RSV SLR-metanalysis manuscript

Title

Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries

Short title

Respiratory syncytial virus burden in older and high-risk adults: a meta-analysis

Authors

- Jonathan S. Nguyen-Van-Tam, University of Nottingham School of Medicine, Division of Epidemiology and Public Health, Nottingham, UK. Jonathan.Van-Tam@nottingham.ac.uk
- Maureen O'Leary, P95 Epidemiology and Pharmacovigilance, Leuven, Belgium maureenoleary01@gmail.com
- Emily T. Martin, University of Michigan School of Public Health, Ann Arbor, MI, USA.
- etmartin@umich.edu;
- Esther Heijnen, Janssen Vaccines & Prevention BV, Leiden, The Netherlands. EHeijnen@its.jnj.com
- Benoit Callendret, Janssen Vaccines & Prevention BV, Leiden, The Netherlands. BCALLEND@its.jnj.com
- Roman Fleischhackl, Janssen Research and Development, Beerse, Belgium rfleischhackl@its.jnj.com
- Christy Comeaux, Janssen Vaccines & Prevention BV, Leiden, The Netherlands. CComeaux@its.jnj.com
- Thao Mai Phuong Tran, P95 Epidemiology and Pharmacovigilance, Leuven, Belgium. Thao.tran@p-95.com
- Karin Weber, Janssen Global Medical Affairs, IDV, Vienna, Austria. Kweber3@its.jnj.com

Corresponding author:

- Thao Mai Phuong Tran, P95 Epidemiology and Pharmacovigilance, Leuven, Belgium. Thao.tran@p-95.com

INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of acute respiratory tract infection (ARI), including upper and lower respiratory tract infection (URTI/LRTI). RSV infection is transmitted by direct or indirect contact with infection rates typically peaking in colder months in temperate climates[1].Prior to COVID-19 pandemic, LRTIs represented globally the fourth cause of overall disability-adjusted life-years (DALYs) at all ages[2] and RSV was the second most common aetiology[3].

The burden of RSV infection is highest in children below five years of age (global incidence: 17.0 (95% uncertainty intervals (UI), 10.6–26.2) per 1000 people)[3,4], older adults (global incidence: 6.3 (95% UI, 4.9–7.8) per 1000 people >70 years old) and adults with underlying comorbidities (such as the immunocompromised and those with an underlying chronic cardiopulmonary disease)[5], who are at risk of severe outcomes of infection (hereafter known as high-risk adults, HR).

Clinical presentation of RSV ranges from a mild cold to a serious respiratory illness with complications comparable to those caused by influenza and other respiratory viruses. These complications can include pneumonia, the need for intensive care unit (ICU) admission[6] and mechanical ventilation, cardiopulmonary complications (in particular exacerbations of congestive heart failure[7] and chronic obstructive pulmonary disease[8]), and might lead to death[9]. These complications are especially observed in hospitalized RSV patients >60 years old and in those with underlying health conditions[9].

Currently, there are no specific treatment options for RSV disease among adults, and consequently, several vaccine and therapeutic candidates are under development [10,11].
To guide this development, robust data on the epidemiology and clinical presentation of RSV infection as well as on associated healthcare utilisation are required. Although research into RSV has increased in recent years, more specific information on the impact of RSV infection in older and HR adults is needed[12].

A recently published meta-analysis estimated that in 2015 RSV caused 1.5 million episodes of illness (95% confidence intervals (CI), 0.3-6.9 million) in adults aged ≥50 years from industrialised countries, of whom an estimated 14.5% (214 000 episodes; 95% CI, 100 000–459 000) were hospitalized and 1.6% (95% CI, 0.7%– 3.8%) died[13]. This meta-analysis provided valuable evidence on disease burden; however, further data on severe outcomes (such as ICU admissions) in older adults as well as on healthcare utilisation are needed. Similarly, overall estimates of the burden of RSV related disease in HR adults are limited.

To strengthen the evidence base on the burden of RSV disease among older and HR adults, we conducted a systematic literature review and meta-analysis of (1) the epidemiological burden and clinical presentation of symptomatic RSV infection, (2) the burden of RSV-related severe outcomes and complications of infection, and (3) the RSV-related healthcare utilisation. We restricted the study to developed countries as they have comparable healthcare systems.

METHODS

We performed a systematic literature review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[14].
We prospectively registered the protocol in PROSPERO (registration number CRD42019156730).

Literature search strategy
We searched Embase (through Ovid) and Medline to identify peer-reviewed articles published between January 2000 and the 10th of December 2019 using predefined terms (**Supplementary Table 1**).

Articles selection criteria and data extraction.
We included original articles reporting on the burden of symptomatic RSV infection, clinical presentation, symptoms, severe outcomes, and RSV-related healthcare utilisation in older adults (≥60 years old) and adults ≥18 years old at risk of complications (high-risk, HR). HR adults refer to those at risk of complications of infection due to underlying conditions[15,16] (for a list of conditions selected in this study, see **Supplementary Table 2,** Definition 1). We defined RSV cases as those with symptomatic laboratory-confirmed infection. RSV clinical outcome definitions are listed in **Supplementary Table 3.** We included studies in English and conducted in developed countries recognised as such by the United Nations [17]. Detailed inclusion criteria are compiled in **Supplementary Table 4.** One reviewer selected the abstract using Rayyan[18] and two reviewers screened the full-texts and selected the articles that were finally included in the analysis. Any disagreements were resolved by consensus among reviewers. Relevant data from the included articles were extracted using EpiData[19]. Extracted items included the study setting, study period, follow-up time, study population, population age, HR group, study design, study outcome, specimen type, testing methodology and the number of study participants. We extracted data on incidence and prevalence of RSV disease burden, clinical presentation (URTI and LRTI), signs and symptoms, severe outcomes (pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), cardiopulmonary complications, hospitalisations, intensive care unit (ICU) admissions, mechanical ventilation and mortality), and healthcare utilisation (outpatient visits, emergency department visits, discharge to care, oxygen therapy, and antibiotic use). When possible, we stratified data by age.

Bias assessment
We used an adapted version of the Newcastle-Ottawa Scale to assess the risk of bias (ROB) (**Supplementary Table 5.A**), using a previously described approach[20]. We assessed the study design, study period, representativeness of the study population, case identification, sampling strategy, specimen type, diagnostic assay, outcome assessment and completeness of outcome assessment to categorise the included studies as having either a low or a high risk of bias. Results for each article are displayed in **Supplementary Table 5.B** and shown in the figures**.**

Meta-analysis
We analysed the data and generated summary tables and forest plots using R.3.4.2.[21].
We calculated pooled estimates for outcomes when there were three or more eligible studies; for outcomes with less than three studies, data were only presented per study. We reported estimates based on five or more studies as main figures and estimates based on less than five studies as supplementary figures or tables. We categorised studies as either annual or seasonal

studies, depending on whether data were collected continuously for one year or more (annual studies) or whether they were restricted to the respiratory virus season (seasonal studies), and we analysed these separately.
For the older adult analyses, we stratified data further by population type (community-based or medically attended), by age (≥60 or ≥65 years old), and by geographic region (North America, Europe, or Western Pacific). We categorised studies as community based if participants were followed up prospectively in the community, or as medically attended if data were only collected at points of contact with the health service (including inpatients, outpatients or both).

For the HR adult analyses, we stratified data by HR subgroup (cardiopulmonary disease, diabetes, chronic kidney disease, immunodeficiency, dementia and functional impairment, as well as institutionalised older adults) and by geographic region. As many studies reported on patients with asthma, an additional specific HR subgroup for asthmatic patients was designated. The cardiopulmonary HR subgroup does not include the asthmatic subgroup. Patients with HIV, cancer, haematological diseases, immunosuppressive treatment, or recipients of transplants were classified as immunodeficient. An overview of included studies is presented in **Supplementary Table 6.**

For the analyses of hospitalisation, we excluded populations comprising solely inpatients; we included mixed populations of inpatients and outpatients and we performed an additional sensitivity analysis that included outpatient populations only. There was little difference in the size of the effect estimates generated by the analyses of outpatient populations only; consequently, we report the results of the analyses including both inpatients and outpatients.

We calculated the incidence rate as the number of RSV cases divided by the total person-time followed up. The population at risk under follow-up was i) the total number of participants in the cohort, for community-based cohort studies, and ii) the total number of participants in the underlying population, for studies recruiting from medical facilities.
We calculated the proportion as the number of RSV cases divided by either the number of study participants, illness episodes, or specimens, depending on the study design. We expressed proportions as percentages.

We used the Wilson 'score' method with asymptotic variance without continuity correction to calculate 95% confidence intervals (CI) for proportions[22]. To infer the uncertainty for incidence rates, we used the exact 95% confidence interval under the Poisson distribution[23]. We employed random-effects meta-analyses using restricted maximum likelihood to pool information regarding proportions from different studies. For the analyses of incidence rates, we used random-effects models within the maximum likelihood estimation framework. We computed Cochran's Q test statistics to test for heterogeneity examining the null hypothesis that all studies produce the same effect. We quantified the between-study heterogeneity using the I^2 statistic, as the power of the Cochran's Q test is low in the analyses with a small number of studies. This I^2 statistic quantifies the proportion of total variation in the estimates of treatment effect due to the heterogeneity between studies and is considered to be a better approach for heterogeneity quantification[24].

Sensitivity analysis for the analysis in HR groups
Most data available for HR groups came from studies conducted on immunodeficient patients. To study the impact of this patient group on the pooled estimates, we calculated pooled estimates

for the HR group with and without the immunodeficient group. Also, some studies reported data for multiple HR groups without specifying if these groups were mutually exclusive. In those cases, we first generated pooled estimates including all the observations in a study. We then conducted a sensitivity analysis whereby only a single observation from each study was included. We used a hierarchical approach to select which observations to include using three types of definitions of HR groups (**Supplementary Table 2**). If a study reported on many HR groups, the HR group that appears first in the provided list was retained (e.g., if the study reported on asthma, diabetes, and chronic kidney disease (CKD), only asthma data were retained (first order)). The sensitivity analysis demonstrated little change in the effect estimates; therefore, we report the estimates based on the inclusion of all HR groups (with the immunodeficient group).

RESULTS

We identified a total of 3429 articles using our search criteria and included 103 in the review (**Supplementary Figure 1**). Of these, 30 studies reported data on older adults, 57 on HR groups, and 16 on both groups. Most studies were conducted in Europe (50.5%) and North America (38.8%), followed by Australia (7.8%) and Japan (2.90%). More than half of the studies (53.40%) reported data collected continuously over the year (annual data), and 46.60% reported data collected during one or more seasons (seasonal data). Seasonal studies were primarily conducted in winter, except for one study that took place in summer, in Southern California from June to August 2015[25]. Most studies reported on medically attended population (77.70%), followed by community-based population (18.40%) and residents of long-term care facilities (3.90%). Complete studies description and extracted outcomes are presented in **Supplementary Table 6**.

RSV disease burden and clinical presentation in older adults

Four studies (two on medically attended population and two in community cohorts) reported on RSV incidence in older adults (≥60 years old) (**Supplementary Table 7**). The seasonal incidence in older adults was reported by three studies, resulting in the pooled estimate of 16.11 cases/1000 persons per year (95% CI, 3.52-73.83). These studies showed a very high heterogeneity (I^2= 99.1%, p=0.00). One study reported on the annual RSV incidence in those ≥65 years old (0.27 cases/1000 persons per year (95% CI, 0.22-0.33))[26].

Forty-one studies reported on the proportion of RSV infection among older adults with symptomatic respiratory infections, including 31 studies conducted on patients ≥65 years old (**Figure 1**). According to annual studies (n=18), the proportion of RSV infection ranged from 0.00% to 21.50%, and the pooled estimate reached 4.66% (95% CI, 3.34-6.48). The included studies were highly heterogeneous (I^2 = 97.5%, p<0.001), and the estimate was largely driven by studies in medically attended populations and by studies in adults ≥ 65 years old. Due to data paucity (n=1)[27], no annual pooled estimate for community-based studies in older adults could be calculated. According to seasonal studies (n= 23), the proportion of RSV infection ranged from 0.00% to 26.50%, and the pooled estimate reached 7.80% (95% CI, 5.77-10.45) with high heterogeneity (I^2 = 96.2%, p<0.001). When stratified by the study population, the seasonal pooled estimate for medically attended populations was higher than for community-cohorts (8.91% (95% CI, 6.68-11.80) and 6.04% (95% CI, 3.21-11.09), respectively).
We observed little variation in the proportion of RSV-positive cases among older adults when compared by geographic region (**Supplementary Table 8**). Among annual studies, the proportion varied from 5.09% (95% CI, 3.42-7.50) in Europe, to 4.49% (95% CI, 1.50-12.67) in North America,

to 3.45% (95% CI, 2.10-5.61) in the Western Pacific region. In seasonal studies, the proportion varied from 6.65% (95% CI, 4.79-8.87) in Europe to 6.72% (95% CI, 4.78-9.38) in North America. No seasonal data were available from the Western Pacific region.

Most of the studies in older adults reported data only on symptomatic RSV infection in general and did not report separate data for patients presenting with URTI or LRTI. Consequently, it was not possible to generate specific estimates on URTI or LRTI proportion among older adults. The available data on these outcomes are presented in **Supplementary Table 9**. Six studies captured self-reported symptoms associated with RSV infection in older adults, and one recorded data on signs on examination (**Supplementary Table 10**). Among older adults, the most frequently self-reported RSV symptoms were cough (with a median of 86.0% patients reporting this symptom across six studies), weakness/malaise (median 86.7%), shortness of breath (median 72.3%), sputum (median 56.1%) and fever (median 53.3%). The most frequently reported sign on examination was wheezing, documented in 20.2% of cases [28].

RSV infection severe outcomes in older adults

Two community-cohort studies and five studies in medically attended populations reported on RSV severe outcomes in older adults (**Supplementary Table 11.A**). Overall, an estimated 27.44% (95% CI, 18.74-38.29) of RSV patients developed pneumonia (4 studies), 24.48% (95% CI, 0.43-96.07) required hospitalisation (3 studies) and 5.01% (95% CI, 0.47-37.36) (3 studies) were admitted to the ICU. These data should be interpreted with caution because the estimates are based on a limited number of studies combining medially attended and community cohort populations.

Using data from five studies in medically attended and one study in community-based older adults, we estimated the overall RSV infection case fatality proportion (CFP) among older adults at 8.18% (95%CI, 5.54-11.94) **(Figure 2**). These studies had low heterogeneity (I^2 =0.0%, p=0.37)**.** There was insufficient data to calculate RSV related CFPs by geographic region.

RSV disease burden and clinical presentation in HR adults

Eleven studies, four annual and seven seasonal, reported RSV incidence rates in three HR groups (≥18 years old adults at risk of complications) **(Supplementary Table 12**). Among immunodeficient patients, combining medically attended population and community cohorts, the annual incidence was 36.88 RSV cases per 1000 person-years (95% CI, 17.82-76.33) and the seasonal incidence was 7-fold higher, reaching 260.89 RSV cases per 1000 person-years (95% CI, 82.33-826.65%)**.** In patients with cardiopulmonary disease, the seasonal incidence was 19.15 RSV cases per 1000 person-years (95% CI, 6.06-60.49). Estimates in patients with immunodeficiency and cardiopulmonary disease were based on three studies each. A single study reported an incidence of 9.78 RSV cases per 1000 person-years (95% CI, 3.18-20.04) in institutionalised older adults[29].

Fifty-eight studies assessed the proportion of RSV-positive cases among HR groups with respiratory infections. Most of the studies reported on patients with cardiopulmonary disease or immunodeficiency (22 and 21 out of 58 studies, respectively) (**Figure 3**).
According to annual studies (n=32), the proportion of RSV infection among HR adults ranged from 0.00% to 45.83%, and the pooled proportion was estimated at 7.03% (95% CI, 5.18-9.48), with high

heterogeneity (I^2 = 92.1%, p <0.01). A sensitivity analysis excluding immunodeficient patients (Definition 2, **Supplementary Table 2**) generated a similar estimated proportion of 7.51% (95% CI, 4.79-11.60). Comparing the annual pooled estimates among HR subgroups, the RSV proportion was higher among patients with cardiopulmonary disease (9.68% (95% CI, 4.77- 18.68)) compared to immunodeficient patients (6.33% (95% CI, 4.31, 9.22)). According to seasonal studies (n=26), the proportion of RSV infection among HR adults ranged from 0.00% to 34.48% and the pooled proportion was estimated at 7.69% (95% CI, 6.23-9.46). The heterogeneity among seasonal studies was high (I^2= 84.5%, p <0.01). Excluding the immunodeficient patients resulted in an estimated RSV proportion of 6.53% (95% CI, 5.24-8.11). Comparing the seasonal pooled estimates among HR subgroups, immunodeficient patients had the highest pooled proportion (11.28% (95% CI, 7.75-16.13)), followed by patients with cardiopulmonary disease (7.22%, (95% CI, 5.20-9.94)) and institutionalised older adults (5.20% (95% CI, 3.27, 8.17)). As in the annual studies, the immunodeficient group accounted for a large proportion of all seasonal studies.

In annual studies, 11.21% (95%CI, 6.45-18.78) of HR adults with symptomatic respiratory infection tested positive for RSV in Europe, 5.44% (95%CI, 3.60- 8.13) in North America, and 5.32% (95%CI, 3.17-8.78) in the Western Pacific Region (**Supplementary Table 8**). In seasonal studies, 6.22% (95%CI, 4.49-8.55) of HR adults with symptomatic respiratory infection tested positive for RSV in Europe and 10.07% (8.05-12.54) in North America.

A total of 56.80% (95%CI, 48.13-65.07) and 44.53% (95%CI, 36.83-52.49%) of RSV-positive immunodeficient patients were estimated to have developed URTI and LRTI, respectively (**Supplementary Table 9**). Self-reported symptoms affecting more than 50% of RSV cases included cough, shortness of breath, sputum, nasal congestion, wheezing, discoloured sputum, and fever in patients with cardiopulmonary disease (2 studies); cough, wheezing and sputum (6 studies) among immunodeficient patients; and cough, weakness/malaise, and fever (1 study) among institutionalised older adults (**Supplementary Table 10**). Upon examination, wheezing and crackles were the signs identified in more than half of cardiopulmonary disease patients with RSV infection.

