

Supplementary material

Adjusting for case under-ascertainment in estimating RSV hospitalisation burden of older adults in high-income countries: a systematic review and modelling study

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List of high-income countries

| | |
|------------------------|---------------------------|
| Andorra | Liechtenstein |
| Antigua and Barbuda | Lithuania |
| Aruba | Luxembourg |
| Australia | Macao SAR, China |
| Austria | Malta |
| Bahamas, The | Mauritius |
| Bahrain | Monaco |
| Barbados | Nauru |
| Belgium | Netherlands |
| Bermuda | New Caledonia |
| British Virgin Islands | New Zealand |
| Brunei Darussalam | Northern Mariana Islands |
| Canada | Norway |
| Cayman Islands | Oman |
| Channel Islands | Palau |
| Chile | Panama |
| Croatia | Poland |
| Curaçao | Portugal |
| Cyprus | Puerto Rico |
| Czech Republic | Qatar |
| Denmark | Romania |
| Estonia | San Marino |
| Faeroe Islands | Saudi Arabia |
| Finland | Seychelles |
| France | Singapore |
| French Polynesia | Sint Maarten (Dutch part) |
| Germany | Slovak Republic |
| Gibraltar | Slovenia |
| Greece | Spain |
| Greenland | St. Kitts and Nevis |
| Guam | St. Martin (French part) |
| Hong Kong SAR, China | Sweden |
| Hungary | Switzerland |
| Iceland | Taiwan, China |
| Ireland | Trinidad and Tobago |
| Isle of Man | Turks and Caicos Islands |
| Israel | United Arab Emirates |
| Italy | United Kingdom |
| Japan | United States |
| Korea, Rep. | Uruguay |
| Kuwait | Virgin Islands (U.S.) |
| Latvia | |

Based on the World Bank Income Classifications (the year 2019):

<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>

Search strategy and results

MEDLINE (Ovid)

| | | |
|----|----------------------------------------------------------------------------------------------------------|---------|
| 1 | exp Pneumonia/ or exp Pneumonia, Bacterial/ or exp pneumonia, viral/ | 218184 |
| 2 | exp Respiratory Tract Infections/ | 492380 |
| 3 | exp Pneumococcal Vaccines/ | 8274 |
| 4 | exp Influenza Vaccines/ | 24846 |
| 5 | ("community acquired pneumonia" or "community-acquired pneumonia" or "community-acquired pneumonia").mp. | 9480 |
| 6 | exp chronic obstructive lung disease/ | 61406 |
| 7 | ("exacerbation of COPD" or "COPD exacerbation" or "worsening of COPD" or "COPD worsening").mp. | 2602 |
| 8 | ("global burden" or "burden of disease" or "disease burden" or "burden").mp. | 225407 |
| 9 | exp Hospitalization/ | 270070 |
| 10 | exp incidence/ | 285564 |
| 11 | exp morbidity/ | 610493 |
| 12 | exp mortality/ | 410782 |
| 13 | ((case-fatality or case fatality) adj (rate or ratio)).mp. | 6067 |
| 14 | exp Prevalence/ | 321497 |
| 15 | proportion*.mp. | 635994 |
| 16 | exp epidemiology/ | 27847 |
| 17 | exp Respiratory Syncytial Virus Infections/ | 7754 |
| 18 | exp Respiratory Syncytial Viruses/ | 9624 |
| 19 | exp Respirovirus/ | 7176 |
| 20 | exp Respirovirus Infections/ | 2639 |
| 21 | RSV.mp. | 11983 |
| 22 | exp Human respiratory syncytial virus/ | 3116 |
| 23 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 561406 |
| 24 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 1931366 |
| 25 | 17 or 18 or 19 or 20 or 21 or 22 | 24099 |
| 26 | 23 and 24 and 25 | 1815 |
| 27 | limit 26 to humans | 1764 |
| 28 | limit 27 to yr="1996 -Current" | 1630 |
| 29 | limit 28 to "middle aged" | 289 |
| 30 | limit 20 to "adults, 80 and over" | 110 |
| 31 | 29 or 30 | 289 |

