

Review Article

Respiratory Syncytial Virus Vaccination Recommendations for Adults Aged 60 Years and Older: The NeumoExperts Prevention Group Position Paper

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ABSTRACT

Respiratory syncytial virus (RSV) is a major cause of respiratory tract infections in adults, particularly older adults and those with underlying medical conditions. Vaccination has emerged as a potential key strategy to prevent RSV-related morbidity and mortality. This NeumoExperts Prevention (NEP) Group scientific paper aims to provide an evidence-based positioning and RSV vaccination recommendations for adult patients. We review the current literature on RSV burden and vaccine development and availability, emphasising the importance of vaccination in the adult population. According to our interpretation of the data, RSV vaccines should be part of the adult immunisation programme, and an age-based strategy should be preferred over targeting high-risk groups. The effectiveness and efficiency of this practice will depend on the duration of protection and the need for annual or more spaced doses. Our recommendations should help healthcare professionals formulate guidelines and implement effective vaccination programmes for adult patients at risk of RSV infection now that specific vaccines are available.

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Introduction


Respiratory syncytial virus (RSV) is a common respiratory pathogen that significantly affects vulnerable populations, including infants, older adults, and individuals with chronic medical conditions and immunocompromised status.¹ More than 158,000 RSV-associated hospitalizations occur annually among adults in the

EU, 92% of which happen in adults ≥ 65 years.² RSV causes 10,000 deaths among the elderly annually in the US alone.³ Furthermore, its mortality rate is comparable to that of influenza.⁴ Given the substantial burden of RSV-related illness in adults,⁵ there is an urgent need to develop effective prevention strategies, particularly through vaccination, and the WHO has emphasised RSV vaccine development as a top priority.^{6,7}

In the last two decades, several vaccine candidates have been designed, targeting young children and older adults.^{8–10} In 2023, three vaccine formulations designed for older adults successfully completed Phase 3 trials and two already received marketing approval.¹¹ These recent approvals have revolutionised the field and warrant the exploration of potential vaccination strategies

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and prophylaxis positioning of available products to prevent and control RSV infections. This paper aims to offer evidence-based recommendations for the vaccination of adult patients against RSV.

Methods

A comprehensive literature review was conducted using electronic databases, including PubMed, Embase, and Cochrane Library until December 2023, to identify relevant studies, clinical trials, and guidelines for RSV infection and vaccination in adults. The search terms included “respiratory syncytial virus”, “adults”, “vaccine”, and related keywords. The selected articles were critically appraised, and data were synthesised to develop evidence-based recommendations.

Epidemiology and Clinical Manifestations

RSV Epidemiology in Adults

RSV has long been recognised as a leading cause of respiratory tract infections in infants and young children. However, recent research has also shed light on the significant burden of RSV infections in adults.^{5,9} Based on data from the Global Burden of Disease report, which covers 204 countries and territories, the mortality rate for individuals aged 70 years and older in 2019 exceeded that of other age groups. It is worth noting that the mortality rate for people aged 70 years and older compared to infants under 5 years old increased from 0.57 in 1990 to 1.85 in 2019.¹² Understanding the epidemiology of RSV in adults is crucial to identifying high-risk populations and implementing effective preventive measures, such as vaccination.

RSV peaks are typically observed during the fall and winter, but inter-seasonal RSV activity exists, and its reservoir is exclusively human.¹³ Occupational exposure is a crucial factor in the epidemiology of RSV in adults. Healthcare and daycare workers are at a higher risk of contracting RSV due to their frequent contact with infected individuals. These occupations play a critical role in the transmission dynamics of RSV, as infected healthcare workers can spread the virus within healthcare settings and vulnerable patient populations.^{14–16}