RSV infection severe outcomes in HR adults

Overall, among all HR RSV-positive patients, 32.82% (95%CI, 23.49-43.74) required hospitalisation and 26.74% (95%CI, 20.40-34.22) were admitted to the ICU (**Supplementary Table 11.B**). Among all RSV-positive immunodeficient patients (including community based and medically attended), 35.33% (95%CI, 29.78-41.30) developed pneumonia (6 studies), 20.62% (95%CI, 2.22-74.82) had a respiratory failure (3 studies), 24.09% (95%CI, 16.35-34.01) were admitted in the ICU (10 studies), 13.65% (95%CI, 7.87-22.63) required ventilatory support (5 studies), and 38.30 % (95%CI, 29.26-48.23) were hospitalized (13 studies).
Based on 29 studies (including 18 studies in immunodeficient populations), the estimated RSV infection case fatality proportion (CFP) was 9.88% (95%CI, 6.66-14.43), with substantial heterogeneity observed between studies (I^2 = 62.7%; p<0.05) mostly attributable to the heterogeneity observed between some studies from the immunodeficiency HR group (**Figure 4**). The CFP in RSV patients with cardiopulmonary disease was estimated at 10.80% (95% CI, 6.45-17.55), and among immunodeficient patients, at 9.27% (95% CI, 5.42-15.39). In Europe, the CFP among RSV-positive HR adults was estimated to be 13.00% (95%CI, 9.16-18.12) and, in North America, 7.73% (95% CI, 4.18-13.88) (**Supplementary Table 8**). We found insufficient data to calculate RSV-related mortality rates among HR adults.

RSV-related healthcare utilisation in older and HR adults

Two studies reported on RSV-related healthcare utilisation in older adults, four in HR adults and one in both groups. Among older adults with RSV infection, the studies showed that 76.95% to 77.91% were treated with antibiotics[5,28], 13.64% to 14.81% required oxygen use[28,30], less than 1% were discharged to care[28], 0.00% to 5.35% visited the emergency department[5,28], and 17.39% were outpatients visitors[5]. Among different HR adults with RSV infection, the studies reported that 23.81% to 50.00% required oxygen use[31-33], 4.17% to 17.29% were discharged to care[34], 8.93% visited the emergency department[5], and 28.57% were treated in outpatients[5]. We could not calculate pooled estimates for any of the groups due to paucity of data. Data are presented in **Supplementary Table 13.**

DISCUSSION

This SLR and meta-analysis comprehensively synthesise the available evidence on RSV disease burden among older adults ≥ 60 years of age and HR adults in developed countries. Our review was based on 103 articles that included about 3341 laboratory-confirmed RSV cases. It should be noted throughout that most data were available in HR and medically attended populations and that pooled estimates reflect those underlying patient populations more than true community estimates. The results showed a substantial burden of RSV in the adult population, especially those with comorbidities. We estimated that the proportion of RSV cases among respiratory infection was 4.66% in older adults and 7.03% in HR adults in annual studies. Severe outcomes were also more frequent among HR adults than among older adults. Hospitalisation and ICU admission in HR adults were reported in 32.82% and 26.74% of cases, compared to 24.48% and 5.01% in older adults, and the estimated CFP was 9.88% in HR adults and 8.18% in older adults.

In older adults, we estimated a seasonal RSV incidence of 16.11 cases/1000 persons per year (95% CI, 3.52,73.83) (including medically attended and community cohort populations).
As reported by others, RSV incidence is lower among the community cohort (6.7 cases/1000 persons per year (95% CI, 1.4–31.5) for adults ≥50 years old in industrialised countries[13]) than among hospitalized patients (23.2 cases per 1000 persons per year among adults ≥65 years old (95% CI, 11.1- 36.8)[4]).

The annual incidence of RSV in HR adults was similar to the one recently estimated out of community cohort studies in adults ≥18 years old with any comorbidity with ARI in industrialised countries (37.6 RSV cases per 1000 persons per year (95% CI, 20.1-70.3)[35]. However, in seasonal studies, we estimated a 9-fold higher incidence as previously reported by Shi et al[35]. (260.89 cases/1000 persons per year (95% CI, 82.33-826.65) compared to 28.4 RSV cases per 1000 person per year (95% CI, 11.4-70.9, respectively)). This difference might be driven by the inclusion of studies on cohorts of immunocompromised patients in our analysis, such as outpatient cohort of adult bone marrow or peripheral blood stem cell transplant recipients with mild RSV manifestation[36]. Thus, these results should be interpreted with caution.

Our estimate on the proportion of RSV-positive cases causing symptomatic respiratory infections in older adults varied from 4.66% in annual studies to 7.80 % in seasonal studies (including community cohort and medically attended). This aligns with previous studies on RSV burden in developed countries where RSV infection was estimated to cause 4.4% (95% CI, 3.0–6.5) of ARI among hospitalized adults ≥65 years old[13], 10% (95% CI, 5–16%) of ARI/ILI or CAP among community cohort or medically attended adults ≥50 years old in Europe and 7% (95% CI 5–9%) in the US[37], and 12% of ARI among medically attended adults ≥50 years old without underlying comorbidities in the US[38]. Two recent studies in those aged >60 years support these estimates, reporting that 5.4% of hospitalized patients with acute respiratory illnesses[9] and 5.6% community-dwelling adults[39] are RSV-infected. Altogether, the proportion of respiratory infection caused by RSV among older adults ranged from 4% to 12%.

The proportion of RSV-positive cases among HR groups with respiratory infection was similar to that previously estimated by two meta-analyses[37,38]. Those studies demonstrated that RSV infection accounted for 8.6% to 20.0% of all respiratory viral infections among

immunocompromised patients[37] and 8% to 13% of infections among adults with chronic cardiopulmonary diseases who were hospitalised during the winter season[38].

Cough was the most frequently reported symptom followed by shortness of breath, sputum, and fever, consistent with previous studies in older and HR adults[40]. Severe outcomes due to RSV infection –pneumonia, hospitalisation, ICU admission, and death- were more frequent among HR patients, mostly immunodeficient, than among older adults. Pneumonia was the most frequent complication in older adults and immunodeficient patients (27.44% and 35.33, respectively). Even higher estimates were recently reported in the study of Tseng, Sy et al. 2020, where it was estimated that >65% of RSV cases of hospitalized patients> 60 years of age (with and without comorbidities) developed pneumonia[9], probably reflecting underlying frailty and age. After pneumonia, hospitalisation was the second most frequent severe outcome, affecting 24.48% older adults and 32.82% HR adults. ICU admission was required five times more often among HR patients than among older adults. According to our pooled estimate from 11 studies (mostly on immunodeficient patients), more than one-quarter of HR patients required ICU admission [9]**.** This indicates the higher risk of severe disease and poor outcome in HR patients, especially among immunodeficient patients.

The case fatality proportion (CFP) among older adults mostly hospitalized reached 8.18% (95% CI, 5.54-11.94). The CFP was 10.80% (95% CI, 6.45%-17.55%) among cardiopulmonary patients and 9.27% (95% CI, 5.42%-15.39%) among immunodeficient adults, demonstrating similar results to those recently estimated for mostly immunocompetent RSV-ARI HR adults (11.7% (5.8%-23.4%))[35]. According to another study, cumulative mortality consistently increases after hospitalisation, reaching 25.8% in adults ≥60 years old after one year of admission[9]. The high CFP among immunocompetent older adults and those with comorbidities suggests that vaccination of at-risk patients could be a useful intervention to prevent RSV-related mortality.

Although RSV is the second most common aetiology of LRTI [3]after pneumococcal pneumonia, and it might lead to severe complications, our SLR identified a paucity of data on disease burden and healthcare utilisation. This limited our ability to estimate the incidence or prevalence of i) different clinical presentations of RSV disease, ii) the RSV-related complications and iii) the healthcare utilisation such as duration of hospitalisation. Data stratification by narrower age groups could not be investigated either due to the lack of data. It has been reported that RSV might have a major impact on hospitalisation and worse outcomes among the elderly and patients with underlying comorbidities compared to influenza [41-43]. Whereas influenza is subject to well-resourced seasonal surveillance and control strategies, including targeted vaccination programmes and treatment, this is not the case for RSV. Improved surveillance, including the adoption of the standardized case definitions, and criteria for testing and reporting, similarly as seen for influenza, would enable the generation of more robust estimates of the burden of disease and the identification of HR patients that needs special management and treatment. This could be achieved in the future as multiplex testing is now more widely adopted in response to the SARS-CoV-2 pandemic.

A good surveillance system is especially important since RSV circulation has been altered due to the COVID-19 pandemic. During 2020-2021, RSV season has been either completely missed (Brazil, Chile, Japan, Canada and South Korea) or delayed by an average of 39 weeks due to the effect of the non-pharmacological contingency interventions (social isolation, movement and gathering restriction, school and workplace closing, face mask policies) [44-47]. The virus resurged after lifting

the restrictions and reopening of schools[48]. According to the largest study that examined clinical outcomes of co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses in 6965 adults with SARS-CoV-2 in UK, RSV-COVID-19 dual infection affected 3.165% (220/6965) of the patients with COVID-19, and was not associated with increased odds of receiving invasive mechanical ventilations, as it was reported for influenza virus or adenovirus coinfection[49].

Our study is strengthened by the application of strict inclusion criteria, the assessment of the risk of bias, and the use of sensitivity and stratified analyses to thoroughly interrogate the available data. However, our study had several limitations. First, the included papers used different methods, and this might affect the comparability of the studies. Second, the true burden of RSV might be underestimated due to inclusion of only laboratory-confirmed cases. Third, medically attended and inpatient populations predominate, which potentially leads to underestimating the true RSV disease burden.

This study strengthens the evidence-base for the impact of RSV in older adults, and especially in adults with comorbidities. Comorbidities in older RSV patients are common, particularly chronic pulmonary and chronic cardiac conditions[50]. The combination of older age and underlying comorbidities may further increase the risk of severe outcomes of infection. Considering the increasingly aging population in high-income countries[51] and the high proportion of adults ≥ 60 years old with comorbidities (estimated at 22-31% of the world's population when considering diseases causing an increased risk of severe COVID-19[52]), the population at risk of RSV severe outcomes is substantial, and RSV intervention should be prioritised. To facilitate the development of RSV vaccines and treatments, increased RSV surveillance and understanding of key RSV epidemiological indicators, healthcare utilisation, risk factors, and severe outcomes across risk groups and older adults is needed to further characterise the RSV disease burden in the elderly.

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CONFLICTS OF INTEREST

J. Nguyen-Van-Tam received no research funding, honoraria, or non-financial benefits, including travel for his role in this or related work. He is seconded to the Department of Health and Social Care, England (DHSC) but performed this in his academic capacity at the University of Nottingham. The view expressed in this article are those of the authors and not necessarily those of DHSC. M. O'Leary and T.M.P Tran are employees of P95, a company that received consulting fees from Janssen, Pharmaceutical Companies of Johnson & Johnson. E. Martin received no research funding, honoraria, or non-financial benefits, including travel for his role in this or related work E. Heijnen, B. Callendret and C. Comeaux are employees of Janssen Vaccines & Prevention BV. R.Fleischhackl is an employee of Janssen Research and Development. K.Weber is an employee of Janssen Global Medical Affairs, IDV.

ACRONYMS AND ABBREVIATIONS

AEC	Acute exacerbation of COPD
AECOPD	Acute exacerbation of COPD
ARDS	Adult / Acute respiratory distress syndrome
ARI	Acute respiratory infection
CAP	Community acquired pneumonia
CFP	Case fatality proportion
CI	Sampling by clinical indication
95% CI	95% confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
GFR	Glomerular filtration rate
HR	High risk
HSCT	Hematopoietic stem-cell transplantation
ICU	Intensive care unit
ILI	Influenza like illness
LRTI	Lower respiratory tract infections
Obs	Observations
PNM	Pneumonia
RSV	Respiratory Syncytial Virus
RVI	Respiratory virus infection
SLR	Systematic literature review
SOT	Solid organ transplant
SS	Systematic sampling
URTI	Upper respiratory tract infection

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FIGURE LEGEND & FOOTNOTES

Figure 1. Proportion of respiratory infections attributable to RSV among older adults; annual and seasonal studies.

For each study, the first author, publication year, country of study, participants age (AgeGrp), population type (Pop), sampling method and respiratory infection (Samp), risk of bias assessment results (ROB), positive RSV cases (n), tested individuals (N), proportion of RSV cases (expressed as %) and its 95% confidence interval is given. Estimates stratified by data collection period, population according to the study setting and age are shown.

Footnote Figure 1: *REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS = systematic sampling; CI = sampling by clinical indication; 95% CI = 95% confidence interval, ILI = influenza like illness; ARI = acute respiratory infection; PNM = pneumonia; SARI = severe ARI; MSILI = moderate to severe ILI; IP = inpatients; OP = outpatients; ED = Emergency department; FLUVAC = Influenza vaccinated study population. Arbefeville 2017: Sampling targeted at inpatients with respiratory distress, immunocompromised or critically ill; Aronen 2019: very high rates of underlying comorbidities; Belongia 2018: Fever & cough included in eligibility criteria most seasons; Campe 2016: Swabbing conducted during influenza season; Huijts 2018: CAPITA trail, no active community-based follow-up, cases detected from medical facilities. Puig Barbera 2012: emergency hospitalisations.*

Figure 2. Case fatality proportion among RSV positive older adults.

For each study, the first author, publication year, country of study, participants age (AgeGrp), population type (Pop), sampling method and respiratory infection (Samp), risk of bias assessment results (ROB), number of deaths (n), positive RSV cases (N), total sample size (Total), proportion of deaths among RSV cases (expressed as %) and its 95% confidence interval is given. Estimates stratified by data collection period are shown.

Footnote Figure 2: *REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS = systematic sampling; CI = sampling by clinical indication; 95% CI = 95% confidence interval, ILI = influenza like illness; ARI = acute respiratory infection; PNM = pneumonia; IP = inpatients; ED = Emergency department; Puig Barbera 2012: emergency hospitalisations*

Figure 3. Proportion of respiratory infections attributable to RSV among high-risk adults; annual and seasonal studies. For each study, the first author, publication year, country of study, participants age (AgeGrp), study setting (Sett), population type (Pop), sampling method and respiratory infection (Samp), risk of bias assessment results (ROB), positive RSV cases (n), tested individuals (N), proportion of RSV cases (expressed as %) and its 95% confidence interval is given. Estimates stratified by data collection period and HR subgroups are shown.

Footnote Figure 3 *: REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, meda = medically attended; comm = community based; SS = systematic sampling; CI = sampling by clinical indication; 95% CI = 95% confidence interval, ILI = influenza like illness; ARI = acute respiratory infection; LRTI=lower respiratory tract infection; PNM = pneumonia; URTI=upper respiratory tract infection; AEA=acute exacerbation of asthma; AEC = acute exacerbation of COPD; RF=respiratory failure; IP = inpatients; OP = outpatients; ED = Emergency department; ICU = intensive care unit; CCU= critical care unit; RVI=respiratory virus infection; CU MV = intensive care unit, mechanically ventilated. Saraya, 2017: excluded COPD, pneumonia, interstitial lung diseases & acute heart failure patients, as well as those with respiratory symptoms due to infections in the last month; Jahn 2018 included immunocompromised patients with suspicion of infection and/or respiratory symptoms and/or radiologically confirmed lung infiltrates undergoing bronchoscopy; Mahan 2017, Slade 2017 & D'Angelo 2016 patients followed in medical facility. Clark, 2014: Inclusion criteria: acute exacerbation of chronic cardiopulmonary illness or acute pulmonary illness (pneumonia, bronchitis, ILI) Belongia, 2018: Fever & cough included in eligibility criteria most seasons; Puig Barbera 2012: emergency hospitalisations; Diaz-Decaro, 2016 – recruitment during summer; Gueller 2013: all inpatient haematopoietic stem cell transplant patients enrolled, regardless of whether they had symptoms.*

Figure 4. Case fatality proportion among RSV positive high-risk groups.

For each study, the first author, publication year, country of study, participants age (AgeGrp), study setting (Sett), population type (Pop), sampling method and respiratory infection (Samp), risk of bias assessment results (ROB), number of deaths (n), positive RSV cases (N), total sample

size (Total), proportion of deaths among RSV cases (expressed as %) and its 95% confidence interval is given. Estimates stratified by HR subgroups are shown.

Footnote Figure 4: REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, meda = medically attended; comm = community based; SS = systematic sampling; CI = sampling by clinical indication; 95% CI = 95% confidence interval, ILI = influenza like illness; ARI = acute respiratory infection; RF=respiratory failure; RVI = respiratory viral infection; IP = inpatients; ICU = intensive care unit.

D'Angelo 2016 patients followed in medical facility, Li 2012 – patients sampled based on clinical indication, but all RSV positives systematically included in analysis.

Title

Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries

SUPPLEMENTARY FIGURE LEGEND

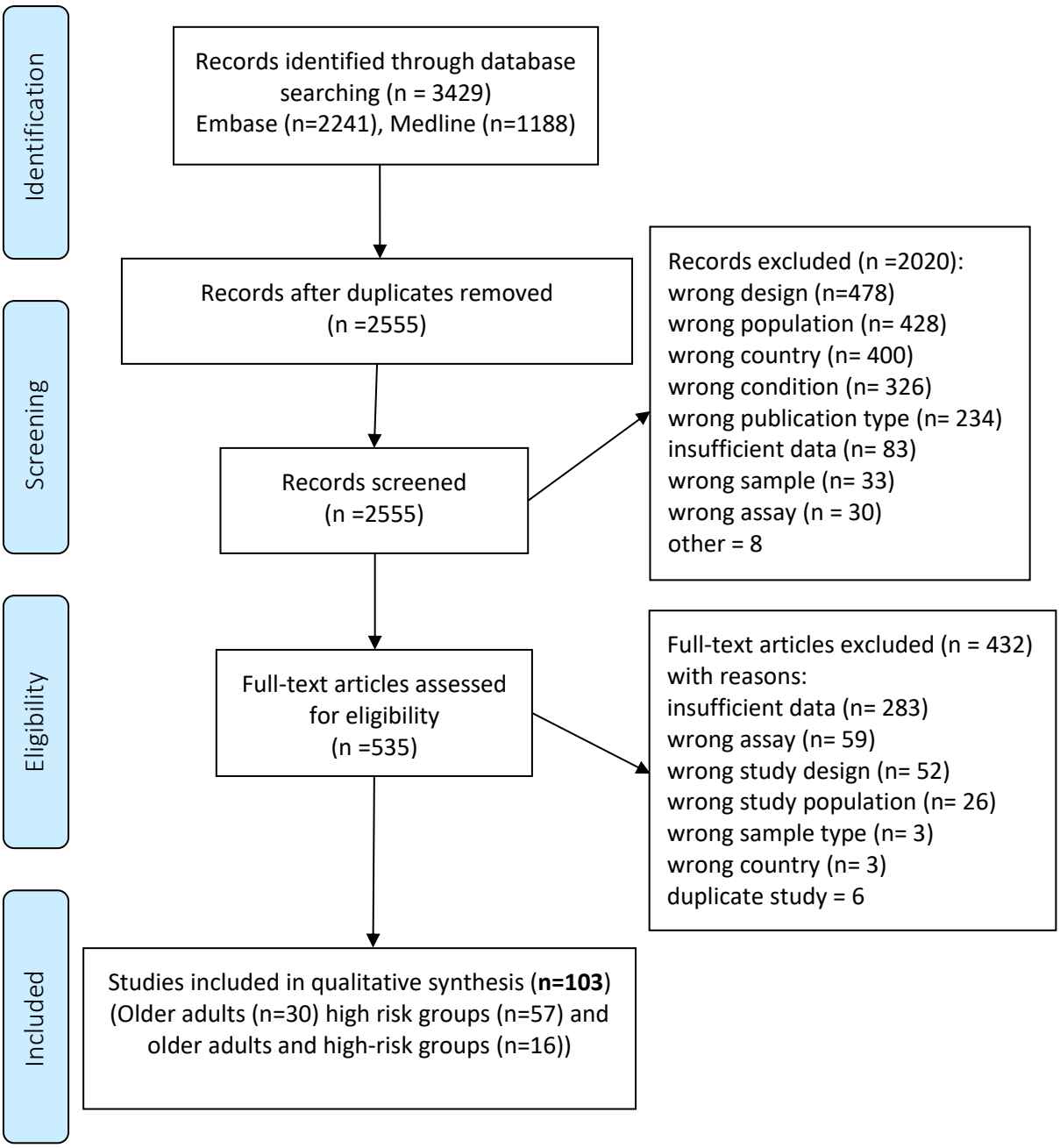
Supplementary Figure 1. PRISMA flow diagram.

