Supplementary Material

Room for improvement in current influenza vaccines? A systematic literature review on the humanistic and economic burden of influenza in an older (≥65 years old) adult population

AUTHORS:

Jakob Langer,[1]
Verna L. Welch,[2]
Mary Moran,[2]
Alejandro Cane,[2]
Santiago M.C Lopez,[2]
Amit Srivastava,[3]
Ashley Enstone,[4]
Amy Sears,[4]
Kristen Markus,[4]
Maria Heuser,[4]
Rachel Kewley,[4]
Isabelle Whittle[4]

AFFILIATIONS:

[1]Pfizer Patient & Health Impact, Lisbon, Portugal
[2]Pfizer Vaccines Medical & Scientific Affairs, Collegeville, PA USA
[3]Pfizer Emerging Markets, Vaccines Medical & Scientific Affairs, Cambridge MA USA
[4]Adelphi Values PROVE, Bollington SK10 5JB, UK

CORRESPONDING AUTHOR:

Name (Inc. prefix): Jakob Langer

Mailing address: Pfizer Portugal, Lagoas Park, Edifício 10, 2740-271 Porto Salvo, Portugal
Email address: Jakob.Langer@pfizer.com

Search strategies

Table S3. Electronic database search strategies

#		Query	Results from 9 Feb 2022
1	Disease terms	exp influenza/	96,506
2		exp influenza A/ or exp Influenza A virus/	41,118
3		exp influenza B/ or exp Influenza B virus/	5,266
4		exp seasonal influenza/	6,766
5		(flu or influenza*).mp.	219,215
6		or/1-5	219,215
7	Clinical burden terms	exp *hospitalization/ or exp *outpatient care/ or exp *outpatient/ or exp *outpatient department/ or exp *hospital patient/ or exp *general practice/ or exp *emergency ward/ or exp *"length of stay"/	195,492
8		*epidemiology/ or *morbidity/ or *mortality/ or *prevalence/ or *incidence/	268,807
9		exp *"pharmacy (shop)"/ or exp *non prescription drug/ or exp *self medication/ or exp *clinical pathway/	22,305
10		exp *social care/ or exp *home care/ or exp *long term care/ or *nursing home/ or exp *elderly care/	238,043
11		(over adj3 counter).ti,ab.	14,213
12		breakthrough.ti,ab.	32,718
13		((social or home or elderly or follow*) adj3 care).ti,ab.	96,091
14		(hospitali$ation or outpatient or inpatient or (length adj5 stay) or (general adj3 practice) or (emergency adj3 (ward or department))).ti,ab.	687,189
15		(disease adj4 (burden or impact)).ti,ab.	90,403
16		(epidemiology or morbidity or mortality or prevalence or incidence).ti.	610,207
17		or/7-16	1,829,395
18	Humanistic burden terms	exp "quality of life"/ or exp quality adjusted life year/ or exp disability-adjusted life year/ or exp absenteeism/ or exp "European Quality of Life 5 Dimensions questionnaire"/	587,623
19		("quality of life" or QoL or patient reported outcome* or ((patient or emotional or treatment) adj3 (satisfaction or dissatisfaction or response)) or "health related quality of life" or HRQoL).ti,ab.	779,536
20		(eq adj3 5d).ti,ab.	19,214
21		exp sleep quality/ or exp sleep/	260,009
22		or/18-21	1,194,925
23	Economic terms	exp *health economics/	283,114
24		exp *"cost of illness"/ or exp *"hospital cost"/ or exp *"hospitalization cost"/ or exp *"cost control"/ or exp *"drug cost"/ or exp *"health care cost"/ or exp *health care utilization/ or exp *productivity/ or exp *medical leave/	113,096

#		Query	Results from 9 Feb 2022
25		exp *economic evaluation/ or exp *"cost benefit analysis"/ or exp *"cost effectiveness analysis"/ or exp *"cost utility analysis"/ or exp *cost minimization analysis/	68,924
26		(Cost* or expen* or financ* or price* or pricing or pharmacoeconomic* or ((economic or societ* or socioeconomic or socio economic or illness or disease or patient* or caregiver* or carer*) adj2 burden)).ti,ab.	1,299,440
27		((resource* adj2 (utili$ation or use*)) or productivity or hospitali#ation* or (leave adj2 (medical or sick or disability))).ti,ab.	432,481
28		(cost adj (effective* or utilit* or minimi* or benefit)).ti,ab.	226,447
29		or/23-28	1,794,474
30	Older population terms	exp aged/ or exp elderly care/ or exp pensioner/ or exp retirement/	3,344,437
31		(("65" or "70" or "75" or "80") adj3 year*).mp.	443,003
32		((old* or elder* or retire* or pensioner* or aged) adj3 (patient or person or people)).mp.	244,179
33		or/30-32	3,638,376
34	Subtotal: clinical burden: 6 and 17 and 33		5,184
35	Subtotal: humanistic burden: 6 and 22 and 33		1,560
36	Subtotal: economic burden: 6 and 29 and 33		4,145
37	Removal of irrelevant study types	(exp Animal/ or nonhuman/) not exp human/	6,743,524
38		exp case study/ or exp case report/ or exp letter/ or exp preliminary communication/ or exp note/ or exp editorial/ or exp editor/ or exp editorial policies/ or exp newspaper/	5,335,700
39	Total combined results: no time limit: 34 or 35 or 36		8,577
40	Total combined results: limit 39 to yr="2012 -Current"		5,156
41		40 not (37 or 38)	4,766

JBI Critical Appraisal checklists

Table S4 JBI critical appraisal checklist for epidemiological/prevalence studies

	Yes	No	Unclear	N/A
1. Was the sample frame appropriate to address the target population?				
2. Were study participants sampled in an appropriate way?				
3. Was the sample size adequate?				
4. Were the study subjects and the setting described in detail?				
5. Was the data analysis conducted with sufficient coverage of the identified sample?				
6. Were valid methods used for the identification of the condition?				
7. Was the conditions measured in a standard, reliable way for all participants?				
8. Was there appropriate statistical analysis?				
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

Table S5 JBI critical appraisal checklists for cohort studies

	Yes	No	Unclear	N/A
1. Were the two groups similar and recruited from the same population?				
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?				
3. Was the exposure measured in a valid and reliable way?				
4. Were confounding factors identified?				
5. Were strategies to deal with confounding factors stated?				
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?				
7. Were the outcomes measured in a valid and reliable way?				
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?				
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?				
10. Were strategies to address incomplete follow up utilized?				
11. Was appropriate statistical analysis used?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

