



Respiratory syncytial virus vaccination in older adults and patients with chronic disorders: A position paper from the Portuguese Society of Pulmonology, the Portuguese Association of General and Family Medicine, the Portuguese Society of Cardiology, the Portuguese Society of Infectious Diseases and Clinical Microbiology, the Portuguese Society of Endocrinology, Diabetes and Metabolism, and the Portuguese Society of Internal Medicine

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Respiratory syncytial virus vaccination in older adults and patients with chronic disorders: A position paper from the Portuguese Society of Pulmonology, the Portuguese Association of General and Family Medicine, the Portuguese Society of Cardiology, the Portuguese Society of Infectious Diseases and Clinical Microbiology, the Portuguese Society of Endocrinology, Diabetes and Metabolism, and the Portuguese Society of Internal Medicine

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ABSTRACT

Background: Respiratory syncytial virus (RSV) is an important cause of lower respiratory tract infection, hospitalisation and death in adults.

Methods: Based on evidence regarding the impact of RSV on adult populations at risk for severe infection and the efficacy and safety of RSV vaccines, the Portuguese Society of Pulmonology, the Portuguese Association of General and Family Medicine, the Portuguese Society of Cardiology, the Portuguese Society of Infectious Diseases and Clinical Microbiology, the Portuguese Society of Endocrinology, Diabetes and Metabolism, and the Portuguese Society of Internal Medicine endorses this position paper with recommendations to prevent RSV-associated disease and its complications in adults through vaccination.

Conclusion: The RSV vaccine is recommended for people aged ≥ 50 years with risk factors (chronic obstructive pulmonary disease, asthma, heart failure, coronary artery disease, diabetes, chronic kidney disease, chronic liver disease, immunocompromise, frailty, dementia, and residence in a nursing home) and all persons aged ≥ 60 years. If it cannot be made available to this population, then the vaccine should be prioritised for individuals aged ≥ 75 years and those aged ≥ 50 years with risk factors. The vaccine should preferably be given between September and November and can be co-administered with the influenza vaccine. Ongoing studies on RSV vaccines may justify extending these recommendations in the future.

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Introduction

Respiratory syncytial virus (RSV) is a single-stranded RNA virus that belongs to the *Pneumoviridae* family.¹ Its genome encompasses 10 genes that encode the following 11 proteins: attachment protein (G), fusion protein (F), small hydrophobic protein (SH), nucleocapsid protein (N), phosphoprotein (P), polymerase protein (L), M2-1 and M2-2 cofactor proteins, matrix protein (M), and non-structural proteins 1 and 2 (NS1 and NS2). Respiratory syncytial virus is classified into the RSV-A and RSV-B subtypes according to variations in the G protein, and a pattern of alternative predominance has been observed between them.^{1,2} Although some studies report that RSV-A infection results in more severe outcomes, the clinical significance between the RSV subtypes remains controversial.³

Respiratory syncytial virus is known for its ability to induce the fusion of respiratory epithelial cells into multinucleated giant cells (syncytia).¹ The clinical manifestations of RSV infection vary from asymptomatic cases to acute pneumonia and severe life-threatening respiratory distress, with exacerbations of underlying chronic conditions.⁴ Because of viral immunomodulatory mechanisms, the immune response against RSV is short-lived, with protective antibodies and T cells waning within weeks or months, rendering reinfections common, even in the absence of antigenic variation.^{1,5} Severe RSV disease has been associated with inappropriate or dysregulated host responses.^{1,5}

The paradigm of RSV-associated disease as a potentially serious condition only in very young children has changed, with RSV being increasingly recognised as a highly relevant pathogen in older people, mainly due to the routine use of molecular diagnostic tests in clinical practice.⁵⁻⁷ Moreover, RSV disease in older adults can now be prevented with vaccines. In a context where no specific treatments are available, physicians should be aware of the importance of RSV infection prevention in this population and in patients with chronic conditions.

Peers from the Portuguese Society of Pulmonology (SPP), the Portuguese Association of General and Family Medicine (APMGF), the Portuguese Society of Cardiology (SPC), the Portuguese Society of Infectious Diseases and Clinical Microbiology (SPDIMC), the Portuguese Society of Endocrinology, Diabetes and Metabolism (SPEDM), and the Portuguese Society of Internal Medicine (SPMI) gathered with the aim of discussing the relevance of RSV vaccination in adults and elaborating recommendations for the prevention of RSV-associated disease and its complications in this population through vaccination. This resulting joint position paper first reviews the current evidence regarding the impact of RSV on adult populations at risk and the efficacy and safety of available vaccines and then proposes recommendations for RSV vaccination in older people and adults with chronic disorders.

Methods

In July 2024, a narrative non-systematic literature search of the MEDLINE/PubMed database was conducted between 2014 and 2024 using the following search terms in the title field: ('respiratory syncytial virus' OR RSV) AND (hospitalisations OR exacerbations OR death OR morbidity OR mortality OR burden OR epidemiology) OR ('respiratory diseases' OR 'pulmonary diseases' OR 'chronic obstructive pulmonary disease' OR COPD OR asthma) OR ('cardiovascular diseases' OR CVD) OR diabetes OR ('chronic kidney disease' OR CKD OR 'end-stage renal disease' OR ESRD) OR ('chronic liver disease' OR CLD) OR (immunodepressed OR immunosuppressed OR immunocompromised) OR (elderly OR 'older adults' OR 'older people' OR geriatrics) OR (vaccination OR vaccine). Only English- or Portuguese-language publications whose full text was available were considered. The authors also proposed other publications throughout the preparation of the present document that were added to the final references, namely, international guidelines and recommendations.

The expert panel was composed of three pulmonologists, two primary care specialists, two cardiologists, two infectious disease specialists, one endocrinologist, and two internal medicine specialists with expertise in geriatrics and respiratory diseases. This panel analysed and selected the articles of each area for their relevance to set a joint position statement on RSV vaccination, with a special focus on more recent publications. The panel members were selected and invited by the president of each scientific society based on their knowledge and expertise in this field. The recommendations were issued after an online meeting, where the experts reviewed the evidence regarding the impact of RSV on adult populations at risk for severe infection and the efficacy and safety of RSV vaccines.

What is the impact of RSV worldwide and in Portugal?

According to recently published data from the Global Burden of Disease Study, RSV infection accounted for 4.59 million cases of lower respiratory tract infection (LRTI) worldwide across all ages in 2021; in 2019, before the COVID-19 pandemic, the number of estimated cases of RSV-associated LRTI was 12.5 million.⁸ In Europe, approximately 3 million cases of RSV-associated acute respiratory infection (ARI) were estimated among adults aged ≥ 60 years in 2019, accounting for 273,753 hospitalisations and 19 527 in-hospital deaths.⁹ In the United States (US), the Centers for Disease Control and Prevention (CDC) estimates the number of annual hospitalisations and deaths due to RSV in adults aged ≥ 65 years to be 60 000–160,000 and 6,000–10,000, respectively.¹⁰

In Portugal, the RSV season typically starts in December, with a median epidemic duration of 10 to 11 weeks, although it can extend from October/November to April/May.^{11,12} An extrapolation from the RSV Consortium in Europe (RESCEU) estimates 3,095 annual RSV-associated hospitalisations in people aged ≥ 65 years in Portugal, accounting for 92.5% of all adult RSV-associated hospital admissions.¹³

Preliminary results from the European Mortality Monitoring Network (EuroMOMO) show that the excess mortality in Europe during weeks 48/2023 to 6/2024 coincided with peaks of COVID-19, influenza and RSV.¹⁴ Notably, RSV seems to compete with influenza as a cause of hospitalisation and death.⁶ A French retrospective study over seven epidemic seasons revealed that, in patients aged ≥ 75 years, RSV had a mortality rate comparable to that of influenza and was associated with higher rates of consolidative pneumonia, hospitalisation, intensive care unit (ICU) admissions, and extended hospital stays.¹⁵ Furthermore, a cohort study in the US compared the severity of RSV disease with that of COVID-19 and influenza, according to the COVID-19 and influenza vaccination status, among hospitalised adults aged ≥ 18 years and before the first RSV vaccine was recommended by the CDC. Respiratory syncytial virus-associated disease was similar in severity compared with COVID-19 (adjusted odds ratio [aOR] = 0.82; $p = 0.22$) and influenza (aOR = 1.20; $p = 0.35$) in unvaccinated patients and more severe than COVID-19 (aOR = 1.38; $p = 0.03$) and influenza (aOR = 2.81; $p < 0.001$) in vaccinated patients, for the composite of invasive mechanical ventilation (IMV) and in-hospital death.¹⁶

Increasing evidence demonstrates the burden of RSV in adults worldwide, including in Portugal.

