High clinical burden of influenza disease in adults aged ≥65 years: Can we do better? A systematic literature review

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Appendix

Appendix A: Index of supplementary tables

Appendix B: Search strategies

Table S1. 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/ 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		exp *health economics/	283,114

24	Economic terms	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
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**

Appendix C: JBI critical appraisal checklists

Table S2 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 S3 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 S4 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 S5 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 S6 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 S7 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):				

Appendix D: Supplementary material

Table S8 Summary of included studies

Study details	Patient population of interest (n=)	Outcomes
Pacis *et al.*, 2022(60) **Country: Germany** **Setting: Clinical or hospital** **Study period: 2019–2020** **Publication type: Conference abstract.** **Title: Social distancing and trends in influenza hospitalization during the COVID-19 outbreak: a difference-in-difference analysis of German claims data.**	Adults aged ≥80 years with an influenza diagnosis (ICD-10-CM codes J10-J11) (n=NR).	> Mean rate of weekly influenza-related hospitalizations among patients aged ≥80 years decreased from 5.8 in 2019, to 2.2 in 2020 (aIRR: 0.36, 95% CI: 0.28–0.46, p<0.001).
Hernandez *et al.*, 2020(48) **Country: Spain** **Setting: Hospital** **Study period: 2017–2018** **Publication type: Conference abstract** **Title: Respiratory syncytial virus, an underestimated disease in the elderly population.**	Adults ≥65 years with either community-acquired or hospital/healthcare-associated ILI (n=842 samples)	> Of the 842 ILI samples, 394 (16%) were influenza A; 289 (12%) were influenza B and 159 (6.5%) were RSV. > Admission rate for influenza was 81.1% (vs 80.5% for RSV). > Median length of stay was 11.2 days for patients with influenza. > Admission to ICU was required by five patients with influenza. > Mortality rate for influenza was 12/159, 7.5%.
Li *et al.*, 2021(35) **Country: China**	Adults aged ≥65 years with influenza-associated respiratory and circulatory morbidity (n=NR).	> Mean annual rate of influenza-associated excess respiratory and circulatory hospitalizations was 696.4 per 100,000 population (95% CI: 396.3–1,026.4).

Setting: Community **Study period: 2010–2017** **Publication type: Peer-reviewed journal article.** **Title: Development of influenza-associated disease burden pyramid in Shanghai, China, 2010–2017: a Bayesian modelling study.**	> Mean annual rate of influenza-associated excess circulatory hospitalizations was 501.9 per 100,000 population (95% CI: 406.5–600.2). > Mean annual rate of influenza-associated excess respiratory hospitalizations was 210.2 per 100,000 population (95% CI: 63.1–404.7). > When stratified into influenza strains A(H1N1), A(H3N2) and B, the mean annual rate of influenza-associated excess respiratory hospitalizations was 97.9 (95% CI: 53.8–146.6), 323.6 (95% CI: 243.9–400.3), and 87.3 (95% CI: 22.9–153.1) per 100,000 population, respectively. > Similarly, the mean annual rate of influenza-associated excess circulatory hospitalizations was 41.4 (95% CI: 2.8–114.2), 95.8 (95% CI: 53.8–146.6), and 65.9 (95% CI: 4.4–173.2) per 100,000, for strains A(H1N1), A(H3N2) and B, respectively. > The influenza-associated excess respiratory disease mortality rate was 35.70 per 100,000 population (95% CI: 27.8–44.2). > The influenza A(H1N1) specific rate was 5.90 per 100,000 population (95% CI: 2.5–9.4). > The influenza A(H3N2) specific rate was 23.13 per 100,000 population (95% CI: 18.0–27.8). > The influenza B specific rate was 7.21 per 100,000 population (95% CI: 1.7–12.6). > The influenza-associated excess Circulatory disease mortality rate was 52.81 per 100,000 population (95% CI: 28.7–79.4). > The influenza A(H1N1) specific rate was 7.00 per 100,000 population (95% CI: 0.3–17.3). > The influenza A(H3N2) specific rate was 36.78 per 100,000 population (95% CI: 15.0–56.8). > The influenza B specific rate was 7.78 per 100,000 population (95% CI: 0.4–22.6). > The influenza-associated excess circulatory and respiratory disease mortality rate was 81.03 per 100,000 population (95% CI: 50.4–117.0). > The influenza A(H1N1) specific rate was 9.73 per 100,000 population (95% CI: 0.9–23.8). > The influenza A(H3N2) specific rate was 57.47 per 100,000 population (95% CI: 31.7–82.6). > The influenza B specific rate was 13.62 per 100,000 population (95% CI: 0.9–34.5).

Chair *et al.*, 2021(36) **Country: China** **Setting: Clinical or hospital** **Study period: 1997–2017** **Publication type: Peer-reviewed journal article.** **Title: Influenza-associated hospitalizations and risk of subsequent heart failure hospital admissions: a 20-year territory-wide registry study in Hong Kong, China.**	Adults aged ≥65 years with laboratory confirmed influenza (n=NR).	> Between 1997 and 2017, there were 27,885 influenza-related hospitalizations. > During the study period, 1,199 patients were admitted for heart failure within 12 months of influenza-associated hospitalization. > The aOR for heart failure-related admittance was 1.1 (95% CI: 1.0–1.2).
Wang *et al.*, 2015(37) **Country: China** **Setting: Clinical or hospital** **Study period: 2004–2010** **Publication type: Peer-reviewed journal article** **Title: Age and sex differences in rates of influenza-associated hospitalizations in Hong Kong.**	Adults aged ≥65 years with an influenza diagnosis (ICD-9-CM codes 480–487) (n=NR).	> Excess rate of influenza A(H1N1)-associated hospitalizations was stratified by sex, with a rate of 26.4 (95% CI: -5.3–58.1) per 100,000 population for men, and 25.7 (95% CI: -0.1–47.3) per 100,000 population for women. > Similarly stratified, excess rate of influenza A(H3N2)-associated hospitalizations was 213.8 (95% CI: 166.3–260.7) and 204.4 (95% CI: 162.4–245.7) per 100,000 population, for men and women respectively. > Excess rate of influenza B associated hospitalizations was 119.8 (95% CI: 84.2–155.0) and 74.9 (95% CI: 48.9–101.4) per 100,000 population, for men and women respectively.
Lee *et al.*, 2021(25) **Country: US** **Setting: Community** **Study period: 2013–2014** **Publication type: Peer-reviewed journal article**	Adults aged ≥65 years with an influenza diagnosis (ICD-9-CM code 487) (n=78,668).	> The proportion of patients readmitted within 30-days of influenza-related hospitalization was higher among patients aged ≥80 years (5.8%, n=2,443) than patients aged 65–79 years (4.8%, n=1,750). > The proportion of 'in-hospital all-cause 30-day mortality' in octogenarians (≥80 years old, n=41,806) was 2.89% (P<0.0001). > The proportion of 'in-hospital all-cause 30-day mortality' in older adults (65–74 years old, n=36,862) was 1.57% (P<0.0001). > The HR for the association between age group and in-hospital all-cause 30-day mortality among individuals aged 65–79 years hospitalized with influenza was 1.03 (95% CI: 0.9-1.2). > The HR for the association between age group and in-hospital all-cause 30-day mortality among individuals aged ≥80 years hospitalized with influenza was 1.91 (95% CI: 1.6–2.2).

Title: Comparison of influenza hospitalization outcomes among adults, older adults, and octogenarians: a US national population-based study.		> The HR for the association between age groups and mortality among patients hospitalized with influenza using young adults as reference group was: - 1.13 (95% CI: 0.8–1.6) in those with diabetes. - (95% CI: 0.7–1.6) in those with heart failure. - 0.93 (95% CI: 0.7–1.3) in those with COPD.
Andrew *et al.*, 2021(54) **Country: Canada** **Setting: Clinical or hospital** **Study period: 2011–2012** **Publication type: Peer-reviewed journal article.** **Title: Persistent functional decline following hospitalization with influenza or acute respiratory illness.**	Adults aged ≥65 years admitted to hospital with influenza (n=346).	> During the study period, 346 patients were hospitalized with influenza-related illness. > Of which, 15% (n=52) were admitted from long-term care facilities. > The proportion of patients requiring ICU admission was 11.3%. > The proportion of '30-day post-discharge mortality' in influenza patients was 12.1% (P<0.01). > The number of influenza patients who were 'alive at 30-day post-discharge' was 304. > The proportion of patients with influenza-related catastrophic disability or influenza-related death was 23.
Chung *et al.*, 2020(26) **Country: US** **Setting: Clinical or hospital** **Study period: 2018–2019** **Publication type: Peer-reviewed journal article.** **Title: Effects of influenza vaccination in the United States during the 2018-2019 influenza season.**	Adults aged ≥65 years admitted to hospital with influenza.	> Using Flu VE Network data, it was estimated that 157,983 (95% UI: 102,336–316,414) hospitalizations could be attributed to Influenza A(H3N2) related illness during the 2018–2019 season. > The estimated number of hospitalizations that could be attributed to Influenza B related illness was 11,524 (95% UI: 7,396–23,360) over the same period. > The 95% UI estimates were generated from 5,000 Monte Carlo simulations. > The influenza number of deaths in patients with A(H3N2) was 14,450/1,520,099. > The influenza number of deaths in patients with influenza B was 1,054/35,460.
Pivette *et al.*, 2020(49) **Country: France** **Setting: Clinical or hospital**	Adults aged ≥80 years with a laboratory confirmed influenza diagnosis (n=NR).	> Between 2012 and 2017 mean annual rate of influenza hospitalization was 134 per 100,000 population. > Over the study period, hospitalization rate ranged between 28 and 358 per 100,000 population, during the 2013–2014 and 2016–2017 seasons, respectively.