Adults aged 60 years and older, especially those residing in long-term care facilities or nursing homes, are at increased risk of severe RSV-related illness.¹⁷ A recent meta-analysis found that in adults aged 60 years and older, the attack rate for RSV-associated acute respiratory infection was estimated at 1.62%; the hospitalisation attack rate was 0.15%, and the in-hospital case fatality rate (hCFR) was 7.13%.³ In Spain, Heppe-Montero et al. estimated an hCFR of 7.91% for patients aged 60 years or older.¹⁸

Additionally, age-related comorbidities, such as chronic obstructive pulmonary disease (COPD), congestive heart failure, stroke, chronic kidney disease and diabetes, further heighten the risk of severe RSV infections and the need for hospitalisation.^{19–23} Furthermore, individuals with compromised immune systems, such as those undergoing immunosuppressive therapy, solid organ transplant recipients, people with HIV infection, and especially those with haematologic malignancies undergoing chemotherapy, are at an elevated risk of severe RSV infections.²⁴ The chronic use of inhaled corticosteroids has also been associated with the increased risk of RSV pneumonia (aOR 2.08 [95% CI: 1.39–3.09]).²⁵ These individuals often experience more prolonged and severe illness and are at an increased risk of complications, including hospitalisation and death.^{26–28}

Complications include bacterial co-infection in up to 29% of adults hospitalised for RSV pneumonia, the most common pathogens being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*.²⁹ This co-infection rate is even higher

than in influenza patients, estimated to occur in 20% of patients.³⁰ RSV infection may also be complicated by cardiovascular events, including acute coronary syndrome, worsening congestive heart failure and arrhythmias in 14–22%.³¹ Finally, acute functional loss has been associated with a significant short- and long-term reduction in quality of life, which may last for months.^{8,32}

In sum, RSV infections in adults represent a significant public health concern and have a substantial impact on morbidity, mortality, and healthcare utilisation. Older adults, individuals with chronic medical conditions, immunocompromised individuals, and those with occupational exposure face an elevated risk of severe RSV-related illness^{14–16,18,33–36}

Adult RSV Clinical Manifestations

RSV infection in adults can present with a wide spectrum of clinical manifestations, ranging from mild respiratory symptoms to severe lower respiratory tract infections. Individual risk factors, comorbidities, and immunological status influence the clinical presentation of RSV in adults.³⁷ The most common clinical symptoms of RSV infection in adults include cough, rhinorrhoea (runny nose), sore throat, nasal congestion, and fever. These symptoms often resemble those of other respiratory viral infections, so clinical diagnosis is challenging without laboratory confirmation. RSV infection may be mistaken for a common cold or influenza, especially during seasonal peaks of respiratory viral activity.^{38,39}

While RSV infections in adults can be self-limiting and resolve without complications, they can also progress to more severe respiratory illnesses, including pneumonia, as a complication of RSV infection that may require hospitalisation.^{22,40} In some individuals, particularly those with underlying chronic respiratory conditions, RSV infection can lead to exacerbations of pre-existing conditions, such as COPD or asthma.⁴¹ In severe cases, RSV infection may result in lower respiratory tract infections, such as bronchiolitis and pneumonia. Bronchiolitis is more commonly observed in infants and young children but can also occur in adults, especially those with compromised lung function or immunocompromised status.⁴² RSV is also a cause of pneumonia in 49.3% of patients with confirmed RSV infection, primarily in the form of consolidations (23.8%) or ground-glass opacities (19.9%).⁴⁰

RSV infections in the elderly are frequent and more severe than those with influenza A/B, especially in vulnerable populations, and can result in hospitalisation and, in rare cases, lead to fatal outcomes. These severe outcomes are more likely in individuals with multiple risk factors, advanced age, and significant comorbidities.^{4,22}

In summary, RSV infection in adults has different presentations, ranging from asymptomatic or mild respiratory symptoms to exacerbations of underlying chronic conditions and severe lower respiratory tract infections, such as bronchiolitis and pneumonia. Clinical manifestations can vary widely, and individual risk factors and comorbidities influence the severity of illness. Early identification through efficient diagnostic testing, suitable treatment and specific preventive measures like vaccination are essential in reducing the morbidity and mortality linked to RSV infection in adults.