Table S6 JBI critical appraisal checklist for cross-sectional studies

	Yes	No	Unclear	N/A
1. Were the criteria for inclusion in the sample clearly defined?				
2. Were the study subjects and the setting described in detail?				
3. Was the exposure measured in a valid and reliable way?				
4. Were objective, standard criteria used for measurement of the condition?				
5. Were confounding factors identified?				
6. Were strategies to deal with confounding factors stated?				
7. Were the outcomes measured in a valid and reliable way?				
8. Was appropriate statistical analysis used?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

Table S7 JBI critical appraisal checklist for randomized controlled trial studies

	Yes	No	Unclear	N/A
1. Was true randomization used for assignment of participants to treatment groups?				
2. Was allocation to treatment groups concealed?				
3. Were treatment groups similar at the baseline?				
4. Were participants blind to treatment assignment?				
5. Were those delivering treatment blind to treatment assignment?				
6. Were outcomes assessors blind to treatment assignment?				
7. Were treatment groups treated identically other than the intervention of interest?				
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?				
9. Were participants analyzed in the groups to which they were randomized?				
10. Were outcomes measured in the same way for treatment groups?				
11. Were outcomes measured in a reliable way?				
12. Was appropriate statistical analysis used?				
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

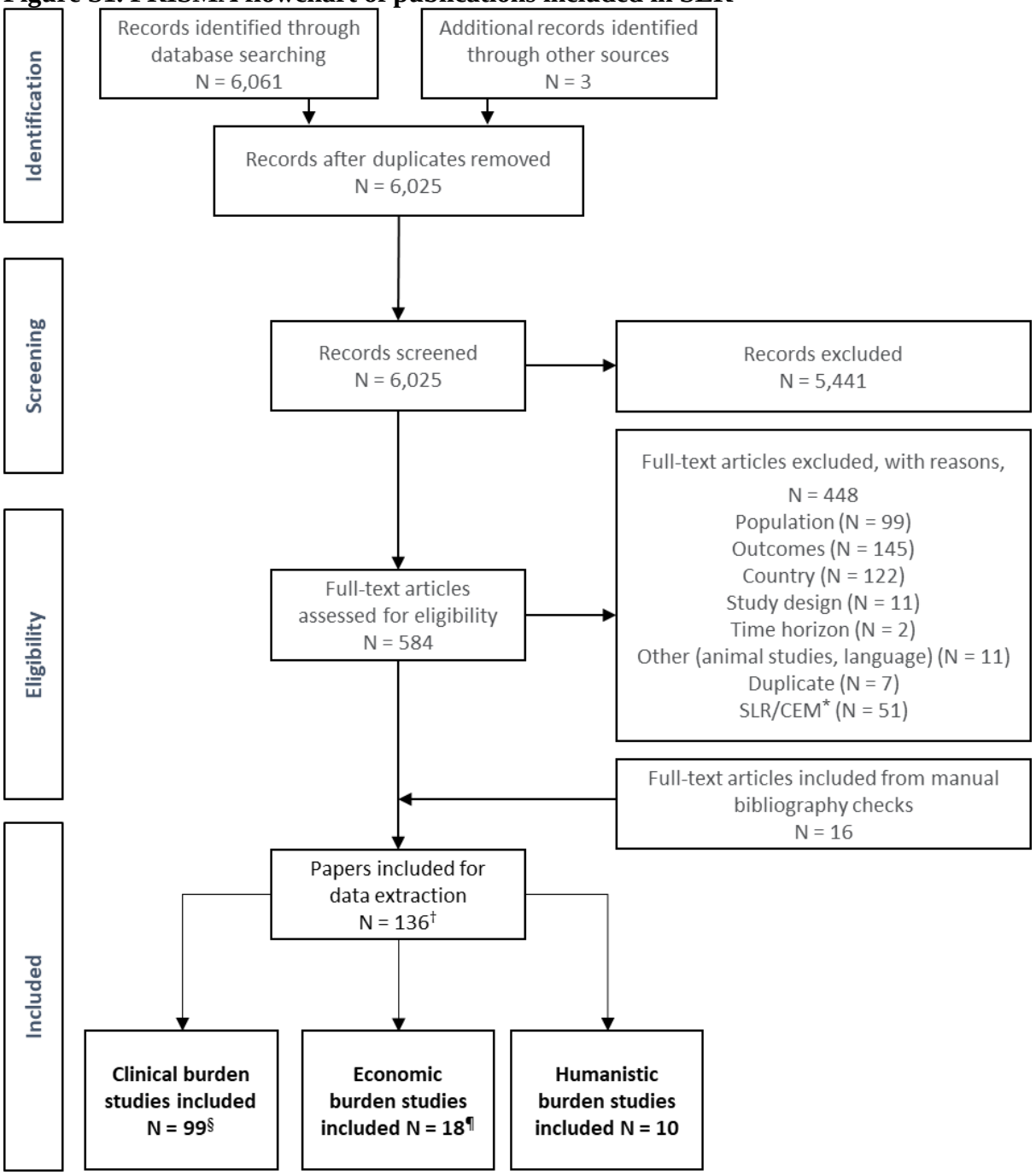
Table S8 JBI critical appraisal checklist for economic evaluation studies

	Yes	No	Unclear	N/A
1. Is there a well-defined question?				
2. Is there comprehensive description of alternatives?				
3. Are all important and relevant costs and outcomes for each alternative identified?				
4. Has clinical effectiveness been established?				
5. Are costs and outcomes measured accurately?				
6. Are costs and outcomes valued credibly?				
7. Are costs and outcomes adjusted for differential timing?				
8. Is there an incremental analysis of costs and consequences?				
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?				
10. Do study results include all issues of concern to users?				
11. Are the results generalizable to the setting of interest in the review?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

Table S9 JBI critical appraisal checklist for case-control studies

	Yes	No	Unclear	N/A
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?				
2. Were cases and controls matched appropriately?				
3. Were the same criteria used for identification of cases and controls?				
4. Was exposure measured in a standard, valid and reliable way?				
5. Was exposure measured in the same way for cases and controls?				
6. Were confounding factors identified?				
7. Were strategies to deal with confounding factors stated?				
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?				
9. Was the exposure period of interest long enough to be meaningful?				
10. Was appropriate statistical analysis used?				
Overall appraisal		Low-risk / High-risk of bias		
Comments (including reason for high-risk of bias):				