Study period: 2012–2017

Publication type: Peer-reviewed journal article.

Title: Characteristics of hospitalizations with an influenza diagnosis, France, 2012-2013 to 2016-2017 influenza seasons.

- Between 2012 and 2017, 6% of patients aged ≥80 years that were hospitalized for influenza were admitted to the ICU.
- The proportion of hospitalizations that led to ICU admission were stratified by season and are presented in the embedded table below:
- The proportion of patients dying of influenza following all hospitalizations (n=24,849) was 10%.
- The proportion of ICU patient dying (n=1,464) of influenza was 32%.

Season	Hospitalizations (n)	ICU admission (%)
2012–2013	1,936	7
2013–2014	1,034	9
2014–2015	6,460	7
2015–2016	2,142	9
2016–2017	13,277	4

- Between 2012 and 2017, 8%–10% of hospitalized patients died of influenza.

Palekar *et al.*, 2019(61)

Country: Brazil, Canada, US

Setting: Clinical or hospital

Study period: 2010–2015

Publication type: Peer-reviewed journal article.

Title: Burden of influenza-associated respiratory hospitalizations in the Americas, 2010-2015.

Adults aged ≥65 years admitted to hospital with influenza.

- The rate of influenza-associated hospitalizations in Brazil ranged from 47–459 per 100,000 population between 2010 and 2015.
- The rates of influenza-associated hospitalizations in the US and Canada ranged from 287–734 and 150–677 per 100,000 population during the timespans 2010–2013 and 2010–2014, respectively.

Yokomichi *et al.*, 2019(56) **Country: Japan** **Setting: Clinical or hospital** **Study period: 2012-2016** **Publication type: Peer-reviewed journal article.** **Title: Incidence of hospitalization for severe complications of influenza virus infection in Japanese patients between 2012 and 2016: A cross-sectional study using routinely collected administrative data**	Adults aged 65-74 years with influenza diagnosis (n=231,120)	> The proportion of influenza infections hospitalized in those aged 65-74 years was 2.21%. > During the study period, 1,919 patients aged 65–74 were hospitalized with influenza. > The incidence of hospitalization with severe complications per 100,000 confirmed influenza infections in those aged 65-74 was 56 for acute respiratory failure, 245 for pneumonia, 1.7 for ARDS, 0 for febrile seizure and 0.4 for Encephalitis/encephalopathy. > The hospitalization rate for influenza and any of the five complications was 271 per 100,000 influenza infections. > During the study period, the rate of pneumonia among adults hospitalized with severe influenza complications was 245 per 100,000 population. > During the study period, the rate of ARI and ARDS diagnoses among adults hospitalized with severe influenza complications was 56 and 1.7 per 100,000 population, respectively. > During the study period, the rate of febrile seizures and encephalitis/encephalopathy was 0 and 0.4 per 100,000 population, respectively.
Oliva *et al.*, 2018(42) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2010–2016** **Publication type: Peer-reviewed journal article.** **Title: Estimating the burden of seasonal influenza in Spain from surveillance of mild and severe influenza disease, 2010-2016.**	Adults aged ≥65 years admitted to hospital with severe and laboratory-confirmed influenza (n=NR).	> Between 2010 and 2016, the rate of influenza-related hospitalizations was 16.5 (95% CI: 15.7–17.4) per 100,000 population. > When stratified by influenza season, there were 472 (95% CI: 430–517) incidences of influenza hospitalization in 2010–2011, 546 (95% CI: 501–594) in 2011–2012, 352 (95% CI: 316–391) in 2012–2013, 2,052 (95% CI: 1,964–2,143) in 2013–2014, 2,366 (95% CI: 2,272–2,463) in 2014–2015, and 2,636 (95% CI: 2,532–2,735) in 2015–2016. > During the study period the mean annual rate of influenza-attributable ICU admissions was 4.5 (95% CI: 4.1–5.0) per 100,000 population. > The proportion of ICU admission among patients with severe hospitalized influenza was 27.3% (95% CI: 26.3–28.2).

<table>
<tr>
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The mean annual number of influenza-attributable ICU admissions stratified by season are presented in the embedded table below:
The average annual rate of death due to influenza was 3.0 per 100,000 population (95% CI: 2.6–3.4).

<table>
<tr><th>Season</th><th>Number of admissions</th><th>95% CI</th></tr>
<tr><td>2010–2011</td><td>137</td><td>115–162</td></tr>
<tr><td>2011–2012</td><td>189</td><td>163–218</td></tr>
<tr><td>2012–2013</td><td>116</td><td>96–139</td></tr>
<tr><td>2013–2014</td><td>553</td><td>508–601</td></tr>
<tr><td>2014–2015</td><td>586</td><td>540–635</td></tr>
<tr><td>2015–2016</td><td>714</td><td>663–768</td></tr>
</table>

The proportion of deaths in hospitalized patients with severe influenza was 18.1% (95% CI: 17.3–18.9).
The annual number of deaths in hospitalized patients ranged from 69 (54–87) to 465 (424–509) between 2010–2016.
The highest rate was reported in 2014/14 and the lowest in 2012/13.

</td>
</tr>
<tr>
<td>Sruamsiri et al., 2017(57)

Country: Japan

Setting: Clinical or hospital

Study period: 2014–2015

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.</td>
<td>Adults aged ≥65 years admitted to hospital with influenza (n=NR).</td>
<td>

Of 3,249 influenza-related hospitalizations, 45% were subcategorized as regular in nature, 50% as emergency, and 173 as requiring ICU admission.
During the study period, 173 patients were admitted to the ICU with influenza-related disease.
The number of deaths was 239 (7%).

</td>
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</table>

Wu *et al.*, 2017(38) **Country: China** **Setting: Clinical or hospital** **Study period: 1998–2013** **Publication type: Peer-reviewed journal article.** **Title: A joint analysis of influenza-associated hospitalizations and mortality in Hong Kong, 1998–2013.**	Adults aged ≥65 years admitted to hospital with influenza (n=NR).	> Mean influenza-related hospitalization rates were 847.2 (95% CI: 775.2–913.2) per 100,000 population. > When stratified by strain, the rate of influenza A(H3N2) was 502.5 (95% CI: 454.0–548.8), influenza A(H1N1) was 51.3 (95% CI: 7.6–89.4), and influenza B was 276.0 (95% CI: 227.5–325.4), each per 100,000 population. > The mean mortality rates were 48.7 (95% CI: 40.4–56.5), 9.2 (95% CI: 4.0–14.1), 26.5 (95% CI: 21.1–31.9), and 11.3 (95% CI: 5.0–17.2) per 100,000 population, in patients with overall influenza, influenza A(H1N1), influenza A(H3N2), and influenza B, respectively. > Excess respiratory death rate was 58.8 per 100,000 population (95% CI: 49.1–69.1).
Matias *et al.*, 2017(39) **Country: US** **Setting: Clinical or hospital** **Study period: 1997–2009** **Publication type: Peer-reviewed journal article.** **Title: Estimates of hospitalization attributable to influenza and RSV in the US during 1997–2009, by age and risk status.**	Adults aged ≥65 years admitted to hospital with influenza (n=NR).	> The mean annual incidence of hospitalizations attributable to influenza was 48,459 (SD: 17,474) among patients aged 65–74 years, and 102,001 (SD:38,054) among patients aged ≥75 years. > The mean annual rate of influenza-attributable hospitalizations was 256 (SD: 91, range: 83–385) per 100,000 population among patients aged 65–74, and 589 (SD: 216, range: 173–864) per 100,000 population among patients aged ≥75 years. > The patient population of interest was also stratified by both influenza strain and age group (see embedded table below)

Influenza strain	Age group (years)	Incidence (SD)	Rate per 100,000 (SD)
A(H1N1)	65–74	4,252 (5,075)	22 (26)
A(H1N1)	≥75	4,760 (5,669)	27 (32)
A(H3N2)	65–74	34,495 (23,184)	183 (124)
A(H3N2)	≥75	71,345 (47,891)	414 (279)
B	65–74	9,712 (6,876)	51 (36)
B	≥75	25,896 (18,344)	148 (104)

Gonzalez *et al.*, 2016(43)

Country: Spain

Setting: Clinical or hospital

Study period: 2009–2015

Publication type: Conference abstract

Title: Evaluation of influenza virus A in elderly hospitalized.

Adults aged ≥75 years with laboratory-confirmed influenza (n=44).

