculated an annual indirect cost of $854 US dollars (USD) (95% CI: $580-$1,127). 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 (52).

A South African study conducted between 2013–2015 estimated the mean annual direct and indirect costs of absenteeism due to influenza-associated illness (35). It was found that 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 (35). When compared to other risk groups within the study, individuals aged [?]65 years were the eighth largest contributor to annual influenza-associated absenteeism, between 2013–2015 (35).

A US-specific study reported losses in productivity for a US Veterans Affairs population aged [?]65 years (34). 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 (34). The cost for lost productivity due to influenza-attributable mortality was $14 million over the same time period (2010–2014) (34). 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) (34).

Discussion

The aims of this SLR were to characterize the humanistic and economic burden of influenza in older adults aged [?]65 years with the aim to assess potential limitations of currently available influenza vaccines. Despite the global impact of influenza, only 40 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 under-recognized or under-reported 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 (32). 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.

Due to 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 (37). These findings may be a result of independent factors such as, frailty or functional status (37). A separate study found that influenza-related headaches were significantly reduced in vaccinated people (38). Interestingly however, a similar reduction was not seen in other symptoms (38). 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 (38). 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). Vaccine technical committees (VTCs), 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 (54, 55). 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 (56). The assessment of humanistic burden, in terms of people-focused perspectives and elements, was not mentioned (56). Moreover, vaccine HTAs are largely driven by efficacy, safety, and cost-effectiveness analyses. The limited focus by VTCs, HTAs, and internationally recognized organizations on people and patient perspectives might explain the lack humanistic evidence identified in this SLR (57). 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, the majority of studies were conducted in the US, 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 economic evaluations, particularly in high-income countries had increased in the past 20 years (56). Applying an age restriction in the eligibility criteria of this SLR may be a plausible explanation for the lack of studies identified. Only studies that explicitly reported data for those aged [?]65 years were extracted, which led to the exclusion of other 'older' age groups where the lower bound of the age range was below 65 years, such as 60–80 years. 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 showed that HCRUs, especially hospitalizations, intensive care unit (ICU) admissions and influenza-related direct costs, were found to be greater in high-risk groups, particularly in those with comorbidities (34, 47). Nevertheless, study limitations such as selection bias due to small sample sizes should be considered when extrapolating results to the general population (34, 47). 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 did not appear to be associated with higher influenza-related direct costs, which was observed across several studies (41, 42, 49, 50). 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 US, Germany and Spain, a comparison of populations with similar healthcare systems is needed.

Two of the three indirect cost studies identified in this SLR utilized absenteeism to characterize the indirect cost of influenza in older adults (34, 35). One of these studies reported absenteeism in patients aged [?]65 years, not including absenteeism in their caregivers. As a significant proportion of individuals aged [?]65 are likely be retired, this might have led to an over estimation of the economic burden in this age group (35). In contrast, not including the indirect cost burden of absenteeism in caregivers, might have led to an under estimation of the economic burden (35). 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. New vaccine technologies may further alleviate this burden. mRNA vaccines may provide an effective solution to some limitations of current influenza vaccines. Recent evidence, such as the growing amount of safety and efficacy data due to the wide-scale use during the COVID-19 pandemic, provides reassurance for the utilization of this technology and demonstrates the place of mRNA vaccines in infectious disease prevention (1, 58-61). As mRNA technology allows a rapid and effective response to seasonal and regional variation in circulating influenza strains, they may provide more targeted and longer protection from serious infection. The potential use of seasonal mRNA vaccines may simplify yearly strain adjustment. In addition, this technology allows for the targeting of multiple strains and the identification of potential novel viral epitopes [1, 58]. Furthermore, it has no significant risk of mismatch compared with vaccine egg-adaption [1, 58]. By reducing strain mismatch, mRNA vaccines could potentially have a positive impact on the influenza burden worldwide (62).

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 search strategy was designed to capture studies with age stratifications reported in the study title or abstract therefore, if further explanation was provided in the main body of the manuscript, it was unlikely to be included. Only data that were explicitly reported for adults aged [?]65 years were extracted. 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, hence representative to evaluate the humanistic and economic burden of disease. Additionally, the search was refined 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 in 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 due to 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 has demonstrated that there is 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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Tables

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:* 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	N/A

Study characteristics	Inclusion criteria	Exclusion criteria
	Economic: 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	N/A
Time frame	Studies published from January 2012 to February 2022	N/A
Study design	Study types to be included are: RCTs Non-randomized interventional studies Observational studies SLRs and meta-analyses	Study types to be excluded are: Editorials Case studies Letters to journals Non-systematic literature reviews Conference minutes
Countries	France, Germany, Italy, Spain, UK, US, Canada, China, Japan, Brazil, Saudi Arabia, South Africa (for economic studies only)	All other countries
Other	Human studies English language	Animal studies 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, US: United States.	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, US: United States.	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, US: United States.

Table 2 Influenza symptoms contributing to overall humanistic burden

Country	**Author**	**Key outcomes**
US	van Wormer, 2014 (40)	The symptom severity scores 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 (31)	*Duration of symptoms after initial consultation in influenza-positive adult acute cough patients:* 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 4–12 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 2–15 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).
Spain	Casado, 2016 (36)	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%.