The Virus and Its Diagnosis

RSV is a negative-sense, non-segmented RNA virus of more than 15,000 nucleotides. Unlike influenza viruses, it cannot reassort segments, so a large-scale pandemic is unlikely.⁴³ RSV has two major specific antigenic subgroups (A and B) that differ in a number of proteins, but the major genetic diversity lies within the attachment glycoprotein G. However, glycoprotein F is highly conserved between RSV A and RSV B, making it an ideal candidate as a vaccine

antigen, once stabilised in its “pre-fusion” structural conformation, which induces more potent neutralising antibodies by presenting more important epitopes.^{43,44}

Clinical features in adults are not sufficiently helpful in distinguishing RSV from other respiratory agents; therefore, laboratory confirmation may be required. Molecular testing, such as polymerase chain reaction (PCR)-based assays, are rapid, highly sensitive and specific, making them the preferred tool in hospitalised adult patients, particularly when using lower respiratory tract samples. The preferred sample for detecting RSV in adults is a nasopharyngeal swab, but adding additional samples such as saliva, sputum, and serology increases diagnosis accuracy by 2.6-fold.⁴⁵ Multiplex PCR-based assays enable the simultaneous detection of several respiratory pathogens, albeit at a higher cost. Rapid antigen detection tests (RADTs) provide a quicker, cheaper and more useful point-of-care diagnostic tool, although their sensitivity is less than 10% compared to serological tests and PCR. Immunochromatographic assays targeting RSV F-glycoprotein are used for most RADTs.⁴⁶ Viral culture is time-consuming and demands trained staff, limiting it to reference labs. Serology offers limited value for immediate diagnosis or patient care, yet when paired with PCR in acute and convalescent phases, its sensitivity is heightened beyond that of viral culture. Whole-genome sequencing and next-generation sequencing techniques are presently unavailable for clinical purposes. These techniques are intended mostly for public health research due to their capacity for detecting evolutionary diversity and potential transmission patterns.⁴⁷

RSV Older Adult Vaccination: Current Status

Vaccine Development for RSV

Historically, the development of an RSV vaccine has been challenging.⁴⁸ In light of recent advances in understanding the biology and structure of the RSV virus, particularly the importance of the pre-fusion configuration of the F antigen (Pre-F Ag),⁴⁹ numerous vaccine candidates have been developed and tested. Each candidate uses a distinct but all use Pre-F Ag. Here, we discuss the current status of RSV vaccine development for the elderly population and highlight key characteristics of various vaccine candidates (Table 1).

Subunit Vaccines

Subunit vaccines are either protein- or particle-based. Protein-based vaccines employ purified RSV antigens, including the F or G protein, often formulated with adjuvants to enhance the immune response. Two vaccines have successfully completed Phase 3 trials and have recently been approved for use in older adults (Tables 2 and 3).^{50,51}

The first one, a prefusion F protein RSV vaccine (RSVPreF3, Arexvy, GSK), reported efficacy results in Phase 3 clinical trial in adults ≥ 60 years (ARESVi 006 Study) of 82.6% (95% CI: 57.9–94.1%) for RSV-associated lower respiratory tract disease (LRTD), and 94.1% (95% CI: 62.4–99.9%) for severe RSV-associated LRTD.⁵² Further analyses stratified by season revealed that one dose of the RSVPreF3 vaccine in preventing symptomatic, laboratory-confirmed RSV-associated LRTD was 82.6% (96.95% CI: 57.9–94.1%) during the first RSV season and 56.1% (95% CI: 28.2–74.4%) during the second full season (Table 3). The cumulative efficacy of a single dose over the two combined seasons was 74.5% (97.5% CI: 60.0–84.5%) in preventing RSV-associated LRTD and 77.5% (95% CI: 57.9–89.0%) in preventing medically attended RSV-associated LRTD. In addition, the vaccine was well tolerated, with no safety concerns.^{53,54}