Embase (Ovid)

| | | |
|---|----------------------------------------------------------------------------------------------------------|--------|
| 1 | exp Pneumonia/ or exp Pneumonia, Bacterial/ or exp pneumonia, viral/ | 339596 |
| 2 | exp Respiratory Tract Infections/ | 426622 |
| 3 | exp Pneumococcal Vaccines/ | 21217 |
| 4 | exp Influenza Vaccines/ | 39143 |
| 5 | ("community acquired pneumonia" or "community-acquired pneumonia" or "community-acquired pneumonia").mp. | 22550 |
| 6 | exp chronic obstructive lung disease/ | 147799 |
| 7 | ("exacerbation of COPD" or "COPD exacerbation" or "worsening of COPD" or "COPD worsening").mp. | 6790 |

| | | |
|----|------------------------------------------------------------------------------|---------|
| 8 | ("global burden" or "burden of disease" or "disease burden" or "burden").mp. | 388430 |
| 9 | exp Hospitalization/ | 431254 |
| 10 | exp incidence/ | 564990 |
| 11 | exp morbidity/ | 388710 |
| 12 | exp mortality/ | 1188441 |
| 13 | ((case-fatality or case fatality) adj (rate or ratio)).mp. | 11162 |
| 14 | exp Prevalence/ | 853526 |
| 15 | proportion*.mp. | 966235 |
| 16 | exp epidemiology/ | 3816668 |
| 17 | exp Respiratory Syncytial Virus Infections/ | 6310 |
| 18 | exp Respiratory Syncytial Viruses/ | 6721 |
| 19 | exp Respirovirus/ | 4041 |
| 20 | exp Respirovirus Infections/ | 296 |
| 21 | RSV.mp. | 17502 |
| 22 | exp Human respiratory syncytial virus/ | 6310 |
| 23 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 777416 |
| 24 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 4958260 |
| 25 | 17 or 18 or 19 or 20 or 21 or 22 | 26118 |
| 26 | 23 and 24 and 25 | 5942 |
| 27 | limit 26 to human | 5511 |
| 28 | limit 27 to yr="1996 -Current" | 5442 |
| 29 | limit 28 to aged <65+ years> | 642 |

Web of Science

| | | |
|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1 | TOPIC: (((RSV OR "respiratory syncytial virus*") OR "respiroviruses") OR "Respiratory syncytial virus infection*") | 24470 |
| 2 | TOPIC: (((((((((((("epidemiology" OR "global burden") OR "burden of disease") OR "disease burden") OR "burden") OR "Hospitali?ation") OR "incidence") OR "mortality") OR "morbidity") OR "case fatality ratio") OR "case-fatality ratio") OR "case fatality rate") OR "case-fatality rate") OR "proportion*") OR "prevalence")) | 4115892 |
| 3 | TOPIC: (((((((((((((((("pneumonia" OR "viral pneumonia") OR "bacterial pneumonia") OR "respiratory tract infection*") OR "respiratory tract disease*") OR "respiratory disease") OR "acute respiratory infection*") OR "community acquired pneumonia") OR "community-acquired pneumonia") OR "community-acquired pneumonia") OR "chronic obstructive lung disease") OR "COPD") OR "exacerbation of COPD") OR "COPD exacerbation") OR "worsening of COPD") OR "COPD worsening")) | 262305 |
| 4 | TOPIC: (((("elderly" OR "older adult*") OR "adult*") OR "aged") OR "middle")) | 3079348 |

| | | |
|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| 5 | <p>TOPIC: (((RSV OR "respiratory syncytial virus*") OR "respiroviruses") OR "Respiratory syncytial virus infection*")</p> <p>AND</p> <p>TOPIC: (((((((((((("epidemiology" OR "global burden") OR "burden of disease") OR "disease burden") OR "burden") OR "Hospitali?ation") OR "incidence") OR "mortality") OR "morbidity") OR "case fatality ratio") OR "case-fatality ratio") OR "case fatality rate") OR "case-fatality rate") OR "proportion*") OR "prevalence"))</p> <p>AND</p> <p>TOPIC: (((((((((((("pneumonia" OR "viral pneumonia") OR "bacterial pneumonia") OR "respiratory tract infection*") OR "respiratory tract disease*") OR "respiratory disease") OR "acute respiratory infection*") OR "community acquired pneumonia") OR "community-acquired pneumonia") OR "community-acquired pneumonia") OR "chronic obstructive lung disease") OR "COPD") OR "exacerbation of COPD") OR "COPD exacerbation") OR "worsening of COPD") OR "COPD worsening"))</p> <p>AND</p> <p>TOPIC: (((("elderly" OR "older adult*") OR "adult*") OR "aged") OR "middle"))</p> | 1183 |
| 6 | <p>TOPIC: (((RSV OR "respiratory syncytial virus*") OR "respiroviruses") OR "Respiratory syncytial virus infection*")</p> <p>AND</p> <p>TOPIC: (((((((((((("epidemiology" OR "global burden") OR "burden of disease") OR "disease burden") OR "burden") OR "Hospitali?ation") OR "incidence") OR "mortality") OR "morbidity") OR "case fatality ratio") OR "case-fatality ratio") OR "case fatality rate") OR "case-fatality rate") OR "proportion*") OR "prevalence"))</p> <p>AND</p> <p>TOPIC: (((((((((((("pneumonia" OR "viral pneumonia") OR "bacterial pneumonia") OR "respiratory tract infection*") OR "respiratory tract disease*") OR "respiratory disease") OR "acute respiratory infection*") OR "community acquired pneumonia") OR "community-acquired pneumonia") OR "community-acquired pneumonia") OR "chronic obstructive lung disease") OR "COPD") OR "exacerbation of COPD") OR "COPD exacerbation") OR "worsening of COPD") OR "COPD worsening"))</p> <p>AND</p> <p>TOPIC: (((("elderly" OR "older adult*") OR "adult*") OR "aged") OR "middle"))</p> <p>AND</p> <p>Index date: 1996/01/01 to 2021/11/20</p> | 1163 |

