



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

The disease burden of respiratory syncytial virus in older adults

Citation for published version:

Kenmoe, S & Nair, H 2024, 'The disease burden of respiratory syncytial virus in older adults', *Current Opinion in Infectious Diseases*. <https://doi.org/10.1097/QCO.0000000000001000>

Digital Object Identifier (DOI):

[10.1097/QCO.0000000000001000](https://doi.org/10.1097/QCO.0000000000001000)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Current Opinion in Infectious Diseases

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.





The disease burden of respiratory syncytial virus in older adults

Sebastien Kenmoe^a and Harish Nair^{a,b,c}

Purpose of review

To highlight the respiratory syncytial virus (RSV) disease burden and the current developments and challenges in RSV prevention for older adults ≥ 60 years through analysis of RSV epidemiology and the effectiveness of emerging vaccines.

Recent findings

In industrialized countries, RSV incidence rates and hospitalization rates among older adults are estimated to be 600.7 cases per 100 000 person-years and 157 hospitalizations per 100 000 person-years, respectively. Yet, accurately determining RSV morbidity and mortality in older adults is challenging, thus resulting in substantially under-estimating the disease burden. The in-hospital fatality rates vary substantially with age and geographies, and can be as high as 9.1% in developing countries. Two promising RSV vaccines for the elderly have been approved, demonstrating efficacies of up to 94.1%, signifying considerable advancement in RSV prevention. However, concerns over potential side effects remain.

Summary

RSV is associated with a significant burden in older adults. While the landscape of RSV prevention in older adults is promising with the licensure of vaccines from two companies, current trial data underscore the need for additional studies. Addressing the real-world effectiveness of these vaccines, understanding potential rare side effects, and ensuring broad inclusivity in future trials are crucial steps to maximize their potential benefits.

Keywords

disease burden, older adults, respiratory syncytial virus, vaccine

INTRODUCTION

Respiratory syncytial virus (RSV), first identified by Robert Chanock in 1956, is a single stranded RNA virus. RSV is a common respiratory pathogen and almost all children are infected by the age of 3 years [1]. RSV is a member of the Pneumoviridae family, characterized by enveloped viral particles. This envelope contains key surface glycoproteins such as the G protein, which allows the virus to attach to and enter host cells and stimulates neutralizing antibodies [2]. The F protein, another crucial component, facilitates attachment and fusion to the host cell membrane. The F protein also undergoes a shift from a prefusion to a postfusion form and remains a central target for vaccine and passive prophylactic measures development [3]. There are two subgroups – A and B. RSV is transmitted primarily through droplets released by coughing and sneezing and involves direct contact with infected persons and contact with contaminated surfaces. Some infants may remain contagious for longer and those with immunocompromised status may remain contagious up to 4 weeks [4]. RSV exhibits

distinct seasonality in most parts of the world [5] and causes severe disease in the very young (infants < 1 year) and the older adults ≥ 60 years [6,7,8^{***}].

RSV infection can result in upper respiratory and/or lower respiratory tract symptoms. The most prevalent upper respiratory tract infection (URTI) symptoms in older adults with RSV include sore throat, runny noses, and nasal congestion (Table 1). In those with lower respiratory tract infections (LRTI)

^aCentre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK, ^bSchool of Public Health, Nanjing Medical University, Nanjing, Jiangsu, China and ^cSchool of Public Health, University of the Witwatersrand, South Africa

Correspondence to Harish Nair, Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh EH8 9AG, UK.
E-mail: harish.nair@ed.ac.uk

Curr Opin Infect Dis 2024, 37:000–000

DOI:10.1097/QCO.0000000000001000

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

KEY POINTS

- Respiratory syncytial virus (RSV) represents a substantial health burden for older adults, with high incidence and hospitalization rates that are often underestimated.
- Emerging vaccines for RSV show promising efficacies up to 94.1%, marking significant progress in prevention efforts for the older adults.
- Despite vaccine approvals, ongoing challenges include the need for further studies to assess real-world effectiveness and understand rare side effects.

symptoms, cough is predominant, along with shortness of breath and sputum. Among the gastrointestinal symptoms, nausea, vomiting, or diarrhea have been reported. Other common symptoms include fever, fatigue or weakness, disturbed sleep, and general malaise. The symptoms are mild and self-resolving in most cases with symptoms usually resolving in one to two weeks. However, a small proportion of cases may result in more severe acute LRTI leading to serious outcomes such as hospitalizations and death [7[•],8^{••}]. The incidence rates, however, show marked variability in any given year (across regions and countries) due to factors like inadequate testing and the potentially suboptimal sensitivity of conventional diagnostic specimens and tools in adults [9^{••},10^{••}]. There is also marked variability in RSV activity year on year [5]. People with chronic conditions such as chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, among others, are more likely to experience hospitalizations and death caused by RSV [11–13]. This vulnerability extends to those living in long-term care facilities, individuals displaying signs of frailty, those above 75 years of age, and immunocompromised patients, including organ transplant recipients [7[•]]. The preventive and therapeutic options against RSV have remained limited until recently when effective immunization strategies have been developed [14^{••},15^{••}]. The purpose of this article is to examine the burden of disease caused by RSV in older adults (60 years and above).