Figure S1. PRISMA flowchart of publications included in SLR



*SLRs and cost-effectiveness models captured in the database search that met inclusion criteria underwent a manual bibliography check, and data were extracted from studies that met inclusion criteria and were not already captured.
†The total number of papers eligible for data extraction include multiple papers reporting on the same study. In such instances, papers were extracted as a single study.
§Clinical burden studies have been reported in a separate manuscript. Vaccine effectiveness studies were captured in this SLR, but results were not presented in the clinical burden manuscript. As such the number of papers included for extraction is higher than the number of clinical, economic, and humanistic burden studies.
¶Economic burden studies include papers reporting on healthcare resource utilization. These outcomes were not reported in the present manuscript.

Table S10. Healthcare resource utilization study characteristics (n= 14 studies)

Study	Country	Healthcare resource utilization type	Study period	Study design
Arriola, 2017(61)	US	Hospital length of stay	2013 – 2014	Retrospective cohort study/analyses
Belk, 2021 (49)	US	Hospital length of stay	2016 - 2018	Retrospective cohort study/analyses
Chaves, 2015 (62)	US	Antiviral treatment use	2010 – 2013	Prospective analyses
Jules, 2014 (63)	US	Antiviral treatment use; receipt of influenza test	2009 – 2011	Retrospective cohort study/analyses
Casado, 2018 (64)	Spain	Hospital length of stay	2013 – 2015	Case control
Hernandez, 2020 (65)	Spain	Hospital length of stay	2017 – 2018	Cross-sectional research
Ramos, 2016 (66)	Spain	Hospital length of stay	2015	Cross-sectional research
Suarez-Varela, 2018 (67)	Spain	ICU length of stay	2013 – 2014	Case control
Pivette, 2019 (68)	France	Hospital and ICU length of stay	2012 – 2017	Retrospective cohort study/analyses
Fleming, 2015 (69)	UK	GP visits	1995 – 2009	Cross-sectional research
Li, 2021 (70)	China	Outpatient visits	2010 – 2017	Modelling study

GP: general practitioner; ICU: intensive care unit; UK: United Kingdom; US: United States.

Table S11 JBI critical appraisal of epidemiological studies

	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall appraisal
Lemaitre 2021										Low risk
Regis 2014										Low risk
Goettler 2022										Low risk
Perrotta 2017										Low risk
Near 2020										Low risk
Bruyndonckx 2020										Low risk

Table S12 JBI critical appraisal of cohort studies

	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?	Overall appraisal
Lee 2020												Low risk
Belk 2021												Low risk
Levin 2021												Low risk
Pelton 2020												Low risk
Postma 2020												Low risk
Mosnier 2017												Low risk
Pelton 2021												Low risk

Table S13 JBI critical appraisal of cross-sectional studies

	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Overall appraisal
Gonzalez 2016									High risk
Torner 2017									Low risk
Sruamsiri 2017									Low risk
Van Wormer 2014									Low risk
Czaja 2019									Low risk