The second one, a bivalent RSV-A and RSV-B stabilised prefusion F protein vaccine (RSVpreF, Abrysvo, Pfizer) reported efficacy

results in Phase 3 clinical trial in adults ≥ 60 years (RENOIR study) of 66.7% (96.66% CI: 28.8–85.8%) for RSV lower respiratory tract infection (LRTI) with at least two signs or symptoms and 85.7% (96.66% CI: 32.0–98.7%) for most severe respiratory disease defined by the presence of three or more symptoms associated with RSV (Table 2).⁵⁵ Analyses by season reported that one dose of the RSVpreF vaccine prevented symptomatic, laboratory-confirmed RSV-associated LRTD with 88.9% efficacy (95% CI: 53.6–98.7%) during the first RSV season and 78.6% (95% CI: 23.2–96.1%) during the partial second season (Table 3). The efficacy of a single dose over the two combined seasons was 84.4% (95% CI: 59.6–95.2%) in preventing RSV-associated LRTD and 81.0% (95% CI: 43.5–95.2%) in preventing medically attended RSV-associated LRTD. In addition, the vaccine was well tolerated, with no safety concerns.^{53,54} Nanoparticle-based vaccines use self-assembling nanoparticles presenting key RSV antigens, such as the F glycoprotein or the RSV prefusion-stabilised F protein. They aim to induce a robust neutralising antibody response and have shown promising results in preclinical and early clinical studies.⁵⁶ IVX-A12, a bivalent vaccine candidate based on nanoparticle technology for treating older adults with RSV and human metapneumovirus (hMPV), started its Phase 3 clinical trial in older adults in June 2023.⁵⁷

Live Attenuated Vaccines

Live attenuated vaccines (LAV) mimic natural infection to induce a strong immune response.^{58,59} RSV-MinL4-0 (modified polymerase gene), a codon-pair deoptimised LAV, has shown a humoral and cellular immune response similar to wild-type infection in non-human primates and has completed Phase 1 trials.⁶⁰

Chimeric Vaccines

Chimeric live virus vaccine candidates express RSV proteins in related attenuated viruses with favourable safety profiles. Unlike vector vaccine candidates, chimeric vaccines show favourable antigen presentation that activates an adaptive immune response. CPI-RSV-F (BLB201), currently in Phase 1 trials, is a chimeric RSV vaccine candidate that includes older adults. Based on an attenuated strain of canine parainfluenza virus expressing the RSV-F protein, a Phase 1 trial is ongoing in the elderly population. The first study cohort showed that 64% of subjects had serum anti-RSV antibody responses above baseline levels.⁶¹

Messenger Ribonucleic Acid (mRNA) Vaccines

mRNA vaccines have revolutionised vaccine development, exemplified by their successful application in COVID-19 vaccines.^{62,63} Moderna’s mRNA-1345, an mRNA candidate encoding stabilised RSV pre-F protein, recently reported efficacy results in Phase II + III trial clinical trial in adults ≥ 60 years of 83.7% (95.88% CI: 66.1–92.2%; $p < 0.0001$) against RSV LRTD as defined by two or more symptoms and 82.4% (96.36% CI, 34.8–95.3) against the disease with at least three signs or symptoms.⁶⁴ In addition, vaccine efficacy was 68.4% (95% CI, 50.9–79.7) against RSV-associated acute respiratory disease. In general, the vaccine was well tolerated, with no safety concerns. Supported by these results, the company requested the market approval of mRNA-1345 in July 2023.