Country	Author	Key outcomes
	Czaja, 2019 (37)	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 [?]85 years, the three most frequently reported symptoms were cough (2,234–3,041 cases), fever (1,754–2,202 cases), shortness of breath/respiratory distress (1,662–2,011 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 [?]85 years. Occurrence increased with age (P<0.01)
France	Mosnier, 2017 (38)	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.

Country	Author	Key outcomes
	Regis, 2014 (39)	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, US: United States.	C: Celsius, CI: confidence interval, ILI: influenza-like illness, IQR: interquartile range, OR: odds ratio, US: United States.	C: Celsius, CI: confidence interval, ILI: influenza-like illness, IQR: interquartile range, OR: odds ratio, US: United States.

Table 3 Direct costs of influenza results

Country	Author	Key outcomes
Inpatient costs	**Inpatient costs**	**Inpatient costs**
US	Belk, 2022 (53)	Median costs of inpatient treatment: $31,237 (IQR: 40,260, P<0.0001)
	Lee, 2020 (42)	Median total cost of first hospital stay by age group: 64–79 years = $5,789.50 (IQR: 5,454,.50, P<0.0001). [?]80 years = $6,220.30 (IQR: 5,556.60, P<0.0001). Median total cost per day by age group: 64–79 years = $1,776.70 (IQR: 1,084.2, P<0.0001). [?]80 years = $1,627.60 (IQR: 930.2, P<0.0001).
France	Lemaitre, 2022 (48)	Total cost (\euro 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

Country	Author	Key outcomes
Germany	Goettler, 2022 (49)	Mean (SD) hospitalization costs per person from 2010–2019 were reported by age group: 70–79 years: \euro4,275 (9,912) 80–89 years: \euro3,489 (5,952) [?]90 years: \euro2,903 (2,230) Median (IQR) hospitalization costs per person from 2010–2019 were reported by age group: 70–79 years: \euro2,408 (1,578–2,741) 80–89 years: \euro2,613 (1,629–2,771) [?]90 years: \euro2,688 (1,722–2,858)
Spain	de Miguel, 2022 (50)	Median and total costs (\euro) for hospitalizations were reported by age group 64–74 years: \euro4,373.48; \euro4,872,057.10 >74 years: \euro3,951.18; \euro12,149,892.20 >74 years: \euro1,817,988.08
	Torner, 2017 (51)	Hospitalization costs (\euro 2015) for unvaccinated patients per annum were \euro1,184,808 and \euro1,152,333 for vaccinated patients.
UK	Moss, 2020 (28)	Cost per influenza admission between September 2017 and March 2018 were: £3,023.70 in those aged 65–74 years (n=7,320). £3,506.06 in those aged [?]75 years (n=16,060). Cost per influenza admission between September 2018 and March 2019 were: PS3,103.75 in those aged 65–74 years (n=4,975). PS3,675.91 in those aged [?]75 years (n=8,495). Cost per admission LOS (12.55 days) between September 2017 and March 2018 were: PS3,100 in those aged 65–74 years (n=7,320). PS3,500 in those aged [?]75 years (n=16,060).
Outpatient costs	**Outpatient costs**	**Outpatient costs**

Country	Author	Key outcomes
US	Young-Xu, 2017 (34)	Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, ED visit: Low-risk = \$176 (thousand) (95% CI: 101–251) High-risk group = \$3,968 (thousand) (95% CI: 3,314–4,623) Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, hospitalization only: Low-risk = \$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 = \$6 (thousand) (95% CI: 0–20) High-risk group = \$5,168 (thousand) (95% CI: 4,167–6,232)
Spain	de Miguel, 2022 (50)	Total costs (\euro) for referrals were reported by age group: 64–74 years: \euro2,308,881.60 >74 years: \euro1,502,578.08 Total costs (\euro) for visits were reported by age group: 64–74 years: \euro2,956,829.17 74 years: \euro1,817,988.08
Total costs	**Total costs**	**Total costs**
US	Levin, 2021 (43)	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 (44)	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 (45)	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).

Country	Author	Key outcomes
	Postma, 2020 (46)	Mean annualized influenza-related costs per patient by vaccine type: aTIV = $23.75. TIV-HD = $21.79.
China	Zhou, 2013 (47)	The median overall costs (USD 2010) for patients at high-risk of severe influenza were $2,340 (n=23,080) vs low-risk patients median cost of $1,295 (n=2,553).
Japan	Sruamsiri, 2017 (52)	Mean overall costs (USD) were reported for procedures (6,546 [SD: 5,793]) and DPC (5,526 [SD: 5,296]).
South Africa	Tempia, 2020 (35)	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.
CI: confidence interval, DPC: diagnosis procedure combination, ED: emergency department, LOS: length of stay, M: million; SD: standard deviation; UK: United Kingdom, USD: United States dollar.	CI: confidence interval, DPC: diagnosis procedure combination, ED: emergency department, LOS: length of stay, M: million; SD: standard deviation; UK: United Kingdom, USD: United States dollar.	CI: confidence interval, DPC: diagnosis procedure combination, ED: emergency department, LOS: length of stay, M: million; SD: standard deviation; UK: United Kingdom, USD: United States dollar.

Table 4 Out-of-pocket expenses associated with influenza

Country	Author	Key outcomes
US	Chua, 2021 (41)	Mean patient out-of-pocket/co-pay by age group in 2018: 65–74 years = $1,065 (SD: 807). 75–84 years = $1,000 (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).

SD: standard deviation; USD: United States dollar.

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