What is the impact of RSV on populations at risk?

What is the impact of RSV on chronic respiratory/pulmonary disease?

Patients with chronic obstructive pulmonary disease (COPD) or asthma are at increased risk of hospitalisation due to RSV infection compared with those without these conditions. A prospective study conducted in the US revealed that RSV hospitalisation rates were 3.2 to 13.4 times higher in adults with COPD and 2.0 to 3.6 times higher in adults with asthma than in those without these conditions.¹⁷ An extension of two surveillance studies in New Zealand also demonstrated that adults with COPD had RSV hospitalisation rates that were 10 times greater than those without COPD, whereas adults with asthma exhibited hospitalisation rates that were 7 to 8 times greater than those without asthma.¹⁸ In a retrospective study, in adults hospitalised with RSV infection, the prevalence of underlying COPD, chronic bronchitis, or emphysema was 29.8%, and the prevalence of underlying asthma was 26.0%.¹⁹ Chronic obstructive pulmonary disease has been identified as a significant predictor of hospitalisation in RSV-infected adults (odds ratio [OR] = 2.12; $p < 0.001$).²⁰

Furthermore, the role of RSV in COPD and asthma exacerbation is gradually becoming more evident. In a cohort of individuals aged ≥ 60 years hospitalised with RSV infection, 80.4% of patients with COPD, chronic bronchitis, or emphysema and 49.5% of patients with asthma experienced disease exacerbation during hospitalisation.²¹ In a prospective epidemiological study in adults aged ≥ 18 years hospitalised with ARI, 33.3% of patients with RSV presented an acute exacerbation of COPD or asthma compared with 24.4% of patients with influenza (unspecified vaccination status).²² In line with these observations, a retrospective study reported that exacerbations of COPD, chronic bronchitis, emphysema, or asthma were more common in older adults hospitalised with RSV than in those with influenza infection, most of whom were vaccinated against influenza (COPD/chronic bronchitis/emphysema exacerbations: OR = 1.7; $p = 0.001$; asthma exacerbations: OR = 1.5; $p = 0.006$).¹⁹ Lee et al. reported that lower respiratory complications were diagnosed in

71.9% of adults aged ≥ 18 years who were hospitalised for RSV infection (pneumonia: 42.3%; acute bronchitis: 21.9%; COPD/asthma exacerbation: 27.3%). Pneumonia and COPD exacerbation were the direct causes of death in 66.7% and 6.9%, respectively, of the patients with RSV who died within 60 days of admission.²³

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recognise RSV vaccination as an effective preventive measure in patients with COPD.²⁴ Similarly, the Global Initiative for Asthma (GINA) encourages adults with asthma to follow their local immunisation schedule, which includes RSV vaccination.²⁵

Adults with COPD or asthma are at increased risk of RSV-associated hospitalization compared with those without these conditions.

Respiratory syncytial virus infection can lead to COPD and asthma exacerbation.

What is the impact of RSV on cardiovascular disease?

The relationship between RSV infection and cardiovascular disease is bidirectional: patients with cardiovascular comorbidities have a higher risk of severe RSV infection, whereas RSV-infected patients are more prone to cardiovascular complications.²⁶ A prospective study in the US revealed that adults with heart failure (HF) exhibited RSV hospitalisation rates 4.0 to 33.2 times higher than those without HF, whereas adults with coronary artery disease (CAD) presented RSV hospitalisation rates 3.7 to 7.0 times greater than those of individuals without CAD.¹⁷ In agreement with these findings, an extension of two surveillance studies in New Zealand reported an increased risk of RSV hospitalisation in adults with HF (5 to 36 times higher) or CAD (3 to 11 times higher) vs. those without the corresponding condition; in this study, no increased risk was observed for adults with a history of stroke.¹⁸ In a retrospective study, 35.3% and 32.2% of adults hospitalised with RSV infection had underlying HF and ischaemic heart disease, respectively.¹⁹ Among patients who presented to the emergency department of a single Italian centre during the 2022–2023 fall/winter season, those with RSV infection had a higher prevalence of HF than those with an influenza A infection ($p = 0.001$); HF was a predictor of RSV infection ($OR = 3.286$; $p = 0.041$).²⁷ Moreover, a real-world analysis of US Medicare beneficiaries with RSV infection identified comorbid HF ($OR = 2.06$; $p < 0.001$) and stroke ($OR = 2.0$; $p = 0.045$) as significant predictors of hospitalisation.²⁰ However, we must highlight that age is a risk factor for both RSV infection and HF.

The cardiac complications of RSV infection have also been revealed. In a cross-sectional study of 6,248 adults aged ≥ 50 years who were hospitalised with RSV infection over five seasons, the weighted estimated prevalence of having a cardiac event was 22.4% (acute HF: 15.8%; acute ischaemic heart disease: 7.5%; hypertensive crisis: 1.3%; ventricular tachycardia: 1.1%; and cardiogenic shock: 0.6%). Acute cardiac events occurred in 33.0% of patients with vs. 8.5% of patients without underlying cardiovascular disease (adjusted risk ratio [aRR] = 3.51; 95% confidence interval [CI]: 2.85, 4.32). Notably, patients who experienced an acute cardiac event had nearly twice the risk of severe outcomes compared with those who did not (ICU admission: 25.8% vs. 16.5%; aRR = 1.54; 95% CI: 1.23, 1.93; in-hospital death: 8.1% vs. 4.0%; aRR = 1.77; 95% CI: 1.36, 2.31).²⁸ In another study, cardiovascular complications (HF exacerbation, atrial fibrillation, acute coronary events, or acute cerebrovascular events) were diagnosed in 14.3% of adults aged ≥ 18 years who were hospitalised for RSV infection; acute cardiovascular events were the direct cause of death in 16.7% of patients with RSV who died within 60 days of admission.²³ The specific incidence of each complication is not known.²³ In addition, Tseng et al. reported that 38.2% of older adults with HF experienced disease exacerbation during RSV-associated hospitalisation; exacerbation of HF during hospitalisation was independently associated with increased mid- to long-term mortality (adjusted hazard ratio [aHR] = 1.86; 95% CI: 1.11, 3.13), whereas atrial fibrillation during hospitalisation was independently associated with increased short-term mortality (aHR = 1.66; 95% CI: 1.01, 2.71).²¹

Adults with underlying cardiovascular disease, especially HF and CAD, are at increased risk of RSV-associated hospitalization and complications compared with those without these conditions.

Cardiovascular complications, including HF exacerbation and coronary events, can occur in adults hospitalized for RSV infection and are associated with an increased risk of a fatal outcome.

What is the impact of RSV on diabetes?