SUPPLEMENTARY TABLES LEGEND

Supplementary Table 1. Embase and Medline search terms.
Supplementary Table 2. HR groups definitions and hierarchy for retention of data from studies reporting data in multiple HR groups in overall pooled analyses.
Supplementary Table 3. Clinical outcome definitions of RSV infection.
Supplementary Table 4. Inclusion and exclusion criteria.
Supplementary Table 5. ROB assessment tool **(A.)** and ROB assessment results per included study **(B.).**
Supplementary Table 6. Characteristics of included studies.
Supplementary Table 7. RSV incidence in older adults (annual and seasonal studies).
Supplementary Table 8. Estimated proportion of symptomatic respiratory infection attributable to RSV and estimated RSV case fatality proportion among older adults and HR adults by geographical location.
Supplementary Table 9. URTI, LRTI and bronchitis proportion among older adults and HR groups.
Supplementary Table 10. RSV signs and symptoms description in older and high-risk adults.
Supplementary Table 11. RSV severe outcomes in older adults **(A.)** and HR adults **(B.).**
Supplementary Table 12. RSV incidence in HR adults (annual and seasonal studies).
Supplementary Table 13. RSV related healthcare utilisation of older and HR adults.

SUPPLMENTARY FIGURE

Supplementary Figure 1. PRISMA flow diagram.



SUPPLEMENTARY TABLE

Supplementary Table 1. Embase and Medline search terms.

Embase search terms (Ovid); 2241 articles	
1	exp Human respiratory syncytial virus/ or exp respiratory syncytial virus infection/ or rsv.mp. or exp Respiratory syncytial pneumovirus/ or exp respiratory syncytial virus vaccine/
2	respiratory syncytial virus.mp.
3	1 or 2
4	respiratory tract infection.mp. or exp respiratory tract infection/
5	ARI.mp.
6	upper respiratory tract infection.mp. or exp upper respiratory tract infection/
7	URTI.mp.
8	lower respiratory tract infection.mp. or exp lower respiratory tract infection/
9	LRTI.mp.
10	ALRTI.mp.
11	ALRI.mp.
12	bronchitis.mp. or exp bronchitis/
13	cough.mp. or exp coughing/
14	exp sputum/ or sputum.mp.
15	haemoptysis.mp. or exp hemoptysis/
16	hemoptysis.mp.
17	wheezing.mp. or exp wheezing/
18	shortness of breath.mp. or exp dyspnea/
19	dyspnea.mp.
20	runny nose.mp. or exp rhinorrhea/
21	rhinorrhea.mp.
22	rhinorrhoea.mp.
23	congested nose.mp.
24	blocked nose.mp.
25	sore throat.mp. or exp sore throat/
26	pharyngitis.mp. or exp pharyngitis/ or exp viral pharyngitis/
27	headache.mp. or exp headache/
28	exp fatigue/ or fatigue.mp.
29	exp fever/ or fever.mp.
30	pyrexia.mp.
31	exp myalgia/ or myalgia.mp.
32	muscle pain.mp.
33	exp respiratory distress/ or respiratory compromise.mp.
34	difficulty breathing.mp.
35	weakness.mp. or exp weakness/
36	malaise.mp. or exp malaise/
37	respiratory distress.mp. or exp respiratory distress/
38	tachypnoea.mp. or exp tachypnea/
39	tachypnea.mp.
40	reduced breath sounds.mp. or exp abnormal respiratory sound/
41	crackles.mp. or exp crackle/
42	rales.mp.
43	rhonchi.mp.
44	oxygen saturation.mp. or exp oxygen saturation/
45	pneumonia.mp. or exp pneumonia/
46	respiratory failure.mp. or exp respiratory failure/
47	hypoxia.mp. or exp hypoxia/
48	hypoxic.mp.

Embase search terms (Ovid); 2241 articles	
49	hypercapnia/ or hypercapnic.mp.
50	hypercapnia.mp.
51	hypercapnoea.mp.
52	hypercapnea.mp.
53	adult respiratory distress syndrome.mp. or exp adult respiratory distress syndrome/
54	ARDS.mp.
55	cardiorespiratory failure.mp. or exp cardiopulmonary insufficiency/
56	cardiopulmonary complications.mp.
57	arrhythmia.mp. or exp heart arrhythmia/
58	congestive heart failure.mp. or exp congestive heart failure/
59	myocardial infarction.mp. or exp heart infarction/
60	stroke.mp. or cerebrovascular accident/
61	chronic obstructive pulmonary disease.mp. or exp chronic obstructive lung disease/
62	copd.mp.
63	chronic obstructive lung disease.mp.
64	exp asthma/ or asthma.mp.
65	exp disease exacerbation/ or exacerbation .mp.
66	exp complication/ or complication .mp.
67	exp hospital readmission/ or hospital .mp. or exp hospital admission/
68	intensive care.mp. or exp intensive care/
69	ICU.mp. or exp intensive care unit/
70	high dependency.mp. or exp high dependency unit/
71	emergency care.mp. or exp emergency care/
72	mechanical ventilation.mp. or exp artificial ventilation/
73	exp mortality/ or mortality.mp. or exp mortality rate/
74	exp death/ or death.mp.
75	case fatality.mp.
76	exp outpatient care/ or outpatient.mp. or exp outpatient/ or exp outpatient department/
77	primary care.mp. or exp primary medical care/
78	general practice.mp. or exp general practice/
79	emergency department.mp. or exp emergency ward/
80	exp emergency health service/ or A&E.mp.
81	exp rehabilitation/ or rehab .mp.
82	nursing.mp. or exp nursing home/
83	long-term care.mp. or exp long term care/
84	exp home oxygen therapy/ or exp oxygen therapy/ or oxygen.mp. or exp oxygen/
85	antibiotic.mp. or exp antibiotic agent/
86	antimicrobial.mp.
87	exp incidence/ or incidence.mp.
88	prevalence.mp. or exp prevalence/
89	morbidity.mp. or exp morbidity/
90	burden.mp. or global disease burden/ or disease burden/
91	utilisation.mp. or exp health care utilisation/
92	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91
93	3 and 92
94	limit 93 to (human and english and yr="2000 -Current" and (adult <18 to 64 years> or aged >65 years>))

Medline search terms (Ovid); 1188 articles	
1	respiratory syncytial virus.mp. or exp Respiratory Syncytial Viruses/
2	exp Respiratory Syncytial Virus Infections/ or RSV.mp.
3	1 or 2
4	respiratory tract infection.mp. or exp Respiratory Tract Infections/
5	acute respiratory tract infection.mp.
6	ARI.mp.
7	upper respiratory tract infection.mp.
8	URTI.mp.
9	lower respiratory tract infection.mp.
10	LRTI.mp.
11	bronchitis.mp.
12	respiratory tract disease.mp. or exp Respiratory Tract Diseases/
13	exp Cough/ or cough.mp.
14	sputum.mp. or exp Sputum/
15	exp Hemoptysis/ or haemoptysis.mp.
16	hemoptysis.mp.
17	wheezing.mp. or exp Respiratory Sounds/
18	shortness of breath.mp. or exp Dyspnea/
19	dyspnea.mp.
20	exp Rhinitis/ or rhinorrhea.mp.
21	rhinorrhoea.mp.
22	nasal congestion.mp.
23	blocked nose.mp.
24	sore throat.mp. or exp Pharyngitis/
25	pharyngitis.mp.
26	headache.mp. or exp Headache/
27	exp Fatigue/ or fatigue.mp.
28	fever.mp. or exp Fever/
29	pyrexia.mp.
30	myalgia.mp. or exp Myalgia/
31	muscle pain.mp.
32	exp Respiratory Insufficiency/ or respiratory compromise.mp.
33	weakness.mp.
34	malaise.mp.
35	exp Tachypnea/ or tachypnea.mp.
36	tachypnoea.mp.
37	reduced breath sounds.mp.
38	crackles.mp. or exp Respiratory Sounds/
39	rales.mp.
40	rhonchi.mp.
41	oxygen saturation.mp.
42	exp Pneumonia/ or pneumonia.mp.
43	respiratory failure.mp.
44	hypoxia.mp. or exp Hypoxia/
45	hypoxic.mp.
46	exp Hypercapnia/ or hypercapn .mp.
47	exp Respiratory Distress Syndrome, Adult/ or respiratory distress.mp.
48	ARDS.mp.
49	cardiorespiratory failure.mp.
50	cardiopulmonary insufficiency.mp.
51	cardiopulmonary complications.mp.
52	arrhythmia.mp. or exp Arrhythmias, Cardiac/
53	congestive heart failure.mp. or exp Heart Failure/

Medline search terms (Ovid); 1188 articles	
54	myocardial infarction.mp. or exp Myocardial Infarction/
55	stroke.mp. or exp Stroke/
56	cerebrovascular accident.mp.
57	COPD.mp. or exp Pulmonary Disease, Chronic Obstructive/
58	chronic obstructive pulmonary disease.mp.
59	asthma.mp. or exp Asthma/
60	exacerbation.mp.
61	complicatio .mp.
62	hospital admission.mp. or exp Hospitalisation/
63	hospital .mp.
64	exp Intensive Care Units/ or exp Critical Care/ or ICU.mp. or exp Critical Illness/
65	intensive care.mp.
66	high dependency.mp.
67	emergency care.mp. or exp Emergency Medical Services/
68	mechanical ventilation.mp. or exp Respiration, Artificial/
69	artificial respiration.mp.
70	exp Mortality/ or mortality.mp.
71	death.mp. or exp Death/
72	case fatality.mp.
73	outpatient.mp. or exp Outpatients/
74	primary care.mp. or exp Primary Health Care/
75	general practice.mp. or exp General Practice/
76	A&E.mp.
77	emergency.mp.
78	emergency department.mp. or exp Emergency Service, Hospital/
79	exp Rehabilitation/ or exp Rehabilitation Centers/ or rehab .mp.
80	nursing care.mp. or exp Nursing Care/
81	long term care.mp. or exp Long-Term Care/
82	exp Oxygen Inhalation Therapy/ or oxygen therapy.mp. or exp Oxygen/
83	antibiotic.mp. or exp Anti-Bacterial Agents/
84	exp Drug Prescriptions/ or exp Prescription Drugs/ or prescri .mp. or exp Prescriptions/
85	antimicrobial.mp.
86	drug utilisation.mp. or exp Drug Utilisation/
87	morbidity.mp. or exp Morbidity/
88	incidence.mp.
89	prevalence.mp.
90	burden of disease.mp.
91	utili#ation.mp.
92	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91
93	3 and 92
94	limit 93 to (english language and humans and yr="2000 -Current" and "all adult (19 plus years)")

Supplementary Table 2. High risk groups definitions and hierarchy for retention of data from studies reporting data in multiple HR groups in overall pooled analyses.

High risk group definition	Includes the following underlying conditions:
Definition 1	- cardiopulmonary disease (chronic obstructive pulmonary disease (COPD), chronic heart disease (coronary heart failure, coronary artery disease (e.g., angina pectoris, ischemic cardiomyopathy, history of myocardial infarct, history of coronary artery bypass graft or coronary artery stent) - asthma - diabetes - chronic kidney disease (CKD) - immunodeficiency or immunosuppressive diseases (severe combined immunodeficiency, leukaemia or hematopoietic cell or lung transplant) - dementia or stroke - institutionalized older adults - functional impairment
Definition 2	- As HR group definition 1 but excluding patients with immunodeficiency or immunosuppressive diseases (severe combined immunodeficiency, leukaemia or hematopoietic cell or lung transplant).
Definition 3	- cardiopulmonary disease (chronic obstructive pulmonary disease (COPD), chronic heart disease (coronary heart failure, coronary artery disease (e.g., angina pectoris, ischemic cardiomyopathy, history of myocardial infarct, history of coronary artery bypass graft or coronary artery stent)) - asthma
Hierarchy among HR group	**Rationale**
1. Asthma 2. Cardiopulmonary	Risk groups included in the most specific definition of HR (definition 3). Asthma prioritised for inclusion as data for this group were less frequently reported
3. Diabetes 4. CKD 5. Dementia 6. Institutionalised older adults	Groups included in the next most specific definition (definition 2). Ordered according to their prevalence in the general population*
7. Immunodeficient	Only included in definition 1, the least specific definition of HR groups.

** 1 in 11 adults worldwide aged 20-79 have diabetes (diabetes atlas https://diabetesatlas.org/en/); Global prevalence of CKD = 9.1%[1]. 5-8% of global population have dementia (WHO https://www.who.int/news-room/fact-sheets/detail/dementia); 3.1% of US[2] and 3.2%of UK[3] adults aged 65+ reside in long term care homes*

Supplementary Table 3. Clinical outcome definitions of RSV infection.

Outcome	**Outcome definition**
Symptomatic RSV infection	Based on clinical diagnosis
Upper respiratory tract infection (URTI)	Based on clinical diagnosis
Lower respiratory tract infection (LRTI)	Based on clinical diagnosis
Bronchitis	Based on clinical diagnosis
Symptoms & signs	Fever will be based on patient self-report and for the assessment of signs fever will be defined as a measured temperature of ≥380C for those aged 18-59 years and ≥37.50C for those aged ≥60 years
Pneumonia	Based on clinical diagnosis
Respiratory failure	Respiratory failure will refer to acute respiratory failure and will include hypoxic (type 1) and hypercapnic (type 2) respiratory failure, as well as unspecified types of acute respiratory failure. Respiratory failure can be based on the definitions used in the source paper. The definition used will be noted in the data extraction form, to aid data interpretation and inform possible additional analyses.
Acute respiratory distress syndrome (ARDS)	ARDS will not be subject to any particular definition but will be based on the definitions used in the source papers; although similar to respiratory failure, the definition used will be noted in the data extraction form.
Cardiopulmonary complications	Cardiopulmonary complications will include lower respiratory tract complications (pneumonia and exacerbations of COPD or asthma) and cardiovascular complications (arrhythmia, congestive heart failure exacerbation, myocardial infarction and stroke), in accordance with the definition used by Volling et al.[4].

Supplementary Table 4. Inclusion and exclusion criteria.

Parameter	**Criteria**
Population	1. The general population of adults aged 60 years and older. 2. High risk adults aged 18 years and older (Definition 1, Supplementary Table2)
Outcomes	1. Incidence and proportion of symptomatic RSV infection 2. RSV-related URTI, LRTI, bronchitis 3. RSV-related signs and symptoms 4. RSV-related CAP, respiratory failure, ARDS, cardiopulmonary complications, hospitalisations, ICU admissions, mechanical ventilation and case fatality rate. 5. RSV related outpatient and emergency department consultations and discharges to skilled nursing care, oxygen therapy and antibiotic use
Time	6. Studies dating from 2000 to 10.12.2020
Study design	Included: − Peer reviewed observational studies on RSV infection, signs and symptoms, outcomes of infection, and healthcare utilisation including cohort, case-control and surveillance reports. − Modelling studies (if data can be extracted on the underlying estimates of RSV burden used to generate the model). − Conference abstracts (if both numerator and denominator data can be extracted on the study outcomes). − Interventional trials (if epidemiological data can be extracted from a control group). − Studies of point of care testing (if PCR test data from a clearly defined unbiased sample were conducted). − Validation studies of laboratory assays based on systematic testing or testing of an unbiased sample of routinely received specimens. − Longitudinal studies of HR groups (such as stem-cell transplant patients), including studies of pharmaceutical interventions such as the use of palivizumab (if the follow-up time is clearly defined and can be used to generate an estimate in person-time). − Longitudinal and surveillance studies in long-term care facilities, reporting annual or seasonal incidence of RSV (as opposed to reporting the attack rate during an outbreak). Excluded: − Literature review articles (reference lists will be scanned to identify relevant articles). − Outbreak reports, including reports of outbreaks in long-term care facilities. − Reports on hospital-acquired infections. − Case reports. − In vitro studies. − Animal studies. − Immunogenicity, safety and human challenge studies. − Environmental studies. − Economic and quality of life studies. − Knowledge, attitude and perception studies. − Studies in travelers & children. − Studies lacking clearly defined denominator data (such as data on the follow-up time). − Studies lacking clearly defined study populations. Studies not reporting data in those aged ≥60 (general population) or in HR groups aged ≥18 (for instance if data are only reported for all adults over 18 years of age and separate estimates for those aged 60 and over or HR groups are not reported)

Parameter	Criteria
Other	Included: – Studies from developed countries[5] including: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia, Slovenia, Iceland, Norway, Switzerland, Australia, Canada, Japan, New Zealand, USA. – English language articles. RT-PCR confirmed RSV cases only (including both rapid molecular tests and multiplex molecular tests of respiratory specimens including nose and throat swabs, nose swabs, oropharyngeal/throat swabs, nasal washes, nasopharyngeal swabs and aspirates, sputum, bronchoscopy and bronchoalveolar lavage samples). Excluded: – RSV cases identified through viral culture, rapid antigen detection tests, direct fluorescent antibody tests. – Studies of asymptomatic RSV infection.

Supplementary Table 5.A. ROB assessment tool.