- Hospital readmission rate within 30 days was 4%.
- The proportion of patients admitted to the ICU and requiring invasive mechanical ventilation was 27%.
- The proportion of patients that were admitted to the ICU and died during hospitalization was 33%.
- The proportion of patients with influenza-related secondary pneumonia infection was 38%.
- The rate of influenza-attributable hospitalizations was stratified by age and risk group.
- High-risk was defined as the presence of COPD, CVD, kidney disorders, diabetes, immunosuppression, liver disorders, stroke, or CNS disorders.
- The number of hospitalizations for the low-risk cohort was higher in patients aged ≥75 years (157 [SD: 68] per 100,000 population), than patients aged 65–74 years (49 [SD: 23] per 100,000 population).
- A similar trend was observed in the high-risk group, with the number of hospitalizations higher in patients aged ≥75 years (769 [SD: 331] per 100,000 population) than patients aged 65–74 years (350 [SD: 163] per 100,000 population).
- The rate of influenza-attributable hospitalizations stratified by age, risk group and influenza strain are presented in the embedded table below:

Strain	Age group (years)	Hospitalizations per 100,000 population (SD)	
		Low-risk	High-risk
Influenza A(H3N2)	65–74	39 (26)	286 (192)
	≥75	117 (80)	587 (388)
Influenza A(H1N1)	65–74	0 (0)	20 (25)
	≥75	0 (0)	21 (27)
Influenza B	65–74	9 (6)	44 (32)
	≥75	40 (28)	161 (116)

Ramos *et al.*, 2016(44) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2015** **Publication type: Peer-reviewed journal article.** **Title: Seasonal influenza in octogenarians and nonagenarians admitted to a general hospital: epidemiology, clinical presentation, and prognostic factors.**	Adults aged ≥65 years with laboratory-confirmed influenza (n=164).	> During the study period, the proportion of influenza hospitalizations was greater among those aged >80 years (n=87, 4.9% of total number of patients admitted to study hospital) compared to those in the 65–79 years age group (n=77, 3.0% of total number of patients admitted). > Therefore, the risk of being hospitalized for influenza was higher among those aged >80 years (5.9; 95% CI: 4.1–8.2) compared to the 65–79 years age group (3.5; 95% CI: 2.5–5.0). > The proportion of influenza mortality in octogenarians and nonagenarians admitted to hospital with influenza was 19% (OR: 9.21; 95% CI: 1.65–51.35, P=0.01). > Proportion of overall influenza death across age group was 78.9% (OR: 7.96; 95% CI: 2.54–24.9, P<0.001). > The proportion of octogenarians and requiring antibiotic treatment and steroid treatment were 64.6% and 40.6%, respectively between January and April 2015.
Reed *et al.*, 2015(27) **Country: US** **Setting: Clinical or hospital** **Study period: 2010–2013** **Publication type: Peer-reviewed journal article.** **Title: Estimating influenza disease burden from population-based surveillance data in the United States.**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> The rate of influenza-related hospitalizations per 100,000 population over the three seasons of study was 335 (95% CI: 208–462) in 2010–2011, 170 (95% CI: 96–245) in 2011–2012, and 1,033 (95% CI: 712–1,355) in 2012–2013. > The proportion of hospitalized patients who were admitted to ICU ranged was 16.1% in 2010–2011, 15.9% in 2011–2012, and 14.7% in 2012–2013. > The estimated rate of ICU admission over the study three seasons (2010–2013) was 53.9 (95% CI: 32.8–75.0), 27.0 (95% CI: 14.5–39.4), and 151 (95% CI: 103–199), per 100,000 population respectively. > The estimated influenza death rate was 22.8 (95% CI: 13.1–32.5), 8.6 (95% CI:3.8–13.3), and 54.6 (95% CI: 36.2–73.0) per 100,000 population in 2010/11, 2011/12, and 2012/13, respectively. > The risk of death if hospitalized was 4.7%, 3.4%, and 3.6% in 2010/11, 2011/12, and 2012/13, respectively.
Chan *et al.*, 2015(40) **Country: China** **Setting: Clinical or hospital**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> Mean annual rate of influenza A-related hospitalizations among adults aged ≥65 years was 17.3 and 19.5 per 10,000 population for female and male patients, respectively. > For female and male patients with influenza B related hospitalization, mean annual rate was 2.9 and 4.2 per 10,000 population, respectively.

Study period: 1998–2012

Publication type: Peer-reviewed journal article.

Title: Hospitalization incidence, mortality, and seasonality of common respiratory viruses over a period of 15 years in a developed subtropical city.

> Mean annual rate of influenza-related hospitalizations in Hong Kong between 1998 and 2012 stratified by influenza strain, age group and sex are presented in the embedded table below:

> Annual influenza A mortality rate per 100,000 hospitalizations:

- In female patients aged ≥65years= 102.4
- In female patients aged 65–74 years= 27.8
- In female patients aged >74 years= 182.7
- In male patients aged ≥65years= 138.0
- In male patients aged 65–74 years= 70.44

Influenza strain (sex)	Age group (years)	Rate per 10,000 population
A (female)	65–74	7.3
	≥75	27.6
A (male)	65–74	10.4
	≥75	33.9
B (female)	65–74	0.9
	≥75	4.9
B (male)	65–74	2.1
	≥75	7.5

- In male patients aged >74 years= 248.10

> Annual influenza B mortality rate per 100,000 hospitalizations:

- In female patients aged ≥65years= 10.6
- In female patients aged 65–74 years= 0.0
- In female patients aged >74 years= 20.7
- In male patients aged ≥65years= 30.6
- In male patients aged 65–74 years= 21.56

> In male patients aged >74 years= 44.47

Appiah *et al.*, 2015(28) **Country: US** **Setting: Community** **Study period: 2014–2015** **Publication type: Epidemiology report.** **Title: Influenza Activity — United States, 2014–15 season and composition of the 2015–16 influenza vaccine.**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> Annual rate of influenza-related hospitalizations during the 2014–2015 season, was 322.8 cases per 100,000 population. > Between 2010 and 2014, the annual rate of influenza-related hospitalizations ranged from 30.2 to 183.2.
Regis *et al.*, 2014(50) **Country: France** **Setting: Clinical or hospital** **Study period: 2004–2009** **Publication type: Peer-reviewed journal article.** **Title: Five years of hospital-based surveillance of ILI and influenza in a short-stay geriatric unit.**	Adults aged ≥65 years with ILI (n=115).	> The number of community-acquired ILI and hospital-acquired ILI cases were 81 and 34, respectively. > The proportion of patients admitted from the community cohort for cardio-respiratory disease without fever was 48.2% (n=39), and for infectious disease with fever was 42.0% (n=34). > The proportion of patients from the hospital-acquired cohort admitted for cardio-respiratory disease without fever 52.9% (n=18), and for infectious disease with fever was 5.9% (n=2). > The proportion of deaths in community-acquired influenza (n=81) aged 69–103 years was 6.2%. between 2005 and 2009. > The proportion of deaths in-hospital-acquired influenza (n=34) aged 77–99 years was 4.8%, between 2005 and 2009. > The rate of respiratory complications among patients with community (n=81) and hospital-acquired (n=34) ILI was 7.4 and 2.9%, respectively. > The rate of cardiac complications in the same subpopulations was 3.7 and 0%, respectively.
Ortiz *et al.*, 2013(30) **Country: US** **Setting: Clinical or hospital** **Study period: 2003–2009**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR), acute respiratory failure was defined by ICD-9-CM codes.	> The number of hospitalizations due to influenza-associated respiratory failure varied by age group. > Total incidence of influenza-associated hospitalizations among patients aged 65–74, 75–84 and >84 years were 1,502, 1,956, and 1,259, respectively. > The equivalent rates of hospitalization for patients aged 65–74, 75–84 and >84 years were 8.7 (95% CI: 0.3–77.7), 16.5 (95% CI: 1.5–126.2) and 27.9 (95% CI: 3.2–170.4) per 100,000 population.

Publication type: Peer-reviewed journal article. **Title: Population-based incidence estimates of influenza-associated respiratory failure hospitalizations, 2003 to 2009.**		
Zhou *et al.*, 2012(31) **Country: US** **Setting: Clinical or hospital** **Study period: 1993–2008** **Publication type: Peer-reviewed journal article.** **Title: Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008).**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> The observed mean rate of influenza-associated hospitalizations during the study period was 48.1 per 100,000 person-years. > Estimated influenza-associated hospitalization rates were derived using Negative Binomial Regression modeling. > The estimated mean rate of influenza-associated hospitalizations during the study period was 309.1 (95% CI: 186.0–1,103.7) per 100,000 person-years. > When stratified by influenza strain, estimated hospitalization rates for influenza A(H1), influenza A(H3) and influenza B were 2.1 (95% CI: 0.0–268.0), 239.9 (95% CI: 164.0–485.5) and 68.4 (95% CI: 22.6–344.6) per 100,000 person-years, respectively. > The proportion of estimated influenza hospitalizations listing an ICD-9-CM code for influenza was 14.7% (range: 6.0–23.3).
D'Mello 2015(41) **Country: US** **Setting: Surveillance** **Study period: 2014–2015** **Publication type: Epidemiology report.** **Title: Update: Influenza activity — United States, September 28, 2014–February 21, 2015.**		> During the 2014–2015 season, the overall rate of influenza-associated hospitalization was 258 per 100,000 population. > Over the previous three seasons, the overall rate of influenza-associated hospitalizations ranged from 30.2–183.2 per 100,000 population.
Moss *et al.*, 2020(58) **Country: UK** **Setting: Clinical or hospital**	Adults aged ≥65 years with laboratory confirmed influenza (n=36,850).	> During the 2017–2018 season, there were 8,140 hospitalizations among patients aged 65–75 years and 17,650 among patients aged ≥75 years. > The number of hospitalizations decreased during the 2018–2019 season, as there were 5,605 hospitalizations among patients aged 65–74 years and 9,350 among patients aged ≥75 years.

<table>
<tr>
<td>Study period: 2017–2019

Publication type: peer-reviewed journal article.

Title: Quantifying the direct secondary health care cost of seasonal influenza in England.</td>
<td></td>
<td>> The proportion of patients aged 65–74 years, dying in-hospital, were 6.2% from 2017–2018 and 6.5% from 2018–2019.
> The proportion of patients aged ≥75 years, dying in-hospital, were 11.0% from 2017–2018 and 11.2% from 2018–2019.</td>
</tr>
<tr>
<td>Soldevila et al., 2021(45)

Country: Spain

Setting: Clinical or hospital

Study period: 2017–2018

Publication type: Peer-reviewed journal article.