In 2021, diabetes was the tenth leading cause of death worldwide, accounting for 19.6 deaths per 100,000 individuals and 78.9 million disability-adjusted life-years (DALYs).^{29,30} In Portugal, in the same year, the prevalence of diabetes was 14.1% in adults aged 20–79 years and 27.1% in those aged 60–79 years.³¹

In a prospective study conducted in the US over three RSV seasons, adults with diabetes presented RSV hospitalisation rates 2.4 to 11.4 times greater than those without this medical condition. The magnitude of increased risk was more pronounced for younger patients (an 11-fold increase for those aged 18–49 years, 3- to 4-fold increase for those aged 50–64 years, and 2- to 6-fold increase for those aged ≥65 years).¹⁷ An extension of two surveillance studies in New Zealand also indicated an increased risk of RSV hospitalisation in adults with diabetes (1.2 to 5.6 times higher) compared with those without diabetes.¹⁸ Furthermore, several studies have reported a prevalence of diabetes ranging from 38.6% to 41.1% in adults hospitalised with RSV infection.^{19–21}

The American Diabetes Association (ADA) recommends RSV vaccination in patients with diabetes aged ≥60 years.³²

Adults with diabetes are at increased risk of RSV-associated hospitalization compared with those without this condition.

What is the impact of RSV on chronic kidney disease?

Chronic kidney disease (CKD) has been reported in 28% of adults aged ≥18 years who were hospitalised with RSV infection.¹⁷ Moreover, a real-world analysis of US Medicare beneficiaries with RSV infection identified CKD as a significant predictor of hospitalisation (OR = 4.37; $p < 0.001$); among high-risk patients hospitalised with RSV (namely, those with chronic lung disease, prior pneumonia, HF, or who were immunocompromised on or within 180 days before the date of RSV diagnosis), CKD was one of the most prevalent comorbid conditions (31%).²⁰ Notably, in a Finnish retrospective cohort study, CKD seemed to be an independent risk factor for death among RSV-infected adult patients.³³

End-stage renal disease (ESRD), in particular, has been found in approximately 6% of older adults hospitalised with RSV infection.^{19,21} Prasad et al. showed that adults aged 50–64 years with ESRD exhibited RSV hospitalisation rates 6.6 times higher than those without this medical condition in the same age group.¹⁸ End-stage renal disease was associated with increased mid- to long-term mortality (aHR = 2.13; 95% CI: 1.08, 4.17) in older adults hospitalised with RSV infection.²¹

Adults with CKD are at increased risk of RSV-associated hospitalization and death compared with those without CKD.

What is the impact of RSV on chronic liver disease?

Studies involving RSV-infected patients with underlying liver disease are scarce. Current evidence indicates that chronic liver disease (CLD) might be present in up to 6% of adults hospitalised for RSV infection.^{17,21}

Adults with CLD might be at increased risk of RSV-associated hospitalization compared with those without this condition.

What is the impact of RSV on immunocompromised patients?

Respiratory syncytial virus infection has been associated with substantial morbidity and mortality in immunocompromised patients. In a prospective cohort study, Kim et al. compared the characteristics and outcomes of severe RSV-associated pneumonia and severe influenza-associated pneumonia in adults who were admitted to the ICU at a single centre from 2010 to 2019. Immunocompromise was significantly more common in the RSV group (57.6% vs. 34.4%; $p < 0.001$), in which 32.6% of patients received immunosuppressants (including corticosteroids), 30.4% received chemotherapy for underlying malignancy, 4.4%

received solid organ transplantation (SOT), and 9.8% received haematopoietic stem cell transplantation (HSCT). Among the immunocompromised patients, the 90-day mortality was high in both the RSV and influenza groups (52.8% vs. 61.0%; $p = 0.25$).³⁴ Other studies reported RSV hospitalisation rates of 1,288 to 1,562 per 100,000 immunosuppressed individuals and ICU admissions of 36% in immunocompromised patients hospitalised with RSV.^{35,36}

The considerable burden of RSV infection in adult HSCT recipients is well established: progression from upper respiratory tract infection (URTI) to LRTI occurs in 40 to 60% of patients, with mortality rates of up to 80%.³⁷ Lung transplant recipients also bear a high RSV-related burden, including hospitalisation, ICU admission, death from LRTI, and long-term complications.^{38,39} Several studies that focus on the outcomes of RSV infection in other subgroups of immunocompromised individuals have also been published. Chatzis et al. observed that RSV-infected adults with solid tumours (OR = 5.2; $p = 0.015$) or those receiving chronic immunosuppressive treatments mainly for rheumatologic conditions (OR = 4.1; $p = 0.034$) were significantly more likely to be hospitalised than HSCT recipients were.⁴⁰ Hematological malignancies were also identified as predictors of hospitalisation in RSV-infected adults (OR = 5.17; $p < 0.001$).²⁰ Furthermore, having lymphoma within 12 months prior to hospitalisation due to RSV infection was associated with increased short-term mortality (aHR = 3.87; 95% CI: 1.32, 11.30) and mid- to long-term mortality (aHR = 3.57; 95% CI: 1.20, 10.60) in older adults.²¹ Indeed, the American Society of Clinical Oncology (ASCO) recommends RSV vaccination in patients with cancer aged ≥ 60 years.⁴¹

Notably, HIV-infected individuals with RSV also appear to be at increased risk of hospitalisation compared with HIV-uninfected individuals (in 2010, aRR = 18; 95% CI: 13, 24; in 2011, aRR = 12; 95% CI: 8, 16; in 2012, aRR = 14; 95% CI: 11, 19).⁴² In this study, among HIV-infected patients who were admitted with RSV-associated severe ARI, 64% and 36% presented CD4⁺ T-cell counts < 200 cells/mm³ and > 200 cells/mm³, respectively; whether these patients were receiving antiretroviral treatment is unknown.⁴² These findings might be particularly important, since HIV-infected patients often exhibit immunosuppression, older age and other comorbidities (e.g., hypertension, diabetes, and cancer), which are even more relevant in the context of the underlying chronic inflammatory state.⁴³

Immunocompromised adults, especially HSCT and lung transplant recipients, are at increased risk of RSV-associated hospitalization and death compared with those without immunosuppression.

Respiratory syncytial virus can also cause severe disease in other immunocompromised patients, namely, those with solid tumors or hematological malignancies, those receiving chronic immunosuppressive therapy, and those who are HIV-positive.

What is the impact of RSV on older adults?

Immunosenescence is a recognised risk factor for RSV infection and severe disease, with a high burden of comorbidities further increasing the susceptibility of older people to this virus.^{4,13} In Portugal, the RESCEU estimates that the rate of RSV-associated hospitalisations is 210 per 100,000 adults among people aged 75–84 years and 343 per 100,000 adults among people aged ≥ 85 years, with 76.3% of all adult RSV-associated hospital admissions occurring in these age groups.¹³

A prospective study conducted in the US showed that the annual incidence rates of RSV infection in hospitalised adults were 7.7 to 11.9 per 100,000 individuals, 33.5 to 57.5 per 100,000 individuals, and 136.9 to 255.6 per 100,000 individuals aged 18–49, 50–64, and ≥ 65 years, respectively.¹⁷ In another study, during 12 consecutive seasons, serious clinical outcomes were reported in 19% of RSV-infected adults aged ≥ 60 years, and the risk of a serious outcome (hospital admission, emergency department visit, or pneumonia) due to RSV infection was significantly greater in people aged ≥ 75 years than in those aged 60–64 years (relative risk [RR] = 3.64; 95% CI: 1.33, 9.95).⁴⁴ Notably, a retrospective study in three New York City hospitals revealed that patients living in a residential facility at admission had a 4.43-fold greater likelihood of severe RSV infection than did those living in the community.⁴⁵

The worse prognosis of RSV infection in older people, particularly those aged ≥ 75 years, is further documented by extensive evidence. A real-world analysis of US Medicare beneficiaries with RSV infection

identified older age as a significant predictor of hospitalisation (OR = 1.73; $p = 0.008$ for 75 to 84 years; OR = 2.53; $p < 0.001$ for ≥ 85 years).²⁰ In hospitalised adults with RSV infection, advanced age (>75 years) was associated with a longer duration of hospitalisation (aHR = 0.74; $p = 0.001$) and poorer survival at 30 days (aHR = 2.85; $p = 0.003$) and 60 days post-admission (aHR = 2.10; $p = 0.011$).²³ Tseng et al. described mortality rates during hospitalisation of 4.6% in people aged 60 to 74 years and 6.1% in people aged ≥ 75 years; the variables independently associated with increased mid- to long-term mortality included age between 75 and 84 years (aHR = 5.37; 95% CI: 1.32, 22.90), age ≥ 85 years (aHR = 5.12; 95% CI: 1.17, 22.40), and dementia (aHR = 1.86; 95% CI: 1.08, 3.19).²¹ Interestingly, a systematic review and meta-analysis including 16 observational studies and 762,084 older participants demonstrated that the incidences of hospitalisation and mortality were similar for RSV and influenza in this population.⁴⁶