EPIDEMIOLOGY OF RESPIRATORY SYNCYTIAL VIRUS

The primary source of RSV infection in older adults are frequently their grandchildren in the community and staff in nursing care homes [16[•]]. Regardless of the region, the variations in RSV season onset, duration, and offset are relatively consistent year-on-year [5,17]. RSV outbreaks have a consistent duration, averaging 4.6–4.8 months. In temperate

Table 1. Respiratory syncytial virus signs and symptoms in older adults

	Mean proportion [range]
Upper respiratory tract infection symptoms	
Runny nose/rhinorhea [1–4]	58.5 [27.7; 81.8]
Nasal congestion [2,3]	56.4 [47.2; 72.7]
Sore throat/pharyngitis [1–5]	53.9 [23.7; 81.3]
Earache [2,4]	34.4 [32.3; 36.4]
Lower respiratory tract infection symptoms	
Cough [1–6]	78.9 [27.3; 97.2]
Sputum production [1–3,5,6]	72.8 [49.4; 94.4]
Shortness of breath/difficulty breathing/dyspnea [1,3–6]	66.9 [19.3; 89.1]
Hemoptysis [3,5]	1.8 [1.2; 2.9]
Chest pain [3,5]	21.1 [7.4; 34.9]
Wheezing [1–6]	55.8 [16.0; 55.8]
Tachypnea [3,5,6]	52.2 [6.6; 93.7]
Decreased breath sounds [3,5]	24.1 [7.8; 33.6]
Crackles/rales [3,5]	33.3 [9.5; 50.0]
Rhonchi [3,5]	33.2 [12.8; 44.4]
SpO ₂ <95% [6]	13.9
Pleuritic pain/pleuritic chest pain [3]	9.1 [6.8; 11.3]
Gastrointestinal symptoms	
Nausea/vomiting/ diarrhea [3,4]	28.4 [15.5; 38.7]
Anorexia/lack of appetite [3,4]	37.5 [22.7; 61.3]
Abdominal pain [3]	12.7 [12.4; 13.0]
Other symptoms	
Fever [1,3–6]	35.8 [5.6; 71.0]
Feverishness [1–3,6]	44.1 [27.3; 59.7]
Chills [3]	38.7 [35.7; 41.6]
Myalgia/muscle ache [1–6]	35.3 [16.0; 64.1]
Arthralgia/joint pains [3]	13.6 [13.0; 14.1]
Headache [1–4,6]	52.5 [16.7; 82.1]
Fatigue/weakness [1,3,4]	68.1 [47.9; 90.3]
Lethargy [3]	56.1 [54.5; 57.6]
Altered mental status [3,4]	32.2 [19.3; 40.0]
Disturbed sleep [6]	72.2
Feeling unwell [6]	91.7
Disturbance in daily activity [6]	75.0
Seizures [3]	1.2 [0.2; 2.1]
Conjunctivitis [3]	1.0 [0.8; 1.2]
Dizziness [3]	16.7 [13.1; 20.2]

areas, RSV epidemics predominantly occur in the winter, but they usually precede influenza outbreaks by about 0.3 months. The influenza season, by contrast, tends to be shorter in temperate zones,

Table 2. RSV burden among older adults in community studies

Settings	Population	Regions	RSV proportion positive	RSV incidence rate	Proportion hospitalized among RSV positive
Community	≥60 years		3.4% to 8.8% [1–7]		
	≥65 years	Industrialized countries		600.7 cases per 100 000 (95% CI: 100.4–3100.5) person-years [8 ^{***}]	
	≥60 years, RSV-positive				0% to 19.5% [2–4]
Outpatients	≥60 years		5.2% to 14.9% [7, 9–16]	500.9 to 2300.2 per 100 000 person-years [17, 18 [*]]	
	≥60 years, RSV-positive				11.9% [10]
Emergency department	≥65 years			300.3 (95% CI: 1100.7–9000.8) per 100 000 person-years [19]	

CI, confidence interval; RSV, respiratory syncytial virus.

averaging around 3.8 months, but extends to 5.2 months in the tropics. RSV epidemics typically start in tropical regions around July, with the onset delayed until January in high-latitude areas. Sub-tropical areas display more varied seasonality with peaks at different time of the year depending on the region. The dominant RSV subtype in circulation does not affect the epidemic's timeline or span [18^{*}].

CHALLENGES TO IDENTIFYING MORBIDITY BURDEN IN OLDER ADULTS

Estimating the RSV burden in older adults is challenging. Similar symptoms between RSV and other respiratory viral infections, coupled with a lack of awareness and access to timely testing by older adults, lead to underestimations of RSV morbidity burden in older adults. Many studies rely on RT-PCR testing of nasopharyngeal swabs from upper respiratory tract, which may not be representative of the LRTI. Older adults often show diminished viral

presence, especially if tested late, and generally have lower viral concentrations than children [44]. Broadening testing to include saliva, sputum, and serology have proven more effective [10^{***}]. A recent study in US has shown that RSV prevalence by nasopharyngeal swab alone was 1.8% but increased to 4.5% when saliva (and sputum) was added [10^{***}]. These data were utilized in the recent meta-analysis by Li *et al.* [8^{***}] to report that the annual estimates RSV hospitalizations in adults ≥65 years industrialized countries could be as high as 787 000 (460–1347). Similarly, the in-hospital annual mortality in this region could be as high as 47 000. Community-based studies provide a varied picture compared to inpatient studies (Tables 2 and 3). While community-based studies provide valuable insights into the range of prevalence/incidence of RSV-ARI in the general older adult population, hospital-based studies offer more precise data on the hospitalization rate, in-hospital deaths, and healthcare impact of RSV.