Domain	Category	Risk of Bias
1. Study design	Prospective enrolment of cases	Low
	Other studies	High
2. Study period	At least one complete year	Low
	Less than a complete year, for instance: One or more influenza seasons	High
3. Representativeness of study population	Largely representative of target population	Low
	Selection of particular groups of participants that might bias estimates including: 1. ILI cases. 2. Hospitalised persons. 3. Vaccinated persons. 4. Other selection criteria that might affect estimates. 5. Selection of participants not described.	High
4. Case identification	Cases identified using standardised case definition & approach	Low
	No standardised case definition or process for case identification, or process not described	High
5. Sampling strategy	≥90% of eligible cases tested or a systematic sample of cases tested	Low
	<90% of eligible cases tested, or non-systematic sampling strategy used, or sampling strategy not described, or proportion of eligible cases tested not reported	High
6. Specimen type	Any of nose & throat swab, nose swab, nasal wash, sputum, nasopharyngeal swab or aspirate, bronchoscopy, bronchoalveolar lavage +/- throat swab	Low
	100% throat swabs	High
6. Diagnostic test	100% PCR testing	Low
	Mix of diagnostic assays including PCR, immunofluorescence, viral culture, antibody tests	High
7. Outcome assessment	Outcomes identified using standardised approach including: 1. Clinical assessment. 2. Medical record review. 3. Patient interview using standardised study instruments.	Low
	Outcome assessment by self-report or approach not described	High
8. Completeness of outcome assessment	≥90% of participants followed up for a sufficient duration of time to allow outcomes to occur	Low
	Complete follow-up for <90% of participants or follow-up of insufficient duration or completeness and duration of follow up not described	High

Supplementary Table 5.B. ROB assessment tool results per included study.

Author, year and country	Study design	Study period	Representativeness	Case identification	Sampling strategy	Specimen	Diagnostic test	Outcome assessment	Completeness of outcome assessment	ROB score (out of 9)
Ambrosioni, 2014, Switzerland	High	Low	High	High	High	Low	Low	Low	Low	4
Ansaldi, 2012, Italy	Low	High	High	Low	Low	Low	Low	Low	Low	2
Antalis, 2018, Greece	Low	High	High	Low	Low	Low	Low	Low	Low	2
Anton, 2016, Spain	Low	High	High	Low	Low	Low	Low	Low	Low	2
Arbefeville, 2017, USA	High	Low	High	High	High	Low	Low	Low	Low	4
Aronen, 2019, Finland	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Belongia, 2018, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Borg, 2003, Germany	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Camargo, 2008, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Cameron, 2006, Australia	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Campe, 2016, Germany	Low	High	High	Low	Low	Low	Low	Low	Low	2
Carrat, 2006, France	Low	High	High	Low	Low	Low	Low	Low	Low	2
Charles, 2008, Australia	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Chasqueira, 2018, Portugal	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Chatzis, 2018, Switzerland	High	Low	High	Low	Low	Low	Low	Low	Low	2
Clark, 2014, UK	Low	High	High	Low	Low	Low	Low	Low	Low	2
Damlaj, 2016, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
D'Angelo, 2016, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
De Serres, 2009 Canada	Low	High	High	Low	Low	Low	Low	Low	Low	2
Diaz-Decaro, 2016, USA	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Dimopoulos, 2014, Greece	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Falsey, 2005, USA	Low	High	Low	Low	Low	Low	High	Low	Low	2
Falsey, 2006 USA	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Falsey, 2014, Belgium, Canada, Czech Rep, Estonia, France, Germany,	Low	High	High	Low	High	Low	Low	Low	Low	3

Author, year and country	Study design	Study period	Representativeness	Case identification	Sampling strategy	Specimen	Diagnostic test	Outcome assessment	Completeness of outcome assessment	ROB score (out of 9)
Netherlands, Norway, Poland, Romania, UK										
Garcia-Noblejas, 2015, Spain	High	Low	High	High	High	Low	Low	Low	High	5
Gaymard, 2018, France	High	High	High	High	High	Low	Low	Low	Low	5
Gaymard, 2019, France	High	High	High	High	High	Low	Low	Low	Low	5
Gilca, 2014, Canada	Low	High	High	Low	Low	Low	Low	Low	Low	2
Gimferrer, 2019, Spain	Low	High	High	Low	Low	Low	High	Low	Low	3
Gorcea, 2015, UK	High	Low	High	Low	High	Low	Low	Low	Low	3
Gorse, 2015, USA	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Graat, 2003, Netherlands	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Gueller, 2013, Germany	High	High	High	Low	Low	High	Low	Low	Low	4
Hequet, 2019, Switzerland	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Hombrouck, 2012, Belgium	Low	High	High	Low	Low	Low	Low	Low	Low	2
Hopkins, 2008, Australia	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Huijts, 2018, Netherlands	Low	Low	High	Low	Low	High	Low	Low	Low	2
Hutchinson, 2007, Australia	Low	High	High	Low	Low	Low	Low	Low	Low	2
Iikura, 2015, Japan	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Jahn, 2018, Switzerland	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Jain, 2015, USA	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Jeannoel, 2019, France	High	High	High	Low	High	Low	Low	Low	Low	4
Johnstone, 2014, Canada	Low	High	Low	Low	Low	Low	Low	High	Low	2
Juretschko, 2017, USA & Canada	Low	High	High	High	High	Low	Low	Low	Low	4
Katsurada, 2017, Japan	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Khanna, 2008, Switzerland	High	Low	High	Low	High	Low	High	Low	Low	4
Kherad, 2010, Switzerland	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Klein, 2007, Canada	Low	High	High	Low	Low	Low	High	Low	Low	3
Kumar, 2005, Canada	Low	Low	High	Low	Low	Low	Low	Low	Low	1

Author, year and country	Study design	Study period	Representativeness	Case identification	Sampling strategy	Specimen	Diagnostic test	Outcome assessment	Completeness of outcome assessment	ROB score (out of 9)
Lee, 2019, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Leibl, 2017, Switzerland	Low	High	High	Low	Low	Low	Low	Low	Low	2
Li, 2012, USA	High	Low	High	Low	Low	Low	Low	Low	Low	2
Lopez-Medrano, 2007, Spain	Low	High	Low	Low	Low	Low	High	Low	Low	2
Loubet, 2017, France	Low	High	High	Low	Low	Low	Low	Low	Low	2
Mahan, 2017, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Malosh, 2017, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Mikulsa, 2014, Italy	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Meerhoff, 2006, Netherlands, England, Scotland	Low	High	High	Low	Low	Low	Low	Low	Low	2
Milstone, 2006, USA	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Minodier, 2014, France	Low	High	High	Low	Low	Low	Low	Low	Low	2
Ong, 2014, Netherlands	Low	High	High	Low	Low	Low	Low	Low	High	3
Paba, 2014, Italy	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Pancer, 2011, Poland	Low	Low	High	High	High	Low	Low	Low	Low	3
Passi, 2019, Italy	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Peghin, 2017, Spain	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Peyrani, 2012, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Pilie, 2015, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Pinana, 2017, Spain	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Price, 2019, Australia	High	Low	High	High	Low	Low	Low	Low	Low	3
Puig-Barbera, 2012, Spain	Low	High	High	Low	Low	Low	Low	Low	Low	2
Puzelli, 2009, Italy	Low	High	High	Low	Low	High	Low	Low	Low	3
Reid, 2017, Australia	High	High	High	Low	High	Low	Low	Low	Low	4
Renaud, 2013, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Roghmann, 2003, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Rohde, 2003, Germany	Low	Low	High	Low	Low	Low	Low	Low	Low	1

Author, year and country	Study design	Study period	Representativeness	Case identification	Sampling strategy	Specimen	Diagnostic test	Outcome assessment	Completeness of outcome assessment	ROB score (out of 9)
Saez-Lopez, 2019, Portugal	Low	High	High	Low	Low	Low	Low	Low	Low	2
Sanghavi, 2012, USA	Low	High	High	High	High	High	Low	Low	Low	5
Saraya, 2017, Japan	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Schmidt, 2019, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Seemungal, 2001, UK	Low	Low	High	Low	Low	Low	High	Low	Low	2
Sellers, 2018, USA	Low	Low	High	Low	Low	Low	Low	Low	Low	1
Slade, 2017, USA	High	Low	Low	Low	High	Low	High	Low	Low	3
Snyder, 2017, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Souty, 2019, France	Low	High	High	Low	Low	Low	Low	Low	Low	2
Spahr, 2018, Switzerland	High	Low	High	High	High	Low	Low	Low	Low	4
Steensels, 2019, Belgium	High	Low	High	Low	High	Low	Low	Low	Low	3
Stolz, 2019, Switzerland	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Sundaram, 2014, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Tanner, 2012, UK	High	High	High	High	High	Low	Low	Low	Low	5
Teh, 2015, Australia	High	Low	High	Low	High	Low	Low	Low	Low	3
Theodoropoulos, 2013, USA	High	Low	High	Low	High	High	Low	Low	Low	4
Thomas, 2019, USA	High	High	High	Low	High	Low	Low	Low	Low	4
Tramuto, 2016, Italy	High	Low	High	Low	Low	Low	Low	Low	Low	2
Van Beek, 2017, Netherlands	Low	High	Low	Low	Low	Low	Low	Low	Low	1
Varghese, 2018, Australia	Low	Low	High	Low	High	Low	Low	Low	Low	2
Visseaux, 2017, France	High	Low	High	Low	High	Low	Low	Low	Low	3
Walker, 2014, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Wansaula, 2016, USA	Low	Low	High	Low	Low	Low	Low	Low	High	2
Weinberg, 2010, USA	Low	Low	Low	Low	Low	Low	Low	Low	Low	0
Widmer, 2012, USA	Low	High	High	Low	Low	Low	Low	Low	Low	2
Widmer, 2014, USA	Low	Low	High	Low	Low	Low	Low	Low	Low	1

Author, year and country	Study design	Study period	Representativeness	Case identification	Sampling strategy	Specimen	Diagnostic test	Outcome assessment	Completeness of outcome assessment	ROB score (out of 9)
Yousaf, 2017, USA	High	Low	High	Low	High	Low	Low	Low	Low	3
Zambon, 2001, UK	Low	High	High	Low	High	Low	Low	Low	Low	3

Supplementary Table 6. Characteristics of included studies.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
1	Ambrosioni, 2014, Switzerland	1039	>65	Medically attended	Older adults	2011-2012	Continuous (annual)	Surveillance	RSV prevalence (Elderly)	Ambrosioni J, Bridevaux P-O, Wagner G, Mamin A, Kaiser L. Epidemiology of viral respiratory infections in a tertiary care centre in the era of molecular diagnosis, Geneva, Switzerland, 2011-2012. Clinical Microbiology and Infection 2014; 20(9): O578-O84.
2	Ansaldi, 2012, Italy	2551	≥60	Community cohort	Older adults	2010-2011	Seasonal	Cohort	Pneumonia proportion (Elderly); RSV proportion (Elderly)	Ansaldi F, De Florentiis D, Parodi V, et al. Bacterial carriage and respiratory tract infections in subjects ≥ 60 years during an influenza season: Implications for the epidemiology of Community Acquired Pneumonia and influenza vaccine effectiveness. Journal of Preventive Medicine and Hygiene 2012; 53(2): 94-7.
3	Antalis, 2018, Greece	129	>65	Medically attended	Older adults	2009-2015	Seasonal	Surveillance	RSV proportion (Elderly)	Antalis E, Oikonomopoulou Z, Kottaridi C, et al. Mixed viral infections of the respiratory tract; an epidemiological study during consecutive winter seasons. Journal of Medical Virology 2018; 90(4): 663-70.
4	Anton, 2016, Spain	339	>65	Medically attended, ILI	Older adults	2006-2012	Seasonal	Surveillance	RSV proportion (Elderly)	Anton A, Marcos MA, Torner N, et al. Virological surveillance of influenza and other respiratory viruses during six consecutive seasons from 2006 to 2012 in Catalonia, Spain. Clinical Microbiology and Infection 2016; 22(6): 564.
5	Arbefeville, 2017, USA	614	≥60	Medically attended	Older adults	2014-2015	Continuous (annual)	Surveillance	RSV proportion (Elderly)	Arbefeville S, Ferrieri P. Epidemiologic analysis of respiratory viral infections mainly in hospitalised children and adults in a Midwest University Medical Center after the implementation of a 14-virus multiplex nucleic acid amplification test. American Journal of Clinical Pathology 2017; 147(1): 43-9.
6	Aronen, 2019, Finland	382	≥65	Medically attended, inpatients	HR older adults, all with underlying comorbidities	2007-2009	Continuous (annual)	Cohort	Pneumonia proportion (Elderly); RSV proportion (Elderly)	Aronen M, Viikari L, Kohonen I, et al. Respiratory tract virus infections in the elderly with pneumonia. BMC geriatrics 2019; 19(1): 111.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
7	Belongia, 2018, USA	1832	≥60	Medically attended	Older adults, cardiopulmonary, asthma, diabetes, immunodeficient (cause not specified), lung disease, cardiac disease	2004-2016	Seasonal	Cohort	Hospitalisation proportion (Elderly); ICU admission proportion (Elderly); RSV proportion (Elderly); RSV incidence (Elderly); Hospitalisation proportion (HR); RSV proportion (HR); RSV incidence (HR)	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(12).
8	Borg, 2003, Germany	125	≥18	Medically attended, COPD inpatients	Cardiopulmonary	1999-2001	Continuous (annual)	Assay validation	RSV proportion (HR)	Borg I, Rohde G, Loseke S, et al. Evaluation of a quantitative real-time PCR for the detection of respiratory syncytial virus in pulmonary diseases. European Respiratory Journal 2003; 21(6): 944-51.
9	Camargo, 2008, USA	76	≥50	Medically attended, AECOPD	Cardiopulmonary, lung disease	2003-2004	Seasonal	Prospective case series	Hospitalisation proportion (HR); proportion (HR); RSV proportion (HR)	Camargo JCA, Ginde AA, Clark S, Cartwright CP, Falsey AR, Niewoehner DE. Viral pathogens in acute exacerbations of chronic obstructive pulmonary disease. Internal and Emergency Medicine 2008; 3(4): 355-9.
10	Cameron, 2006, Australia	105	>45	Medically attended, AECOPD ICU ventilated patients	Cardiopulmonary, lung disease	2000-2003	Continuous (annual)	Prospective case series	RSV proportion (HR)	Cameron RJ, de Wit D, Welsh TN, Ferguson J, Grissell TV, Rye PJ. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. Intensive Care Med 2006; 32(7): 1022-9.
11	Campe, 2016, Germany	28	≥60	Medically attended, sentinel surveillance	Older adults	2013-2013	Seasonal	Surveillance	RSV proportion (Elderly)	Campe H, Heinzinger S, Hartberger C, Sing A. Clinical symptoms cannot predict influenza infection during the 2013 influenza season in Bavaria, Germany. Epidemiology and infection 2016; 144(5): 1045-51.
12	Carrat, 2006, France	122	≥18	Medically attended, critical care inpatients with cardiorespiratory failure	Cardiopulmonary	2002-2014	Seasonal	Prospective case series	RSV proportion (HR)	Carrat F, Leruez-Ville M, Tonnellier M, et al. A virologic survey of patients admitted to a critical care unit for acute cardiorespiratory failure. Intensive Care Medicine 2006; 32(1): 156-9.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
13	Charles, 2008, Australia	865	≥18; ≥65	Medically attended (Emergency department), pneumonia patients	Older adults, cardiopulmonary, asthma, chronic kidney disease, diabetes, immunodeficient (defined as occurring in patients who took ≤10 mg prednisolone per day, who were pregnant, who had undergone splenectomy, or who had received an autologous stem cell transplant years earlier), dementia, care home	2004-2006	Continuous (annual)	Prospective case series	Case fatality rate (Elderly); Hospitalisation proportion (Elderly); RSV proportion (Elderly); RSV proportion (HR)	Charles PG, Whitby M, Fuller AJ, et al. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2008; 46(10): 1513-21.
14	Chasqueira, 2018, Portugal	1022	≥59	Care home	Care home	2013-2014	Seasonal	Cohort	RSV proportion (HR); RSV incidence (HR)	Chasqueira M-J, Paixao P, Rodrigues M-L, et al. Respiratory infections in elderly people: Viral role in a resident population of elderly care centers in Lisbon, winter 2013-2014. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2018; 69: 1-7.
15	Chatzis, 2018, Switzerland	175	≥18	Medically attended, RSV positive	Immunodeficient (allogeneic or autologous hematopoietic stem cell transplant recipients, solid organ transplant recipients, patients on cancer chemotherapy or long-term immunosuppression for any chronic disease)	2005-2014	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); Pneumonia proportion (HR); URTI proportion (HR); Mechanical ventilation proportion (HR)	Chatzis O, Darbre S, Pasquier J, et al. Burden of severe RSV disease among immunocompromised children and adults: a 10 year retrospective study. BMC infectious diseases 2018; 18(1): 111.
16	Clark, 2014, UK	780	≥18	Medically attended, inpatients	Asthma, lung disease, cardiac disease	2005-2008	Seasonal	Assay validation	RSV proportion (HR)	Clark TW, Medina MJ, Batham S, Curran MD, Parmar S, Nicholson KG. Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample. The Journal of infection 2014; 69(5): 507-15.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
17	Damlaj, 2016, USA	45	≥18	Medically attended	Immunodeficient (allogeneic stem cell transplant recipients)	2008-2014	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); URTI proportion (HR)	Damlaj M, Bartoo G, Cartin-Ceba R, et al. Corticosteroid use as adjunct therapy for respiratory syncytial virus infection in adult allogeneic stem cell transplant recipients. Transplant Infectious Disease 2016; 18(2): 216-26.
18	D'Angelo, 2016, USA	118	≥50	Medically attended, HSCT	Immunodeficient (allogeneic hematopoietic cell transplant recipients)	2009-2013	Continuous (annual)	Cohort	Case fatality rate (HR); Hospitalisation proportion (HR); LRTI proportion (HR); RSV proportion (HR)	D'Angelo CR, Kocherginsky M, Pisano J, et al. Incidence and predictors of respiratory viral infections by multiplex PCR in allogeneic hematopoietic cell transplant recipients 50 years and older including geriatric assessment. Leukemia and Lymphoma 2016; 57(8): 1807-13.
19	De Serres, 2009 Canada	108	≥50	Medically attended, AECOPD	Cardiopulmonary, lung disease	2003-2004	Seasonal	Prospective case series	RSV proportion (HR)	De Serres G, Lampron N, La Forge J, et al. Importance of viral and bacterial infections in chronic obstructive pulmonary disease exacerbations. Journal of Clinical Virology 2009; 46(2): 129-33.
20	Diaz-Decaro, 2016, USA	52	≥18	Care home	Care home	2015-2015	Seasonal (Summer)	Cohort	RSV proportion (HR)	Diaz-Decaro J, Launer B, Mckinnell JA, et al. Prevalence of respiratory viruses, including influenza, among nursing home residents and high-touch room surfaces. Open forum infectious diseases 2016; 3.
21	Dimopoulos, 2014, Greece	247	≥18; ≥65	Medically attended, AECOPD inpatients	Cardiopulmonary, lung disease	2008-2010	Continuous (annual)	Cohort	RSV proportion (HR)	Dimopoulos G, Tsiodras S, Lerikou M, et al. Viral profile of COPD exacerbations according to patients. Open Respiratory Medicine Journal 2014; 9(1): 1-8.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
22	Falsey, 2005, USA	2536	≥21, ≥65	Community cohort & medically attended	Older adults, cardiopulmonary, lung disease, cardiac disease	1999-2003	Seasonal	Cohort	Case fatality rate (Elderly); Hospitalisation proportion (Elderly); RSV proportion (Elderly); RSV incidence (Elderly); Case fatality rate (HR); Emergency consultation proportion (HR); Hospitalisation proportion (HR); Outpatient proportion (HR); Pneumonia proportion (HR); RSV proportion (HR); RSV incidence (HR)	Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and HR adults. The New England journal of medicine 2005; 352(17): 1749-59.
23	Falsey, 2006 USA	112	≥40	Community cohort, COPD	Cardiopulmonary, lung disease	2004-2005	Continuous (annual)	Cohort	RSV proportion (HR)	Dimopoulos G, Tsiodras S, Lerikou M, et al. Viral profile of COPD exacerbations according to patients. Open Respiratory Medicine Journal 2014; 9(1): 1-8.
24	Falsey, 2014, Belgium, Canada, Czech Rep, Estonia, France, Germany, Netherlands, Norway, Poland, Romania, UK	404	≥65	Community cohort, ILI	Older adults	2008-2010	Seasonal	Trial	RSV proportion (Elderly); RSV proportion (Elderly)	Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. The Journal of infectious diseases 2014; 209(12): 1873-81.
25	Garcia-Noblejas, 2015, Spain	211	≥18	Medically attended, haematology patients	Immunodeficient (haematological disease patients)	2012-2014	Continuous (annual)	Retrospective case series	Case fatality rate (HR); LRTI proportion (HR); RSV proportion (HR); URTI proportion (HR)	Garcia-Noblejas A, Lorenzo A, Cardenoso L, Villanueva M, De La Camara R. Community acquiered respiratory virus in adults patients with hematological disease: Clinical characteristics and outcome in RSV and HPIV infection. Haematologica 2015; 100: 296-7.