Other outcomes of RSV infection, in addition to hospitalisation and death, have been investigated in older people, namely, changes in functional status and the impact of frailty in terms of morbidity and mortality. Branche et al. reported an acute functional decline in adults aged ≥ 60 years hospitalised with RSV, with prolonged loss of function in some patients. Moreover, the authors suggested that frailty, assessed by the pre-hospitalisation living situation, may be a predictor of long-term morbidity and mortality, given that the 6-month Lawton – Brody Instrumental Activities of Daily Living (IADL) scores declined by 66% for those admitted from a skilled nursing facility.⁴⁷

Older people, particularly those aged ≥ 75 years, are at increased risk of RSV-associated hospitalization and death compared with younger individuals, and they account for a large proportion of all adult hospital admissions for RSV.

Respiratory syncytial virus infection might negatively impact the functional status of older adults, potentially increasing their overall burden and indirect costs. This should be taken into account in the overall assessment of these patients at all levels of care and acted upon accordingly.

What RSV vaccines are available, and how effective and safe are they?

What RSV vaccines are available in Portugal?

Currently, two RSV vaccines are available in Portugal (Table 1): the vaccine containing the recombinant RSV pre-fusion F protein adjuvanted with AS01_E (RSVPreF3)⁴⁸ and the vaccine containing the recombinant bivalent RSV-A and RSV-B pre-fusion F protein (RSVpreF).⁴⁹ RSVPreF3 is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults aged ≥ 60 years and in adults aged 50–59 years at increased risk for RSV disease.⁴⁸ RSVpreF is indicated for active immunisation for the prevention of LRTD caused by RSV in adults aged ≥ 60 years and for passive protection against LRTD caused by RSV in infants from birth through six months of age following maternal immunisation during pregnancy.⁴⁹ Both vaccines are administered in a single dose via intramuscular injection.^{48,49} At present, none of the RSV vaccines are included in the National Vaccination Program.⁵⁰

A third RSV vaccine has been approved in Europe, although it is not available in Portugal.⁵¹ This vaccine contains a single-stranded 5' capped mRNA that encodes the RSV glycoprotein F, which is stabilised in the prefusion conformation.⁵¹ It is indicated for active immunisation for the prevention of LRTD caused by RSV in adults aged ≥ 60 years, and it is administered in a single dose via intramuscular injection.⁵¹

How effective are RSV vaccines?

Adults ≥ 60 years old

The efficacy of the RSVPreF3 vaccine against RSV-associated LRTD in adults aged ≥ 60 years was evaluated in the AReSVi-006 study, a phase III, randomised, placebo-controlled trial.^{48,52} Respiratory syncytial virus-associated LRTD, confirmed by reverse transcriptase-polymerase chain reaction (RT–PCR), was defined as follows: the participant had experienced at least two lower respiratory symptoms or signs, including at least one lower respiratory sign for at least 24 hours or had experienced at least three lower respiratory symptoms for at least 24 hours.^{48,52} During the first RSV season, RSVPreF3 showed an efficacy of 82.6% (96.95% CI: 57.9,

Table 1. Respiratory syncytial virus vaccines available in Portugal.

	RSVPreF3	RSVpreF
Type	Recombinant RSV pre-fusion F protein adjuvanted with AS01 _E ⁴⁸	Recombinant bivalent RSV-A and RSV-B pre-fusion F protein ⁴⁹
Indication	Active immunisation for the prevention of LRTD caused by RSV in adults aged ≥60 years and in adults aged 50–59 years at increased risk for RSV disease ⁴⁸ 1/7/2025 2:46:00 PM	Active immunisation for the prevention of LRTD caused by RSV in adults aged ≥60 years, and passive protection against LRTD caused by RSV in infants from birth through 6 months of age following maternal immunisation during pregnancy ⁴⁹
Posology and administration	Single dose, intramuscular injection ⁴⁸	Single dose, intramuscular injection ⁴⁹
Season 1 efficacy in adults ≥60 years old (%) [*]	RSV-associated LRTD [†] : 82.6 (96.95% CI: 57.9, 94.1) ^{48,52} Severe RSV-associated LRTD: 94.1 (95% CI: 62.4, 99.9) ^{48,52} RSV-associated LRTD [†] in participants with ≥ 1 pre-existing comorbidity of interest [‡] : 94.6 (96.95% CI: 65.9, 99.9) ^{48,59} RSV-associated LRTD [†] in participants aged 60–69 years: 81.0 (95% CI: 43.6, 95.3) ^{48,52} RSV-associated LRTD [†] in participants aged 70–79 years: 93.8 (95% CI: 60.2, 99.9) ^{48,52} RSV-associated LRTD [†] in participants aged ≥80 years: 33.8 (95% CI: –477.7, 94.5) ⁵² 1/7/2025 2:46:00 PM	RSV-associated LRTD [§] : With ≥2 symptoms: 65.1 (95% CI: 35.9, 82.0) ⁴⁹ With ≥3 symptoms: 88.9 (95% CI: 53.6, 98.7) ⁴⁹ RSV-associated LRTD [§] in participants with ≥ 1 high-risk condition [¶] : With ≥2 symptoms: 62.5 (96.66% CI: –8.4, 89.1) ⁵⁶ With ≥3 symptoms: 75.0 (96.66% CI: –39.1, 97.9) ⁵⁶ RSV-associated LRTD [§] in participants aged 60–69 years: With ≥2 symptoms: 57.9 (96.66% CI: –7.4, 85.3) ⁵⁶ With ≥3 symptoms: 77.8 (96.66% CI: –18.7, 98.1) ⁵⁶ RSV-associated LRTD [§] in participants aged 70–79 years: With ≥2 symptoms: 77.8 (96.66% CI: –18.7, 98.1) ⁵⁶ With ≥3 symptoms: 100.0 (96.66% CI: –573.8, 100.0) ⁵⁶ RSV-associated LRTD [§] in participants aged ≥80 years: With ≥2 symptoms: 80.0 (96.66% CI: –104.3, 99.7) ⁵⁶ With ≥3 symptoms: 100.0 (96.66% CI: –191.2, 100.0) ⁵⁶ RSV-associated LRTD [§] : With ≥2 symptoms: 55.7 (95% CI: 34.7, 70.4) ⁵⁷ With ≥3 symptoms: 77.8 (95% CI: 51.4, 91.1) ⁵⁷ RSV-associated LRTD [§] in participants with ≥ 1 high-risk condition [¶] : With ≥2 symptoms: 42.9 (95% CI: 7.3, 65.4) ⁵⁷ With ≥3 symptoms: 69.6 (95% CI: 26.7, 89.0) ⁵⁷ RSV-associated LRTD [§] in participants aged 60–69 years: With ≥2 symptoms: 56.4 (95% CI: 28.3, 74.2) ⁵⁷ With ≥3 symptoms: 81.5 (95% CI: 51.2, 94.4) ⁵⁷ RSV-associated LRTD [§] in participants aged 70–79 years: With ≥2 symptoms: 60.7 (95% CI: 18.6, 82.4) ⁵⁷ With ≥3 symptoms: 57.1 (95% CI: –87.7, 92.8) ⁵⁷ RSV-associated LRTD [§] in participants aged ≥80 years: With ≥2 symptoms: 20.0 (95% CI: –271.7, 84.1) ⁵⁷ With ≥3 symptoms: 100 (95% CI: –432.5, 100) ⁵⁷
Season 2 efficacy in adults ≥60 years old (%) [*]	RSV-associated LRTD [†] : 56.1 (95% CI: 28.2, 74.4) ⁵³ Severe RSV-associated LRTD: 64.2 (95% CI: 6.2, 89.2) ⁵³ RSV-associated LRTD [†] in participants with ≥ 1 pre-existing comorbidity of interest [‡] : 51.5 (95% CI: 7.4, 76.6) ⁵³ RSV-associated LRTD [†] in participants aged 60–69 years: 50.9 (95% CI: 6.1, 76.3) ⁵³ RSV-associated LRTD [†] in participants aged 70–79 years: 66.2 (95% CI: 18.9, 88.3) ⁵³ RSV-associated LRTD [†] in participants aged ≥80 years: 41.0 (95% CI: –209.9, 94.0) ⁵³	ND
Season 3 efficacy in adults ≥60 years old (%)	RSV-associated LRTD [†] : 48.0 (95% CI: 8.7, 72.0) ^{54,55} Severe RSV-associated LRTD: 43.3 (95% CI: –45.3, 81.3) ^{54,55} RSV-associated LRTD [†] in participants with ≥ 1 pre-existing comorbidity of interest [‡] : 57.8 (95% CI: 8.0, 83.0) ⁵⁵	ND