Global Index Medicus

| | | |
|---|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| 1 | Title, abstract, subject: Respiratory syncytial virus | 1312 |
| 2 | Title, abstract, subject: adult OR elderly OR middle aged OR middle-aged | 484249 |
| 3 | <p>Title, abstract, subject: Respiratory syncytial virus</p> <p>AND</p> <p>Title, abstract, subject: adult OR elderly OR middle aged OR middle-aged</p> | 183 |
| 4 | <p>Title, abstract, subject: Respiratory syncytial virus</p> <p>AND</p> <p>Title, abstract, subject: adult OR elderly OR middle aged OR middle-aged</p> | 174 |

| | | |
|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| | Year range: 1996 to 2021 | |
| 5 | Title, abstract, subject: Respiratory syncytial virus AND Title, abstract, subject: adult OR elderly OR middle aged OR middle-aged Year range: 1996 to 2021; Language: English | 67 |

Global Health (CABI)

| | | |
|----|-------------------------------------------------------------------------------------------------------|--------|
| 1 | exp pneumonia/ or "bacterial pneumonia".mp. or "viral pneumonia".mp.Advanced | 25267 |
| 2 | exp respiratory diseases/ or "respiratory tract infection*".mp. or "acute respiratory infection*".mp. | 134916 |
| 3 | "Pneumococcal Vaccine*".mp. | 1354 |
| 4 | "Influenza Vaccines*".mp. | 1919 |
| 5 | exp community acquired pneumonia/ | 3161 |
| 6 | ("chronic obstructive lung disease" or "COPD").mp. | 6036 |
| 7 | ("exacerbation of COPD" or "COPD exacerbation" or "worsening of COPD" or "COPD worsening").mp. | 345 |
| 8 | ("global burden" or "burden of disease" or "disease burden" or "burden").mp. | 64130 |
| 9 | Hospitali?ation.mp. | 28933 |
| 10 | exp incidence/ | 94182 |
| 11 | exp morbidity/ | 29726 |
| 12 | exp mortality/ | 126131 |
| 13 | ((case-fatality or case fatality) adj (rate or ratio)).mp. | 3327 |
| 14 | exp disease prevalence/ | 140243 |
| 15 | proportion*.mp. | 118951 |
| 16 | exp epidemiology/ | 264038 |
| 17 | exp Human respiratory syncytial virus/ | 4876 |
| 18 | RSV.mp. | 4352 |
| 19 | exp Respirovirus/ | 640 |
| 20 | exp elderly/ | 55388 |
| 21 | elderly.mp. | 63723 |
| 22 | adult*.mp. | 273707 |
| 23 | "older adult*".mp. | 56800 |
| 24 | "middle aged".mp. | 13757 |
| 25 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 137928 |
| 26 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 555500 |
| 27 | 17 or 18 or 19 | 6354 |
| 28 | 20 or 21 or 22 or 23 or 24 | 284439 |

| | | |
|----|--------------------------------|-----|
| 29 | 25 and 26 and 27 and 28 | 432 |
| 30 | limit 29 to yr="1996 -Current" | 432 |