Table 3. RSV burden among older adults in inpatient studies

Settings	Population	Regions	RSV hospitalization rate	RSV in hospital case fatality rate
Inpatients	≥65 years	Industrialized countries	157 (95% CI: 98–252) RSV infections per 100 000 person-years [20]	6.1% (95% CI: 3.3–11.0) [20]
	≥65 years	Industrialized countries	100 (95% CI: 50–210) RSV infections per 100 000 person-years [8 ^{***}]	1.6% (95% CI: 0.7–3.8%) [8 ^{***}]
	≥65 years	Developing countries	30 (95% CI: 10–70) RSV infections per 100 000 person-years [8 ^{***}]	9.1% (95% CI: 2.6–31.8%) [8 ^{***}]
	≥60 years	Industrialized countries		7.1% (95% CI: 5.4–9.3) [21]

CI, confidence interval; RSV, respiratory syncytial virus.

MORBIDITY BURDEN

Community burden

Very few community-based studies have reported RSV disease burden in older adults. These are largely from industrialized countries. A meta-analysis by RESCEU investigators identified five studies (with a clear denominator population at risk) from industrialized countries in older adults and reported that the pooled estimate of RSV related acute respiratory infections (ARI) incidence rate was 600.7 [95% confidence interval (CI): 100.4–3100.5] cases per 100 000 person-years [19] (Table 2). Other studies, without a clear denominator population at risk have reported the proportion of older adults with ARI cases testing positive for RSV in community settings; these are highly variable and range from 3.4% to 8.8% depending on the study settings [20–26]. The proportion of ARI cases testing positive for RSV in community and subsequently hospitalized ranged from 0% to 19.5% [21–23]. There is a clear age dependent increase in incidence of RSV-ARI in older adults. The incidence rate of RSV-ARI in older adults per 1000 per year varies by age group: for those aged ≥ 65 years it ranges from 0.7 to 151.1, for ≥ 70 years it ranges from 1.6 to 175.0, for ≥ 75 years it ranges from 6.6 to 175.4, and for those aged ≥ 80 years, the rates span from 0.9 to 259.7 [27]. In a meta-analysis from industrialized countries examining the incidence of RSV-ARI in adults with comorbidities, the annual incidence rate was found to be 3700.6 (95% CI: 20.1–70.3) per 100 000 persons, while the seasonal incidence rate was 2800.4 (95% CI: 11.4–70.9) per 100 000 persons [12]. In a community-based cohort study involving older adults aged 50 years or older in United States across two RSV seasons (2019–2021), the incidence of RSV-positive ARI before the COVID-19 pandemic was found to be substantial at 4800.6 per 100 000 person-years [28*]. No cases were identified during the pandemic RSV season, though cases re-emerged in the summer of 2021.

Studies in industrialized countries among outpatients aged 60 years and above have reported that RSV positive proportions among those seeking care with ARI varied from 5.2% to 14.9% [26,29–36]. Studies in United States where a reliable population denominator could be estimated have reported an incidence rate of 500.9 to 2300.2 per 100 000 person-years for RSV-ARI in outpatient settings [37,38]. About 11.9% of these RSV-positive older adults in outpatient settings were subsequently hospitalized [30]. In two studies conducted in United States and a multicentre European study, the RSV positive proportions across age groups were relatively consistent [30,31]. Those aged 60–64 years had a proportion of 10% [30]. For the 60–74 years age group,

proportions were recorded at 5.18% and 10.78% [30,31]. In the same studies, individuals aged 75 years and above, 8.4% and 11.3% of those with ARI tested positive for RSV [30,31]. In a study conducted in the United States in emergency departments, those aged 65 and over had an RSV incidence rate of 330.9 per 100 000 person-years (95% CI: 110.7–9000.8).