(Continued)

Table 1. (Continued).

	RSVPreF3	RSVpreF
Cumulative efficacy over 2 seasons in adults ≥ 60 years old (%) [*]	RSV-associated LRTD [†] : 67.2 (97.5% CI: 48.2, 80.0) ^{48,53} Severe RSV-associated LRTD: 78.8 (95% CI: 52.6, 92.0) ⁵³ RSV-associated LRTD [†] in participants with ≥ 1 pre-existing comorbidity of interest [‡] : 66.7 (95% CI: 41.8, 82.0) ⁵³ RSV-associated LRTD [†] in participants aged 60–69 years: 65.4 (95% CI: 40.4, 80.9) ⁵³ RSV-associated LRTD [†] in participants aged 70–79 years: 74.9 (95% CI: 48.4, 89.2) ⁵³ RSV-associated LRTD [†] in participants aged ≥ 80 years: 38.4 (95% CI: –118.2, 86.1) ⁵³	RSV-associated LRTD [§] : With ≥ 2 symptoms: 58.8 (95% CI: 43.0, 70.6) ⁵⁷ With ≥ 3 symptoms: 81.5 (95% CI: 63.3, 91.6) ⁵⁷ RSV-associated LRTD [§] in participants with ≥ 1 high-risk condition [¶] : With ≥ 2 symptoms: 49.3 (95% CI: 23.2, 67.0) ⁵⁷ With ≥ 3 symptoms: 73.5 (95% CI: 43.6, 88.8) ⁵⁷ RSV-associated LRTD [§] in participants aged 60–69 years: With ≥ 2 symptoms: 57.5 (95% CI: 35.8, 72.4) ⁵⁷ With ≥ 3 symptoms: 81.6 (95% CI: 58.2, 93.1) ⁵⁷ RSV-associated LRTD [§] in participants aged 70–79 years: With ≥ 2 symptoms: 62.5 (95% CI: 30.6, 80.8) ⁵⁷ With ≥ 3 symptoms: 72.7 (95% CI: –3.2, 95.1) ⁵⁷ RSV-associated LRTD [§] in participants aged ≥ 80 years: With ≥ 2 symptoms: 54.5 (95% CI: –41.9, 87.6) ⁵⁷ With ≥ 3 symptoms: 100 (95% CI: –9.1, 100) ⁵⁷
Cumulative efficacy over 3 seasons in adults ≥ 60 years old (%)	RSV-associated LRTD [†] : 62.9 (97.5% CI: 46.7, 74.8) ^{54,55} Severe RSV-associated LRTD: 67.4 (95% CI: 42.4, 82.7) ^{54,55} RSV-associated LRTD [†] in participants with ≥ 1 pre-existing comorbidity of interest [‡] : 64.7 (95% CI: 45.1, 78.1) ^{54,55} RSV-associated LRTD [†] in participants aged 60–69 years: 60.3 (95% CI: 39.5, 74.8) ^{54,55} RSV-associated LRTD [†] in participants aged 70–79 years: 70.6 (95% CI: 48.4, 84.3) ^{54,55}	ND
Safety in adults ≥ 60 years old [*]	Well tolerated in the overall population, with a clinically acceptable safety profile over 3 seasons ^{52–54,63} SAEs: RR ^{**} : 1.02 (95% CI: 0.91, 1.15) ⁶⁴ Severe reactogenicity events: RR ^{**} : 4.10 (95% CI: 1.99, 8.45) ⁶⁴ Inflammatory neurologic events ^{††} : 3/17,922 RSVPreF3 recipients ⁶⁴ GBS events in post-marketing analysis: 1.8/million doses of RSVPreF3 ⁶⁷	Well tolerated in the overall population, with a clinically acceptable safety profile over 2 seasons ^{56,65,66} SAEs: RR ^{**} : 1.04 (95% CI: 0.94, 1.15) ⁶⁴ Severe reactogenicity events: RR ^{**} : 1.43 (95% CI: 0.85, 2.39) ⁶⁴ Inflammatory neurologic events ^{††} : 3/20,255 RSVpreF recipients ⁶⁴ GBS events in post-marketing analysis: 4.4/million doses of RSVpreF ⁶⁷

CI, confidence interval; GBS, Guillain – Barré syndrome; LRTD, lower respiratory tract disease; ND, not determined; RR, relative risk; RSV, respiratory syncytial virus; SAEs, serious adverse events. ^{*}There are no clinical trials comparing the head-to-head efficacy between RSV vaccines; therefore, these data cannot be interpreted as comparative. [†]RSV-LRTD, confirmed by reverse transcriptase-polymerase chain reaction, was defined as follows: the participant had experienced at least two lower respiratory symptoms or signs, including at least one lower respiratory sign for at least 24 hours, or experienced at least three lower respiratory symptoms for at least 24 hours. [‡]Cardiorespiratory conditions (including chronic obstructive pulmonary disease, asthma, and chronic heart failure) and endocrine or metabolic conditions (diabetes and advanced renal or liver disease). [§]Reverse transcriptase-polymerase chain reaction-confirmed RSV illness with two or more or three or more respiratory symptoms within seven days of symptom onset and lasting more than one day during the same illness. [¶]Lung disease (including chronic obstructive pulmonary disease and asthma), heart disease (including chronic heart failure), diabetes, renal or liver disease, and current tobacco use. ^{**}RSV vaccine recipients compared with placebo recipients. ^{††}All inflammatory neurologic events occurred in trials without placebo recipients. ^{‡‡}No inflammatory neurologic events were observed in the placebo-controlled comparator arm.