Table S14 JBI critical appraisal economic evaluations

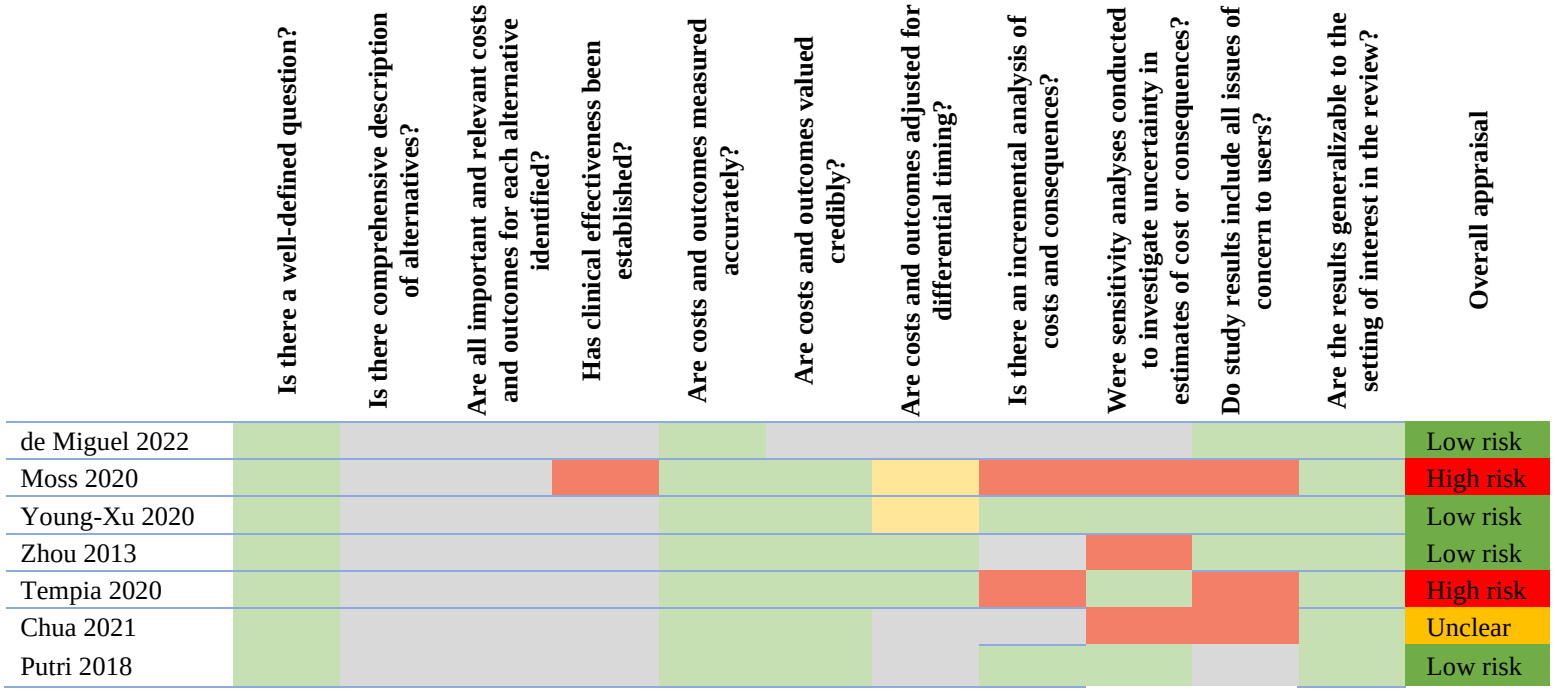


Table 15 JBI critical appraisal RCT studies

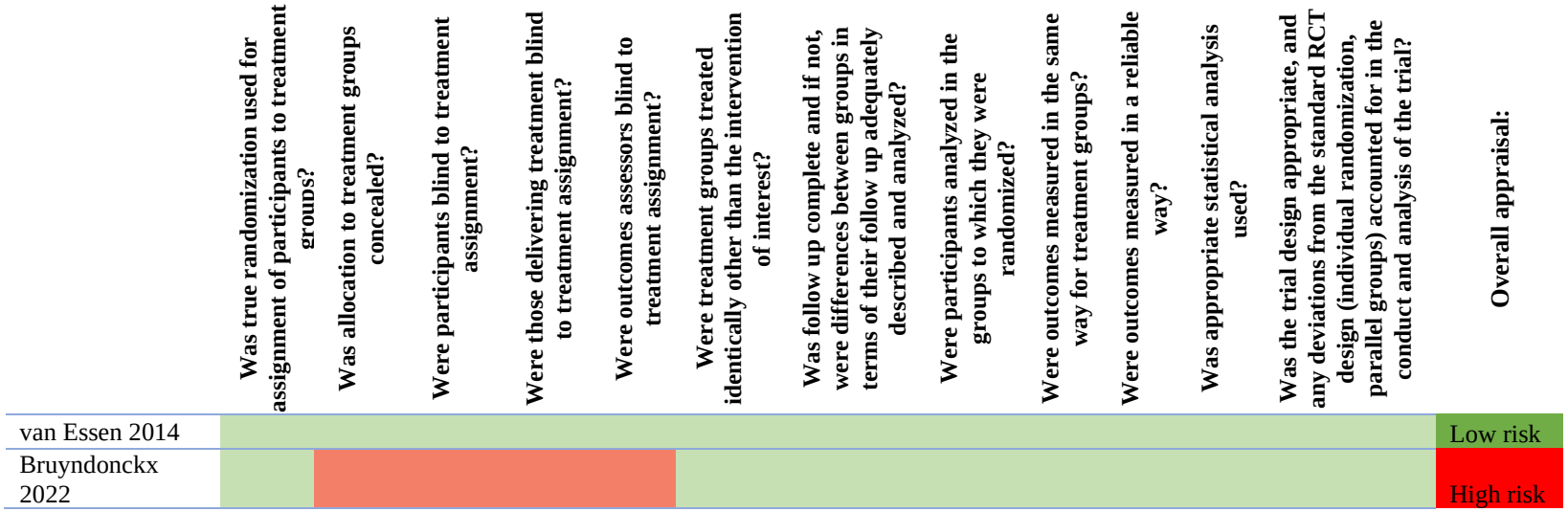
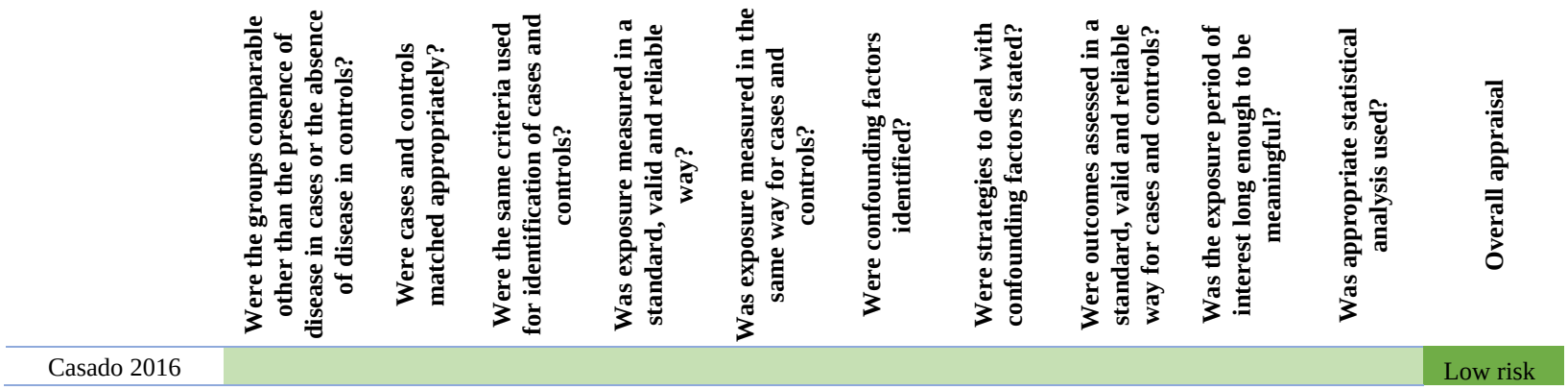


Table 16 JBI critical appraisal case-control studies



Economic and humanistic burden results identified in this SLR

Table S17 Study characteristics (n= 28 studies)

Study	Country	Burden type	Study period	Study design
Belk, 2022 (49)	US	Economic	2016–2018	Retrospective cohort study/analyses
Chua, 2021 (35)	US	Economic	2018	Retrospective cohort study/analyses
Lee, 2021 (36)	US	Economic	2013─2014	Retrospective cohort study/analyses
Levin, 2021 (37)	US	Economic	February 2019─March 2020	Retrospective cohort study/analyses
Pelton, 2021 (38)	US	Economic	August 2018─July 2019	Retrospective cohort study/analyses
Pelton, 2020 (39)	US	Economic	August 2017–August 2018	Retrospective cohort study/analyses
Postma, 2020 (40)	US	Economic	2018─2019	Retrospective cohort study/analyses
Putri, 2018 (47)	US	Economic	2015	Cost-of-illness study
Near, 2020 (48)	US	Economic	2014─2018	Retrospective cohort study/analyses
Young-Xu, 2017 (28)	US	Economic/Humanistic	2010─2014	Cost-of-illness study
Zhou, 2013 (41)	China	Economic	December 2009─June 2011	Retrospective cohort study/analyses
Lemaitre, 2022 (42)	France	Economic	2010─2018	Retrospective cohort study/analyses
Goettler, 2022 (43)	Germany	Economic	January 2010─December 2019	Observational
de Miguel, 2022 (44)	Spain	Economic	2015	Cost-of-illness study
Torner, 2017 (45)	Spain	Economic	2013–2015	Cross-sectional research
Moss, 2020 (22)	UK	Economic	September 2017─March 2019	Retrospective cohort study/analyses