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26	Gaymard, 2018, France	4232	>65	Medically attended	Older adults	2010-2014	Seasonal	Surveillance	RSV proportion (Elderly)	Gaymard A, Bouscambert-Duchamp M, Pichon M, et al. Genetic characterisation of respiratory syncytial virus highlights a new BA genotype and emergence of the ON1 genotype in Lyon, France, between 2010 and 2014. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology 2018; 102: 12-8.
27	Gaymard, 2019, France	6931	>65	Medically attended	Older adults	2014-2018	Seasonal	Surveillance	RSV proportion (Elderly)	Gaymard A, Pichon M, Ibranosyan M, et al. Epidemiology of respiratory syncytial virus circulating in Lyon, France, between 2014 and 2018. Virologie 2019; 23(2): 93.
28	Gilca, 2014, Canada	474	≥65	Medically attended, inpatients	Older adults	2012-2013	Seasonal	Trial	RSV proportion (Elderly)	Gilca R, Amini R, Douville-Fradet M, et al. Other respiratory viruses are important contributors to adult respiratory hospitalisations and mortality even during peak weeks of the influenza season. Open forum infectious diseases 2014; 1(2).
29	Gimferrer, 2019, Spain	6534	>64	Medically attended	Older adults	2013-2018	Continuous (annual)	Surveillance	RSV proportion (Elderly)	Gimferrer L, Vila J, Pinana M, et al. Virological surveillance of human respiratory syncytial virus A and B at a tertiary hospital in Catalonia (Spain) during five consecutive seasons (2013-2018). Future Microbiology 2019; 14(5): 373-81.
30	Gorcea, 2015, UK	407	≥18	Medically attended, HSCT	Immunodeficient (haematopoietic stem cell transplant recipient)	2010-2014	Continuous (annual)	Retrospective case series	Hospitalisation proportion (HR); ICU admission proportion (HR)	Gorcea CM, Tholouli E, Turner A, Flaum N, Dignan F. The clinical and financial impact of respiratory syncytial virus infection post-haematopoietic stem cell transplantation. Bone Marrow Transplantation 2015; 50: S194-S5.
31	Gorse, 2015, USA	100	≥60	Community cohort, patients with cardiopulmonary disease	Cardiopulmonary	2009-2013	Continuous (annual)	Cohort	RSV proportion (HR)	Gorse GJ, Donovan MM, Patel GB, Balasubramanian S, Lusk RH. Coronavirus and Other Respiratory Illnesses Comparing Older with Young Adults. American Journal of Medicine 2015; 128(11): 1251e11-e20.
32	Graat, 2003, Netherlands	97	≥60	Community cohort	Older adults	1998-2000	Continuous (annual)	Case control	RSV proportion (Elderly)	Graat JM, Schouten EG, Heijnen ML, et al. A prospective, community-based study on virologic assessment among elderly people with and without symptoms of acute respiratory infection. J Clin Epidemiol 2003; 56(12): 1218-23.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
33	Gueller, 2013, Germany	29	≥18	Medically attended, HSCT	Immunodeficient (haematopoietic stem cell transplant recipient)	2008-2009	Seasonal	Retrospective case series	Bronchitis proportion (HR); LRTI proportion (HR); Oxygen therapy proportion (HR); Pneumonia proportion (HR); RSV proportion (HR); URTI proportion (HR)	Gueller S, Duenzinger U, Wolf T, et al. Successful systemic high-dose ribavirin treatment of respiratory syncytial virus-induced infections occurring pre-engraftment in allogeneic hematopoietic stem cell transplant recipients. Transplant Infectious Disease 2013; 15(4): 435-40.
34	Hequet, 2019, Switzerland	509	≥18	Care home	Care home	2016-2018	Seasonal	Cohort	Antibiotic use proportion (HR); Case fatality rate (HR); Hospitalisation proportion (HR); Oxygen therapy proportion (HR); RSV proportion (HR)	Hequet D, Rochat A, Petignat C. Respiratory syncytial virus, a threat for nursing homes residents? Antimicrobial Resistance and Infection Control 2019; 8.
35	Hombrouck, 2012, Belgium	18	≥65	Medically attended, influenza negative ILI cases	Older adults	2009-2010	Seasonal	Surveillance	RSV proportion (Elderly)	Hombrouck A, Sabbe M, Van Casteren V, et al. Viral aetiology of influenza-like illness in Belgium during the influenza A(H1N1)2009 pandemic. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2012; 31(6): 999-1007.
36	Hopkins, 2008, Australia	89	≥18	Community cohort, SOT	Immunodeficient (lung transplant recipients)	2003-2006	Continuous (annual)	Cohort	Case fatality rate (HR); Respiratory failure proportion (HR); RSV proportion (HR); URTI proportion (HR)	Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. American journal of respiratory and critical care medicine 2008; 178(8): 876-81.
37	Huijts, 2018, Netherlands	84496	≥65	Community cohort, pneumonia patients	Older adults	2008-2013	Continuous (annual)	Trial	RSV proportion (Elderly); RSV incidence (Elderly)	Huijts SM, Coenjaerts FEJ, Bolkenbaas M, et al. The impact of 13-valent pneumococcal conjugate vaccination on virus-associated community-acquired pneumonia in elderly: Exploratory analysis of the CAPiTA trial. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2018; 24(7): 764-70.

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38	Hutchinson, 2007, Australia	92	≥18	Community cohort, AECOPD patients	Cardiopulmonary, lung disease	2003-2005	Seasonal	Case control	RSV proportion (HR); RSV incidence (HR)	Hutchinson AF, Ghimire AK, Thompson MA, et al. A community-based, time-matched, case-control study of respiratory viruses and exacerbations of COPD. Respiratory Medicine 2007; 101(12): 2472-81.
39	Iikura, 2015, Japan	48	≥18	Medically attended, asthma exacerbation inpatients	Asthma	2011-2012	Continuous (annual)	Prospective case series	RSV proportion (HR)	Iikura M, Hojo M, Koketsu R, et al. The importance of bacterial and viral infections associated with adult asthma exacerbations in clinical practice. PloS one 2015; 10(4): e0123584.
40	Jahn, 2018, Switzerland	1303	≥18	Medically attended, immunocompromised	Immunodeficient (haematological disease patients and solid organ transplant recipients)	2009-2017	Continuous (annual)	Prospective case series	RSV proportion (HR)	Jahn K, Schumann D, Tamm M, et al. Respiratory viral infection in immunocompromised patients. Respiration 2018; 95(6): 506-7.
41	Jain, 2015, USA	805	≥65	Medically attended, pneumonia inpatients	Older adults	2010-2012	Seasonal	Cohort	RSV proportion (Elderly)	Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. The New England journal of medicine 2015; 373(5): 415-27.
42	Jeannoel, 2019, France	14792	≥18, ≥65	Medically attended	Older adults, immunodeficient (reason not specified)	2013-2016	Seasonal	Retrospective case series	Case fatality rate (Elderly); ICU admission proportion (Elderly); Pneumonia proportion (Elderly); Antibiotic use proportion (HR); ARDS proportion (HR); ARDS proportion (HR); ARDS proportion (HR); Case fatality rate (HR); ICU admission proportion (HR)	Jeannoel M, Lina G, Rasigade JP, Lina B, Morfin F, Casalegno JS. Microorganisms associated with respiratory syncytial virus pneumonia in the adult population. European Journal of Clinical Microbiology and Infectious Diseases 2019; 38(1): 157-60.
43	Johnstone, 2014, Canada	1072	≥65	Care home	Care home	2009-2012	Seasonal	Cohort	RSV proportion (HR)	Johnstone J, Parsons R, Botelho F, et al. Immune biomarkers predictive of respiratory viral infection in elderly nursing home residents. PLoS ONE 2014; 9(10): e108481.

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44	Juretschko, 2017, USA & Canada	732	>65	Medically attended	Older adults	2015-2016	Seasonal	Assay validation	RSV proportion (Elderly)	Juretschko S, Mahony J, Buller RS, et al. Multicenter clinical evaluation of the luminex aries flu A/B and RSV assay for pediatric and adult respiratory tract specimens. Journal of clinical microbiology 2017; 55(8): 2431-8.
45	Katsurada, 2017, Japan	2037	≥65	Medically attended, pneumonia	Older adults	2011-2014	Continuous (annual)	Surveillance	RSV proportion (Elderly)	Katsurada N, Suzuki M, Aoshima M, et al. The impact of virus infections on pneumonia mortality is complex in adults: a prospective multicentre observational study. BMC infectious diseases 2017; 17(1): 755.
46	Khanna, 2008, Switzerland	34	≥18	Medically attended, haematology patients	Immunodeficient (haematological disease patients)	2002-2007	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); Respiratory failure proportion (HR); URTI proportion (HR); Mechanical ventilation proportion (HR)	Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological diseases: Single-center study and review of the literature. Clinical Infectious Diseases 2008; 46(3): 402-12.
47	Kherad, 2010, Switzerland	86	≥60	Medically attended, AECOPD inpatients	Cardiopulmonary, lung disease	2007-2008	Continuous (annual)	Cohort	RSV proportion (HR)	Kherad O, Kaiser L, Bridevaux P-O, et al. Upper-respiratory viral infection, biomarkers, and COPD exacerbations. Chest 2010; 138(4): 896-904.
48	Klein, 2007, Canada	50	≥18	Medically attended, HIV	Immunodeficient (HIV patients)	2003-2006	Seasonal	Surveillance	RSV proportion (HR)	Klein MB, Lu Y, DelBalso L, Cote S, Boivin G. Influenza virus infection is a primary cause of febrile respiratory illness in HIV-infected adults, despite vaccination. Clinical Infectious Diseases 2007; 45(2): 234-40.
49	Kumar, 2005, Canada	50	≥18	Medically attended, SOT patients	Immunodeficient (lung transplant recipients)	2001-2003	Continuous (annual)	Cohort	LRTI proportion (HR); Pneumonia proportion (HR); RSV proportion (HR); URTI proportion (HR)	Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. American Journal of Transplantation 2005; 5(8): 2031-6.

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50	Lee, 2019, USA	326	≥18; >65	Medically attended, RSV-positive inpatients	Older adults, cardiopulmonary, asthma, immunodeficient (reason not specified)	2014-2016	Continuous (annual)	Retrospective case series	Antibiotic use proportion (HR)	Lee N, Walsh EE, Sander I, et al. Delayed Diagnosis of Respiratory Syncytial Virus Infections in Hospitalized Adults: Individual Patient Data, Record Review Analysis and Physician Survey in the United States. The Journal of infectious diseases 2019; 220(6): 969-79.
51	Leibl, 2017, Switzerland	100	≥18	Medically attended, SOT patients	Immunodeficient (lung transplant recipients)	2016-2017	Seasonal	Assay validation	RSV proportion (HR)	Leibl M, Robinson C, Boeni J, et al. Diagnostic performance of rapid and standard polymerase chain reaction laboratory tests for influenza and respiratory syncytial virus detection in nasopharyngeal swabs from symptomatic lung transplant recipients. Chest 2017; 152(4): A1110.
52	Li, 2012, USA	21	≥18	Medically attended, SOT patients	Immunodeficient (lung transplant recipients	2006-2010	Continuous (annual)	Retrospective case series	Case fatality rate (HR); LRTI proportion (HR); Oxygen therapy proportion (HR); URTI proportion (HR)	Li L, Avery R, Budev M, Mossad S, Danziger-Isakov L. Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation. Journal of Heart and Lung Transplantation 2012; 31(8): 839-44.
53	Lopez-Medrano, 2007, Spain	152	≥18	Community cohort, SOT patients	Immunodeficient (solid organ transplant patients)	2002-2003	Seasonal	Cohort	Case fatality rate (HR); RSV proportion (HR); RSV incidence (HR)	Lopez-Medrano F, Aguado JM, Lizasoain M, et al. Clinical implications of respiratory virus infections in solid organ transplant recipients: A prospective study. Transplantation 2007; 84(7): 851-6.
54	Loubet, 2017, France	1452	≥65	Medically attended, ILI	Older adults, cardiopulmonary, asthma, CKD, diabetes, immunodeficient (immunosuppressive treatment)	2012-2015	Seasonal	Prospective case series	Case fatality rate (Elderly); RSV proportion (Elderly); Case fatality rate (HR)	Loubet P, Lenzi N, Valette M, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clinical Microbiology and Infection 2017; 23(4): 253-9.
55	Mahan, 2017, USA	66	≥18	Medically attended, SOT patients	Immunodeficient (lung transplant recipients	2013-2014	Continuous (annual)	Retrospective case series	RSV proportion (HR); RSV incidence (HR)	Mahan L, Mohanka M, Mullins J, et al. Community-acquired respiratory virus infections during the first year after lung transplantation. Chest 2017; 152(4): A1108.
56	Malosh, 2017, USA	1261	≥18; >65	Medically attended	Older adults, lung and cardiovascular disease	2014-2016	Seasonal	Prospective case series	Case fatality rate (Elderly); RSV proportion (Elderly)	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.
57	Mikulska, 2014, USA	193	>=18	Medically attended	Immunodeficient XX	2011	Seasonal	Cohort	Case fatality rate (HR); RSV prevalence (HR)	Mikulska M, Del Bono V, Gandolfo N, et al. Epidemiology of viral respiratory tract infections in an outpatient haematology facility. Ann Hematol 2014; 93(4): 669-76.

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58	Meerhoff, 2006, Netherlands, England, Scotland	110	≥65	Medically attended, ILI	Older adults	2002-2003	Seasonal	Surveillance	Case fatality rate (HR); RSV proportion (HR)	Meerhoff TJ, Fleming D, Smith A, Mosnier A, van Gageldonk-Lafeber AB, W.J. P. Surveillance recommendations based on an exploratory analysis of respiratory syncytial virus reports derived from the European Influenza Surveillance System. BMC infectious diseases 2006; 6: 128.
59	Milstone, 2006, USA	50	≥18	Community cohort, SOT patients	Immunodeficient (lung transplant recipients	1999-2000	Seasonal	Cohort	Case fatality rate (HR); Hospitalisation proportion (HR); proportion (HR); LRTI proportion (HR); Pneumonia proportion (HR); RSV proportion (HR); RSV incidence (HR)	Milstone AP, Brumble LM, Barnes J, et al. A single-season prospective study of respiratory viral infections in lung transplant recipients. European Respiratory Journal 2006; 28(1): 131-7.
60	Minodier, 2014, France	10	≥65	Medically attended, ILI	Older adults	2012-2013	Seasonal	Surveillance	RSV proportion (Elderly)	Minodier L, Arena C, Heuze G, et al. Epidemiology and viral etiology of the influenza-like illness in Corsica during the 2012-2013 Winter: an analysis of several sentinel surveillance systems. PLoS One 2014; 9(6): e100388.
61	Ong, 2014, Netherlands	158	≥18	Medically attended, ICU patients with respiratory failure	Cardiopulmonary, immunodeficient (immunosuppressive treatment)	2010-2013	Seasonal	Prospective case series	Case fatality rate (HR); RSV proportion (HR)	Ong DSY, Faber TE, Klein Klouwenberg PMC, et al. Respiratory syncytial virus in critically ill adult patients with community-acquired respiratory failure: A prospective observational study. Clinical Microbiology and Infection 2014; 20(8): O505-O7.
62	Paba, 2014, Italy	107	≥60	Medically attended, ILI	Older adults, immunodeficient (reason not specified)	2009-2011	Continuous (annual)	Assay validation	RSV proportion (Elderly); RSV proportion (HR)	Paba P, Farchi F, Mortati E, et al. Screening of respiratory pathogens by Respiratory Multi Well System (MWS) r-geneTM assay in hospitalized patients. New Microbiologica 2014; 37(2): 231-6.
63	Pancer, 2011, Poland	96	>18	Medically attended, chronic respiratory diseases	Cardiopulmonary	2008-2010	Continuous (annual)	Prospective case series	RSV proportion (HR)	Pancer K, Ciacka A, Gut W, et al. Infections caused by RSV among children and adults during two epidemic seasons. Polish Journal of Microbiology 2011; 60(3): 253-8.