94.1) against RSV-LRTD and a 94.1% efficacy (95% CI: 62.4, 99.9) against severe RSV-LRTD.^{48,52} During the second season post-vaccination (median follow-up of 17.8 months), the efficacy of RSVPreF3 was 56.1% (95% CI: 28.2, 74.4) against RSV-LRTD and 64.2% (95% CI: 6.2, 89.2) against severe RSV-LRTD, with a cumulative efficacy over two seasons of 67.2% (97.5% CI: 48.2, 80.0) and 78.8% (95% CI: 52.6, 92.0), respectively.^{48,53} A second dose of RSVPreF3 administered 12 months after the first dose did not confer

additional efficacy benefits.^{48,53} During the third season post-vaccination (median follow-up of 30.6 months), the efficacy of RSVPreF3 was 48.0% (95% CI: 8.7, 72.0) against RSV-LRTD and 43.3% (95% CI: -45.3, 81.3) against severe RSV-LRTD, with a cumulative efficacy over three seasons of 62.9% (97.5% CI: 46.7, 74.8) and 67.4% (95% CI: 42.4, 82.7), respectively.^{54,55}

The RENOIR study, a phase III, randomised, placebo-controlled trial, assessed the efficacy of RSVpreF against RSV-associated LRTD in individuals aged ≥ 60 years.^{49,56} Respiratory syncytial virus-associated LRTD was defined as RT-PCR-confirmed RSV illness in patients with two or more or three or more respiratory symptoms within seven days of symptom onset that last more than one day during the same illness.⁴⁹ During the first RSV season, the efficacy of RSVpreF against RSV-LRTD in patients with at least two symptoms and with at least three symptoms was 65.1% (95% CI: 35.9, 82.0) and 88.9% (95% CI: 53.6, 98.7), respectively.⁴⁹ During the second season following vaccine administration (median follow-up of 16.4 months), the efficacy of RSVpreF against RSV-LRTD in patients with at least two symptoms and with at least three symptoms was 55.7% (95% CI: 34.7, 70.4) and 77.8% (95% CI: 51.4, 91.1), respectively; the cumulative efficacy of RSVpreF against RSV-LRTD in patients with at least two symptoms and with at least three symptoms over two seasons was 58.8% (95% CI: 43.0, 70.6) and 81.5% (95% CI: 63.3, 91.6), respectively.⁵⁷

Finally, the ConquerRSV study, a phase II/III, randomised, placebo-controlled trial, evaluated the efficacy of the mRNA vaccine against RSV-associated LRTD in adults aged ≥ 60 years.⁵⁸ Respiratory syncytial virus-associated LRTD was defined as a RT-PCR-confirmed RSV infection and radiologic evidence of pneumonia or new or worsening lower respiratory symptoms for at least 24 hours.^{51,58} After a median follow-up of 3.7 months, the efficacy of the mRNA vaccine was 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD in patients with at least two symptoms and 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD in patients with at least three symptoms.^{51,58} After a median follow-up of 8.6 months, the vaccine efficacy was 63.3% (95% CI: 48.7, 73.7) against RSV-LRTD in patients with at least two symptoms and 63.0% (95% CI: 37.3, 78.2) against RSV-LRTD in patients with at least three symptoms.⁵¹ The vaccine efficacy was generally consistent across subgroups defined according to age and comorbidities.^{51,58}

Adults ≥ 60 years old by age and underlying medical conditions

The efficacy of recombinant RSV vaccines was also evaluated in specific populations of adults aged ≥ 60 years. In participants with at least one cardiorespiratory condition (including COPD, asthma or chronic HF), RSVPreF3 demonstrated an efficacy against RSV-LRTD of 92.1% (95% CI: 46.7, 99.8) and 73.8% (95% CI: 47.9, 88.2) over one and two seasons, respectively.^{53,59} In participants with at least one endocrine or metabolic condition (including diabetes or advanced renal or liver disease), the efficacy of RSVPreF3 against RSV-LRTD was 100% (95% CI: 74.0, 100) and 63.1% (95% CI: 17.4, 85.4) over one and two seasons, respectively.^{53,59} Over three seasons, the efficacy of RSVPreF3 against RSV-LRTD was 64.7% (95% CI: 45.1, 78.1) in participants with at least one pre-existing comorbidity of interest.^{54,55} Finally, RSVPreF3 showed an efficacy against RSV-LRTD of 81.0% (95% CI: 43.6, 95.3), 93.8% (95% CI: 60.2, 99.9) and 33.8% (95% CI: -47.7, 94.5) in participants aged 60 to 69 years, 70 to 79 years and ≥ 80 years, respectively, over one season; RSVPreF3 efficacy over two seasons was 65.4% (95% CI: 40.4, 80.9), 74.9% (95% CI: 48.4, 89.2) and 38.4% (95% CI: -118.2, 86.1) in the corresponding age groups.^{52,53} Over three seasons, the efficacy of RSVPreF3 against RSV-LRTD was 60.3% (95% CI: 39.5, 74.8) in participants aged 60 to 69 years and 70.6% (95% CI: 48.4, 84.3) in those aged 70 to 79 years.^{54,55}

Over one season, the efficacy of RSVpreF against RSV-LRTD with at least two symptoms and with at least three symptoms was 62.5% (96.66% CI: -8.4, 89.1) and 75.0% (96.66% CI: -39.1, 97.9), respectively, in participants aged ≥ 60 years with at least one high-risk condition, including COPD, asthma, chronic HF, diabetes, and renal or liver disease.⁵⁶ Over two seasons, the efficacy of RSVpreF against RSV-LRTD with at least two symptoms and with at least three symptoms was 49.3% (95% CI: 23.2, 67.0) and 73.5% (95% CI: 43.6, 88.8), respectively, in participants aged ≥ 60 years with at least one high-risk condition.⁵⁷ Specifically, in participants with at least one chronic cardiopulmonary condition (including COPD, asthma and chronic HF), over one season, RSVpreF revealed an efficacy of 33.3% (96.66% CI: -213.7, 87.9) against RSV-LRTD with at least two symptoms and 50.0% (96.66% CI: -302.1, 96.4) against RSV-LRTD with at least three symptoms.⁵⁶ Over two seasons, RSVpreF showed an efficacy of 29.0% (95% CI: -26.6, 60.8) against RSV-LRTD with at least two symptoms and 63.2% (95% CI: 8.5, 86.9) against RSV-LRTD with at least three symptoms in participants with at least one chronic cardiopulmonary condition.⁵⁷ Furthermore, during

the first season, the efficacy of RSVpreF against RSV-LRTD with at least two symptoms was 57.9% (96.66% CI: -7.4, 85.3), 77.8% (96.66% CI: -18.7, 98.1) and 80.0% (96.66% CI: -104.3, 99.7) in participants aged 60 to 69 years, 70 to 79 years and ≥ 80 years, respectively; RSVpreF efficacy against RSV-LRTD with at least three symptoms was 77.8% (96.66% CI: -18.7, 98.1), 100% (96.66% CI: -573.8, 100.0) and 100% (96.66% CI: -191.2, 100.0) in the corresponding age groups.⁵⁶ Over two seasons, the efficacy of RSVpreF against RSV-LRTD with at least two symptoms was 57.5% (95% CI: 35.8, 72.4), 62.5% (95% CI: 30.6, 80.8) and 54.5% (95% CI: -41.9, 87.6) in participants aged 60 to 69 years, 70 to 79 and ≥ 80 years, respectively; the efficacy of RSVpreF against RSV-LRTD with at least three symptoms was 81.6% (95% CI: 58.2, 93.1), 72.7% (95% CI: -3.2, 95.1) and 100% (95% CI: -9.1, 100) in the corresponding age groups.⁵⁷ The wide confidence intervals reflect the small subgroup sizes in this trial.^{56,57}

Adults 50–59 years old

The noninferiority of the humoral immune response to RSVPreF3 in adults aged 50–59 years compared with those aged ≥ 60 years has recently been demonstrated in the RSV OA=ADJ-18 study, a phase III, randomised, placebo-controlled trial.⁶⁰ Noninferiority was shown both for participants 50–59 years old without and for those with chronic conditions that increase the risk for RSV disease, such as chronic pulmonary disease (including COPD and asthma), chronic cardiovascular disease (including chronic HF, CAD, and cardiac arrhythmia), diabetes, CKD, and CLD.⁶⁰ Although these data suggest that RSVPreF3 might be efficacious in adults aged 50–59 years with or without underlying medical conditions, this study did not evaluate the efficacy of the vaccine against RSV-associated LRTD in this population.⁶⁰

Vaccine effectiveness

Post-licensure data were reviewed from four observational studies on the effectiveness of RSVPreF3 and RSVpreF against RSV-associated hospitalisation in adults aged ≥ 60 years during the first season after vaccination.^{61,62} Vaccine effectiveness ranged from 75% (95% CI: 50, 87) to 82% (95% CI: 69, 89), and it was similar across vaccine products and patient age groups (60–74 years and ≥ 75 years).^{61,62} The effectiveness of RSV vaccines against RSV-associated hospitalisation was also shown in adults aged ≥ 60 years with immunocompromising conditions (73% [95% CI: 48, 85]) and those with ESRD (72% [95% CI: 41, 87] in adults otherwise immunocompetent and 83% [95% CI: 45, 95] in those with additional immunocompromise).⁶¹ Furthermore, RSVPreF3 and RSVpreF demonstrated high effectiveness against documented RSV infection and against RSV-associated emergency department visits and critical illness (ICU admission and/or death) in adults aged ≥ 60 years.⁶¹

Two RSV vaccines are currently available in Portugal, with proven efficacy against RSV-associated LRTD in adults aged ≥ 60 years, including those with comorbidities and those of more advanced age.