Title: Behavior of hospitalized severe influenza cases according to the outcome variable in Catalonia, Spain, during the 2017–2018 season.</td>
<td>Adults aged ≥65 years admitted to ICU with laboratory confirmed influenza (n=NR).</td>
<td>> Severe influenza was defined as a case requiring hospitalization for pneumonia, septic shock, multi-organ failure, acute respiratory distress, and death.
> The adjusted odds ratio of ICU admission for patients with severe influenza aged 65–74 years was 0.41 (95% CI: 0.23–0.74, p<0.01).
> The adjusted odds ratio for patients with severe influenza aged ≥75 years was 0.3 (95% CI: 0.17–0.53, p<0.01).
> During the study period, 37 patients aged 65–74 years and 61 aged ≥75 years were admitted to the ICU admission with severe influenza.
> The number of in-hospital death of patients aged ≥75 years with severe influenza was 120 (adjusted OR: 6.95; 95% CI: 2.8–1.8).
> The number of in-hospital death of patients aged 65–74 years with severe influenza was 27 (adjusted OR: 3.19; 95% CI: 1.2–8.5).</td>
</tr>
<tr>
<td>Lemaitre et al., 2022(51)

Country: France

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.</td>
<td>Adults aged ≥65 years admitted to the ICU with laboratory-confirmed influenza (n=NR), defined by ICD-9-CM and ICD-10-CM codes.</td>
<td>> The number of influenza-associated hospitalizations stratified by age group and season are presented in the embedded table below:

<table>
<tr><th rowspan="2">Season</th><th colspan="3">Hospitalization incidence</th></tr>
<tr><th>65–74</th><th>75–84</th><th>≥85</th></tr>
<tr><td>2010–2011</td><td>525</td><td>507</td><td>332</td></tr>
<tr><td>2011–2012</td><td>710</td><td>1,190</td><td>1,077</td></tr>
<tr><td>2012–2013</td><td>1,069</td><td>1,306</td><td>1,035</td></tr>
<tr><td>2013–2014</td><td>784</td><td>860</td><td>544</td></tr>
<tr><td>2014–2015</td><td>2,346</td><td>3,717</td><td>3,602</td></tr>
</table>
</td>
</tr>
</table>

2015–2016	1,911	1,770	1,137
2016–2017	3,619	6,556	8,335
2017–2018	6,115	8,332	8,528
All seasons	17,079	24,238	24,590

- The median proportion of in-hospital deaths was 6.1 (range: 3.9–6.9) in patients aged 65–74 years, 6.6 (range: 5.1–7.5) in patients aged 75–84 years, and 9.3 (range:7.1–11.6) in patients aged ≥85 years.
- The proportion of patients in the age groups 65–74, 75–84 and ≥85 years with all-cause readmittance to hospital within 3 months of discharge was 27.7% (range: 25.4–28.9), 26.0% (range: 24.4–28.0) and 21.9% (20.6–24.2), respectively.
- The proportion of patients in the age groups 65–74, 75–84 and ≥85 years readmitted to hospital within 3 months of discharge for cardiac conditions was 6.3% (range:5.1–8.8), 6.3% (range: 5.6–8.8), and 5.8% (range: 5.2–6.4), respectively.
- Similarly, for respiratory causes of hospital readmittance, the proportion of patients aged 65–74, 75–84 and ≥85 years was 6.8 (range: 5.9–7.5), 6.0 (range: 5.1–7.4) and 5.5 (range: 4.3–6.0), respectively.
- During the 2012–2013 season, the proportion of patients requiring an escalation of care, was reported for each of the age groups 65–74, 75–84 and ≥85 years.
- Escalation of care was defined as transfer from the emergency unit and occurred in 21.8% (range: 20.0–23.2), 23.7 (range: 21.3–24.9) and 25.2 (range: 22.8–25.6) of cases among those aged 65–74, 75–84 and ≥85 years, respectively.

Casado *et al.*, 2016(46)

Country: Spain

Setting: Clinical or hospital

Study period: 2013–2014

Adults aged ≥65 years admitted to the ICU with laboratory-confirmed influenza (n=433).

- The proportion of patients requiring ICU admission was 10.2% (n=44).
- The proportion of ‘in-hospital or within 30-days post-hospital admission mortality’ was 12.5%.
- The proportion of ‘in-hospital mortality’ was 9.2%.
- The proportion of patients requiring antiviral treatment was 90.3%.

Publication type: Peer-reviewed journal article. **Title: Effect of influenza vaccination on the prognosis of hospitalized influenza patients.**		
Nguyen *et al.*, 2016(33) **Country: US** **Setting: Clinical or hospital** **Study period: 2006–2012** **Publication type: Peer-reviewed journal article.** **Title: Seasonal influenza infections and cardiovascular disease mortality.**	Adults aged ≥65 years with ILI (n=NR).	> During the study period in New York, the mean rate of daily ILI emergency department visits among adults aged ≥65 years was 6.8 (SD: 4.2).
Jules *et al.*, 2014(29) **Country: US** **Setting: Clinical or hospital** **Study period: 2009–2011** **Publication type: Peer-reviewed journal article.** **Title: Age-specific influenza-related emergency department visits and hospitalizations in 2010–2011 compared with the pandemic year 2009–2010.**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> The annual incidence of influenza-related ED visits in Middle Tennessee was 1,015 in 2010–2011, an increase from 111 in 2009–2010. > The annual rate of hospitalization in the 2020–2011 season was 6.7 (95% CI: 2.4–16.5) per 1,000 population. > Annual influenza-associated hospitalization incidence among Middle Tennessee residents aged ≥65 years was 1,667 during the 2010–2011 season. > The rate of hospitalizations within this population was 4.5 (95% CI: 3.1–6.5) per 1,000 residents for the 2010–2011 season. > During the 2009–2010 and 2010–2011 influenza seasons, 10% of the cohorts developed influenza-associated pneumonia.
Gruneir *et al.*, 2014(55) **Country: Canada** **Setting: Clinical or hospital**	Adults aged ≥65 years with laboratory-confirmed influenza (n=NR).	> The rate of influenza-associated ED visits was stratified by living arrangements and age. > Among long-term care residents aged 66–105, 66–85 and 86–105 years, rate of influenza-associated ED visits was 300.5, 290.6 and 310.0, respectively per 100,000 population. > The rate of influenza-associated ED visits among community residents in the same age groups was 124.7, 113.5 and 210.9, respectively per 100,000 population.

Study period: 2002–2008 **Publication type: Peer-reviewed journal article.** **Title: Influenza and seasonal patterns of hospital use by older adults in long-term care and community settings in Ontario, Canada.**		> Stratified by living arrangements and age. > The rate of influenza-associated hospitalizations among long-term care residents aged 66–85, 86–105 and 66–105 years was 319.5, 325.4 and 322.5 per 100,000 population, respectively. > Among community residing patients within the same age groups, rate of hospitalization was lower at 69.1, 215.7 and 86.0 per 100,000 population, respectively.
Cheysson *et al.*, 2021(52) **Country: France** **Setting: Clinical or hospital** **Study period: 2010–2017** **Publication type: Peer-reviewed journal article.** **Title: Outpatient antibiotic use attributable to viral acute lower respiratory tract infections during the cold season in France, 2010–2017.**	Adults aged ≥75 years with ILI (n=NR).	> The proportion of patients with an ILI diagnosis who visited the ER was 0.18% (SD: 0.0).
Machado *et al.*, 2021(34) **Country: US** **Setting: Clinical or hospital** **Study period: 2011–2018** **Publication type: peer-reviewed journal article.** **Title: Relative effectiveness of influenza vaccines in elderly persons in the United States, 2012/2013–2017/2018 seasons.**	Adults aged ≥65 years with laboratory confirmed influenza (n=2,374,857).	> When looking at hospitalization or ER visits with a principal or secondary diagnosis of influenza between 2011-2018, 33.3% of events were ER visits.
Chaves *et al.*, 2015(32)	Adults aged ≥65 years with laboratory confirmed influenza (n=6,593).	> During the study period, 4% (n=252) of patients with influenza had required mechanical ventilation. > A total of 847 (13%) patients were admitted to the ICU with influenza-associated illness.

Country: US **Setting: Community** **Study period: 2010–2013** **Publication type: Peer-reviewed journal article.** **Title: Impact of prompt influenza antiviral treatment on extended care needs after influenza hospitalization among community-dwelling older adults.**		
Arrieta *et al.*, 2021(47) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2015–2017** **Publication type: Peer-reviewed journal article.** **Title: Influenza A-associated in-hospital mortality in very older people: does inflammation also play a role?**	Adults aged ≥85 years with diagnosed influenza A (n=117)	> 0.9% of patients ≥85 years required non-invasive mechanical ventilation (1/117). > The proportion of in-hospital mortality was 10.3% (P=0.03). > The proportion of patients with influenza-associated pneumonia was 20.5%. > 7.7% of patients with influenza experienced influenza-associated respiratory failure. > The proportion of patients with influenza-associated respiratory failure was 7.7%.
Bernadou *et al.*, 2020(53) **Country: France** **Setting: Hospital** **Study period: 2012–2018** **Publication type: Conference abstract** **Title: Estimating the burden of influenza on hospitals using severe acute respiratory infections in metropolitan France, 2012-2018.**	Adults aged ≥85 years with influenza-associated hospitalizations (n=NR)	> Influenza-associated SARI hospitalization rate in the subgroup of patients aged ≥85 years was 475 per 100,000 population.

Boddington *et al.*, 2017(59)

Country: England

Setting: Hospital

Study period: 2011–2015

Publication type: Peer-reviewed journal article

Title: Developing a system to estimate the severity of influenza infection in England: findings from a hospital-based surveillance system between 2010/2011 and 2014/2015.