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64	Passi, 2019, Italy	151	≥18	Medically attended, haematology patients	Immunodeficient (haematological patients with acute leukemia, lymphoma, myeloma or other haem diseases)	2011-2019	Continuous (annual)	Surveillance	RSV proportion (HR)	Passi A, Pagani C, Gramegna D, et al. Respiratory viruses infections are a significant clinical problem in haematological patients with underestimated adverse outcome: A single institution 9-years experience. Haematologica 2019; 104: 29-30.
65	Peghin, 2017, Spain	98	≥18	Community cohort, SOT patients	Immunodeficient (lung transplant recipients	2009-2014	Continuous (annual)	Cohort	Bronchitis proportion (HR); Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); Pneumonia proportion (HR); RSV proportion (HR); RSV incidence (HR); URTI proportion (HR)	Peghin M, Hirsch HH, Len O, et al. Epidemiology and Immediate Indirect Effects of Respiratory Viruses in Lung Transplant Recipients: A 5-Year Prospective Study. American Journal of Transplantation 2017; 17(5): 1304-12.
66	Peyrani, 2012, USA	48	≥60	Medically attended, AECOPD & pneumonia inpatients	Cardiopulmonary	2010-2011	Seasonal	Trial	RSV proportion (HR)	Peyrani P, Nahas A, Giovini V, et al. Respiratory viruses are significant etiologic agents in hospitalized patients with lower respiratory tract infections: Results from the rapid empiric treatment with oseltamivir study (RETOS). American Journal of Respiratory and Critical Care Medicine 2012; 185.
67	Pilie, 2015, USA	69	≥18	Medically attended, RSV-positive HSCT & SOT inpatients	Immunodeficient (hematopoietic stem cell transplant and solid organ transplant recipients)	2009-2012	Continuous (annual)	Retrospective case series	Case fatality rate (HR); ICU admission proportion (HR); LRTI proportion (HR); Pneumonia proportion (HR); URTI proportion (HR); Mechanical ventilation proportion (HR)	Pilie P, Werbel WA, Riddell J, Shu X, Schaubel D, Gregg KS. Adult patients with respiratory syncytial virus infection: Impact of solid organ and hematopoietic stem cell transplantation on outcomes. Transplant Infectious Disease 2015; 17(4): 551-7.

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68	Pinana, 2017, Spain	35	≥18	Medically attended, RSV-positive HSCT patients	Immunodeficient (allogeneic hematopoietic stem cell transplantation) recipients)	2013-2015	Continuous (annual)	Trial	Antibiotic use proportion (HR); Hospitalisation proportion (HR); LRTI proportion (HR); URTI proportion (HR)	Pinana JL, Hernandez-Boluda JC, Calabuig M, et al. A risk-adapted approach to treating respiratory syncytial virus and human parainfluenza virus in allogeneic stem cell transplantation recipients with oral ribavirin therapy: A pilot study. Transplant infectious disease: an official journal of the Transplantation Society 2017; 19(4).
69	Price, 2019, Australia	7777	≥65	Medically attended	Older adults	2002-2015	Continuous with gaps (annual)	Surveillance	RSV proportion (Elderly)	Price OH, Sullivan SG, Sutterby C, Druce J, Carville KSA-POH, http://orcid.org/---735X O. Using routine testing data to understand circulation patterns of influenza A, respiratory syncytial virus and other respiratory viruses in Victoria, Australia. Epidemiology and infection 2019; 147: e221.
70	Puig-Barbera, 2012, Spain	799	≥60	Medically attended, ILI inpatients	Older adults, cardiopulmonary, CKD, diabetes, immunodeficient (immunosuppressive treatments)	2010-2011	Seasonal	Vaccine efficacy study	Case fatality rate (Elderly); ICU admission proportion (Elderly); Pneumonia proportion (Elderly); RSV proportion (Elderly); RSV proportion (HR)	Puig-Barbera J, Diez-Domingo J, Arnedo-Pen aA, et al. Effectiveness of the 2010-2011 seasonal influenza vaccine in preventing confirmed influenza hospitalizations in adults: A case-case comparison, case-control study. Vaccine 2012; 30(39): 5714-20.
71	Puzelli, 2009, Italy	37	≥65	Medically attended, ILI	Older adults	2004-2007	Seasonal	Surveillance	RSV proportion (Elderly)	Puzelli S, Valdarchi C, Ciotti M, et al. Viral causes of influenza-like illness: Insight from a study during the winters 2004-2007. Journal of Medical Virology 2009; 81(12): 2066-71.
72	Reid, 2017, Australia	184	≥18	Medically attended, AECOPD	Cardiopulmonary, lung disease	2015-2015	Seasonal	Retrospective case series	RSV proportion (HR)	Reid DW, Tse T, Jong T, Masel P, Smith DJ. Profile of bacterial and viral pathogens in patients presenting to hospital with an acute exacerbation of copd. Respirology 2017; 22: 138.
73	Renaud, 2013, USA	23	≥18	Medically attended, RSV positive	Immunodeficient (haematopoietic stem cell transplant recipients)	2007-2011	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Respiratory failure proportion (HR)	Renaud C, Xie H, Seo S, et al. Mortality rates of human Metapneumovirus and respiratory syncytial virus lower respiratory tract infections in hematopoietic cell transplantation recipients. Biology of Blood and Marrow Transplantation 2013; 19(8): 1220-6.

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74	Roghmann, 2003, USA	62	≥18	Community cohort, HSCT & bone marrow patients	Immunodeficient (bone marrow or peripheral blood stem cell transplant recipients)	2001-2001	Seasonal	Cohort	Hospitalisation proportion (HR); LRTI proportion (HR); Respiratory failure proportion (HR); RSV proportion (HR); RSV incidence (HR); URTI proportion (HR)	Roghmann M, Ball K, Erdman D, Lovchik J, Anderson LJ, Edelman R. Active surveillance for respiratory virus infections in adults who have undergone bone marrow and peripheral blood stem cell transplantation. Bone Marrow Transplantation 2003; 32(11): 1085-8.
75	Rohde, 2003, Germany	85	≥18	Medically attended, AECOPD inpatients	Cardiopulmonary, lung disease	1998-1999	Continuous (annual)	Cohort	RSV proportion (HR)	Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: A case-control study. Thorax 2003; 58(1): 37-42.
76	Saez-Lopez, 2019, Portugal	952	≥65	Medically attended, ILI	Older adults	2010-2018	Seasonal	Surveillance	RSV proportion (Elderly)	Saez-Lopez E, Pechirra P, Costa I, et al. Performance of surveillance case definitions for respiratory syncytial virus infections through the sentinel influenza surveillance system, Portugal, 2010 to 2018. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2019 ; 24(45).
77	Sanghavi, 2012, USA	105	≥18	Medically attended, SOT	Immunodeficient (solid organ transplant recipients)	2006-2007	Seasonal	Prospective case series	LRTI proportion (HR); RSV proportion (HR); URTI proportion (HR)	Sanghavi SK, Bullotta A, Husain S, Rinaldo CR. Clinical evaluation of multiplex real-time PCR panels for rapid detection of respiratory viral infections. Journal of Medical Virology 2012; 84(1): 162-9.
78	Saraya, 2017, Japan	106	≥18	Medically attended, asthma patients	Asthma	2012-2015	Continuous (annual)	Cross-sectional	Hospitalisation proportion (HR); RSV proportion (HR)	Saraya T, Kimura H, Kurai D, Ishii H, Takizawa H. The molecular epidemiology of respiratory viruses associated with asthma attacks. Medicine (United States) 2017; 96(42): e8204.
79	Schmidt, 2019, USA	489	≥18; >65	Medically attended, RSV-positive inpatients	Older adults, CKD, diabetes, immunodeficient (immunosuppressive treatment), lung disease, cardiac disease	2009-201	Continuous (annual)	Cohort	Case fatality rate (HR); Discharge to care proportion (HR); ICU admission proportion (HR); Mechanical ventilation proportion (HR)	Schmidt H, Das A, Nam H, Yang A, Ison MGA-I, Michael G., http://orcid.org/--- O. Epidemiology and outcomes of hospitalized adults with respiratory syncytial virus: A 6-year retrospective study. Influenza and other respiratory viruses 2019; 13(4): 331-8.

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80	Seemungal, 2001, UK	83	≥18	Community cohort, AECOPD	Cardiopulmonary, lung disease		Continuous (annual)	Cohort	RSV proportion (HR)	Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001; 164(9): 1618-23.
81	Sellers, 2018, USA	70	≥18	Medically attended, HIV	Immunodeficient (HIV patients)	2015-2018	Continuous (annual)	Cross-sectional	RSV proportion (HR)	Sellers S, Dover K, Wohl DA, Miller M, Dittmer D, Fischer W. The burden of respiratory viral illness in HIV-infected patients. Open forum infectious diseases 2018; 5: S670.
82	Slade, 2017, USA	104	≥18	Community cohort, HSCT patients	Immunodeficient (haploidentical peripheral blood hematopoietic cell transplant recipients)	2009-2015	Continuous (annual)	Cohort	LRTI proportion (HR); RSV proportion (HR); RSV incidence (HR); URTI proportion (HR)	Slade M, Goldsmith S, Romee R, et al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. Transplant Infectious Disease 2017; 19(1): e12629.
83	Snyder, 2017, USA	250	≥18	Medically attended, AECOPD	Cardiopulmonary, lung disease	2013-2014	Continuous (annual)	Retrospective case series	RSV proportion (HR)	Snyder ME, Aaron CP, Regalbuto R, et al. Impact of virulent viral pathogens on hospital length of stay and readmissions after an acute exacerbation of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2017; 195.
84	Souty, 2019, France	337	≥65	Medically attended, ILI	Older adults	2015-2017	Seasonal	Surveillance	RSV proportion (Elderly)	Souty C, Masse S, Valette M, et al. Baseline characteristics and clinical symptoms related to respiratory viruses identified among patients presenting with influenza-like illness in primary care. Clinical Microbiology and Infection 2019; 25(9): 1147-53.
85	Spahr, 2018, Switzerland	33	≥18	Community cohort, HSCT patients	Immunodeficient (allogeneic hematopoietic cell transplant recipients)	2010-2014	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); URTI proportion (HR); Mechanical ventilation proportion (HR)	Spahr Y, Tschudin-Sutter S, Baettig V, et al. Community-acquired respiratory paramyxovirus infection after allogeneic hematopoietic cell transplantation: A single-center experience. Open forum infectious diseases 2018; 5(5).

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
86	Steensels, 2019, Belgium	397	≥18	Medically attended, immunocompromised	Immunodeficient (patients with any disease and/or treatment known to impair the immune system, such as solid organ transplant under immunosuppressive therapy, solid or hematological malignancy under chemotherapy, or other underlying disease needing long-term high-dose corticosteroid therapy or immunosuppressive therapy Patients infected with HIV with a CD4 count < 200/ mm3 were also included).	2014-2015	Continuous (annual)	Cohort	RSV proportion (HR)	Steensels D, Reynders M, Descheemaeker P, et al. Epidemiology and clinical impact of viral, atypical, and fungal respiratory pathogens in symptomatic immunocompromised patients: a two-center study using a multi-parameter customized respiratory Taqman array card. European Journal of Clinical Microbiology and Infectious Diseases 2019; 38(8): 1507-14.
87	Stolz, 2019, Switzerland	445	>40	Community cohort, COPD	Cardiopulmonary, lung disease	2011-2015	Continuous (annual)	Trial	Cardiopulmonary complications proportion (HR); RSV proportion (HR); URTI proportion (HR)	Stolz D, Papakonstantinou E, Grize L, et al. Time-course of upper respiratory tract viral infection and COPD exacerbation. Eur Respir J 2019; 54(4).
88	Sundaram, 2014, USA	992	≥50; ≥65	Medically attended	Older adults, CKD, lung disease, cardiac disease	2004-2010	Seasonal	Cohort	RSV proportion (HR)	Sundaram ME, Meece JK, Sifakis F, Gasser RAJ, Belongia EA. Medically attended respiratory syncytial virus infections in adults aged ≥ 50 years: clinical characteristics and outcomes. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2014; 58(3): 342-9.
89	Tanner, 2012, UK	449	≥65	Medically attended	Older adults	2009-2010	Seasonal	Surveillance	RSV proportion (Elderly)	Tanner H, Boxall E, Osman H. Respiratory viral infections during the 2009-2010 winter season in Central England, UK: Incidence and patterns of multiple virus co-infections. European Journal of Clinical Microbiology and Infectious Diseases 2012; 31(11): 3001-6.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
90	Teh, 2015, Australia	75	≥18	medically attended, haematology patients	Immunodeficient (multiple myeloma patients)	2009-2012	Continuous (annual)	Retrospective case series	Case fatality rate (HR); Hospitalisation proportion (HR); ICU admission proportion (HR); LRTI proportion (HR); RSV proportion (HR); URTI proportion (HR)	Teh BW, Worth LJ, Harrison SJ, Thursky KA, Slavin MA. Risks and burden of viral respiratory tract infections in patients with multiple myeloma in the era of immunomodulatory drugs and bortezomib: experience at an Australian Cancer Hospital. Supportive Care in Cancer 2015; 23(7): 1901-6.
91	Theodoropoulos, 2013, USA	249	≥18	Medically attended, SOT patients	immunodeficient (solid organ transplant patients)	2009-2012	Continuous (annual)	Cohort	RSV proportion (HR)	Theodoropoulos N, Martin S, Ho B, Ison M. Non-influenza respiratory viral infections in solid organ transplant patients at two midwestern transplant centers, 2009-2012. American Journal of Transplantation 2013; 13: 214.
92	Thomas, 2019, USA	27489	≥65	Medically attended, influenza vaccinated	Older adults	2010-2017	Seasonal	Vaccine efficacy study	RSV proportion (Elderly)	Thomas Ray G, Lewis N, Klein NP, et al. Intraseason waning of influenza vaccine effectiveness. Clinical Infectious Diseases 2019; 68(10): 1623-30.
93	Tramuto, 2016, Italy	75	≥65	Medically attended, ILI, ICU inpatients	Older adults	2009-2012	Continuous (annual)	Cross-sectional	RSV proportion (Elderly)	Tramuto F, Maida CM, Napoli G, et al. Burden and viral aetiology of influenza-like illness and acute respiratory infection in intensive care units. Microbes and Infection 2016; 18(4): 270-6.
94	Van Beek, 2017, Netherlands	3119	≥60	Community cohort	Older adults	2011-2013	Seasonal	Cohort	RSV proportion (Elderly); RSV incidence (Elderly)	Van Beek J, Veenhoven RH, Bruin JP, et al. Influenza-like illness incidence is not reduced by influenza vaccination in a cohort of older adults, despite effectively reducing laboratory-confirmed influenza virus infections. Journal of Infectious Diseases 2017; 216(4): 415-24.
95	Varghese, 2018, Australia	447	≥65	Medically attended, ILI	Older adults	2010-2013	Continuous (annual)	Surveillance	RSV proportion (Elderly)	Varghese BM, Dent E, Chilver M, Cameron S, Stocks NP. Epidemiology of viral respiratory infections in Australian working-age adults (20-64 years): 2010-2013. Epidemiology and infection 2018; 146(5): 619-26.
96	Visseaux, 2017, France	2449	>60	Medically attended	Older adults	2011-2016	Continuous (annual)	Surveillance	RSV proportion (Elderly)	Visseaux B, Burdet C, Voiriot G, et al. Prevalence of respiratory viruses among adults, by season, age, respiratory tract region and type of medical unit in Paris, France, from 2011 to 2016. PLoS ONE 2017; 12(7): e0180888.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
97	Walker, 2014, USA	502	≥18, ≥60	Medically attended, inpatients	Older adults, CKD, diabetes, immunodeficient (patients with hematologic malignancy, solid tumour malignancy, autoimmune or rheumatologic disease, asplenia, primary immunodeficiency, or were the recipient of a solid organ transplant), lung disease, cardiac disease)	2009-2010	Continuous (annual)	Retrospective case series	RSV proportion (Elderly); RSV proportion (HR)	Walker E, Ison MG. Respiratory viral infections among hospitalized adults: Experience of a single tertiary healthcare hospital. Influenza and other respiratory viruses 2014; 8(3): 282-92.
98	Wansaula, 2016, USA	156	≥18; >65	Medically attended, SARI inpatients	Older adults, immunosuppression (reason not specified), lung disease, cardiac disease	2010-2014	Continuous (annual)	Surveillance	RSV proportion (Elderly); RSV proportion (HR)	Wansaula Z, Olsen SJ, Casal MG, et al. Surveillance for severe acute respiratory infections in Southern Arizona, 2010-2014. Influenza and other respiratory viruses 2016; 10(3): 161-9.
99	Weinberg, 2010, USA	60	≥18	Community cohort, SOT patients	Immunodeficient (lung transplant recipients)	2005-2007	Continuous (annual)	Cohort	Case fatality rate (HR); Hospitalisation proportion (HR); proportion (HR); RSV proportion (HR)	Weinberg A, Lyu DM, Li S, Marquesen J, Zamora MR. Incidence and morbidity of human metapneumovirus and other community-acquired respiratory viruses in lung transplant recipients. Transplant Infectious Disease 2010; 12(4): 330-5.
100	Widmer, 2012, USA	508	≥65	Medically attended, inpatients	Older adults, diabetes, immunodeficient (patients with transplants, cancer, splenectomy, HIV/AIDS, steroid use or chemotherapy, immunosuppression), institutionalised older adults, lung disease, cardiac disease	2006-2009	Seasonal	Vaccine efficacy study	RSV proportion (Elderly); RSV proportion (HR)	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. Journal of Infectious Diseases 2012; 206(1): 56-62.

Num	Author, Year & country	Overall Sample Size	Age-group	Population according to study setting	Older adults or risk group	Study Years	Data collection	Study design	Outcome reported	Full citation
101	Widmer, 2014, USA	1248	≥18; ≥65	Medically attended	Older adults, diabetes, immunodeficient (Transplant, cancer, splenectomy, HIV/AIDS, steroid use, chemotherapy, haemoglobinopathy, immunosuppression), institutionalised older adults, lung disease, cardiac disease	2009-2010	Continuous (annual)	Vaccine efficacy study	RSV proportion (HR)	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(3): 347-52.
102	Yousaf, 2017, USA	23	≥18	Medically attended, RSV-positive inpatients	Cardiopulmonary	2015-2017	Continuous (annual)	Retrospective case series	Case fatality rate (HR)	Yousaf H, Ramage J. Severe respiratory syncytial virus (RSV) in the adult (dec 2015-jan 2017). Chest 2017; 152(4): A343.
103	Zambon, 2001, UK	167	≥65	Medically attended, ILI	Older adults	1995-1998	Seasonal	Surveillance	RSV proportion (Elderly)	Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: An observational study. Lancet 2001; 358(9291): 1410-6.