CINAHL (Ebsco)

| | | |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| S1 | (MH "Pneumonia+") | 32380 |
| S2 | (MH "Pneumonia, Bacterial") OR (MH "Pneumonia, Viral") | 12644 |
| S3 | (MH "Respiratory Tract Infections+") OR (MH "Respiratory Tract Diseases+") | 324735 |
| S4 | (MH "Influenza Vaccine") | 11060 |
| S5 | (MH "Pneumococcal Vaccine") | 3150 |
| S6 | (MH "Community-Acquired Pneumonia") | 1314 |
| S7 | (MH "Pulmonary Disease, Chronic Obstructive+") | 21321 |
| S8 | ""exacerbation of COPD" or "COPD exacerbation" or "worsening of COPD" or "COPD worsening"" | 956 |
| S9 | ""global burden" or "burden of disease" or "disease burden" or "burden"" | 96933 |
| S10 | (MH "Hospitalization+") | 112183 |
| S11 | (MH "Incidence") | 77209 |
| S12 | (MH "Morbidity+") | 183019 |
| S13 | (MH "Mortality+") | 78926 |
| S14 | (MH "Prevalence") | 102478 |
| S15 | (MH "Epidemiology+") | 7 69070 |
| S16 | ""case-fatality rate" OR "case fatality rate" OR "case-fatality ratio" OR "case fatality ratio"" | 742 |
| S17 | ""proportion*"" | 177678 |
| S18 | (MH "Respiratory Syncytial Virus Infections") | 2094 |
| S19 | (MH "Respiratory Syncytial Viruses") | 1115 |
| S20 | ""RSV"" | 2046 |
| S21 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 | 330941 |
| S22 | S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S1 | 938768 |
| S23 | S18 OR S19 OR S20 | 3168 |
| S24 | S21 AND S22 AND S23 | 793 |
| S24 AND PY 1996- 2021 | Limiters - Publication Year: 1996-2021; Narrow by SubjectAge: - aged, 80 & over; Narrow by SubjectAge: - middle aged: 45-64 years; Narrow by SubjectAge: - aged: 65+ years | 106 |

Total search results retrieved

| | | |
|----|----------------------------------------------|-------------|
| 1. | Medline | 285 |
| 2. | Embase | 634 |
| 3. | Web of Science | 1159 |
| 4. | Global Index Medicus | 67 |
| 5. | Global Health | 431 |
| 6. | CINAHL | 106 |
| | Total results (without deduplication) | 2682 |

Quality assessment

The Joanna Briggs Institute (JBI) critical appraisal tools [1] were applied. JBI grants use of these tools for research purposes.

Cohort study

| Questions | Yes | No | Unclear | Not applicable |
|------------------------------------------------------------------------------------------------------------|-----|----|---------|----------------|
| 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? | | | | |

Cross-sectional study

| Questions | Yes | No | Unclear | Not applicable |
|--------------------------------------------------------------------------|-----|----|---------|----------------|
| 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? | | | | |
| Were the criteria for inclusion in the sample clearly defined? | | | | |

Detection proportions used for obtaining adjustment ratios

Testing approaches (step 1)

| Candidate approach | Gold standard approach | Detection proportion posterior distribution | Reference |
|--------------------|--------------------------|---------------------------------------------|-----------------------------|
| Serology + PCR | Serology + PCR + culture | 1 | Falsey et al. 2002 [2] |
| PCR | Serology + PCR + culture | Beta(88, 31) | Falsey et al. 2002 [2] |
| Serology + culture | Serology + PCR + culture | Beta(111,8) | Falsey et al. 2002 [2] |
| Serology | Serology + PCR + culture | Beta(105,14) | Falsey et al. 2002 [2] |
| Rapid antigen test | PCR | Beta(33,19) | Onwuchekwa et al. 2023 [3] |
| Rapid antigen test | Serology + PCR + culture | Beta(88,31) * Beta(33,19) | (calculated based on above) |

PCR = polymerase chain reaction. Assuming a single nasopharyngeal swab taken for PCR, culture and rapid antigen test.

Clinical specimens (step 2)

| Candidate approach | Gold standard approach | Detection proportion posterior distribution | Reference |
|--------------------|-------------------------------|---------------------------------------------|-------------------------|
| NPS | Serum + NPS + Saliva + Sputum | Beta(32,20) | Ramirez et al. 2022 [4] |
| Serum + NPS | Serum + NPS + Saliva + Sputum | Beta(32,20) | See note |
| Serum | Serum + NPS + Saliva + Sputum | Beta(32,20) | See note |

Note: these were set arbitrarily to be identical to NPS alone as serum (i.e., serology) had been already adjusted for in step 1 (i.e., adjusting for testing approaches), to avoid double counting. NPS = nasopharyngeal swab. Assuming a single PCR test used for NPS, saliva and sputum.

Adjustment ratios used in the analysis

| Clinical specimen | Testing approach | Adjustment ratio (95% CI) |
|--------------------------|--------------------------|----------------------------------|
| NPS | PCR | 2.19 (1.72–2.97) |
| NPS | Rapid antigen test | 3.47 (2.59–4.99) |
| Serum + NPS | Serology + Culture | 1.75 (1.46–2.24) |
| Serum + NPS | Serology + PCR + Culture | 1.63 (1.36–2.08) |
| Unclear* | PCR | 2.19 (1.72–2.97) |
| Unclear* | Rapid antigen test | 3.47 (2.59–4.99) |

*Assuming same sensitivity to NPS.