HOSPITAL BURDEN

There is substantial variability in the estimates for RSV hospitalizations in older adults. The RESCEU investigators reported a pooled hospitalization rate of 157 (95%CI 98–252) per 100 000 persons per year for industrialized countries [8**] (Table 3). This translates to about 356 000 (222–572) hospitalizations in industrialized countries in 2019. Another meta-analysis by Savic *et al.* [39] estimated that the hospitalization attack rate for RSV-ARI in older adults in industrialized countries was 0.15% and this translates to about 466 000 (302–720) hospitalizations in industrialized countries in 2019. They estimate about 274 000 (177–423) and 109 000 (71–168) hospitalizations in Europe and USA in 2019. By contrast, Osei-Yeboah *et al.* [40**] utilized RSV hospitalization data from RESCEU studies which included multiyear national hospitalization data linked to laboratory reports to develop modelled estimates for Europe and reported 145 000 hospitalizations in older adults in 27 EU countries and the UK. Conversely, RESCEU investigators reported in developing countries, the RSV hospitalization rate for this age group was 30 (95% CI: 10–70) per 100 000 person-years based on data from six studies [19]. This translates to about 109 000 (45–266) hospitalizations in developing countries. In Europe, the average annual number of hospitalizations for the age groups 65–74 years, 75–84 years, and ≥ 85 years were 32 679 (95% CI: 27 594; 37 764), 74 519 (95% CI: 69 923; 79 115), and 37 904 (95% CI: 32 444; 43 363), respectively [40**]. The hospitalization rate of RSV-ARI in older adults per 100 000 per year increases with age: for those aged ≥ 65 years, the rate ranges from 10 to 320; for ≥ 70 years, it varies from 10 to 460; for ≥ 75 years, it spans from 0.0 to 710; and for those aged ≥ 80 years, it's between 0.0 and 1410 [27]. A meta-analysis from industrialized countries reported that the odds ratio for RSV-ARI hospitalization in patients with comorbidities (asthma, CHF, COPD, diabetes, and immunocompromised) compared to those without was 4.1 (95% CI: 1.6–10.4). [12]. Moyes *et al.* [41] from South Africa reported that the hospitalization rates for RSV-ARI in adults with HIV (in 2012) were 400.8, 200.0, and 200.0 per 100 000 persons/year for age groups ≥ 65 years, 45–64 years, and 18–44 years, respectively. Falsey *et al.* [42] from the United States reported a

hospitalization rate of 1300.2 per 100 000 persons/year for adults aged ≥ 65 with chronic heart failure or chronic obstructive pulmonary diseases due to RSV-ARI.

MORTALITY BURDEN

In industrialized countries, the in-hospital case fatality rate (hCFR) attributed to RSV infections for older adults shows substantial variation, with estimates from three meta-analyses ranging from 1.6% (95% CI: 0.7–3.8) [19] to 6.1% (95% CI: 3.3–11.0) [8^{***}] and 7.1% (95% CI: 5.4–9.3) [39]. The latter estimate (7.1%) from of Savic *et al.* [19] study translates to about 33 000 (16–67) deaths. In developing countries, the hCFR for this age group was 9.1% (95% CI: 2.6–31.8). This translates to about 10 000 (2–46) deaths, largely driven by the low number of RSV hospitalizations in this region. Among older adults, the hCFR of RSV-ARI varies with age: 4.6% for those aged 60–74 years and 7.3% for those aged ≥ 75 years [43]. In a systematic review examining the burden of RSV in older adults with comorbidities in both industrialized and developing countries, the hCFR for RSV-ARI in adults with any comorbidity stood at 11.0% (95% CI, 6.8; 17.9) [12].

COMPARISON WITH INFLUENZA BURDEN

Several reports have shown that while RSV disease burden is well recognized in young children, it is under appreciated in older adults. Therefore, seasonal influenza that causes substantial morbidity and mortality in older adults, offers a useful anchor point for comparing disease burden and impact on healthcare systems. Studies have shown that in general RSV disease burden may be slightly lower or even comparable to influenza. For example, Falsey *et al.* [20] analyzed data over four consecutive winters from their cohort in Rochester, New York and reported that although RSV infection generated fewer clinic visits than influenza (17% and 29% in healthy and high risk older adults respectively, compared to 42% and 60% respectively for influenza A), use of healthcare services by high-risk adults was similar in both groups (9% and 16% for emergency room visits and hospitalizations respectively for RSV compared to 16% and 20% respectively for influenza A). In the hospitalized cohort, RSV and influenza A infections resulted in similar lengths of stay, rates of use of intensive care (15% and 12% respectively), and mortality (8% and 7%, respectively). A timeseries modelling study from the United Kingdom using data from the Public Health England (PHE) weekly pathogen surveillance for influenza and RSV,

the Clinical Practice Research Datalink (CPRD), the Hospital Episode Statistics (HES), and the Office of National Statistics (ONS) databases for the period 1997 to 2009 showed that the RSV: Influenza ratio for GP episodes and hospitalizations for respiratory disease in adults ≥ 65 years was 1.6 : 1 and 0.8–0.9 : 1 [45]. The antibiotic prescriptions ratio for RSV and influenza was 2 : 1. A recent timeseries including data over a 20 year period from US reported that mean excess respiratory and circulatory deaths associated with RSV in adults ≥ 65 years was 12604 (95% CI 11808–139999) compared to 14496 (13465–15528) for influenza [46]. In the UK, ratio of deaths due to respiratory and cardiorespiratory disease in adults ≥ 65 years from RSV and influenza was broadly comparable (0.9 : 1) [45].