Study	Country	Burden type	Study period	Study design
Sruamsiri, 2017 (46)	Japan	Economic	April 2014─March 2015	Cross-sectional research
Tempia, 2020 (29)	South Africa	Economic/Humanistic	2013─2015	Retrospective cohort study/analyses
van Essen, 2014 (26)	Belgium, Canada, Czech Republic, Estonia, France, Germany, Mexico, Norway, Poland, Romania, Russia, Taiwan, Netherlands, UK, US	Humanistic	September 2008─November 2008	Randomized control trial
Perrotta, 2017 (27)	Italy	Humanistic	2012─2015	Questionnaire, surveillance
Bruyndonckx, 2022 (24)	Belgium, Czech Republic, Denmark, France, Greece, Hungary, Ireland, Lithuania, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, UK	Humanistic	2015─2018	Randomized control trial
van Wormer, 2014 (34)	US	Symptoms	2007─2011	Cross-sectional research
Gonzalez, 2016 (5)	Spain	Symptoms	2009─2015	Retrospective cohort study/analyses
Bruyndonckx, 2020 (25)	Belgium, England, France, Germany, Italy, Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, Wales	Symptoms	October 2007─April 2010	Observational
Casado, 2016 (30)	Spain	Symptoms	2013─2014	Case-control
Czaja, 2019 (31)	Spain	Symptoms	2011─2015	Cross-sectional research
Mosnier, 2017 (32)	France	Symptoms	2003─2014	Retrospective cohort study/analyses

Study	Country	Burden type	Study period	Study design
Regis, 2014 (33)	France	Symptoms	2004–2009	Prospective analyses

UK: United Kingdom, US: United States.

Table S18 Economic study characteristics

	No. (%) of studies
Publication year	
2013	1 (6)
2017	3 (17)
2018	1 (6)
2020	6 (33)
2021	4 (22)
2022	3 (17)
Country	
US	10 (56)
China	1 (6)
France	1 (6)
Germany	1 (6)
Spain	2 (11)
UK	1 (6)
Japan	1 (6)
South Africa	1 (6)
Study design	
Retrospective cohort	12 (67)
Cost-of-illness	3 (17)
Cross-sectional	2 (11)
Observational	1 (6)
Cost outcome[†a]	
Direct costs	18 (100)
Indirect costs	4 (22)

UK: United Kingdom, US: United States.
[†a]Percentages may add up to more than 100%, due to rounding and due to studies reporting on more than one outcome type.

Table S19 Economic and humanistic burden results identified in this SLR

Study details	Patient population of interest (n=)	Outcomes
Belk et al. 2022 (49) Country: US Setting: Clinical or hospital Study period: 2016–2018 Publication type: Conference poster Title: Hospital Utilization for Elderly Patients Diagnosed with Respiratory Syncytial Virus (RSV) Versus Influenza in the US	People aged ≥65 years with laboratory confirmed influenza (n= NR).	Median inpatient charges (USD) incurred for influenza patients were $31,237 (IQR: 40,260, P<0.0001).
Chua et al. 2021 (35) Country: US Setting: Clinical or hospital Study period: 2018 Publication type: Peer-reviewed journal article Title: Out-of-pocket spending for influenza hospitalizations in Medicare advantage.	People aged ≥65 years with laboratory confirmed influenza (n= 14,585).	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 severity of influenza (2018 USD): • No ICU care required = $928 (SD: 754). • ICU care required = $1,106 (SD: 871). Mean patient out-of-pocket/co-pay by sex (2018 USD): • Male = $971 (SD: 790). • Female = $999 (SD: 806).
Lee et al. 2021 (36) Country: US Setting: Community Study period: 2013─2014 Publication type: Peer-reviewed journal article Title: Comparison of influenza hospitalization outcomes among adults, older adults, and octogenarians: a US national population-based study.	People aged ≥65 years with laboratory confirmed influenza (n=NR).	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).

Study details	Patient population of interest (n=)	Outcomes
Levin et al. 2021 (37) Country: US Setting: Clinical or hospital Study period: February 2019─March 2020 Publication type: Peer-reviewed journal article Title: Comparing the clinical and economic outcomes associated with adjuvanted versus high-dose trivalent influenza vaccine among adults aged ≥65 years in the US during the 2019–20 influenza season—A retrospective cohort Analysis.	People aged ≥65 years who received influenza vaccination for season of study (n=NR).	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). Predicted mean annualized cost per patient by vaccine type. Influenza-related ER visits: • aIIV3 (n=798,987) = $4.15 (95% CI: 3.7–4.6). • HDIIV3e (n=798,987) = $4.44 (95% CI: 4.2–4.7). Predicted mean annualized cost per patient by vaccine type. Influenza-related office visits: • aIIV3 (n=798,987) = $2.01 (95% CI: 1.8–2.3). • HDIIV3e (n=798,987) = $1.92 (95% CI: 1.8–2.1). Predicted mean annualized pharmacy cost per patient by vaccine type: • aIIV3 (n=798,987) = $2.75 (95% CI: 2.7–2.8). • HDIIV3e (n=798,987) = $2.77 (95% CI: 2.7–2.8).
Pelton et al. 2021 (38) Country: US Setting: Clinical or hospital Study period: August 2018─July 2019 Publication type: Peer-reviewed journal article Title: A retrospective cohort study assessing relative effectiveness of adjuvanted versus high-dose trivalent influenza vaccines among older adults in the United States during the 2018-19 influenza season.	People aged ≥65 years who received influenza vaccination for season of study (n=22,340,40).	Mean influenza-related ER costs per person by vaccine type: • aTIV (n=561,243) = $2.18 (95% CI: 1.9–2.4). • TIV-HD (n=561,243) = $2.32 (95% CI: 2.1–2.6). Mean influenza-related hospitalizations costs per person by vaccine type: • TIV-HD (n=561,243) = $18.13 (95% CI: 15.2–21.6). • aTIV (n=561,243) = $20.28 (95% CI: 17.6–23.8). Mean influenza-related office costs per person by vaccine type: • TIV-HD (n=561,243) = $1.29 (95% CI: 1.2–1.5). • aTIV (n=561,243) = $1.34 (95% CI: 1.2–1.5). Mean influenza-related pharmacy costs per person by vaccine type: • TIV-HD (n=561,243) = $1.86 (95% CI: 1.8–1.9). • aTIV (n=561,243) = $1.75 (95% CI: 1.7–1.8). Mean influenza-related total costs per person by vaccine type: • TIV-HD (n=561,243) = $18.74 (95% CI: 17.4–20.6).