Characteristics of included studies

| Study | Design | Study period | Number of seasons | Country / territory | Clinical specimen | Testing approach | Quality assessment score (%) |
|--------------------------|---------------------------------|-------------------------------|-------------------|---------------------|-------------------|--------------------------|------------------------------|
| Aronen et al. 2019 [5] | Cohort (prospective) | July 2007 to April 2009 | 2 | Finland | NPS | PCR | 90 |
| Auvinen et al. 2021 [6] | Cohort (prospective) | November 2016 to May 2020 | 4 | Finland | Unclear | PCR | 90 |
| Belongia et al. 2018 [7] | Cohort (prospective) | 2004 to 2016 | 12 | USA | NPS | PCR | 80 |
| Branche et al. 2022 [8] | Cross-sectional (prospective) | October 2017 to March 2020 | 3 | USA | NPS | PCR | 88 |
| Falsey et al. 2005 [9] | Cohort (prospective) | 1999 to 2003 | 4 | USA | Serum + NPS | Serology + PCR + Culture | 70 |
| Malosh et al. 2017 [10] | Cohort (prospective) | November 2014 to April 2016 | 2 | USA | Unclear | PCR | 70 |
| Nolen et al. 2020 [11] | Cohort (prospective) | November 2016 to October 2018 | 2 | USA | NPS | PCR | 70 |
| Prasad et al. 2020 [12] | Cross-sectional (retrospective) | April 2012 to December 2015 | 3 | New Zealand | NPS | PCR | 100 |
| Prasad et al. 2021 [13] | Cross-sectional (retrospective) | April 2012 to December 2015 | 3 | New Zealand | NPS | PCR | 100 |
| Tseng et al. 2020 [14] | Cohort (retrospective) | January 2011 to June 2015 | 4 | USA | Unclear | PCR | 80 |
| Widmer et al. 2012 [15] | Cross-sectional (prospective) | November 2006 to April 2009 | 3 | USA | NPS | PCR | 88 |
| Widmer et al. 2014 [16] | Cohort (prospective) | May 2009 to April 2010 | 1 | USA | NPS | PCR | 80 |

NPS = nasopharyngeal swab; PCR = polymerase chain reaction.

Quality assessment results

Cohort study

| Questions | Aronen et al. 2019 [5] | Auvinen et al. 2021 [6] | Belongia et al. 2018 [7] | Falsey et al. 2005 [9] | Malosh et al. 2017 [10] | Nolen et al. 2020 [11] | Tseng et al. 2020 [14] | Widmer et al. 2014 [16] |
|------------------------------------------------------------------------------------------------------------|------------------------|-------------------------|--------------------------|------------------------|-------------------------|------------------------|------------------------|-------------------------|
| Were the exposures measured similarly to assign people to both exposed and unexposed groups? | Yes | Yes | Yes | No | Yes | Yes | No | Yes |
| Was the exposure measured in a valid and reliable way? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Were confounding factors identified? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Were strategies to deal with confounding factors stated? | Yes | No | No | No | Yes | No | Yes | No |
| Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | Yes | Yes | No | No | No | No | Yes | No |
| Were the outcomes measured in a valid and reliable way? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Was the follow up time reported and sufficient to be long enough for outcomes to occur? | No | Yes | Yes | Yes | No | No | Yes | Yes |
| Was follow up complete, and if not, were the reasons to loss to follow up described and explored? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Were strategies to address incomplete follow up utilized? | NA | NA | NA | NA | NA | NA | NA | NA |
| Was appropriate statistical analysis used? | Yes | Yes | Yes | Yes | NA | Yes | Yes | Yes |

NA = not applicable.

Cross-sectional study

| Questions | Branche et al. 2022 [8] | Prasad et al. 2020 [12] | Prasad et al. 2021 [13] | Widmer et al. 2012 [15] |
|--------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Were the criteria for inclusion in the sample clearly defined? | No | Yes | Yes | Yes |
| Were the study subjects and the setting described in detail? | Yes | Yes | Yes | Yes |
| Was the exposure measured in a valid and reliable way? | Yes | Yes | Yes | Yes |
| Were objective, standard criteria used for measurement of the condition? | Yes | Yes | Yes | Yes |
| Were confounding factors identified? | Yes | Yes | Yes | Yes |
| Were strategies to deal with confounding factors stated? | Yes | Yes | Yes | No |
| Were the outcomes measured in a valid and reliable way? | Yes | Yes | Yes | Yes |
| Was appropriate statistical analysis used? | Yes | Yes | Yes | Yes |

NA = not applicable.