COSTS RELATED TO RESPIRATORY SYNCYTIAL VIRUS HOSPITALIZATIONS OR RESPIRATORY SYNCYTIAL VIRUS ILLNESS IN OLDER ADULTS

A community study across Belgium, the UK, and the Netherlands for two RSV seasons highlighted varied direct mean costs for GP visits per RSV episode: €11.7 (median and IQR: 3.4; 0; 12.2) from the patient's perspective, €14.6 (median and IQR: 0; 0; 23.2) healthcare provider's, and €26.3 (median and IQR: 5.5; 0; 47.3) healthcare payer's. Comparable influenza costs were slightly higher, though interquartile ranges showed substantial overlaps [47^{***}]. Several studies from various regions have evaluated the cost burden and hospitalization duration associated with RSV in older adults. A United States study of 601 patients hospitalized with RSV revealed that 57% were older adults with an average hospitalization cost of \$8241 (95% CI: 6957; 9758) and duration of hospitalization for 8 days (95% CI: 7; 9) [48]. This implies an estimated U.S. annual cost burden of \$743.9 million (95% CI: 542.2; 945.7) for RSV associated hospitalizations in older adults. Another United States comparison between RSV (579 patients) and influenza (1511 patients) showed that RSV hospitalizations incurred a slightly longer stay of 0.68 days (0.02 to 1.37) and cost \$16 034 (14 684; 17 440), compared to \$15 163 (14 192; 16 225) for influenza with a nonsignificant difference of \$871 (–811–2547) [49]. Additionally, immunocompromised U.S. RSV patients had longer hospital stays (geometric mean 7.3 vs. 5.4 days) and higher costs (geometric mean \$66 476.1 vs. \$29 316.2) compared to their nonimmunocompromised counterparts and similar patterns were noted for influenza [50]. In China, RSV patients (median LOS: 14.0 days, IQR: 10.0; 23.0 days) had a longer stay (P value < 0.001) but lower cost (P value < 0.001) (\$2919.1, IQR:

\$1172.1–15627.4) than influenza patients (median LOS: 10.0 days, IQR: 8.0; 14.0 days; cost: \$3367.5, IQR: \$1896.1 to \$10767.0) [51]. A New Zealand study estimated the yearly RSV hospitalization cost at \$525 137.85, translating to an average of \$3053.13 per hospitalization [52]. They reported that the median length of hospital stay for RSV positive patients was 4 days (IQR: 2; 6 days). A Korean study reported an average RSV hospital stay of 20.4 days (± 33.6) with a median cost per each admission of \$2933.17 (IQR: \$1748.26; \$6339.93) [53]. In Canada in multiple care settings, RSV-attributable ARI healthcare costs varied based on age, with the 65–79 age group incurring \$1491 (\pm \$5675) and those aged 80 and above \$2878 (\pm \$7230) per episode [54].

LOOKING FORWARD

Considerable progress was made in developing RSV vaccines for older adults [14[■], 15[■]]. The United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA) recently approved two RSV vaccines for this age group: RSVpreF (unadjuvanted bivalent RSV vaccine with F protein in prefusion conformation) and RSVPreF3 (adjuvanted monovalent RSV vaccine with F protein in prefusion conformation), both of which demonstrated very high efficacy rates along with durable protection for at least 2 years. The RSVPreF3 vaccine has been also licensed in Japan and Canada. RSVpreF, tested on 34 284 participants enrolled between August 31, 2021, and July 14, 2022, showed 66.7% (96.6% CI: 28.8; 85.8) efficacy against RSV-associated LRTI with at least two symptoms and 85.7% (96.6% CI: 32.0; 98.7) with at least three symptoms at the end of the first season [15[■]]. RSVPreF3, evaluated on participants enrolled in 2021–2023, demonstrated an efficacy of 74.5% (95% CI: 60.0; 84.5) against RSV-associated LRTI over combined seasons 1 and 2. In season 1, the efficacy against RSV-associated LRTI was 82.6% (95% CI: 57.9; 94.1) and 87.5% (95% CI: 58.9; 97.6) against RSV-associated medically attended LRTI. In the season 2, the efficacy against RSV-associated LRTD was 56.1% (95% CI: 28.2; 74.4) [14[■], 15[■]]. Both vaccines demonstrated similar efficacies in adults ≥ 75 years as well as those with comorbidities. Concerns emerged regarding certain side effects, such as Guillain–Barré syndrome and atrial fibrillation, observed postvaccination in trials of both vaccines [55[■]]. Based on the safety and efficacy data as well as current disease burden data, the US Centres for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended single dose of RSV vaccine in adults ≥ 60 years based on shared clinical

decision-making considering individual risk factors, health status, and preferences [55[■]]. The ACIP estimates that in the US alone, every one million vaccine doses given over two seasons would prevent 41 000–44 000 outpatient visits, 3190 to 3460 hospitalisations and 155 to 167 deaths in adults ≥ 60 years of age [55[■]]. In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) has recommended a single dose of RSV vaccine in all adults ≥ 75 years. These developments, along with the promising efficacy of mRNA-1345 against RSV-related LRTI, represent an exciting opening chapter in RSV prevention for the elderly [56–58].

CONCLUSION

The prevalence and severity of RSV among older adults, particularly those aged 60 and over, are becoming increasingly recognized, with several studies highlighting its widespread nature both in industrialized and developing countries. The disease burden is likely to be comparable to seasonal influenza. The frail elderly and those with multimorbidities are at substantial risk of severe disease (including prolonged hospitalization) and death. As a result, RSV vaccines displaying efficacies of up to 94.1% with duration of protection extending at least two seasons offer hope. However, concerns about possible side effects require continued monitoring and rigorous research to ensure the safe and effective management of RSV among the older adults.