Study details	Patient population of interest (n=)	Outcomes
		• aTIV (n=561,243) = $17.28 (95% CI: 15.9–18.9).
Pelton et al. 2020 (39) Country: US Setting: Clinical or hospital Study period: August 2017 - August 2018 Publication type: Peer-reviewed journal article Title: Evaluating the relative vaccine effectiveness of adjuvanted trivalent influenza vaccine compared to high-dose trivalent and other egg-based influenza vaccines among older adults in the US during the 2017–2018 influenza season.	People aged ≥65 years who received influenza vaccination for season of study (n=234,313).	Mean annual influenza-related ER visit cost by vaccine type: • aTIV = $3.97 (95% CI: 3.5–4.3). • TIV-HD = $4.49 (95% CI: 3.99–4.97). Mean annual influenza-related hospitalizations cost by vaccine type: • aTIV = $27.59 (95% CI: 23.0–32.9). • TIV-HD = $26.29 (95% CI: 22.4–30.8). Mean annual influenza-related office visit + oseltamivir cost by vaccine type: • aTIV = $1.1 (95% CI: 1.0–1.2). • TIV-HD = $1.36 (95% CI: 1.3–1.5). Mean annual total influenza-related cost by vaccine type: • aTIV = $28.21 (95% CI: 24.6–32.4). • TIV-HD = $31.77 (95% CI: 27.7–36.3).
Postma et al. 2020 (40) Country: US Setting: Clinical or hospital Study period: 2018─2019 Publication type: Conference abstract Title: Impact of enhanced influenza vaccines on direct healthcare costs for the US elderly: A comprehensive real-world evaluation of adjuvanted trivalent influenza vaccine compared to trivalent high-dose influenza vaccine for the 2018-19 influenza season.	People aged ≥65 years who received influenza vaccination for season of study (n=1,122,486).	Predicted mean annualized costs for influenza-related hospitalizations per patient by vaccine type: • aTIV = $20.28. • TIV-HD = $18.13. Predicted mean annualized costs for influenza-related office visits per patient by vaccine type: • aTIV = $1.29. • TIV-HD = $1.34. Predicted mean annualized influenza-related costs per patient by vaccine type: • aTIV = $23.75. • TIV-HD = $21.79.
Putri et al. 2018 (47) Country: US Setting: Community Study period: 2015	People with influenza aged ≥65 years (n=NR).	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

Study details	Patient population of interest (n=)	Outcomes
Publication type: Journal article Title: Economic burden of seasonal influenza in the United States.		• Hospitalization = $1,273.73/$40.45/$1,314.18 • Deaths = NR/$710.1/$710.1 • Total = $1,370.64/$1,044.24/$2,414.88 Total days of productivity loss (excludes from death) • Base case= 1,756,517 • Lower limit= 1,167,114 • Upper limit= 2,830,190
Near et al. 2020 (48) Country: US Setting: *Clinical or hospital* Study period: 2014─*2018* Publication type: Abstract Title: *Incidence and Costs of Influenza-Related Hospitalizations by Comorbidity in the United States*	Patients aged ≥65 years hospitalized with influenza (n=NR)	Mean influenza-related hospitalization cost: $18,770
Young-Xu et al. 2017 (28) Country: US Setting: Clinical or hospital Study period: 2010─2014 Publication type: Peer-reviewed journal article Title: The annual burden of seasonal influenza in the US veterans affairs population.	People aged ≥65 years with unconfirmed influenza and low- or high-risk of influenza complications (n=NR).	Mean annual estimate of influenza-attributed direct medical costs for healthcare encounters, ED visit: • Both risk groups = $4,143 (thousand) (95% CI: 3,416–4,874). • 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: • Both risk groups = $28,966 (thousand) (95% CI: 24,112–33,940). • 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: • Both risk groups = $5,174 (thousand) (95% CI: 4,167–6,253). • Low-risk = $6 (thousand) (95% CI: 0–20).

Study details	Patient population of interest (n=)	Outcomes
		• High-risk group = $5,168 (thousand) (95% CI: 4,167–6,232). Mean cost for hospitalization with extended care, high-risk patients = $63,921 (95% CI: 61,309–66,534). Mean cost for hospitalization with extended care, low-risk patients = $63,526 (95% CI: 55,570–65,482). Mean cost for hospitalization, high-risk patients = $14,839 (95% CI: 14,720–14,958). Mean cost for hospitalization, low-risk patients = 14,723 (95% CI: 14,454–14,992) Mean cost per ED visit, high-risk patients = $592 (95% CI: 591–593). Mean cost per ED visit, low-risk patients = $590 (95% CI: 589–592). Productivity loses were caused by hospitalizations, hospitalizations with extended care, and mortality (56%, 53% and 52%, respectively). Annual estimate (2010–2014) of influenza-attributed QALYs lost in patients at; • High-risk: N=38.2 (95% CI: 33.8–42.6). • Low-risk: N= 3.1 (95% CI: 2.4–3.7). • Both risk groups: N= 41.3 (95% CI: 36.2–46.3).
Zhou et al. 2013 (41) Country: China Setting: Community Study period: December 2009─June 2011 Publication type: Peer-reviewed journal article Title: Direct medical cost of influenza-related hospitalizations among severe acute respiratory infections cases in three provinces in China.	People with laboratory confirmed influenza (n=19)	The median overall costs (USD 2010) for high-risk patients were $2,340 (n=23,080) vs low-risk patients median cost of $1,295 (n=2,553). Median costs for diagnostics, examinations, and laboratory testing were reported for high- and low-risk patients, respectively: $643 vs $358; $175 vs $85; and $395 vs $280. Cost of therapeutics were reported for high-risk and low-risk patients, resulting in median costs of $1,816 (n=16,432) vs $933 (n=2,367). No costs were reported for antiviral treatment. Physician median costs between high- and low-risk group had very little difference ($8 vs $7), while median costs for nursing were $52 vs $17, respectively.
Lemaitre et al. 2022 (42) Country: France	Patients aged ≥65 years hospitalized with influenza (n=NR)	Total cost (€ million) of excess influenza-attributable hospitalizations was reported across eight influenza seasons: • 2010–11: 13.5M