Adults aged ≥65 years with laboratory confirmed influenza (n=NR)

> The aORs of hospitalization in patients aged ≥65 years by season are listed in table below:

Season	aOR	95% CI
2010–2011	6.1	4.3-8.8
2011–2012	1.8	1.3-2.7
2012–2013	4.6	3.4-6.2
2013–2014	2.1	1.5-3.0
2014–2015	7.5	5.7-10.0

> The aOR (95% CI) of hospitalization by influenza strain was 2.1 (1.6-2.6) for A/H3N3, 1.9 (1.5-2.4) for A/unknown, and 1.12 (0.9-1.5) for B

> The proportion of hospitalized cases admitted to ICU by season and strain in those aged ≥65 years is in the table below:

Season	Strain	Proportion cases admitted to ICU (%)
2010–2011	A/H3N2	0
	B	9.1
	A/unknown	0
2011–2012	A/H3N2	23.3
	B	0
	A/unknown	5.4
2012–2013	A/H3N2	16.1
	B	22.6
	A/unknown	13.1

Cheng *et al.*, 2015(67)

Country: US, Southern Brazil

Setting: Community

Study period: 2002─2008

Publication type: Peer-reviewed journal article

Title: Burden of influenza-associated deaths in the Americas, 2002–2008.

Adults aged ≥65 years who died of influenza (n=NR).

> People from the US who died due to the respiratory influenza:
- Aged 65–74 years = 8.2 per 100,000 population (95% CI: 6.0–16.0)
- Aged ≥75 years = 59.7 per 100,000 population (95% CI: 51.8–77.9)

> People from the US who died due to the circulatory influenza:
- Aged 65–74 years = 10.8 per 100,000 population (95% CI: 8.9–15.6)
- Aged ≥75 years = 52.0 per 100,000 population (95% CI: 47.4–62.1)

> People from the US who died due to the circulatory and respiratory influenza:
- Aged 65–74 years = 19.0 per 100,000 population (95% CI: 14.9–31.6)
- Aged ≥75 years = 111.7 per 100,000 population (95% CI: 99.3–140.1)

> People from Southern Brazil who died due to the respiratory influenza:

		- Aged 65–74 years = 15.9 per 100,000 population (95% CI: 3.9–17.4) - Aged ≥75 years = 70.0 per 100,000 population (95% CI: 15.0–187.5) > People from Southern Brazil who died due to the circulatory influenza: - Aged 65–74 years = 22.3 per 100,000 population (95% CI: 5.0–62.9) - Aged ≥75 years = 91.4 per 100,000 population (95% CI: 19.5–257.4) > People from Southern Brazil who died due to the circulatory and respiratory influenza: - Aged 65–74 years = 32.8 per 100,000 population (95% CI: 8.9–102.3) - Aged ≥75 years = 161.4 per 100,000 population (95% CI: 34.5–444.9)
Czaja *et al.*, 2018(68) **Country: US** **Setting: Clinical or hospital** **Study period: 2011─2015** **Publication type: Peer-reviewed journal article** **Title: Association of increasing age with hospitalization rates, clinical presentation, and outcomes among older adults hospitalized with influenza—US Influenza Hospitalization Surveillance Network.**	Adults aged ≥65 years with laboratory confirmed influenza (n=19,760).	> When comparing 75–84 year-olds to ≥85-year-olds, the OR for an increased risk of influenza mortality was 1.4 (95% CI: 1.2–1.7, P<0.01). > When comparing ≥85-year-olds to 75–84 year-olds, the OR for an increased risk of influenza mortality was 2.1 (95% CI: 1.7─2.6, P<0.01). > The risk of developing influenza-related pneumonia for patients aged ≥85 years compared to patients aged 65–74 years was 1.2 (95% CI: 1.0–1.3, p=0.01).
Czaja *et al.*, 2019(69) **Country: US** **Setting: Clinical or hospital** **Study period: 2011─2015**	Adults aged ≥65 years with laboratory confirmed influenza (n=19,760).	> 225/5,956 patients aged 65–74 years died in the hospital or were transferred to hospice. > 370/6,998 patients aged 75–84 years died in the hospital or were transferred to hospice. > 588/6,806 patients aged ≥85 years died in the hospital or were transferred to hospice. > The OR for in-hospital death or transfer to hospice in patients aged 75–84 years was 1.4 (95% CI: 1.2–1.7).

Publication type: Peer-reviewed journal article **Title: Age-related differences in hospitalization rates, clinical presentation, and outcomes among older adults hospitalized with influenza—U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET).**		> The OR for in-hospital death or transfer to hospice in patients aged ≥85 years was 2.1 (95% CI: 1.7–2.6).
De Miguel *et al.*, 2022(70) **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.**	Adults aged ≥65 years with laboratory confirmed influenza (n=7,058).	> The influenza mortality proportion was 3.9% in people aged 64–74 years. > The influenza mortality proportion was 7.1% in people aged >74 years.
Feng *et al.*, 2012(91) **Country: China** **Setting: Clinical or hospital** **Study period: 2003─2008** **Publication type: Peer-reviewed journal article** **Title: Influenza-associated mortality in temperate and subtropical Chinese cities, 2003–2008.**	Adults aged ≥65 years who died from an influenza-associated conditions (n=NR).	> The mean annual number of all-cause influenza-associated excess deaths in the Northern cities - temperate climate (Dalian, Qingdao & Zhaoyuan) were 1,711 (95% CI: 751–5,701). > The mean annual number of all-cause influenza-associated excess deaths in Southern cities, subtropical climate (Shanghai, Wuhan, Yichang, Ningbo & Guangzhou) were 2,111 (95% CI: 307–8,781).
Hardelid *et al.*, 2013(113) **Country: England and Wales** **Setting: Community**	Adults aged ≥75 years with laboratory confirmed influenza (n=NR).	> The number of seasonal deaths caused by influenza; n (% of total deaths) between 1999–2010 was 107 (4.3%). > The highest rate was reported in 1999/2000 with 19,713 cases (8.2% of total deaths). > The lowest rate was reported in 2009/2010 with 988 (0.04% of total deaths).

Study period: 1999─2010 **Publication type: Peer-reviewed journal article** **Title: Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999–2010.**		> A particularly high increase of cases compared to the previous year was seen in 2004/2005 with 14,396 (4.0% of total deaths) and 2008/2009 with 14,137 (6.2% of total deaths).
Jin *et al.*, 2020(74) **Country: China (Shanghai)** **Setting: Clinical or hospital** **Study period: 2010─2015** **Publication type: Peer-reviewed journal article** **Title: Age- and sex-specific excess mortality associated with influenza in Shanghai, China, 2010–2015.**	Adults aged ≥65 years with ILI (n=NR).	> The influenza-associated excess mortality rate with any cause of death as underlying cause of death was: - 23.29 per 100,000 population in people with A(H1N1) influenza. - 97.02 per 100,000 population in people with A(H3N2) influenza. - 10.28 per 100,000 population in people with influenza B (Victoria). - 25.83 per 100,000 population in people with influenza B (Yamagata). - 154.97 per 100,000 population in in people with any influenza type. > The influenza-associated excess mortality rate with 'influenza and pneumonia' as underlying cause of death was: - 0.48 per 100,000 population in people with A(H1N1) influenza. - 1.60 per 100,000 population in people with A(H3N2) influenza. - -0.93 per 100,000 population in people with influenza B (Victoria). - 0.57 per 100,000 population in people with influenza B (Yamagata). - 1.71 per 100,000 population in in people with any influenza type. > The influenza-associated excess mortality rate with 'respiratory and circulatory influenza' as underlying cause of death was: - 15.79 per 100,000 population in people with A(H1N1) influenza. - 67.79 per 100,000 population in people with A(H3N2) influenza. - 7.07 per 100,000 population in people with influenza B (Victoria). - 15.88 per 100,000 population in people with influenza B (Yamagata).

		- 105.31 per 100,000 population in in people with any influenza type. > The influenza-associated excess mortality rate with 'respiratory diseases' as underlying cause of death was: - 7.54 per 100,000 population in people with A(H1N1) influenza. - 26.91 per 100,000 population in people with A(H3N2) influenza. - 4.55 per 100,000 population in people with influenza B (Victoria). - 8.95 per 100,000 population in people with influenza B (Yamagata). - 46.72 per 100,000 population in in people with any influenza type. > The influenza-associated excess mortality rate with 'ischemic heart disease' as underlying cause of death was: - 4.87 per 100,000 population in people with A(H1N1) influenza. - 19.67 per 100,000 population in people with A(H3N2) influenza. - 3.83per 100,000 population in people with influenza B (Victoria). - 5.51 per 100,000 population in people with influenza B (Yamagata). - 33.36 per 100,000 population in in people with any influenza type. > The influenza-associated excess mortality rate with 'COPD' as underlying cause of death was: - 6.89 per 100,000 population in people with A(H1N1) influenza. - 23.91 per 100,000 population in people with A(H3N2) influenza. - 4.10 per 100,000 population in people with influenza B (Victoria). - 8.47 per 100,000 population in people with influenza B (Yamagata). - 42.19 per 100,000 population in in people with any influenza type.
Iuliano *et al.*, 2018(2) **Country: Europe, Spain, Germany, UK, Americas, US, Canada, Brazil, Japan, China, Hong Kong,**	Adults aged ≥65 years with laboratory confirmed influenza (n=NR).	> The worldwide annual influenza-associated mortality in people aged 65–74 years ranged between 13.3–27.8 per 100,000 population. > The EU wide annual influenza-associated mortality in people aged 65–74 years ranged between 5.0–17.2 per 100,000 population. > The worldwide annual influenza-associated mortality in people aged >74 years ranged between 51.3–99.4 per 100,000 population.