List of included studies with RSV-associated ARI hospitalisation rate estimates

| Study | Country | Location | Age group | Year(s) of reporting | Hospitalisation rate (95% CI), per 100,000 |
|--------------------------------|---------|----------------|-----------|----------------------|--------------------------------------------|
| Auvinen et al. 2021 [6] | Finland | Jorvi hospital | 65-99 | 2016-2017 | 19.3 (8.8-36.6) |
| | Finland | Jorvi hospital | 65-99 | 2017-2018 | 117.6 (89.1-152.3) |
| | Finland | Jorvi hospital | 65-99 | 2018-2019 | 43.9 (27.5-66.5) |
| | Finland | Jorvi hospital | 65-99 | 2019-2020 | 52.3 (34.5-76.1) |
| | Finland | Jorvi hospital | 65-84 | 2016-2017 | 9.5 (2.6-24.3) |
| | Finland | Jorvi hospital | 65-84 | 2017-2018 | 89 (63.3-121.6) |
| | Finland | Jorvi hospital | 65-84 | 2018-2019 | 31 (16.9-51.9) |
| | Finland | Jorvi hospital | 65-84 | 2019-2020 | 34.4 (19.7-55.9) |
| | Finland | Jorvi hospital | 85-99 | 2016-2017 | 112.3 (36.5-261.9) |
| | Finland | Jorvi hospital | 85-99 | 2017-2018 | 386.5 (229.2-610.2) |
| | Finland | Jorvi hospital | 85-99 | 2018-2019 | 165.5 (71.5-325.8) |
| | Finland | Jorvi hospital | 85-99 | 2019-2020 | 214.8 (107.3-384) |
| Branche et al. 2022 [8] | USA | Rochester, NY | 65-99 | 2017-2018 | 138.2 (114.46-166.86) |
| | USA | New York City | 65-99 | 2017-2018 | 212 (168.58-266.6) |
| | USA | Rochester, NY | 65-99 | 2018-2019 | 136.92 (113.3-165.46) |
| | USA | New York City | 65-99 | 2018-2019 | 255.56 (207.43-314.86) |
| | USA | Rochester, NY | 65-99 | 2019-2020 | 139.48 (115.62-168.26) |
| | USA | New York City | 65-99 | 2019-2020 | 214.9 (171.16-269.83) |
| | USA | Rochester, NY | 65-74 | 2017-2018 | 112.47 (85.25-148.37) |
| | USA | New York City | 65-74 | 2017-2018 | 98.8 (62.26-156.78) |
| | USA | Rochester, NY | 65-74 | 2018-2019 | 83.23 (60.31-114.85) |
| | USA | New York City | 65-74 | 2018-2019 | 115.27 (75.17-176.74) |
| | USA | Rochester, NY | 65-74 | 2019-2020 | 103.47 (77.51-138.12) |
| | USA | New York City | 65-74 | 2019-2020 | 126.24 (83.91-189.93) |
| | USA | Rochester, NY | 75-84 | 2017-2018 | 154.96 (111.29-215.76) |

| Study | Country | Location | Age group | Year(s) of reporting | Hospitalisation rate (95% CI), per 100,000 |
|--------------------------------|-------------|----------------------------|-----------|----------------------|--------------------------------------------|
| | USA | New York City | 75-84 | 2017-2018 | 253.27 (173.77-369.14) |
| | USA | Rochester, NY | 75-84 | 2018-2019 | 159.38 (115-220.9) |
| | USA | New York City | 75-84 | 2018-2019 | 281.41 (196.85-402.28) |
| | USA | Rochester, NY | 75-84 | 2019-2020 | 154.96 (111.29-215.76) |
| | USA | New York City | 75-84 | 2019-2020 | 272.03 (189.13-391.26) |
| | USA | Rochester, NY | 85-99 | 2017-2018 | 207.15 (137.71-311.59) |
| | USA | New York City | 85-99 | 2017-2018 | 504.11 (348.39-729.44) |
| | USA | Rochester, NY | 85-99 | 2018-2019 | 306.22 (218.91-428.34) |
| | USA | New York City | 85-99 | 2018-2019 | 666.15 (483.17-918.43) |
| | USA | Rochester, NY | 85-99 | 2019-2020 | 255.18 (174.2-365.07) |
| | USA | New York City | 85-99 | 2019-2020 | 396.09 (261.02-601.05) |
| Nolen et al. 2020 [11] | USA | Bethel and Anchorage | 65-99 | 2016-2018 | 356 (178-637) |
| Prasad et al. 2020 [12] | New Zealand | Auckland | 65-99 | 2012-2015 | 99.2 (82.4-115.9) |
| | New Zealand | Auckland | 65-79 | 2012-2015 | 72.9 (57.4-88.3) |
| | New Zealand | Auckland | 80-99 | 2012-2015 | 190.8 (137.6-244.4) |
| Widmer et al. 2012 [15] | USA | Tennessee, Davidson County | 65-99 | 2006-2009 | 254 (131-380) |
| Widmer et al. 2014 [16] | USA | Tennessee, Davidson County | 65-99 | 2009-2010 | 189.6 (104-340) |

ARI = acute respiratory infection.