Study details	Patient population of interest (n=)	Outcomes
Setting: Clinical or hospital Study period: 2010─2018 Publication type: Peer-reviewed journal article Title: Estimating the burden of influenza-related and associated hospitalizations and deaths in France: An eight-season data study, 2010–2018.		• 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
Goettler et al. 2022 (43) Country: Germany Setting: Clinical or hospital Study period: January 2010─December 2019 Publication type: Peer-reviewed journal article Title: Epidemiology and direct healthcare costs of Influenza-associated hospitalizations – nationwide inpatient data (Germany 2010-2019).	Patients aged ≥70 years hospitalized with influenza (n=NR)	Mean (SD) hospitalization costs per person from 2010–2019 were reported by age group: • 70–79 years: €4,275 (9,912). • 80–89 years: €3,489 (5,952). • ≥90 years: €2,903 (2,230). Median (IQR) hospitalization costs per person from 2010–2019 were reported by age group: • 70–79 years: €2,408 (1,578–2,741). • 80–89 years: €2,613 (1,629–2,771). • ≥90 years: €2,688 (1,722–2,858).
de Miguel et al. 2022 (44) Country: Spain Setting: Clinical or hospital Study period: 2015 Publication type: Peer-reviewed journal article Title: Direct medical costs of four vaccine-preventable infectious diseases in older adults in Spain.	People aged ≥65 years with laboratory confirmed influenza (n=NR)	Median and total costs (€) for hospitalizations were reported by age group • 64–74 years: €4,373.48; 4,872,057.10. • >74 years: €3,951.18; 12,149,892.20. 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.
Torner et al. 2017 (45) Country: Spain	People aged ≥65 years with laboratory confirmed influenza (n=728)	Overall costs were reported for influenza-associated hospital admission by vaccination status, per annum: • Unvaccinated: €1,184,808 • Vaccinated: €1,152,333

Study details	Patient population of interest (n=)	Outcomes
Setting: Clinical or hospital Study period: 2013–2015 Publication type: Peer-reviewed journal article Title: Costs associated with influenza-related hospitalization in the elderly		The cost, per annum, of the total influenza-related hospitalizations was €2,337,141.
Moss et al. 2020 (22) Country: UK Setting: Clinical or hospital Study period: September 2017─March 2019 Publication type: Peer-reviewed journal article Title: Quantifying the direct secondary health care cost of seasonal influenza in England.	People aged ≥65 years with laboratory confirmed influenza (n=NR)	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: • £3,103.75 in those aged 65–74 years (n=4,975). • £3,675.91 in those aged ≥75 years (n=8,495). Cost per admission LOS (12.55 days) between September 2017 and March 2018 were: • £3,100 in those aged 65–74 years (n=7,320). • £3,500 in those aged ≥75 years (n=16,060). Cost per admission LOS (9.04 days) between September 2017 and March 2018 were £3,100 in those aged 65–74 years (n=7,320). Cost per admission LOS (9.08 days) between September 2018 and March 2019 were £3,000 in those aged 65–74 years (n=4,975). Cost per admission LOS (12.55 days) between September 2018 and March 2019 were £3,700 in those aged ≥75 years (n=8,495). Cost per admission LOS (12.55 days) between September 2017 and March 2018 were £3,500 in those aged ≥75 years (n=16,060).
Sruamsiri et al. 2017 (46) Country: Japan Setting: Clinical or hospital Study period: April 2014─March 2015	People aged ≥65 years with laboratory confirmed influenza (n=3,249)	Mean overall costs (USD) were reported for procedures (6,546 [SD: 5,793]) and DPC (5,526 [SD: 5,296]). Total healthcare cost, unstandardized coefficient of $854 (95% CI $580-$1,127).

Study details	Patient population of interest (n=)	Outcomes
Publication type: Peer-reviewed journal article Title: Impact of patient characteristics and treatment procedures on hospitalization cost and length of stay in Japanese patients with influenza: A structural equation modelling approach.		
Tempia et al. 2020 (29) Country: South Africa Setting: Clinical or hospital Study period: 2013─2015 Publication type: Peer-reviewed journal article Title: Influenza economic burden among potential target risk groups for immunization in South Africa, 2013–2015.	Patients aged ≥65 years with unconfirmed influenza (n=NR)	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. Mean absenteeism for caregivers per illness episode was 0.5 days (95% CI 0.2–1.5) showing a total absenteeism (13,224,876 days) of 4.5%. From 2013–2015, the study reported 35,601 (95% CI: 23,853–47,349) life years lost in the population of interest.
van Essen et al., 2014 (26) Country: Belgium, Canada, Czech Republic, Estonia, France, Germany, Mexico, Norway, Poland, Romania, Russia, Taiwan, Netherlands, UK, US Setting: Community Study period: September 2008─November 2008 Publication type: Peer-reviewed journal article Title: Influenza symptoms and their impact on elderly adults: Randomised trial of AS03-adjuvanted or non-adjuvanted inactivated trivalent seasonal influenza vaccines.	People aged ≥65 years with confirmed influenza, who received either the AS03-TIV or TIV as part of a phase III trial (n=43,695)	*FluiiQ*™ results: Mean systemic symptom, total symptom and impact on activities scores were lower with AS03-TIV vs TIV. • Mean score for total symptoms: 1.50 (SE: 0.043) and 1.64 (SE: 0.040) for the AS03-TIV and TIV cohorts, respectively. • Mean score for impact on daily activities: 1.27 (SE: 0.1) and 1.54 (SE: 0.1) for the AS03-TIV and TIV cohorts, respectively. Mean respiratory symptom, impact on emotions and impact on relationships scores were similar with AS03-TIV vs TIV. • The mean score for impact on emotions was 0.89 (SE: 0.05) and 1.02 (SE: 0.06) for the AS03-TIV and TIV cohorts, respectively. • The mean score for impact on relationships was 0.67 (SE: 0.05) and 0.74 (SE: 0.47) for the AS03-TIV and TIV cohorts, respectively.