Setting: Community **Study period: 2015** **Publication type: Peer-reviewed journal article** **Title: Estimates of global seasonal influenza-associated respiratory mortality: a modelling study.**		> The EU wide annual influenza-associated mortality in people aged v years ranged between 23.4–70.7 per 100,000 population. > The influenza-associated excess mortality rate in Canada, in people aged 65–74 years and >74 years was 6.1 (±2.2) per 100,000 population and 44.5 (±12.5) per 100,000 population, respectively. > The influenza-associated excess mortality rate in Canada, in people aged 65–74 years and >74 years was 6.1 (±2.2) per 100,000 population and 44.5 (±12.5) per 100,000 population, respectively. > The influenza-associated excess mortality rate in China, in people aged 65–74 years and >74 years was 19.1 (±7.0) per 100,000 population and 112.7 (±34.3) per 100,000 population, respectively. > The influenza-associated excess mortality rate in Hong Kong, in people aged 65–74 years and >74 years was 12.0 (±1.3) per 100,000 population and 84.6 (±9.3) per 100,000 population, respectively. > The influenza-associated excess mortality rate in Japan, in people aged 65–74 years and >74 years was 3.5 (±0.4) per 100,000 population and 27.5 (±2.9) per 100,000 population, respectively. > The influenza-associated excess mortality rate in South Africa, in people aged 65–74 years and >74 years was 123.3 (±7.5) per 100,000 population and 37.4 (±4.0) per 100,000 population, respectively. > The influenza-associated excess mortality rate in South Korea, in people aged 65–74 years and >74 years was 3.8 (±1.0) per 100,000 population and 24.9 (±6.6) per 100,000 population, respectively. > The influenza-associated excess mortality rate in Southern Brazil, in people aged 65–74 years and >74 years was 19.8 (±5.6) per 100,000 population and 111.1 (±40.5) per 100,000 population, respectively. > The influenza-associated excess mortality rate in Spain, in people aged 65–74 years and >74 years was 6.8 (±1.6) per 100,000 population and 54.7 (±15.0) per 100,000 population, respectively. > The influenza-associated excess mortality rate in UK, in people aged 65–74 years and >74 years was 17.3 (±13.2) per 100,000 population and 66.6 (±39.9) per 100,000 population, respectively. > The influenza-associated excess mortality rate in US, in people aged 65–74 years and >74 years was 8.6 (±1.0) per 100,000 population and 49.4 (±6.2) per 100,000 population, respectively. >
McGowan *et al.*, 2017(114) **Country: US**	Adults aged ≥65 years with laboratory confirmed influenza (n=NR).	> There is a likelihood of 88% of patients ≥65 with influenza die after hospital discharge.

Setting: Clinical or hospital **Study period: 2014─2015** **Publication type: Conference abstract** **Title: Causes of in-hospital and post-discharge mortality among patients hospitalized with laboratory confirmed influenza, influenza hospitalization surveillance network, 2014–2015.**		
Paget *et al.*, 2022(115) **Country: Israel, Norway, Serbia, Switzerland, Austria, Czech Republic, Denmark, Germany, Netherlands, Poland, Portugal, Romania, Spain, Sweden, UK** **Setting: Clinical or hospital** **Study period: 2002─2011** **Publication type: Peer-reviewed journal article** **Title: Estimates of mortality associated with seasonal influenza for the European Union from the GLaMOR project.**	Adults aged ≥65 years who died from influenza-associated respiratory illness (n=NR).	> The influenza-associated respiratory mortality in the EU was 29.0 (16.6–41.2) per 100,000 population. > The influenza-associated respiratory mortality in the France was 29.1 (14.9–39.4) per 100,000 population. > The influenza-associated respiratory mortality in Germany was 29.3 (15.4–39.9 per 100,000 population. > The influenza-associated respiratory mortality in Italy was 28.4 (11.7–52.9) per 100,000 population. > The influenza-associated respiratory mortality in Spain was 28.3 (14.4–41.4) per 100,000 population. > The influenza-associated respiratory mortality in the UK was 25.5 (11.7–39.7) per 100,000 population.
Paget *et al.*, 2019(75) **Country: Europe, global** **Setting: Clinical or hospital** **Study period: 2002─2011** **Publication type: Peer-reviewed journal article**	Adults aged ≥65 years who died from influenza-associated respiratory illness (n=NR).	> The global influenza-associated excess mortality in patients with A(H1N1) influenza was 3.04 (±1.89) per 100,000 population. > The global influenza-associated excess mortality in patients with A(H3N2) influenza was 9.13 (±1.14) per 100,000 population. > The influenza-associated excess mortality in Europe was -28.03 (±3.35) per 100,000 population.

Title: Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project.		
Pebody *et al.*, 2018(80) **Country: UK** **Setting: Community** **Study period: 2008─2016** **Publication type: Peer-reviewed journal article** **Title: Significant spike in excess mortality in England in winter 2014/15 - Influenza the likely culprit.**	Adults aged ≥65 years with ILI (n=NR).	> The number of influenza-attributable deaths by ranged from 0–26,542 between 2008–2016. > The highest number of deaths was reported in 2015/16 and the lowest in 2014/15.
Qi *et al.*, 2020(79) **Country: China** **Setting: Clinical or hospital** **Study period: 2012─2018** **Publication type: Peer-reviewed journal article** **Title: Mortality burden from seasonal influenza in Chongqing, China, 2012–2018.**	Adults aged ≥65 years with laboratory confirmed influenza (n=NR).	> The annual rate of patients with influenza A(H3N2) dying from all-cause was 13.8 per 100,000 population (95% CI: 7.2–20.3). > The annual rate of patients with influenza B dying from all-cause was 82.03 per 100,000 population (95% CI:78.6–85.5). > The annual rate of patients with influenza A(H3N2) dying from circulatory and respiratory disease was 17.8 per 100,000 population (95% CI:13.0–22.6). > The annual rate of patients with influenza B dying from circulatory and respiratory disease was 61.8 per 100,000 population (95% CI:59.3–64.3). > The annual rate of patients with influenza B dying from pneumonia and influenza was 2.1 per 100,000 population (95% CI: 2.0–2.2). > The annual rate of patients with influenza A(H3N2) dying from pneumonia and influenza was 0.6 per 100,000 population (95% CI:59.3–64.3). > The annual rate of patients with influenza A(H3N2) dying from COPD was 7.9 per 100,000 population (95% CI: 6.3–9.5). > The annual rate of patients with influenza B dying from COPD was 23.1 per 100,000 population (95% CI: 22.3–24.0). > The annual rate of patients with influenza A(H3N2) dying from ischemic heart disease was 5.5 per 100,000 population (95% CI: 4.5–6.5). > The annual rate of patients with influenza B dying from ischemic heart disease was 11.1 per 100,000 population (95% CI: 10.6–11.6).

Rosano *et al.*, 2019(71) **Country: Italy** **Setting: Community** **Study period: 2013─2017** **Publication type: Peer-reviewed journal article** **Title: Investigating the impact of influenza on excess mortality in all ages in Italy during recent seasons (2013/14–2016/17 seasons).**	Adults aged ≥65 years who died from influenza (n=NR).	> The ILI mortality rate in people aged ≥65 years was 184.89 (95% CI: 173.8–196.2), 292.76 (95% CI: 279.7–306.0), 197.39 (95% CI: 186.7–208.2), and 304.78 (95% CI: 290.4–319.4) per 100,000 population in 2013/14, 2014/15, 2015/16, 2016/17, respectively. > The estimated ILI rate by winter season in people aged ≥65 years ranged from 30.3–49.1 per 100,000 population between 2013–2017, with the highest rate reported in 2016/17. > The estimated ILI rate by winter season in people aged 65–74 years ranged from 7.37–7.86 per 100,000 population between 2013–2017, with the highest rate reported in 2016/17. > The estimated ILI rate by winter season in people aged ≥75 years ranged from 39.47–42.94 per 100,000 population between 2013–2017, with the highest rate reported in 2016/17. > The estimated influenza-attributable mortality rate in people aged ≥75 years ranged from 65.01 (95% CI: 55.2–75.3) to 143.43 (95% CI: 130.1–157.7) per 100,000 population between 2013–2017, with the highest rate reported in 2016/17.
Torner *et al.*, 2017(110) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2013─2015** **Publication type: Peer-reviewed journal article** **Title: Costs associated with influenza-related hospitalization in the elderly.**	Adults aged ≥65 years hospitalized with laboratory confirmed influenza (n=728).	> The OR for deaths in persons <80 years was 0.28 (95% CI: 0.1–0.7, P=0.005). > The number of 30-day mortalities in people aged ≥65 years was 83 (11.4%).
Troeger *et al.*, 2017(116) **Country: Spain** **Setting: Community** **Study period: 1990─2017** **Publication type: Peer-reviewed journal article**	Adults aged >70 years with laboratory confirmed influenza (n=728).	> The LRTI mortality rate in 2017 was 16.4 per 100,00 population (UI: 11.6–21.9).