Acknowledgements

None.

Author contributions: Both authors contributed equally to the article. Both authors approve this manuscript.

Financial support and sponsorship

None.

Conflicts of interest

H.N. reports grants outside the submitted work from the Innovative Medicines Initiative, WHO, the National Institute for Health Research, Pfizer and Icosavax; and personal fees from the Bill & Melinda Gates Foundation, Pfizer, GSK, Merck, Abbvie, Janssen, Icosavax, Sanofi, Novavax, outside the submitted work.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. *Am J Hyg* 1957; 66:281–290.

2. Smith EC, Popa A, Chang A, *et al.* Viral entry mechanisms: the increasing diversity of paramyxovirus entry. *FEBS J* 2009; 276:7217–7227.
3. Falsey AR, Walsh EE. Respiratory syncytial virus prefusion F vaccine. *Cell* 2023; 186:3137–13137; e1.
4. CDC. RSV transmission 2023 [updated 2023/09/25]. Available at: <https://www.cdc.gov/rsv/about/transmission.html>.
5. Li Y, Reeves RM, Wang X, *et al.* Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *Lancet Global Health* 2019; 7:e1031–e1045.
6. Li Y, Wang X, Blau DM, *et al.* Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; 399:2047–2064.
7. Cong B, Dighero I, Zhang T, *et al.* Understanding the age spectrum of respiratory syncytial virus associated hospitalisation and mortality burden based on statistical modelling methods: a systematic analysis. *BMC Med* 2023; 21:224.
- The study informs a crucial deficit in recognizing the RSV burden among older adults, with statistical models showing notably high mortality rates for those 75 and older. The study also highlights the inadequacy of clinical databases in capturing the true extent of RSV hospitalizations for adults, particularly those over 50, suggesting that current data significantly underreports the disease burden.
8. Li Y, Kulkarni D, Begier E, *et al.* Adjusting for case under-ascertainment in estimating RSV hospitalisation burden of older adults in high-income countries: a systematic review and modelling study. *Infect Dis Ther* 2023; 12:1137–1149.
- This research refines the understanding of RSV's impact on older adults by adjusting for diagnostic under-ascertainment, revealing hospitalization rates approximately 2.2 times higher than previously reported (unadjusted 157 per 100 000; 95% CI 98–252 vs. adjusted 347 per 100 000; 95% CI 203–595).
9. Onwuchekwa C, Moreo LM, Menon S, *et al.* Underascertainment of respiratory syncytial virus infection in adults due to diagnostic testing limitations: a systematic literature review and meta-analysis. *J Infect Dis* 2023; 228:173–184.
- This study provides insights into the underascertainment of adult RSV infections, demonstrating that RT-PCR remains the most sensitive diagnostic test. It reveals that the inclusion of additional specimen types, beyond nasal/nasopharyngeal swabs, significantly increases RSV detection rates.
10. Ramirez J, Carrico R, Wilde A, *et al.* Diagnosis of respiratory syncytial virus in adults substantially increases when adding sputum, saliva, and serology testing to nasopharyngeal swab RT-PCR. *Infect Dis Ther* 2023; 12:1593–1603.
- This study advances the understanding of RSV detection in adults, showing that diagnostic rates increase significantly when multiple specimen types are used alongside traditional nasopharyngeal swab RT-PCR. With a nearly two-fold higher detection rate using a combination of NP swab, saliva, sputum, and serology, the research suggests current RSV incidence rates are underestimated and highlights the need for a multifaceted diagnostic approach to accurately assess RSV burden in hospitalized older adults.
11. Nguyen-Van-Tam JS, O'Leary M, Martin ET, *et al.* Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. *Eur Respir Rev* 2022; 31:220105.
12. Shi T, Vennard S, Jasiewicz F, *et al.* Disease burden estimates of respiratory syncytial virus related acute respiratory infections in adults with comorbidity: a systematic review and meta-analysis. *J Infect Dis* 2022; 226(Suppl 1): S17–S21.
13. Havers FP, Whitaker M, Melgar M, *et al.* Characteristics and outcomes among adults aged ≥ 60 years hospitalized with laboratory-confirmed respiratory syncytial virus – RSV-NET, 12 States, July 2022–June 2023. *Am J Transplant* 2023; 23:2000–2007.
14. Papi A, Ison MG, Langley JM, *et al.* Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med* 2023; 388:595–608.
- This phase 3 trial reveals the high efficacy of the RSVPreF3 vaccine in preventing RSV-related respiratory infections in older adults. Demonstrating a vaccine efficacy of over 82% against RSV-related lower respiratory tract disease and 94.1% against severe cases.
15. Walsh EE, Pérez Marc G, Zareba AM, *et al.* Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med* 2023; 388:1465–1477.
- This phase 3 trial evaluates the RSVPreF vaccine's efficacy in older adults. The vaccine showed 66.7% efficacy against RSV with at least two symptoms and 85.7% with at least three. The vaccine maintained a comparable safety profile to the placebo, suggesting its potential as a safe and effective measure against RSV in the older population.
16. Korsten K, Adriaenssens N, Coenen S, *et al.* Contact with young children increases the risk of respiratory infection in older adults in Europe—the RESCEU Study. *J Infect Dis* 2022; 226(Suppl 1):S79–S86.