Study details	Patient population of interest (n=)	Outcomes
		Influenza tended to be less severe with AS03-TIV, but the MID was reached only for impact on activities (mean 9.0%).
Perrotta et al., 2017 (27) Country: Italy Setting: Surveillance Study period: 2012─2015 Publication type: Peer-reviewed journal article Title: Participatory online surveillance as a supplementary tool to sentinel doctors for influenza-like illness surveillance in Italy	People aged ≥65 years with ILI episode	Approximately 27.71% of patients aged ≥65 years reported a change in their daily routine across influenza seasons from 2012–2015.
Bruyndonckx et al., 2022 (24) Country: Belgium, Czech Republic, Denmark, France, Greece, Hungary, Ireland, Lithuania, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, UK Setting: Clinical or hospital Study period: 2015─2018 Publication type: Peer-reviewed journal article Title: Impact of adding oseltamivir to usual care on quality-adjusted life years during influenza-like illness.	Patients ≥65 years with ILI in usual care with or without oseltamivir (n= 997)	14 days follow up: patients treated with oseltamivir gained a total of 0.0006 QALYs (range: 0.0002–0.0010) compared to those without. 28 days follow up: patients treated with oseltamivir gained a total of 0.0008 QALYs (range: 0.0003–0.0014) compared to those without.
Gonzalez et al., 2016 (5) Country: Spain Setting: Clinical or hospital Study period: 2009─2015 Publication type: Peer-reviewed journal article Title: Evaluation of influenza virus A in elderly hospitalized.	Patients aged ≥75 years hospitalized with laboratory confirmed influenza (n=44)	Proportion of non-specific symptoms such as agitation or disorientation: 16%. Proportion of dyspnea: 84%.

Study details	Patient population of interest (n=)	Outcomes
Bruyndonckx et al., 2020 (25) Country: Belgium, England, France, Germany, Italy, Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden, Wales Setting: Clinical or hospital Study period: October 2007─April 2010 Publication type: Peer-reviewed journal article Title: Respiratory syncytial virus and influenza virus infection in adult primary care patients: Association of age with prevalence, diagnostic features and illness course.	Primary care acute cough patients aged ≥75 years with laboratory confirmed influenza (n=NR)	<u>Duration of symptoms after initial consultation in influenza-positive adult acute cough patients:</u> 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).
Casado et al., 2016 (30) Country: Spain Setting: Clinical or hospital Study period: 2013─2014 Publication type: Peer-reviewed journal article Title: Effect of influenza vaccination on the prognosis of hospitalized influenza patients.	Patients aged ≥65 years hospitalized with laboratory confirmed influenza (n=433)	The proportion of hospitalized patients with influenza vaccination with: • Cough: 82.1% • Sore throat: 14.1% • Shortness of breath: 82.6% • Fever: 75.7% • Headache: 20.8% • Myalgia: 26.6% • Malaise: 70.9%
Czaja et al., 2019 (31) Country: Spain Setting: Clinical or hospital Study period: 2011─2015 Publication type: Peer-reviewed journal article Title: Age-related differences in hospitalization rates, clinical presentation, and	People aged ≥65 years admitted to hospital with laboratory confirmed influenza (65–74 years n= 2,796; 75–84 years n= 3,741; ≥85 years n= 4,011)	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).

Study details	Patient population of interest (n=)	Outcomes
outcomes among older adults hospitalized with influenza—U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET).		Altered mental status/confusion was detected in: • 401 patients aged 65–74 years. • 773 patients aged 75–84 years. • 921 patients aged ≥85 years.
Mosnier et al., 2017 (32) Country: France Setting: Clinical or hospital Study period: 2003─2014 Publication type: Peer-reviewed journal article Title: Does seasonal vaccination affect the clinical presentation of influenza among the elderly? A cross-sectional analysis in the outpatient setting in France, 2003–2014.	Outpatients aged ≥65 years with laboratory confirmed influenza (vaccinated n=385; unvaccinated n=290)	Symptoms reported included: Adenopathy, asthenia, bronchitis/bronchiolitis, conjunctivitis, cough, dyspnea, expectoration, fever, gastrointestinal symptoms, headache, myalgia, otitis/earache, pharyngitis, rhinitis, and shivering. The only symptom that was statistically less prevalent when comparing vaccinated to non-vaccinated people was headaches. The OR for headaches was 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. Across vaccinated people, the highest prevalent symptom was cough (96.1%). Across unvaccinated people, the highest prevalent symptom was fever (97.1%).
Regis et al., 2014 (33) Country: France Setting: Clinical or hospital Study period: 2004─2009 Publication type: Peer-reviewed journal article Title: Five years of hospital based surveillance of influenza-like illness and influenza in a short-stay geriatric unit.	People aged ≥69 years with ILI (n=1,353)	Among people with community-acquired ILI, 85.2%, 73.7%, and 12.3% had cough, fever (>37.88C), and sore throat. Among people with hospital-acquired ILI, 88.2%, 67.6%, and 14.7% had cough, fever (>37.88C), and sore throat.
van Wormer et al., 2014 (34) Country: US Setting: Clinical or hospital Study period: 2007─2011 Publication type: Peer-reviewed journal article	Adults aged ≥65 years with influenza and other acute respiratory illness in the outpatient setting (n=NR)	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

Study details	Patient population of interest (n=)	Outcomes
Title: A cross-sectional analysis of symptom severity in adults with influenza and other acute respiratory illness in the outpatient setting.		

aIIV3: Adjuvanted trivalent influenza vaccine; aTIV: Adjuvanted trivalent influenza vaccine; CI: Confidence interval; C: Celsius, ED: Emergency department; ER: Emergency room; FluiiQ™: Influenza intensity and impact questionnaire™; HDIIV3e: High-dose trivalent influenza vaccine; HD-TIV: High-dose trivalent influenza vaccine; ICU: intensive care unit; IQR: Interquartile range; OR, Odds ratio, SD: Standard deviation; US: United States; USD: US dollar.