List of included studies with proportion of RSV in all-cause ARI hospitalisations

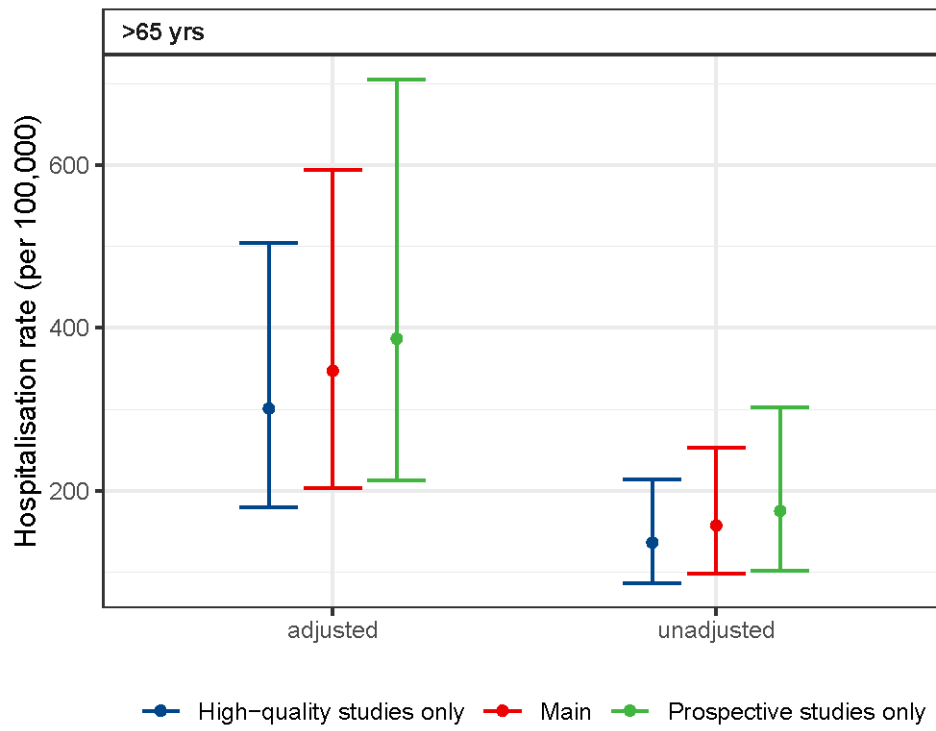
| Study | Country | Location | Case definition | Age group | Year(s) of reporting | Number of tests | Number of RSV positives |
|--------------------------------|-------------|-----------------------------------------------------------------------------|-----------------|-----------|----------------------|-----------------|-------------------------|
| Aronen et al. 2019 [5] | Finland | Turku City Hospital | ARI | 65- | 2007-2009 | 382 | 22 |
| Auvinen et al. 2021 [6] | Finland | Jorvi hospital | ARI | 65-84 | 2016-2020 | 427 | 73 |
| | Finland | Jorvi hospital | ARI | 85- | 2016-2020 | 199 | 42 |
| | Finland | Jorvi hospital | ARI | 65- | 2016-2020 | 626 | 115 |
| Falsey et al. 2005 [9] | USA | Rochester General Hospital | ARI | 65- | 1999-2003 | 1388 | 142 |
| Malosh et al. 2017 [10] | USA | two Southeast Michigan hospitals. | ARI | 65- | 2014-2016 | 426 | 28 |
| Nolen et al. 2020 [11] | USA | YKD Regional Hospital (Bethel) and Alaska Native Medical Center (Anchorage) | ARI | 65- | 2016-2018 | 153 | 4 |
| Prasad et al. 2020 [12] | New Zealand | Auckland | ARI | 65- | 2012-2015 | 2104 | 191 |
| | New Zealand | Auckland | ARI | 65-79 | 2012-2015 | 1308 | 118 |
| | New Zealand | Auckland | ARI | 80- | 2012-2015 | 796 | 73 |
| Prasad et al. 2021 [13] | New Zealand | 2 public hospitals in Auckland | ARI | 65-79 | 2012-2015 | 1379 | 124 |
| Widmer et al. 2012 [15] | USA | Tennessee, Davidson County (2 hospitals) | ARI | 65- | 2006-2009 | 282 | 19 |

ARI = acute respiratory infection; SARI = severe acute respiratory infection; LRTI = lower respiratory tract infection; COPD = chronic obstructive pulmonary disease.