Title: Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017.		
Wong *et al.*, 2019(76) **Country: Hong Kong** **Setting: Community** **Study period: 2006─2016** **Publication type: Peer-reviewed journal article** **Title: Real-time estimation of the influenza-associated excess mortality in Hong Kong.**	Adults aged ≥65 years with influenza (n=NR).	> The annual excess all-cause mortality rate in patients with A(H3N2) influenza was 55.52 per 100,000 population (95% CI: 37.18–73.55). > The annual excess all-cause mortality rate in patients with influenza B was 40.39 per 100,000 population (95% CI: 15.69–62.47).
Wu *et al.*, 2018(81) **Country: China** **Setting: Clinical or hospital** **Study period: 2007─2013** **Publication type: Peer-reviewed journal article** **Title: Mortality burden from seasonal influenza and 2009 H1N1 pandemic influenza in Beijing, China, 2007-2013.**	Adults aged ≥65 years with either laboratory-confirmed influenza or ILI (n=NR).	> The influenza-associated all-cause death rates was 113.6 per 100,000 population (95% CI: 49.5–397.4) from 2007–2013. - The highest annual influenza-associated all-cause death rate was reported in 2007/8 (164.1 per 100,000 [95% CI: 101.2–499.9]). - The lowest annual influenza-associated all-cause death rate was reported in 2012/13 (75.6 per 100,000 [95% CI: 15.2–349.5]). > The influenza-associated respiratory and circulatory death rate was 96.4 per 100,000 population (95% CI: 44.1–323.8) from 2007–2013. - The highest annual influenza-associated respiratory and circulatory death rate was reported in 2007/8 (140.6 per 100,000 [95% CI: 86.1–414.3]). - The lowest annual influenza-associated respiratory and circulatory death rate was reported in 2008/9 (59.3 per 100,000 [95% CI: 12.4–294.0]). > The number of influenza-associated excess all-cause deaths was 2,375 (95% CI: 1,002–8,688) from 2007–2013. > The number of influenza-associated excess respiratory and circulatory deaths was 1,616 (95% CI: 736-5,445) from 2007–2013.
Wu *et al.*, 2012(77)	Adults aged ≥65 years with influenza (n=NR).	> The excess all-cause mortality rates were 89.68 (95% CI: 61.8–113.7), 8.42 (95% CI: -6.0–21.7), 58.79 (95% CI: 40.5–76.0) and 20.28 (95% CI: 0.1–41.5) per 100,000 population, in patients with

Country: Hong Kong **Setting: Clinical or hospital** **Study period: 1998─2009** **Publication type: Peer-reviewed journal article** **Title: Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009.**		overall influenza, influenza A(H1N1), influenza A(H3N2), and influenza B, respectively. > The influenza-associated cause-specific excess mortality rate in people with chronic liver disease was -0.45 per 100,000 population (95% CI: -1.48–1.01). > The influenza-associated cause-specific excess mortality rate in people with diabetes mellitus was 3.22 per 100,000 population (95% CI: -1.21–5.07). > The influenza-associated cause-specific excess mortality rate in people with renal disease was 3.59 per 100,000 population (95% CI: 1.12–6.44). > The influenza-associated cause-specific excess mortality rate in people with respiratory disease was 49.64 per 100,000 population (95% CI: 37.06–61.03). > The influenza-associated cause-specific excess mortality rate in people with cardiovascular disease was 18.96 per 100,000 population (95% CI: 9.61–31.18).
Young-Xu *et al.*, 2017(82) **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.**	US veterans aged ≥65 years with unconfirmed influenza (n=14,270,402).	> The influenza mortality was 79.3%. > The mean annual rate of influenza-attributed hospitalization was 71 (95% CI: 60–83) per 100,000. > Patients were stratified into high and low-risk groups, with those defined as high-risk having had at least one diagnosis code for chronic cardiac, pulmonary, renal, metabolic, liver, neurological diseases, diabetes, hemoglobinopathies, immunosuppressive conditions or malignancy assigned during the influenza season. > The mean annual rate of influenza-attributed hospitalizations was higher in the high-risk group of patients (144 [95% CI: 121–167] per 100,000 population) than the low-risk group (0 [95% CI: 0–1] per 100,000). > Of note, the high and low-risk group sample sizes were 2,029 and 4, respectively. > The mean annual rate of influenza-attributed hospitalization was 245 (95% CI: 203–288) per 100,000 population. > Patients were stratified into high and low-risk groups, with those defined as high-risk having had at least one diagnosis code for chronic cardiac, pulmonary, renal, metabolic, liver, neurological diseases, diabetes, hemoglobinopathies, immunosuppressive conditions or malignancy assigned during the influenza season. > The mean annual rate of influenza-attributed hospitalizations was higher in the high-risk group of patients (476 [95% CI: 398–554]

		per 100,000 population) than the low-risk group (21 [95% CI: 12–29] per 100,000). > Of note, the high and low-risk group sample sizes were 6,702 and 298, respectively.
Zhang-Xu *et al.*, 2018(78) **Country: China** **Setting: Clinical or hospital** **Study period: 2011─2015** **Publication type: Peer-reviewed journal article** **Title: Influenza-associated mortality in Yancheng, China, 2011-15.**	Adults aged ≥65 years with either laboratory-confirmed influenza or ILI (n=NR).	> The estimated excess influenza-associated all-cause mortality rate was 9.74 (95% CI: -10.0–38.2), 27.02 (95% CI: 8.7–55.5), 12.81 (95% CI: -8.5–43.1), and 49.57 (95% CI: 19.8–102.5) per 100,000 population in those with influenza A(H1N1), A(H3N2), B, and overall influenza, respectively. > The estimated excess influenza-associated respiratory mortality rates were12.25 (95% CI: 7.5–23.6), 18.68 (95% CI: 14.2–31.1), 4.70 (95% CI: -2.6–15.1), and 35.63 (95% CI:30.5–57.3) per 100,000 population in those with influenza A(H1N1), A(H3N2), B, and overall influenza, respectively. > The estimated influenza-associated annual excess mortality rate was 12.25 (95% CI: 7.5–23.6), 18.68 (95% CI: 14.2–31.1), 4.70 (95% CI: -2.6–15.1), and 35.63 (95% CI:30.5–57.3) per 100,000 population in those with influenza A(H1N1), A(H3N2), B, and overall influenza, respectively. > The estimated influenza-associated annual excess mortality rate was 35.63 (95% CI:30.5–57.3) and 45.86 (95% CI: 26.4–89.7) per 100,000 population in those with respiratory disease and cardiovascular disease and respiratory disease, respectively.
Arriola, *et al.*, 2015(117) **Country: US** **Setting: Clinical or hospital** **Study period: 2012─2013** **Publication type: Peer-reviewed journal article** **Title: Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012−2013 season in the United States.**	Adults aged ≥65 years with laboratory confirmed influenza (n=5,614).	> Mortality rate was reported by age group and vaccination status. In adults aged 65–74, 2.3% of vaccinated adults died versus 2.7% of those who had not received the influenza vaccine. > In adults aged ≥75 years, mortality rate was higher than the younger cohort however, vaccination had a similar impact with 5% of vaccinated adults dying versus 5.7% of unvaccinated.

Matias, *et al.*, 2014(63) **Country: US** **Setting: Clinical or hospital** **Study period: 1997–2009** **Publication type: Peer-reviewed journal article** **Title: Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status.**	Target population part of total population (n=10,682).	> Mortality rates were stratified by age (65–74 vs ≥75), influenza strain, and by patients' risk status (low- or high-risk). > Mortality rates in 65–74 years age group: - A(H1N1): Zero deaths were reported in the low-risk subgroup, vs one death in high-risk adults. - A(H3N2): High-risk adults had a substantially higher mortality rate than low-risk (1,709 vs 294). - Influenza B: 541 high-risk adults died compared to 91 low-risk adults. > Mortality rates in ≥75 years age group: - A(H1N1): no deaths reported in either risk group - A(H3N2): This influenza strain was associated with the highest number of deaths (7,166 in high-risk adults' vs 2,695 in low-risk). > Influenza B: High-risk subgroup had an increased mortality rate (2,968 vs 990). > Mortality rates were stratified by age (65–74 vs ≥75), influenza strain, and by patients' risk status (low- or high-risk). > Mortality rates in 65–74 years age group: - A(H1N1): Zero deaths were reported in the low-risk subgroup, vs one death in high-risk adults. - A(H3N2): High-risk adults had a substantially higher mortality rate than low-risk (1,709 vs 294). - Influenza B: 541 high-risk adults died compared to 91 low-risk adults. > Mortality rates in ≥75 years age group: - A(H1N1): no deaths reported in either risk group - A(H3N2): This influenza strain was associated with the highest number of deaths (7,166 in high-risk adults' vs 2,695 in low-risk). > Influenza B: High-risk subgroup had an increased mortality rate (2,968 vs 990).
Pebody, *et al.*, 2018(87) **Country: UK** **Setting: Clinical or hospital** **Study period: 2010–2017**	Target population part of total population (n=NR).	> Mortality rates were reported by age group and influenza strain, across five influenza seasons (2011–2017). > In patients aged 65–74, influenza A(H3N2) was associated with the highest mortality rate in both 2014 – 2015 and 2016 – 2017 seasons (2,378 and 1,828 deaths, respectively). > Similarly, in adults ≥75 influenza A(H3N2) had the highest mortality rate with 18,680 deaths reported in 2014–2015 and 9,628 deaths in 2016–2017.

Publication type: Peer-reviewed journal article **Title: Uptake and effectiveness of influenza vaccine in those aged 65 years and older in the United Kingdom, influenza seasons 2010/11 to 2016/17.**		
Arriola *et al.*, 2017(118) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2013–2014** **Publication type: Peer-reviewed journal article.** **Title: Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza.**	Adults aged ≥65 years with laboratory confirmed influenza (n=732).	> In the study cohort of influenza vaccinated patients, the risk of developing influenza-related pneumonia was 1.0 (95% CI: 0.8–1.3).
Andrew *et al.*, 2016(119) **Country: Canada** **Setting: Clinical or hospital** **Study period: 2011–2012** **Publication type: Conference abstract.** **Title: Impact of frailty on influenza vaccine effectiveness and clinical outcomes: experience from the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) network 2011/12 season.**	Adults aged ≥65 years with laboratory confirmed influenza (n=320).	> Influenza-associated persistent catastrophic disability was observed in 15.1% (p=0.047) of the cohort.
Cowling *et al.*, 2018(120) **Country: China**	Adults aged ≥65 years with influenza (n=NR).	> Between 2011 and 2015, 66% of influenza-related hospitalizations in which oseltamivir was dispensed were for patients aged ≥65 years.