HR= high-risk group; SS = systematic sampling; CI = sampling by clinical indication; ILI = influenza like illness; ARI = acute respiratory infection; PNM=pneumonia; IP = inpatients; ICU= intensive care unit; AECOPD = acute exacerbation of COPD; HSCT =Hematopoietic stem-cell transplantation; SOT= Solid organ transplant;

Supplementary Table 7. RSV incidence in older adults (annual and seasonal studies).

Study	Country	Data collection	Setting	Age Group	Sampling	Positive	Person-years	Incidence (/1000 person-years) [95% CI]
Huijts, 2018*	NL	Annual	Medically attended	≥65	SS PNM	91	335449	0.27 [0.22, 0.33]
Belongia, 2018*	US	Seasonal	Medically attended	≥60	SS ARI	243	32261	7.53 [6.62, 8.51]
Falsey, 2005	US	Seasonal	Community cohort	≥65	SS ARI	46	426	108 [79.07; 141.37]
Van Beek, 2017	NL	Seasonal	Community cohort	≥60	SS ILI	25	4723	5.29 [3.42, 7.56]
RE Model for seasonal data (Q=288.15, p=0.00; I^2= 99.1%)								16.11 (3.52,73.83)

REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS= systematic sampling, CI = sampling by clinical indication, 95% CI = 95% confidence interval, ILI = influenza like illness, ARI = acute respiratory infection, PNM=pneumonia, IP = inpatients, Huijts, 2018: Capita trial population; no active community-based follow-up. Cases ascertained when they presented to healthcare facilities so classifying as medically attended. Belongia, 2018: Fever & cough included in eligibility criteria most seasons.

Supplementary Table 8. Estimated proportion of symptomatic respiratory infection attributable to RSV and estimated RSV case fatality proportion among older adults and HR adults by geographical location.

Region	Proportion				CFP	
	Annual		Seasonal			
	Obs	Proportion % (95% CI)	Obs	Proportion % (95% CI)	Obs	Proportion % (95% CI)
Older adults						
North America	4	4.49 [1.50-12.67]	8	6.72 [4.78, 9.38]		-
Europe	12	5.09 [3.42-7.50]	24	6.65 [4.79, 8.87]		-
Western Pacific	3	3.45 [2.10-5.61]	0	-		-
High-risk adults						
North America	17	5.44 [3.60, 8.13]	18	10.07 [8.05, 12.54]	13	7.73 [4.18,13.88]
Europe	15	11.21 [6.45, 18.78]	18	6.22 [4.49, 8.55]	14	13.00 [9.16, 18.12]
Western Pacific	10	5.32 [3.17, 8.78]	2	-	2	-

Obs= Observations, CFP= case fatality proportion, 95% CI = 95% confidence interval.

Supplementary Table 9. URTI, LRTI and bronchitis proportion among older adults and HR groups.

Study	Country	Data collection	Population & age	Sampling	n	RSV+	Total participants	Proportion [95% CI]	Group or risk group
1. Older adults									
URTI									
Van Beek, 2017	NL	Seasonal	Community cohort; ≥60	SS ILI	25	25	4360	100.00 [86.68 – 100.00]	Older adults
2. HR adults									
URTI									
Stolz, 2019	CH	Annual	Community cohort; >40	SS ARI	16	16	450	100.00 [80.64, 100]	Cardiopulmonary
Hopkins, 2008	AU	Annual	Community cohort; ≥18	SS ILI	5	18	89	27.78 [12.50, 50.87]	Institutionalised older adults
Kumar, 2005	CA	Annual	Medically attended; ≥18, OP	SS RVI	1	6	6	100 [60.97, 100]	Immunodeficiency
Damlaj, 2016	US	Annual	Medically attended; ≥18, RSV+	CI	3	35	45	77.78 [63.73, 87.46]	Immunodeficiency
Spahr, 2018	CH	Annual	Medically attended; ≥18, RSV+	CI ARI	4	22	33	66.67 [49.61, 80.25]	Immunodeficiency
Teh, 2015	AU	Annual	Medically attended; ≥18,	CI RVI	3	10	15	66.67 [41.71, 84.82]	Immunodeficiency
Garcia-Noblejas, 2015	ES	Annual	Medically attended; ≥18,	CI ARI	5	21	32	65.62 [48.31, 79.59]	Immunodeficiency
Pinana, 2017	ES	Annual	Medically attended; ≥18, RSV+	CI	1	15	23	65.22 [44.89, 81.19]	Immunodeficiency
Khanna, 2018	CH	Annual	Medically attended; ≥18, RSV+	SS ARI	4	22	34	64.71 [47.91, 78.51]	Immunodeficiency
Slade, 2017*	US	Annual	Medically attended; ≥18,	SS ARI	3	3	5	60 [23.07, 88.24]	Immunodeficiency
Chatzis, 2018	CH	Annual	Medically attended; ≥18, RSV+	CI ARI	2	90	175	51.43 [44.07, 58.72]	Immunodeficiency
Gueller, 2013*	DE	Seasonal	Medically attended; ≥18, IP	SS	4	5	10	50 [23.66, 76.34]	Immunodeficiency
Sanghavi, 2012	US	Seasonal	Medically attended; ≥18,	CI ARI	5	8	17	47.06 [26.17, 69.04]	Immunodeficiency
Li, 2012*	US	Annual	Medically attended; ≥18, RSV+	CI	2	9	21	42.86 [24.47, 63.45]	Immunodeficiency
Pilie, 2015	US	Annual	Medically attended; ≥18, RSV+ IP	CI	3	21	69	30.43 [20.85, 42.08]	Immunodeficiency
Roghmann, 2003	US	Seasonal	Community cohort; ≥18,	SS ARI	2	6	11	54.55 [28.01, 78.73]	Immunodeficiency
Peghin, 2017	ES	Annual	Community cohort; ≥18,	SS ARI	0	2	7	28.57 [8.22, 64.11]	Immunodeficiency
URTI: REM for Immunodeficiency (Q=37.24, p=0.00, I^2=61.9%)								*56.80 [48.13, 65.07]*	Immunodeficiency
LRTI									
D'Angelo, 2016*	US	Annual	Medically attended; ≥50	SS ARI	3	5	6	83.33 [43.65, 96.99]	Immunodeficiency
Pilie, 2015	US	Annual	Medically attended; ≥18, RSV+ IP	CI	3	48	69	69.57 [57.92, 79.15]	Immunodeficiency
Li, 2012*	US	Annual	Medically attended; ≥18, RSV+	CI	2	12	21	57.14 [36.55, 75.53]	Immunodeficiency
Sanghavi, 2012	US	Seasonal	Medically attended; ≥18	CI ARI	5	9	17	52.94 [30.96, 73.83]	Immunodeficiency
Gueller, 2013*	DE	Seasonal	Medically attended; ≥18, IP	SS	4	5	10	50 [23.66, 76.34]	Immunodeficiency

Study	Country	Data collection	Population & age	Sampling	n	RSV+	Total participants	Proportion [95% CI]	Group or risk group
Chatzis, 2018	CH	Annual	Medically attended; ≥18, RSV+	CI ARI	2	85	175	48.57 [41.28, 55.93]	Immunodeficiency
Damlaj, 2016	US	Annual	Medically attended; ≥18, RSV+	CI	3	21	45	46.67 [32.94, 60.92]	Immunodeficiency
Slade, 2017*	US	Annual	Medically attended; ≥18	SS ARI	3	2	5	40 [11.76, 76.93]	Immunodeficiency
Khanna, 2018	CH	Annual	Medically attended; ≥18, RSV+	SS ARI	4	12	34	35.29 [21.49, 52.09]	Immunodeficiency
Pinana, 2017	ES	Annual	Medically attended; ≥18, RSV+	CI	1	8	23	34.78 [18.81, 55.11]	Immunodeficiency
Garcia-Noblejas, 2015	ES	Annual	Medically attended; ≥18	CI ARI	5	11	32	34.38 [20.41, 51.69]	Immunodeficiency
Teh, 2015	AU	Annual	Medically attended; ≥18	CI RVI	3	5	15	33.33 [15.18, 58.29]	Immunodeficiency
Spahr, 2018	CH	Annual	Medically attended; ≥18, RSV+	CI ARI	4	9	33	27.27 [15.07, 44.22]	Immunodeficiency
Kumar, 2005	CA	Annual	Medically attended; ≥18, OP	SS RVI	1	0	6	0 [0, 39.03]	Immunodeficiency
Peghin, 2017	ES	Annual	Community cohort; ≥18	SS ARI	0	5	7	71.43 [35.89, 91.78]	Immunodeficiency
Roghmann, 2003	US	Seasonal	Community cohort; ≥18	SS ARI	2	3	11	27.27 [9.75, 56.56]	Immunodeficiency
Milstone, 2006	US	Seasonal	Community cohort; ≥18	SS ARI	1	2	8	25 [7.15, 59.07]	Immunodeficiency
LRTI: REM for Immunodeficiency (Q=35.48, p=0.00, I^2=54.9%)								*44.53 [36.83, 52.49]*	Immunodeficiency
Bronchitis									
Peghin, 2017	ES	Annual	Community cohort; ≥18	SS ARI	2	7	98	28.57 [8.22, 64.11]	Immunodeficiency
Gueller, 2013	DE	Seasonal	IP; ≥18	SS	9	10	29	90.00 [59.58, 98.21]	Immunodeficiency

REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS = systematic sampling, CI = sampling by clinical indication, 95% CI = 95% confidence interval, ARI = acute respiratory infection, ILI = influenza like illness, AEC = acute exacerbation of COPD, RVI = respiratory virus infection.

Supplementary Table 10. RSV signs and symptoms description in older and HR adults. The table shows mean, min, and max number of percentages of patients reporting signs and symptoms and the amount of studies (#Studies column) and specific studies identified (Citation) informing on RSV signs and symptoms percentages. Signs and symptoms affecting >50% of patients are in red. #Patients column shows the total number of patients reporting on a specific sign or symptom from all included studies from #Studies column.

Signs & symptoms	#Studies (citations)	Citation	#Patients	RSV cases with symptom (%)			
				Median	Mean	Min	Max
1.Older adults							
1.1. Self-reported symptoms							
Cough	6	Volling, 2014; Saez-Lopez, 2019; Puig-Barbera, 2012; Lee, 2019; Lee, 2011; Belongia, 2018	407	86.0	81.5	44.9	97.8
Weakness/Malaise	3	Volling, 2014; Saez-Lopez, 2019; Puig-Barbera, 2012	131	86.7	75.8	50.0	90.7
Shortness of breath	6	Volling, 2014; Saez-Lopez, 2019; Puig-Barbera, 2012; Lee, 2019; Lee, 2011; Belongia, 2018	309	72.3	67.7	19.3	94.0
Sputum	4	Volling, 2014; Lee, 2019; Lee, 2011; Belongia, 2018	260	56.1	59.3	39.1	86.0
Fever	5	Volling, 2014; Saez-Lopez, 2019; Puig-Barbera, 2012; Lee, 2019; Belongia, 2018	252	53.3	53.4	34.6	74.1
Sore throat	5	Volling, 2014; Saez-Lopez, 2019; Puig-Barbera, 2012; Lee, 2019; Belongia, 2018	270	57.4	49.0	18.6	71.1
Wheezing	4	Volling, 2014; Lee, 2019; Lee, 2011; Belongia, 2018	169	45.1	46.6	16.1	80.0
Runny nose	1	Lee, 2019	46	41.8	41.8	41.8	41.8
Myalgia	3	Saez-Lopez, 2019; Lee, 2019; Belongia, 2018	107	23.6	40.7	18.5	80.0
Headache	2	Saez-Lopez, 2019; Lee, 2019	47	39.8	39.8	17.3	62.2
Hoarseness	1	Lee, 2019	43	39.1	39.1	39.1	39.1
Productive cough	2	Volling, 2014; Belongia, 2018	137	35.7	35.7	23.3	48.2
Congested nose	2	Volling, 2014; Lee, 2019	65	32.0	32.0	22.1	41.8
Fatigue	1	Lee, 2019	33	30.0	30.0	30.0	30.0
Vomiting	2	Volling, 2014; Lee, 2019	28	14.5	14.5	12.7	16.3
Chest pain	3	Volling, 2014; Lee, 2019; Belongia, 2018	40	7.4	10.4	6.4	17.4
Sweating	1	Lee, 2019	6	5.5	5.5	5.5	5.5
Haemoptysis	1	Belongia, 2018	3	5.5	1.2	1.2	1.2
1.2. Signs on examination							
Wheezing	1	Belongia, 2018	49	20.2	20.2	20.2	20.2
Rhonchi	1	Belongia, 2018	31	12.8	12.8	12.8	12.8
Crackles	1	Belongia, 2018	23	9.5	9.5	9.5	9.5
Fever	1	Belongia, 2018	20	8.2	8.2	8.2	8.2
Reduced breath sounds	1	Belongia, 2018	19	7.8	7.8	7.8	7.8
Tachypnoea	1	Belongia, 2018	16	6.6	6.6	6.6	6.6
Reduced oxygen saturation	1	Belongia, 2018	11	4.5	4.5	4.5	4.5
Respiratory Distress	1	Belongia, 2018	6	2.5	2.5	2.5	2.5
2. HR adults: patients with cardiopulmonary disease							
2.1 Self-reported symptoms							
Cough	2	Walsh, 2007; Camargo, 2008	121	98.7	98.7	97.5	100.0
Shortness of breath	2	Walsh, 2007; Camargo, 2008	118	97.5	97.5	94.9	100.0

Signs & symptoms	#Studies (citations)	Citation	#Patients	RSV cases with symptom (%)			
				Median	Mean	Min	Max
Sputum	1	Camargo, 2008	5	83.3	83.3	83.3	83.3
Nasal congestion	2	Walsh, 2007; Camargo, 2008	85	75.6	75.6	67.8	83.3
Wheezing	1	Walsh, 2007	86	72.9	72.9	72.9	72.9
Discoloured sputum	1	Camargo, 2008	4	66.7	66.7	66.7	66.7
Fever	2	Walsh, 2007; Camargo, 2008	67	52.1	52.1	50.0	54.2
ConstSympt	1	Walsh, 2007	47	39.8	39.8	39.8	39.8
Hoarseness	1	Walsh, 2007	33	28.0	28.0	28.0	28.0
Sore throat	2	Walsh, 2007; Camargo, 2008	35	22.7	22.7	16.7	28.8
Chest pain	1	Walsh, 2007	22	18.6	18.6	18.6	18.6
Runny nose	1	Walsh, 2007	13	11.0	11.0	11.0	11.0
2.2. Signs on examinations							
Wheezing	1	Walsh, 2007	97	82.2	82.2	82.2	82.2
Crackles	1	Walsh, 2007	74	62.7	62.7	62.7	62.7
Fever	1	Walsh, 2007	15	12.7	12.7	12.7	12.7
3. HR adults: immunodeficient patients							
3.1 Self-reported symptoms							
Cough	3	Lee, 2019; Gueller, 2013; Garcia-Noblejas, 2015	93	72.2	71.6	62.5	80.0
Wheezing	1	Lee, 2019	55	61.1	61.1	61.1	61.1
Sputum	1	Lee, 2019	47	52.2	52.2	52.2	52.2
Nasal congestion	2	Lee, 2019; Gueller, 2013	52	46.7	46.7	40.0	53.3
Fatigue	1	Lee, 2019	39	43.3	43.3	43.3	43.3
Runny nose	2	Lee, 2019; Garcia-Noblejas, 2015	56	42.2	42.2	34.4	50.0
Fever	5	Pinana, 2017; Pilie, 2015; Mikulsa, 2014; Lee, 2019; Garcia-Noblejas, 2015	114	34.4	38.0	16.7	66.7
Myalgia	1	Lee, 2019	34	37.8	37.8	37.8	37.8
Shortness of breath	3	Lee, 2019; Gueller, 2013; Garcia-Noblejas, 2015;	73	12.5	32.7	10.0	75.6
Sore throat	1	Lee, 2019	28	31.1	31.1	31.1	31.1
Hoarseness	1	Lee, 2019	23	25.6	25.6	25.6	25.6
Headache	1	Lee, 2019	21	23.3	23.3	23.3	23.3
Sweating	1	Lee, 2019	11	12.2	12.2	12.2	12.2
Odynophagia	1	Garcia-Noblejas, 2015	3	9.4	9.4	9.4	9.4
Vomiting	1	Lee, 2019	8	8.9	8.9	8.9	8.9
Chest Pain	1	Lee, 2019	6	6.7	6.7	6.7	6.7
3.2 Signs on examinations							
Fever	2	Pinana, 2017; Pilie, 2015	40	36.2	36.2	21.7	50.7
4. HR adults: institutionalised patients							
4.1 Self-reported symptoms							
Cough	1	Hequet, 2019	34	89.5	89.5	89.5	89.5
Weakness/Malaise	1	Hequet, 2019	28	73.7	73.7	73.7	73.7
Fever	1	Hequet, 2019	27	71.1	71.1	71.1	71.1

Supplementary Table 11.A. RSV severe outcomes in older adults.