- This study from the RESCEU consortium highlights the impact that regular contact with young children not living in the same household has on the risk of acute respiratory tract infections (ARTI) in older adults. Findings indicate that such exposure accounts for one in ten ARTI cases in these older adults.
17. Staadegaard L, Caini S, Wangchuk S, *et al.* Defining the seasonality of respiratory syncytial virus around the world: national and subnational surveillance data from 12 countries. *Influenza Other Respir Viruses* 2021; 15:732–741.
18. Deng S, Guo L, Cohen C, *et al.* Impact of subgroup distribution on seasonality of human respiratory syncytial virus: A global systematic analysis. *J Infect Dis* 2023. doi: 10.1093/infdis/jjad192.
- This global systematic analysis enhances the understanding of RSV seasonality by considering the influence of meteorological factors and RSV subgroup distribution. The study concludes that RSV subgroup distribution has a minimal impact on the onset and offset of RSV seasons. The findings suggest that both RSV subgroup distribution and meteorological factors together account for only a small fraction of the variations in RSV seasonality.
19. Shi T, McAllister DA, O'Brien KL, *et al.* Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet* 2017; 390:946–958.
20. Falsey AR, Hennessey PA, Formica MA, *et al.* Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; 352:1749–1759.
21. 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. *J Infect Dis* 2014; 209:1873–1881.
22. Korsten K, Adriaenssens N, Coenen S, *et al.* Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. *Eur Respir J* 2021; 57:2002688.
23. Kurai D, Natori M, Yamada M, *et al.* Occurrence and disease burden of respiratory syncytial virus and other respiratory pathogens in adults aged ≥ 65 years in community: a prospective cohort study in Japan. *Influenza Other Respir Viruses* 2022; 16:298–307.
24. Nicholson KG, Kent J, Hammersley V, *et al.* Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *Br Med J* 1997; 315:1060–1064.
25. Smithgall M, Maykowski P, Zachariah P, *et al.* Epidemiology, clinical features, and resource utilization associated with respiratory syncytial virus in the community and hospital. *Influenza Other Respir Viruses* 2020; 14:247–256.
26. Zuurbier RP, Korsten K, Verheij TJM, *et al.* Performance assessment of a rapid molecular respiratory syncytial virus point-of-care test: a prospective community study in older adults. *J Infect Dis* 2022; 226(Suppl 1):S63–S70.
27. Shi T, Denouel A, Tietjen AK, *et al.* Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. *J Infect Dis* 2020; 222(Suppl 7):S577–S583.
28. Juhn YJ, Wi Cl, Takahashi PY, *et al.* Incidence of respiratory syncytial virus infection in older adults before and during the COVID-19 pandemic. *JAMA Network Open* 2023; 6:e2250634.
- This study provides insights into the incidence and long-term impact of RSV-positive acute respiratory infections (ARI) in older adults, both before and during the COVID-19 pandemic. It reveals a significant decrease in RSV cases during the pandemic, followed by a resurgence in the summer of 2021.
29. Ang L, Mak TM, Cui L, *et al.* Characterisation of respiratory syncytial virus activity in children and adults presenting with acute respiratory illness at primary care clinics in Singapore, 2014–2018. *Influenza Other Respir Viruses* 2020; 14:412–419.
30. 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 Infect Dis* 2018; 5:ofy316; 1–10.
31. Bruyndonckx R, Coenen S, Butler C, *et al.* Respiratory syncytial virus and influenza virus infection in adult primary care patients: Association of age with prevalence, diagnostic features and illness course. *Int J Infect Dis* 2020; 95:384–390.
32. Galli C, Pellegrinelli L, Bubba L, *et al.* When the COVID-19 pandemic surges during influenza season: Lessons learnt from the sentinel laboratory-based surveillance of influenza-like illness in Lombardy during the 2019–2020 season. *Viruses* 2021; 13:695.
33. Meerhoff TJ, Fleming D, Smith A, *et al.* Surveillance recommendations based on an exploratory analysis of respiratory syncytial virus reports derived from the European Influenza Surveillance System. *BMC Infect Dis* 2006; 6:1–7.
34. Pellegrinelli L, Galli C, Bubba L, *et al.* Respiratory syncytial virus in influenza-like illness cases: epidemiology and molecular analyses of four consecutive winter seasons (2014–2015/2017–2018) in Lombardy (northern Italy). *J Med Virol* 2020; 92:2999–3006.
35. Varghese BM, Dent E, Chilver M, *et al.* Epidemiology of viral respiratory infections in Australian working-age adults (20–64 years): 2010–2013. *Epidemiol Infect* 2018; 146:619–626.
36. Zambon MC, Stockton JD, Clewley JP, *et al.* Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001; 358:1410–1416.
37. Jackson ML, Scott E, Kuypers J, *et al.* Epidemiology of respiratory syncytial virus across five influenza seasons among adults and children one year of age and older—Washington State, 2011/2012–2015/2016. *J Infect Dis* 2021; 223:147–156.
38. McClure DL, Kieke BA, Sundaram ME, *et al.* Seasonal incidence of medically attended respiratory syncytial virus infection in a community cohort of adults ≥ 50 years old. *PLoS One* 2014; 9:e102586.
39. Savic M, Penders Y, Shi T, *et al.* Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: A systematic literature review and meta-analysis. *Influenza Other Respir Viruses* 2018; 17:e13031; 1–10.