List of included studies with CFR data on RSV-associated ARI hospitalisations

| Study | Country | Location | Case definition | Age group | Year(s) of reporting | Number of deaths | Number of hospitalisations |
|---------------------------------|---------|----------------------------|-----------------|-----------|----------------------|------------------|----------------------------|
| Aronen et al. 2019 [5] | Finland | Turku city | ARI | 65- | 2007-2009 | 0 | 22 |
| Belongia et al. 2018 [7] | USA | Marshfield, WI | ARI | 60- | 2004-2016 | 0 | 29 |
| Falsey et al. 2005 [9] | USA | Rochester General Hospital | ARI | 65- | 1999-2003 | 10 | 142 |
| Tseng et al. 2020 [14] | USA | Southern California | ARI | 60- | 2011-2015 | 37 | 664 |
| | USA | Southern California | ARI | 60-74 | 2011-2015 | 11 | 238 |
| | USA | Southern California | ARI | 75- | 2011-2015 | 26 | 426 |

Results from sensitivity analyses that included only prospective studies and included only high-quality studies



Reference

1. JBI. CRITICAL APPRAISAL TOOLS. Available at: <https://jbi.global/critical-appraisal-tools>. Accessed 30th November 2022.
2. Falsey AR, Formica MA, Walsh EE. Diagnosis of respiratory syncytial virus infection: comparison of reverse transcription-PCR to viral culture and serology in adults with respiratory illness. *J Clin Microbiol* **2002**; 40:817-20.
3. Onwuchekwa C, Moreo LM, Menon S, et al. Under-ascertainment of Respiratory Syncytial Virus infection in adults due to diagnostic testing limitations: A systematic literature review and meta-analysis. *J Infect Dis* **2023**.
4. Ramirez JA, Carrico R, Wilde AM, et al. Adding sputum and saliva to nasopharyngeal swab samples for PCR detection of Respiratory Syncytial Virus in adults hospitalized with acute respiratory illness may double case detection. *Open Forum Infectious Diseases* **2022**; 9.
5. Aronen M, Viikari L, Kohonen I, et al. Respiratory tract virus infections in the elderly with pneumonia. *BMC Geriatrics* **2019**; 19:111.
6. Auvinen R, Syrjänen R, Ollgren J, Nohynek H, Skogberg K. Clinical characteristics and population-based attack rates of respiratory syncytial virus versus influenza hospitalizations among adults-An observational study. *Influenza Other Respir Viruses* **2022**; 16:276-88.
7. Belongia EA, King JP, Kieke BA, et al. Clinical Features, Severity, and Incidence of RSV Illness During 12 Consecutive Seasons in a Community Cohort of Adults ≥ 60 Years Old. *Open Forum Infectious Diseases* **2018**; 5:ofy316.
8. Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017-2020. *Clin Infect Dis* **2022**; 74:1004-11.
9. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* **2005**; 352:1749-59.
10. Malosh RE, Martin ET, Callear AP, et al. Respiratory syncytial virus hospitalization in middle-aged and older adults. *Journal of Clinical Virology* **2017**; 96:37-43.
11. Nolen LD, Seeman S, Desnoyers C, et al. Respiratory syncytial virus and influenza hospitalizations in Alaska native adults. *J Clin Virol* **2020**; 127:104347.
12. Prasad N, Newbern EC, Trenholme AA, et al. The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. *PLoS One* **2020**; 15:e0234235.
13. Prasad N, Walker TA, Waite B, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Adults With Chronic Medical Conditions. *Clin Infect Dis* **2021**; 73:e158-e63.
14. Tseng HF, Sy LS, Ackerson B, et al. Severe Morbidity and Short- and Mid- to Long-term Mortality in Older Adults Hospitalized with Respiratory Syncytial Virus Infection. *J Infect Dis* **2020**; 222:1298-310.
15. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of Hospitalizations for Respiratory Syncytial Virus, Human Metapneumovirus, and Influenza Virus in Older Adults. *The Journal of Infectious Diseases* **2012**; 206:56-62.
16. Widmer K, Griffin MR, Zhu Y, Williams JV, Talbot HK. Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. *Influenza and Other Respiratory Viruses* **2014**; 8:347-52.