The efficacy of RSVPreF3 was maintained for at least three seasons in adults aged ≥ 60 years. Moreover, RSVPreF3 was immunologically noninferior in adults aged 50–59 years compared with those aged ≥ 60 years.

The efficacy of RSVpreF was maintained for at least two seasons in adults aged ≥ 60 years.

Both vaccines showed high effectiveness against RSV-associated hospitalization, emergency department visits, and critical illness in adults aged ≥ 60 years.

Are RSV vaccines safe?

Adults ≥ 60 years old

Evidence regarding the safety of RSVPreF3 in adults aged ≥ 60 years consists of data from two randomised, double-blind, placebo-controlled clinical trials: the AReSVi-006 study and a phase I/II trial in participants ≥ 60 years old who received either the vaccine formulation used in the phase III trial or a placebo.^{52,63} RSVPreF3 was well tolerated in the overall population, with a clinically acceptable safety profile over three seasons.^{52–}

^{54,63} Most solicited adverse events (AEs) were transient and mild to moderate in severity; injection-site pain and fatigue were the most common AEs reported in those who received the vaccine.^{52,63}

Across both RSVPreF3 trials, the frequency of serious adverse events (SAEs) was similar in the intervention (4.4%) and control (4.3%) groups (pooled RR = 1.02; 95% CI: 0.91, 1.15).⁶⁴ Atrial fibrillation was reported as an unsolicited event within 30 days after injection in 10 (0.1%) RSVPreF3 recipients and in 4 (<0.1%) placebo recipients; 8 of these events were SAEs (RSVPreF3: 7; placebo: 1), and 3 of the SAEs corresponded to new-onset atrial fibrillation (RSVPreF3: 2; placebo: 1).⁶⁴ Severe reactogenicity events occurred in 3.8% of RSVPreF3 recipients vs. 0.9% of placebo recipients (pooled RR = 4.10; 95% CI: 1.99, 8.45).⁶⁴ Across all RSVPreF3 vaccine clinical trials in older adults, inflammatory neurologic events were reported in 3 of 17 922 participants within 42 days after receipt of the RSVPreF3 vaccine, including 1 case of Guillain – Barré syndrome (GBS) and 2 cases of acute disseminated encephalomyelitis (ADEM).⁶⁴ These inflammatory neurologic events occurred in trials without placebo recipients.⁶⁴

Evidence regarding the safety of RSVpreF in adults aged ≥60 years consists of data from two randomised, double-blind, placebo-controlled clinical trials: the RENOIR trial and a phase I/II trial in individuals ≥65 years old who received either the vaccine formulation used in the phase III trial or a placebo.^{56,65} RSVpreF was well tolerated in the overall population, with a clinically acceptable safety profile over two seasons.^{56,65,66} Most AEs were self-limiting and mild to moderate in severity; fatigue, headache, and injection-site pain were the most common AEs reported in those who received the vaccine.⁵⁶

Across both RSVpreF trials, the frequency of SAEs was similar in the intervention (4.3%) and control (4.1%) groups (pooled RR = 1.04; 95% CI: 0.94, 1.15).⁶⁴ Atrial fibrillation was reported as an unsolicited event within 30 days after injection in 10 (<0.1%) RSVpreF recipients and in 4 (<0.1%) placebo recipients; 7 of these events were SAEs (RSVpreF: 4; placebo: 3).⁶⁴ Severe reactogenicity events occurred in 1.0% of RSVpreF recipients vs. 0.7% of placebo recipients (pooled RR = 1.43; 95% CI: 0.85, 2.39).⁶⁴ Across all RSVpreF vaccine clinical trials in older adults, inflammatory neurologic events were reported in 3 of 20 255 participants within 42 days after receiving the vaccine, including 1 patient with GBS, 1 patient with Miller Fisher syndrome (a GBS variant), and 1 patient with undifferentiated motor-sensory axonal polyneuropathy.⁶⁴ No inflammatory neurologic events were observed in the placebo-controlled comparator arm.⁶⁴

Since GBS was identified as a potential safety concern for both recombinant RSV vaccines in clinical trials, the CDC reviewed data reported after RSV vaccination to V-safe (N = 16,220), an active US surveillance system, and to the Vaccine Adverse Event Reporting System (VAERS; N = 3,200), a passive, voluntary surveillance system, from 3 May 2023 to 14 April 2024.⁶⁷ The findings of this post-marketing analysis were consistent with those from the clinical trials, with reports of GBS (1.8 and 4.4 reports per million doses of RSVPreF3 and RSVpreF administered, respectively) being more common than the expected background rates.⁶⁷ Population-based surveillance will evaluate the potential risk for GBS.⁶⁷

Finally, two randomised, placebo-controlled trials contributed safety data on the mRNA RSV vaccine: the ConquerRSV study and a phase I trial in participants aged 65–79 years who received either the phase II/III trial vaccine formulation or a placebo.^{58,68} The mRNA vaccine was generally well tolerated.^{58,68} Severe reactogenicity events were more common among mRNA vaccine recipients than among placebo recipients (pooled RR = 1.54; 95% CI: 1.40, 1.68).⁶⁹ The frequency of SAEs was similar in both groups (pooled RR = 1.00; 95% CI: 0.95, 1.05).⁶⁹ No cases of GBS, other inflammatory neurologic events, myocarditis, or pericarditis were recorded within 42 days after vaccination.⁶⁹

Adults 50–59 years old

In the RSV OA=ADJ-18 study, several solicited AEs following RSVPreF3 vaccination were reported at higher rates in adults aged 50–59 years than in those aged ≥60 years, including injection-site pain, fatigue, myalgia, and headache; these symptoms were mostly transient and had mild to moderate intensity.⁶⁰ The rates of unsolicited AEs, SAEs, and potential immune-mediated diseases (pIMDs) were similar across the study groups.⁶⁰ Specifically, up to six months post-vaccination, 0.5 to 3.6% of participants aged 50–59 years and 2.4% of those aged ≥60 years reported SAEs; 0.0 to 1.0% of participants aged 50–59 years and 0.8% of those

aged ≥ 60 years reported pIMDs.⁶⁰ However, this study was not powered to identify rare AEs following vaccination.⁶⁰ Taken together, these data indicate that the overall safety profile of RSVPreF3 in adults aged 50–59 years was consistent with that in adults aged ≥ 60 years.⁶⁰

The two RSV vaccines currently available in Portugal are generally well tolerated, with an acceptable safety profile in adults aged ≥ 60 years. The report of an AE does not establish a causal relationship but alerts to the need for further studies.

The safety profile of RSVPreF3 in adults aged 50–59 years was consistent with that in adults aged ≥ 60 years.

Can RSV vaccines be administered concomitantly with other vaccines?