Setting: Clinical or hospital **Study period: 2000-2015** **Publication type: Peer-reviewed journal article.** **Title: Use of influenza antivirals in patients hospitalized in Hong Kong, 2000-2015.**		
Soldevila *et al.*, 2020(73) **Country: Spain** **Setting: Clinical or hospital** **Study period: 2013–2015** **Publication type: Peer-reviewed journal article.** **Title: Effect of antiviral treatment in older patients hospitalized with confirmed influenza.**	Adults aged ≥65 years with laboratory confirmed influenza (n=715).	> ICU admission has been associated with antiviral use in patients with influenza aged 65–74 (aOR: 0.65, 95% CI: 0.2–2.2, p=0.46) and >74 years (aOR: 5.78, 95% CI: 0.1–1.5, p=0.09). > Of patients aged 65–74 years who received antiviral treatment for influenza, 87.1% were admitted to the ICU. > Similarly, 97.8% of patients aged >74 years who received antiviral treatment for influenza were admitted to the ICU. > The proportion of influenza deaths in patients treated with antivirals (n=640) was 8.6%. > The proportion of influenza deaths in patients not treated with antivirals (n=75) was 14.7%. > The OR for influenza deaths treated or not treated with antivirals was 0.55 (95% CI: 0.3–1.1). > The proportion of patients treated with antivirals dying, was higher in those aged >74 years than those aged 65-74 years (87.0% and 75.0%, respectively). > The proportion of patients admitted to ICU dying (n=77) was 43.1% (OR: 9.25; 95% CI: 5.2–16.4). > The proportion of patients with influenza A or B dying (n=676) was 45.5% and 6.3%. > The OR for dying of influenza B was 1.24; 95% CI: 0.4–3.6. > The proportion of influenza deaths in patients with AIDS (n=1) was 0%. > The proportion of influenza deaths in patients with autoimmune disease (n=47) was 12.1% (OR: 2.16; 95% CI: 1.0–4.9). > The proportion of influenza deaths in patients with chronic liver disease (n=28) was 6.1% (OR: 1.68; 95% CI:0.6–5.0). > The proportion of influenza deaths in patients with chronic respiratory failure (n=117) was 24.2% (OR: 1.74; 95% CI:1.0–3.2). > The proportion of influenza deaths in patients with congestive heart disease (n=218) was 50.0% (OR: 2.50; 95% CI: 1.5–4.2).

		> The proportion of influenza deaths in patients with COPD (n=193) was 31.8% (OR: 1.29; 95% CI: 0.8–2.2). > The proportion of influenza deaths in patients with diabetes (n=230) was 30.3% (OR: 20.91; 95% CI: 0.5–1.6). > The proportion of influenza deaths in patients with disabling neurological disease (n=51) was 9.1% (OR: 1.34; 95% CI: 0.6–3.3). > The proportion of influenza deaths in patients with HIV infection (n=1) was 0%. > The proportion of influenza deaths in patients with immunosuppressive treatment (n=32) was 7.6% (OR: 1.89; 95% CI: 0.7–5.1. > The proportion of influenza deaths in patients with obesity (n=169) was 24.2% (OR: 1.04; 95% CI: 0.6–1.9). > The proportion of influenza deaths in patients with other lung disease (n=235) was 22.7% (OR: 0.57; 95% CI: 0.3–1.0).
Dahlgren *et al.*, 2018(121) **Country: US** **Setting: Community** **Study period: 2010–2015** **Publication type: Evaluating oseltamivir prescriptions in Centers for Medicare and Medicaid Services medical claims records as an indicator of seasonal influenza in the United States**	Adults aged ≥65 years treated with oseltamivir (n=1,037,157)	> Spearman's correlation coefficients between therapeutic prescriptions of oseltamivir and proportion of people with ILI that require outpatient visits during the 2010-11 to 2014-15 seasons across different states in the US ranged between 0.76–0.94. > Spearman's correlation coefficients between therapeutic prescriptions of oseltamivir and pproportion of influenza-positive specimens during the 2010-11 to 2014-15 seasons across different states in the US ranged between 0.63–0.85.
Near *et al.*, 2020(86) **Country: US** **Setting: Community** **Study period: 2014–2019** **Publication type: Conference abstract**	Adults aged ≥65 years with laboratory confirmed influenza (n=NR).	> The presence of comorbidities in patients with influenza is associated with an increased rate of ED visits. > The proportion of patients visiting the ER with CKD stage 5/ESRD/dialysis and influenza was higher than CKD stage 5/ESRD/dialysis only (60 vs 28%, p<0.5). > Similar trends were observed for influenza with and without CAD (37 vs 14%, p<0.5), COPD (44 vs 18%, p<0.5), CHF (49 vs 23, p<0.5). The presence of comorbidities in patients with influenza is associated with an increased rate of ED visits. > As depicted in the embedded table below, influenza infection increases the hospitalization burden exerted by this population.

Title: Health resource burden of influenza among the elderly with underlying conditions in the United States.

Existing Condition	Proportion hospitalized (%)	
	Condition only	Condition + influenza
CKD stage 3/4	5.9	28.6
CKD stage 5/ESRD/dialysis	13.1	44.1
CAD	3.8	22.8
Old MI	5.3	26.4
Valvular disease	5.1	28.0
Stroke	4.7	30.9
Acute MI	7.6	31.5
Atherosclerosis	8.4	33.2
CHF	7.9	41
Asthma	2.7	18.8
Chronic pulmonary disease	4.6	27.5
COPD	6.1	34.6

Near *et al.*, 2020(62)

Country: US

Setting: Clinical or hospital

Study period: 2014–2018

Publication type: Conference abstract

Adults aged ≥65 years with laboratory confirmed influenza (n=NR).

> The rate of influenza-related hospitalizations among patients aged ≥65 and ≥75 years was 9.4% and 25.7%, respectively.

> The rate of influenza-related hospitalizations among patients aged ≥65 increased to 27.4% when patients presented with pre-existing COPD or CHF.

Title: Incidence and costs of influenza-related hospitalizations by comorbidity in the United States.		
Owusu *et al.*, 2020(85) **Country: US** **Setting: Clinical or hospital** **Study period: 2012–2017** **Publication type: Conference abstract** **Title: Risk of influenza-associated hospitalization among older adults living with diabetes — United States, 2012–2017.**	Adults aged ≥65 years with laboratory confirmed influenza (n=31,934).	> Mean annual rate of influenza-related hospitalization was higher among patients with diabetes mellitus (276 [95% CI: 230–330] per 100,000 population) than without (181 [95% CI: 150–217] per 100,000 population).
Cromer *et al.*, 2014(72) **Country: England** **Setting: Hospital** **Study period: 2000–2008** **Publication type: Peer-reviewed journal article** **Title: The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy.**	Adults aged ≥65s with influenza (n=NR)	> Patients with an acute respiratory illness code and with ICD-10 codes in other diagnostic fields for conditions indicated for seasonal influenza vaccination were flagged as being in a clinical risk group. > Among adults aged ≥65 years, being in a risk group increased the hospital admission rate by 1.8-fold (from 0.46 to 0.84/1000). > Average annual admissions in those at clinical risk vs not at clinical risk were 368,489 vs 53,254, respectively. > Mortality rate of hospitalized patients and number of deaths per influenza-related hospital admission were reported in adults ≥65 years by clinical risk level. - The annual prevalence of adults ≥65 years not at clinical risk dying in-hospital was 378.0 (95% CI: ±11) compared 1,298 (95% CI: ±56) at clinical at risk. > Deaths per 1,000 influenza admissions were 185 (95% CI: 179–192) vs 428 (95% CI: 391–473) in the same populations.
Guesneau *et al.*, 2021(83) **Country: France** **Setting: Clinical or hospital** **Study period: January 2015─April 2015**	Adults aged ≥75 years with laboratory confirmed influenza (n=114).	> The number of 30-day influenza mortalities in the overall population was 14 (12.3%). > The OR of influenza mortality associated with: - Diabetes was 0.6 (95% CI: 0.06–5.91, P=0.662). - Chronic respiratory disease was 0.27 (95% CI: 0.02–3.91, P=0.334). - Chronic cardiac disease was 6.48 (95% CI: 0.56–74.69, P=0.134). > Immunosuppression was 1.62 (95% CI: 0.16–16.40, P=0.683).

Publication type: Peer-reviewed journal article

Title: Risk factors associated with 30-day mortality in older patients with influenza.

aIRR: Adjusted incidence rate ratio; aOR: Adjusted odds ratio; ARDS: Acute respiratory distress syndrome; ARI: Acute respiratory infections; CHF: Congestive heart failure; CI: Confidence interval; CIRN: Canadian Immunization Research Network; CKD: Chronic kidney disease; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ER: Emergency room; ESRD: End-stage renal disease; EU: European Union; GLaMOR: Global influenza mortality; HR: Hazard ratio; ICD: International Classification of Disease; ICU: Intensive care unit; ILI: Influenza-like illness; LRTI: Lower respiratory tract infection; MI: Myocardial infarction; NR: Not reported; OR: Odds ratio; RSV: Respiratory syncytial virus; SARI: Severe acute respiratory infections; SOS: Serious Outcomes Surveillance; UK: United Kingdom; US: United States VE: Vaccine effectiveness