Study	Country	Data collection	Population & age	Sampling	n	N	Total participants	Proportion [95% CI]
Pneumonia								
Ansaldi, 2012	IT	Seasonal	Community cohort; ≥60	SS ILI	0	2	45	0.00 [0.00, 65.76]
Jeannoel, 2019	FR	Seasonal	Medically attended; ≥65	CI	56	165	165	33.94 [27.15, 41.46]
Puig-Barbera, 2012	ES	Seasonal	Medically attended; ≥60	SS ILI	14	54	799	25.93 [16.12, 38.93]
Aronen, 2019	FI	Annual	Medically attended; ≥65	SS ARI	3	22	382	13.64 [4.75, 33.33]
Pneumonia: REM for older adults (Q=4.41, p=0.22, I^2=40.4%)								*27.44 [18.74, 38.29]*
Respiratory failure								
Jeannoel, 2019	FR	Seasonal	Medically attended, RSV+ ARI; ≥65	CI	33	165	165	20.00 [14.61, 26.75]
ARDS								
Jeannoel, 2019	FR	Seasonal	Medically attended, RSV+ ARI; ≥65	CI	33	165	165	20.00 [14.61, 26.75]
Cardiopulmonary complications								
Belongia et al, 2018	US	Seasonal	Medically attended; ≥60	SS ARI/ILI	27	243	2257	11.11 [7.75, 15.68]
Hospitalisation								
Charles, 2008	AU	Annual	Medically attended; ≥65	SS PNM	13	13	587	100 [77.19, 100]
Belongia, 2018	US	Seasonal	Medically attended; ≥60	SS ARI	29	243	2257	11.93 [8.44, 16.61]
Falsey, 2005	US	Seasonal	Community cohort; ≥65	SS ARI	0	46	608	0.00 [0.00, 7.71]
Hospitalisation of older adults: REM for older adults (Q=16.63, p=0.00, I^2=92.7%)								*24.48 [0.43, 96.07]*
Admissions to ICU								
Jeannoel, 2019	FR	Seasonal	Medically attended; ≥65	CI	41	165	165	24.85 [18.88, 31.96]
Belongia, 2018	US	Seasonal	Medically attended; ≥60	SS ARI	0	29	2257	0.00 [0.00, 11.7]
Puig-Barbera, 2012	ES	Seasonal	Medically attended; ≥60	SS ILI	0	54	799	0.00 [0.00, 6.64]
ICU admission of older adults: REM for older adults (Q=10.38, p=0.01, I^2=76.8%)								*5.01 [0.47, 37.36]*
Ventilatory support								
Belongia, 2018	US	Seasonal	Medically attended; ≥60	SS ARI	0	29	2257	0.00 [0.00, 11.70]
Charles, 2008	AU	Annual	Medically attended; ≥65	SS PNM	0	13	587	0.00 [0.00, 22.81]

REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS = systematic sampling, CI = sampling by clinical indication, 95% CI = 95% confidence interval, ILI = influenza like illness, ARI = acute respiratory infection, PNM: pneumonia.

Supplementary Table 11.B. RSV severe outcomes in HR adults.

Study	Country	Data collection	Population & age	Sampling	n	N	Total participants	Proportion [95% CI]	Risk group
Pneumonia									
Falsey, 2005	US	Seasonal	Medically attended, IP; ≥65	SS ARI	41	142	1388	28.87 [22.05, 36.81]	Cardiopulmonary
Chatzis, 2018	US	Seasonal	Medically attended, ≥18, RSV+	CI ARI	2	62	175	35.43 [28.72, 42.76]	Immunodeficient
Gueller, 2013	CH	Annual	Medically attended, ≥18, IP	SS	4	1	10	10 [1.79, 40.42]	Immunodeficient
Kumar	DE	Seasonal	Medically attended, ≥18, OP	SS RVI	1	0	6	0.00 [0.00, 39.03]	Immunodeficient
Milstone, 2006	CA	Annual	Community cohort; ≥18,	SS ARI	1	0	8	0.00 [0.00, 32.44]	Immunodeficient
Peghin, 2017	US	Seasonal	Community cohort; ≥18,	SS ARI	0	3	7	42.86 [15.82, 74.95]	Immunodeficient
Pile	ES	Annual	Medically attended, ≥18, RSV+ IP	CI	3	27	69	39.13 [28.48, 50.93]	Immunodeficient
Pneumonia: REM for immunodeficient (Q=7.02, p=0.22, I^2=0.0%)								*35.33 [29.78, 41.30]*	*Immunodeficiency*
Pneumonia: REM for all risk groups (Q=7.02, p=0.22, I^2= 0.0%)								*33.00 [27.99, 38.43]*	*All risk-groups combined*
Respiratory failure									
Hopkins, 2008	AU	Annual	Community cohort; ≥18	SS ILI	2	18		11.11 [3.1, 32.8]	Institutionalised older adults
Renaud, 2013	US	Annual	Medically attended, RSV+ ≥18	CI	16	23		69.57 [49.13, 84.4]	Immunodeficiency
Khanna, 2018	CH	Annual	Medically attended, RSV+ ≥18	SS ARI	3	34		8.82 [3.05, 22.96]	Immunodeficiency
Roghmann, 2003	US	Seasonal	Medically attended, ≥18	SS ARI	0	11		0.00 [0.00, 25.88]	Immunodeficiency
Respiratory failure: REM for immunodeficient (Q=21.11, p=0.00, I^2=89.1%)								*20.62 [2.22, 74.82]*	*Immunodeficiency*
Respiratory failure: REM for all risk groups (Q=24.85, p= 0.00, I^2= 84.8 %)								*18.40 [3.65, 57.31]*	*All risk-groups combined*
ARDS									
Jeannoel, 2019	FR	Seasonal	RSV+ ARI ≥18	CI	9	55	14792	16.36 [8.86, 28.26]	Cardiopulmonary
Jeannoel, 2019	FR	Seasonal	RSV+ ARI ≥18	CI	5	16	14792	31.25 [14.16, 55.6]	Diabetes
Jeannoel, 2019	FR	Seasonal	RSV+ ARI ≥18	CI	9	37	14792	24.32 [13.36, 40.12]	Immunodeficient
ARDS: REM for all risk groups (Q=1.90, p= 0.39, I^2= 0.0%)								21.79 [14.89, 30.72]	*All risk-groups combined*
Cardiopulmonary complications									
Stolz, 2019	CH	Annual	Community cohort; >40	SS ARI	6	16	450	37.5 [18.48, 61.36]	Cardiopulmonary
ICU admissions									
Jeannoel, 2019	FR	Seasonal	RSV+ ARI; ≥18	CI	16	55	14792	29.09 [18.77, 42.14]	Cardiopulmonary
Schmidt, 2019	US	Annual	RSV+ IP; ≥18	CI	30	107	489	28.04 [20.40, 37.20]	Chronic Kidney Disease
Schmidt, 2019	US	Annual	RSV+ IP; ≥18	CI	40	133	489	30.08 [22.93, 38.34]	Diabetes
Jeannoel, 2019	FR	Seasonal	RSV+ ARI; ≥18	CI	8	16	14792	50.00 [28.00, 72.00]	Diabetes
Chatzis, 2018	CH	Annual	Medically attended; ≥18; RSV+	CI ARI	2	17	58	29.31 [19.18, 42.01]	Immunodeficient
Damlaj, 2016	US	Annual	Medically attended; ≥18; RSV+	CI	3	9	27	33.33 [18.64, 52.18]	Immunodeficient
Gorcea, 2015	GB	Annual	Medically attended; ≥18; RSV+	CI	3	6	20	30 [14.55, 51.9]	Immunodeficient

Study	Country	Data collection	Population & age	Sampling	n	N	Total participants	Proportion [95% CI]	Risk group
Jeannoel, 2019	FR	Seasonal	Medically attended; ≥18; RSV+ ARI	CI	4	13	37	35.14 [21.83, 51.24]	Immunodeficient
Khanna, 2018	CH	Annual	Medically attended; ≥18; RSV+	SS ARI	4	5	16	31.25 [14.16, 55.6]	Immunodeficient
Peghin, 2017	ES	Annual	Community cohort; ≥18	SS ARI	0	2	3	66.67 [20.77, 93.85]	Immunodeficient
Pilie, 2015	US	Annual	Medically attended; ≥18; RSV+ IP	CI	3	11	69	15.94 [9.14, 26.33]	Immunodeficient
Schmidt, 2019*	US	Annual	Medically attended; ≥18; RSV+ IP	CI	3	18	216	8.33 [5.34, 12.79]	Immunodeficient
Spahr, 2018	CH	Annual	Medically attended; ≥18; RSV+	CI ARI	4	2	10	20 [5.67, 50.98]	Immunodeficient
Teh, 2015	AU	Annual	Medically attended; ≥18;	CI RVI	3	1	6	16.67 [3.01, 56.35]	Immunodeficient
ICU admission: REM for immunodeficient (Q=33.82, p=0.00, I^2=67.5%)								*24.09 [16.35, 34.01]*	*Immunodeficient*
ICU admission: REM for all risk groups (Q=45.05, p=0.00, I^2=69.95%)								*26.74 [20.40, 34.22]*	*All risk-groups combined*
Ventilatory support									
Schmidt, 2019	US	Annual	RSV+ IP ≥18	CI	12	107	489	11.21 [6.53, 18.59]	Chronic Kidney Disease
Schmidt, 2019	US	Annual	RSV+ IP ≥18	CI	2	133	489	1.5 [0.41, 5.32]	Diabetes
Khanna, 2018	CH	Annual	Medically attended; ≥18; RSV+	SS ARI	4	4	16	25 [10.18, 49.5]	Immunodeficient
Chatzis, 2018	CH	Annual	Medically attended; ≥18; RSV+	CI ARI	2	13	58	22.41 [13.59, 34.66]	Immunodeficient
Pilie, 2015	US	Annual	Medically attended; ≥18; RSV+ IP	CI	3	7	69	10.14 [5, 19.49]	Immunodeficient
Spahr, 2018	CH	Annual	Medically attended; ≥18; RSV+	CI ARI	4	1	10	10 [1.79, 40.42]	Immunodeficient
Schmidt, 2019*	US	Annual	Medically attended; ≥18; RSV+ IP	CI	3	17	216	7.87 [4.97, 12.24]	Immunodeficient
Ventilatory support: REM for immunodeficient (Q=33.82, p=0.00, I^2=63.7%)								*13.65 [7.87, 22.63]*	*Immunodeficient*
Ventilatory support: REM for all risk groups (Q=21.01, p=0.00, I^2=77.0%)								*10.68 [5.87, 18.65]*	*All risk-groups combined*
Hospitalisation									
Hequet, 2019	CH	Seasonal	Community cohort; ≥18	SS ILI	1	3	38	7.89 [2.72, 20.8]	Institutionalised older adults
Belongia, 2018	US	Seasonal	Medically attended; ≥60	SS ARI	2	9	51	17.65 [9.57, 30.25]	Diabetes
Camargo, 2008	US	Seasonal	Medically attended; ≥50	SS AEC	2	5	6	83.33 [43.65, 96.99]	Cardiopulmonary
Falsey, 2005	US	Seasonal	Community cohort; ≥21	SS ARI	2	9	56	16.07 [8.69, 27.81]	Cardiopulmonary
Falsey, 2006	US	Annual	Community cohort; ≥40	SS ARI	0	1	11	9.09 [1.62, 37.74]	Cardiopulmonary
Saraya, 2017	JP	Annual	Medically attended; ≥18	SS AEA	0	3	3	100 [43.85, 100]	Asthma
D'Angelo, 2016	US	Annual	Medically attended; ≥50	SS ARI	3	5	6	83.33 [43.65, 96.99]	Immunodeficiency
Damlaj, 2016	US	Annual	Medically attended; ≥18	CI	3	27	45	60 [45.45, 72.98]	Immunodeficiency
Gorcea, 2015	GB	Annual	Medically attended; ≥18	CI	3	20	35	57.14 [40.86, 72.02]	Immunodeficiency
Khanna, 2018	CH	Annual	Medically attended; ≥18	SS ARI	4	16	34	47.06 [31.45, 63.26]	Immunodeficiency
Teh, 2015	AU	Annual	Medically attended; ≥18	CI RVI	3	6	15	40 [19.82, 64.25]	Immunodeficiency
Belongia, 2018	US	Seasonal	Medically attended; ≥60	SS ARI	2	5	15	33.33 [15.18, 58.29]	Immunodeficiency
Chatzis, 2018	CH	Annual	Medically attended; ≥18	CI ARI	2	58	175	33.14 [26.6, 40.41]	Immunodeficiency
Spahr, 2018	CH	Annual	Medically attended; ≥18	CI ARI	4	10	33	30.3 [17.38, 47.34]	Immunodeficiency

Study	Country	Data collection	Population & age	Sampling	n	N	Total participants	Proportion [95% CI]	Risk group
Pinana, 2017	ES	Annual	Medically attended; ≥18	CI	1	2	23	8.7 [2.42, 26.8]	Immunodeficiency
Peghin, 2017	ES	Annual	Community cohort; ≥18	SS ARI	0	3	7	42.86 [15.82, 74.95]	Immunodeficiency
Roghmann, 2003	US	Seasonal	Community cohort; ≥18	SS ARI	2	3	11	27.27 [9.75, 56.56]	Immunodeficiency
Weinberg, 2010	US	Annual	Community cohort; ≥18	SS ARI	0	3	13	23.08 [8.18, 50.26]	Immunodeficiency
Milstone, 2006	US	Seasonal	Community cohort; ≥18	SS ARI	1	1	8	12.5 [2.24, 47.09]	Immunodeficiency
Hospitalisation: REM for immunodeficient (Q=31.25, p=0.00, I^2=62%)								*38.30 [29.26, 48.23]*	*Immunodeficiency*
Hospitalisation: REM for all risk groups (Q=66.89, p=0.00, I^2=77.7%)								*32.82[23.49, 43.74]*	*All risk-groups combined*

REM= random-effect model, Q= Cochran's Q test, I^2 = I^2 statistic, SS = systematic sampling, CI = sampling by clinical indication, 95% CI = 95% confidence interval, ILI = influenza like illness; ARI = acute respiratory infection, ARDS= acute respiratory distress syndrome, URTI=upper respiratory tract infection, LRTI=lower respiratory tract infection, AEC = acute exacerbation of COPD, RVI=respiratory virus infection, IP = inpatients, OP = outpatients, ED = Emergency department, ICU MV = intensive care unit, mechanically ventilated.

Supplementary Table 12. RSV incidence in HR adults (annual and seasonal studies).

Study	Data collection	Risk Group	Setting	Country	Age Group	Sampling	Positive	Person-years	Incidence (/1000 person-year) [95% CI]
Slade, 2017*	Annual	Immunodeficiency	Medically attended	US	≥18	SS ARI	5	62	80.55 [26.15, 164.99]
Mahan, 2017*	Annual	Immunodeficiency	Medically attended	US	≥18	CI ARI	3	66	45.45 [9.37, 109.47]
Peghin, 2017	Annual	Immunodeficiency	Community cohort	ES	≥18	SS ARI	7	333	21.01 [8.45, 39.19]
Overall estimate for immunodeficient (annual) (Q=5.4, I^2 = 43.3%; p=0.07)									*36.88 (17.82, 76.33)*
Stolz, 2019	Annual	Cardiopulmonary	Community cohort	CH	>40	SS ARI	16	1013	15.8 [9.03, 24.43]
Chasqueira, 2018	Seasonal	Institutionalised older adults	Community cohort	PT	≥59	SS ARI	5	511	9.78 [3.18, 20.04]
Roghmann, 2003	Seasonal	Immunodeficiency	Community cohort	US	≥18	SS ARI	11	15	755.05 [376.92, 1262.34]
Milstone, 2006	Seasonal	Immunodeficiency	Community cohort	US	≥18	SS ARI	8	21	384 [165.78, 692.29]
Lopez-Medrano, 2007	Seasonal	Immunodeficiency	Community cohort	ES	≥18	SS RVI	6	89	67.67 [24.83, 131.6]
Overall estimate for immunodeficient (seasonal) (Q=22.76, .98; p=0.00; I^2 = 88.0%)									*260.89 [82.33,826.65]*
Falsey, 2005	Seasonal	Cardiopulmonary	Community cohort	US	≥21	SS ARI	56	900	62.26 [47.03, 79.59]
Hutchinson, 2007	Seasonal	Cardiopulmonary	Community cohort	AU	≥18	SS AEC	1	82	12.17 [0.31, 44.88]
Belongia, 2018*	Seasonal	Cardiopulmonary	Medically attended	US	≥60	SS ARI	109	13017	8.37 [6.88, 10.02]
Overall estimate for cardiopulmonary (seasonal) (Q=148.98, p=0.00; I^2 = 97.0%)									*19.15 [6.06, 60.49]*

SS = systematic sampling, CI = sampling by clinical indication, 95% CI = 95% confidence interval, ARI = acute respiratory infection, AEC = acute exacerbation of COPD; RVI = respiratory virus infection. Belongia, 2018: Fever & cough included in eligibility criteria most seasons.

Supplementary Table 13. RSV related healthcare utilisation of older and HR adults.

Study	Country	Data collection	Population & age	Sampling	n	RSV+	Total participants	Proportion [95% CI]
Healthcare utilisation in older adults								
Outpatient visits among RSV-positive older adults								
Falsey, 2005	US	Seasonal	Community cohort, ≥65	SS ARI	8	46	608	17.39 [9.09, 30.72]
Emergency department visits among RSV-positive older adults								
Belongia, 2018	US	Seasonal	Medically attended, ≥65	SS ARI	13	243	2257	5.35 [3.15, 8.94]
Falsey, 2005	US	Seasonal	Community cohort, ≥60	SS ARI	0	46	608	0.00 [0.00, 7.71]
Discharge to care among RSV-positive older adults								
Belongia, 2018	US	Seasonal	Medically attended, ≥60	SS ARI	2	243	2257	0.82 [0.23, 2.95]
Oxygen use among RSV-positive older adults								
Aronen, 2019	FI	Annual	IP ≥65	SS ARI	3	22	382	13.64 [4.75, 33.33]
Belongia, 2018	US	Seasonal	Medically attended, ≥60	SS ARI	36	243	2257	14.81 [10.90, 19.83]
Antibiotic use among RSV-positive older adults								
Falsey, 2005	US	Seasonal	Community cohort, ≥65	SS ARI	67	86	86	77.91 [68.05, 85.38]
Belongia, 2018	US	Seasonal	Medically attended, ≥60	SS ARI	187	243	2257	76.95 [71.27, 81.81]
Healthcare utilisation in HR adults								
Outpatient visits among RSV-positive HR adults								
Cardiopulmonary								
Falsey, 2005	US	Seasonal	Community cohort, ≥21	SS ARI	16	56	540	28.57 [18.42, 41.48]
Emergency department visits among RSV-positive HR adults								
Cardiopulmonary								
Falsey, 2005	US	Seasonal	Community cohort, ≥21	SS ARI	5	56	540	8.93 [3.87, 19.26]
Discharge to care among RSV-positive HR adults								
Chronic Kidney Disease								
Schmidt, 2019	US	Annual	RSV+ IP ≥18	CI	12	107	489	11.21 [6.53, 18.59]
Diabetes								
Schmidt, 2019	US	Annual	RSV+ IP ≥18	CI	23	133	489	17.29 [11.81, 24.61]
Immunodeficient								
Schmidt, 2019	US	Annual	RSV+ IP ≥18	CI	9	216	489	4.17 [2.21, 7.73]
Oxygen use among RSV-positive HR adults								
Immunodeficiency								
Li, 2012	US	Annual	RSV+ ≥18	CI	5	21	21	23.81 [10.63, 45.09]
Gueller, 2013	DE	Seasonal	IP ≥18	SS	5	10	29	50.00 [23.66, 76.34]
Institutionalized older adults								
Hequet, 2019	CH	Annual	Community cohort, ≥18	SS ILI	12	38	509	31.58 [19.08, 47.46]

IP = inpatients, SS = systematic sampling, CI = sampling by clinical indication, ILI = influenza like illness, ARI = acute respiratory infection.