The RSVPreF3 vaccine may be administered concomitantly with seasonal inactivated influenza vaccines (standard dose unadjuvanted, high dose unadjuvanted, or standard dose adjuvanted).^{48,70–72} Upon concomitant administration of RSVPreF3 with seasonal influenza vaccines, numerically lower RSV-A and RSV-B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed compared with separate administration. These findings are not consistent across studies, and their clinical relevance is unknown.^{48,70–72}

The RSVpreF vaccine may be administered concomitantly with a seasonal quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted).^{49,73} In a randomised trial in adults aged ≥ 65 years, the criteria for non-inferiority of the immune responses in the co-administration group vs. the separate administration group were met. However, upon concomitant administration of RSVpreF with the inactivated adjuvanted seasonal influenza vaccine, numerically lower RSV-A and RSV-B neutralising titres and numerically lower influenza A and B haemagglutination inhibition titres were observed compared with when the vaccines were administered separately. The clinical relevance of these findings is unknown.^{49,73}

When given at the same time, vaccines should always be administered at different injection sites. Concomitant administration of RSVPreF3 and RSVpreF with vaccines other than those listed above (e.g., COVID-19) has not been studied.^{48,49}

Recombinant RSV vaccines may be administered concomitantly with seasonal inactivated influenza vaccines.

Data on the efficacy and safety of the coadministration of RSVPreF3 and RSVpreF with vaccines other than influenza vaccines are lacking.

Table 2. Recommendations for respiratory syncytial virus vaccination in older adults and patients with chronic disorders.

Who should be vaccinated	The RSV vaccine is recommended for people aged ≥ 50 years with risk factors (chronic obstructive pulmonary disease, asthma, heart failure, coronary artery disease, diabetes, chronic kidney disease, chronic liver disease, immunocompromise, frailty, dementia, and residence in a nursing home) and all those aged ≥ 60 years.* If it cannot be made available to this population, then it should be prioritised for individuals aged ≥ 75 years and those aged ≥ 50 years with risk factors.
Timing of vaccination	Although it can be given on any date, the RSV vaccine should preferably be administered between September and November.
Co-administration with other vaccines	The RSV vaccine can be administered concurrently with the influenza vaccine.

LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus. *In adults aged 50–59 years at increased risk of RSV disease, RSVPreF3 is the only vaccine approved for active immunisation for the prevention of RSV-LRTD⁴⁸; in pregnant individuals (between weeks 24 and 36 of gestation), RSVpreF is the only vaccine approved to protect infants from birth through 6 months of age.⁴⁹

Conclusions

Considering the scientific evidence presented, the SPP, APMGF, SPC, SPDIMC, SPEDM, and SPMI present the following conclusions and recommendations:

- Respiratory syncytial virus is an important cause of LRTI, with a major burden on adults worldwide, including in Portugal.
- Older adults and people with certain medical conditions, including COPD, asthma, HF, CAD, diabetes, CKD, and CLD, and those who are immunocompromised are at increased risk for severe RSV infection.
- Advanced age (≥ 75 years) is associated with a higher incidence of RSV infection, increased hospitalisation rates and duration, greater clinical severity, and higher mortality; certain conditions common in older adults, such as living in a nursing home, frailty, and dementia, are linked to poorer outcomes.
- Given that there are currently no specific treatments for RSV-associated disease, RSV vaccination in older people and in adults with chronic disorders represents an opportunity to prevent this infection and its associated burden for patients and the health system.
- Two RSV vaccines are currently available in Portugal, with proven efficacy, effectiveness, and safety in adults aged ≥ 60 years, including those with comorbidities and those of more advanced age.
- In adults aged ≥ 60 years, the efficacy of RSVPreF3 was maintained for at least three seasons, and the efficacy of RSVpreF was maintained for at least two seasons.
- RSVPreF3 was immunologically noninferior in adults aged 50–59 years compared with those aged ≥ 60 years, with a consistent safety profile.
- The panel's recommendations for RSV vaccination in adults are summarised in [Table 2](#).

Further research is needed to evaluate the efficacy and safety of RSV vaccines in certain populations, such as immunocompromised individuals, and to better understand the potential interactions with other vaccines (e.g., pneumococcal, herpes zoster, and COVID-19). Several ongoing studies are addressing these issues and may justify extending RSV vaccination recommendations in the future.^{74–77}

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Appendix

Table A1. Recommendations for respiratory syncytial virus vaccination in adults in several countries (30 October 2024).

Country	Recommendations
Austria <i>BMSGPK</i> ⁷⁸	RSV vaccination is recommended in adults ≥60 years of age. It may also be considered in those aged ≥18 years with increased risk of disease (severe organ disease, oncologic disease, immunodeficiency, severe respiratory, cardiac, renal or endocrine, metabolic, neurological underlying disease, body mass index ≥30, HIV infection or other immunosuppressive disease, and people cared for in retirement and nursing homes).
Belgium <i>SHC</i> ⁷⁹	RSV vaccination can be offered on an individual basis to high-risk patients ≥60 years old with ≥1 risk factor for severe RSV disease (chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung disease, chronic respiratory failure, chronic heart failure, chronic kidney disease, diabetes, obesity, immunodeficiency, including solid cancer/hematologic malignancy, use of immunosuppressive medications, solid organ transplantation, allogenic hematopoietic cell transplant, and institutionalized patients).
France <i>HAS</i> ⁸⁰ <i>RespiFIL</i> ⁸¹	HAS recommends seasonal RSV vaccination in people aged ≥75 years and people aged ≥65 years with chronic respiratory disease (particularly chronic obstructive pulmonary disease) or cardiac disease (particularly heart failure) likely to decompensate during an RSV infection. RespiFIL recommends one dose of RSVPreF3 in patients with chronic respiratory disease aged ≥60 years.
Germany <i>STIKO</i> ⁸² <i>Several medical societies</i> ⁸³	STIKO recommends RSV vaccination in people aged ≥75 years and people aged 60–74 years with a serious underlying disease (chronic respiratory, cardiovascular, or kidney disease, hemato-oncological disease, diabetes with complications, chronic neurological or neuromuscular disease, and severe congenital or acquired immunodeficiency) or who live in a care facility. Several medical societies recommend RSV vaccination in persons aged ≥60 years. They also recommend it, after individual consultation, in adults of any age with severe pulmonary or cardiovascular pre-existing conditions and in adults who are significantly immunocompromised.
Ireland <i>NIAC</i> ⁸⁴	RSV vaccination is recommended in adults aged ≥65 years. If there is a limited supply of vaccines, then priority should be given to those of more advanced age, those with significant comorbidities (chronic pulmonary disease, chronic cardiac conditions, cerebrovascular disease, chronic kidney disease, and other immunocompromising conditions) and those living in long-term care facilities for older adults.
Italy <i>Calendario per la Vita</i> ⁸⁵	RSV vaccination is recommended in all subjects aged ≥75 years and in subjects aged ≥60 years with chronic conditions.
Spain <i>NEP</i> ⁸⁶	Individual protection perspective: any individual aged ≥60 years can benefit from RSV vaccination. Public health perspective: RSV vaccination is recommended at least in adults aged ≥60 years in risk groups (institutionalized individuals, chronic cardiovascular, pulmonary or renal disease, diabetes, immunosuppression, and neurological impairments).
UK <i>JCVI</i> ^{87,88}	An RSV vaccination program is advised for people aged ≥75 years, likely not routinely run as a seasonal campaign but rather offered at a given age birthday.
USA <i>CDC'S ACIP</i> ⁸⁹	A single dose of RSV vaccine is recommended in adults ≥75 years of age and in adults 60–74 years of age who are at increased risk of severe RSV disease (chronic cardiovascular disease, chronic lung/respiratory disease, end-stage renal disease, diabetes, neurologic/neuromuscular conditions, chronic liver disease, chronic hematologic conditions, severe obesity, moderate/severe immunocompromise, and residence in a nursing home).

ACIP, Advisory Committee on Immunization Practices; BMSGPK, Federal Ministry of Social Affairs, Health, Care and Consumer Protection; CDC, Centers for Disease Control and Prevention; HAS, High Authority for Health; HIV, human immunodeficiency virus; JCVI, Joint Committee on Vaccination and Immunisation; NEP, NeumoExperts Prevention Group; NIAC, National Immunisation Advisory Committee; RespiFIL, Healthcare Network for Rare Respiratory Diseases; RSV, respiratory syncytial virus; SHC, Superior Health Council; STIKO, Standing Committee on Vaccination.