40. Osei-Yeboah R, Spreeuwenberg P, Del Riccio M, *et al.* Estimation of the number of RSV-associated hospitalisations in adults in the European Union. *J Infect Dis* 2023; 228:1539–1548.
- This study offers a comprehensive assessment of the RSV-associated hospitalization burden among adults in the Europe, revealing significant annual hospitalization rates, particularly in older adults aged 65 and above. The findings challenge the traditional perception of RSV as primarily a pediatric disease, showing that the hospitalization rates in adults are comparable to those in young children.
41. Moyes J, Walaza S, Pretorius M, *et al.* Respiratory syncytial virus in adults with severe acute respiratory illness in a high HIV prevalence setting. *J Infect* 2017; 75:346–355.
42. Falsey AR, Walsh EE, Esser MT, *et al.* Respiratory syncytial virus-associated illness in adults with advanced chronic obstructive pulmonary disease and/or congestive heart failure. *J Med Virol* 2019; 91:65–71.
43. Tseng HF, Sy LS, Ackerson B, *et al.* Severe morbidity and short- and mid- to long-term mortality in older adults hospitalized with respiratory syncytial virus infection. *J Infect Dis* 2020; 222:1298–1310.
44. Talbot HK, Falsey AR. The diagnosis of viral respiratory disease in older adults. *Clin Infect Dis* 2010; 50:747–751.
45. Fleming DM, Taylor RJ, Lustig RL, *et al.* Modelling estimates of the burden of respiratory syncytial virus infection in adults and the elderly in the United Kingdom. *BMC Infect Dis* 2015; 15:443.
46. Hansen CL, Chaves SS, Demont C, *et al.* Mortality associated with influenza and respiratory syncytial virus in the US, 1999–2018. *JAMA Network Open* 2022; 5:e220527.
47. Mao Z, Li X, Korsten K, *et al.* Economic burden and health-related quality of life of respiratory syncytial virus and influenza infection in european community-dwelling older adults. *J Infect Dis* 2022; 226(Suppl 1):S87–S94.
- This study is pivotal in contextualizing the economic and quality of life impacts of RSV in older adults, especially when compared to influenza. By assessing healthcare costs and changes in health-related quality of life in older adults with RSV versus influenza, the research underscores RSV's significant but often overlooked burden.
48. Choi Y, Hill-Ricciuti A, Branche AR, *et al.* Cost determinants among adults hospitalized with respiratory syncytial virus in the United States. *Influenza Other Respir Viruses* 2022; 16:151–158.
49. Ackerson B, An J, Sy LS, *et al.* Cost of hospitalization associated with respiratory syncytial virus infection versus influenza infection in hospitalized older adults. *J Infect Dis* 2020; 222:962–966.
50. Pastula ST, Hackett J, Coalson J, *et al.* Hospitalizations for respiratory syncytial virus among adults in the United States, 1997–2012. *Open Forum Infect Dis* 2017; 4:ofw270.
51. Chen L, Han X, Li Y, *et al.* Comparison of clinical characteristics and outcomes between respiratory syncytial virus and influenza-related pneumonia in China from 2013 to 2019. *Eur J Clin Microbiol Infect Dis* 2021; 40:1633–1643.
52. Prasad N, Newbern EC, Trenholme AA, *et al.* The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. *PLoS One* 2020; 15:e0234235.
53. Yoon JG, Noh JY, Choi WS, *et al.* Clinical characteristics and disease burden of respiratory syncytial virus infection among hospitalized adults. *Sci Rep* 2020; 10:12106.
54. Rafferty E, Paulden M, Buchan SA, *et al.* Evaluating the individual healthcare costs and burden of disease associated with RSV across age groups. *Pharmacoeconomics* 2022; 40:633–645.
55. Melgar M, Britton A, Roper LE, *et al.* Use of respiratory syncytial virus vaccines in older adults: recommendations of the advisory committee on immunization practices – United States, 2023. *MMWR Morbid Mortal Weekly Rep* 2023; 72:793–801.
- The United States Food and Drug Administration's approval of the first RSV vaccines for older adults, as detailed in this report, signifies an innovational advancement in public health. The US Centres for Disease Control and Prevention Advisory Committee on Immunization Practices's decision, based on rigorous review of the vaccines' safety and effectiveness, paves the way for a major step in combating RSV-associated respiratory diseases in older adults.
56. Moderna Inc. Moderna announces global regulatory submissions for its respiratory syncytial virus (RSV) vaccine, MRNA-1345. *ACCESSWIRE News Room*. 2023.
57. Widmer K, Zhu Y, Williams JV, *et al.* Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis* 2012; 206:56–62.
58. Widmer K, Griffin MR, Zhu Y, *et al.* Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. *Influenza Other Respir Viruses* 2014; 8:347–352.