Recombinant Vector Vaccines

Recombinant vector vaccines use a genetically modified, replication-deficient virus as a vehicle to elicit both humoral and cellular immune responses by delivering genes encoding specific RSV antigens. Two candidates in clinical development in the elderly population were discontinued due to strategic decisions (Ad26.RSV.preF)⁶⁵ or failure to meet one of the primary endpoints (MVA-BN-RSV).⁶⁶

Table 1
Summary of Vaccine Candidates in Development for Older Adults Categorised by Design Strategy.¹¹

Type of vaccine	Candidate vaccine sponsor	Antigen	Adjuvant	Mechanism of action	Phase 1 trial (no. participants)	Phase 2 trial (no. participants)	Phase 3 trial (no. participants)
Subunit vaccine	VN-0200 Daiichi Sankyo DPX-RSV Immunovaccine	VAGA-9001a SHe	MABH-9002b DepoVax aluminium hydroxide	Protein-based Protein-based: SHe generates a non-neutralising Ab and CD4+ T-cell response	NCT04914520 (48) NCT02472548 (40)		
	BARS13 Advaccine	G	None or cyclosporine A	Protein-based: RSV G; immunosuppressant	NCT04851977 and ACTRN12618-000948291 (60)	NCT04681833 (120)	
	RSVPre - F3/GSK3844766A GSK	PreF	AS01E	Protein-based: Induce immune response with stabilised preF	NCT04090658, NCT03814590, and NCT04657198 (1055)	NCT04090658 and NCT04657198 (1055)	NCT04886596 (25,000) NCT04732871 (1720) NCT05059301 (750)
	RSVPreF Pfizer	PreF	None	Protein-based: Induce immune response with stabilised preF		NCT03529773 (1235) NCT04785612 (62) NCT04071158 (713)	NCT04032093 (1153) NCT05035212 (30,000)
	IVX-121 Icosavax	Stabilised Pre-F DS-Cav1	None or aluminium hydroxide	Particle-based: Presentation of DS-Cav1 on computationally designed VLP generates a neutralising Ab response against preF	2020-003633-38 (90)		
Nucleic acid vaccine	IVX-A12 (RSV/hMPV) Icosabax mRNA-1345 Moderna	RSV-F/hMPV-F PreF	MF59 None	Particle-based mRNA encodes for a stabilised preF glycoprotein eliciting neutralising antibodies	NCT05664334, 120 NCT04528719 (100 healthy adults, 300 older adults, 180 women, and 40 children)	NCT05903183 (264) Phase 2 and 3; NCT05127434 (34,000)	NCT05127434 (34,000) NCT05330975 (1350)
	mRNA LNP Sanofi	PreF	None	mRNA encodes for a stabilised preF glycoprotein eliciting neutralising antibodies	NCT05639894 (790)		
Live attenuated vaccine	RSV-MinL4.0 Codagenix	All viral proteins	None	L altered for attenuation	NCT04295070 (36)		
Chimeric	CPI-RSV-F Vaccine (BLB-201) Blue Lake Biotechnology Inc.	PreF	None	Parainfluenza virus type 5-vectored live attenuated RSV vaccine	NCT05281263 (30)		

Ab: antibodies; GSK: GlaxoSmithKline; hMPV: human metapneumovirus; mRNA: messenger ribonucleic; RSV: respiratory syncytial virus; SHe: small hydrophobic glycoprotein; VLP: virus-like particle.

Positioning and Recommendations for Vaccination in Older Adult Patients

The rationale for the recommendations to use RSV vaccines in older adults is based on the known burden of the disease and the evidence of moderate to high efficacy in preventing symptomatic RSV-associated LRTD.^{52,55} It is important to note that the trials had limited enrollment of individuals at highest risk for RSV disease, and that protection duration and eventual need for additional doses have not yet been established. From an individual protection perspective, healthcare providers should consider individual risk factors, patient preferences, and vaccine characteristics when deciding whether to vaccinate. Post-marketing surveillance and additional studies will provide further information on the safety

and effectiveness of RSV vaccines in older adults, which will guide future recommendations.⁵⁴

Target Population for RSV Vaccination

Age-based Indication Strategy

The age-based indication strategy involves recommending RSV vaccination for all individuals within a specific age range, regardless of their individual risk levels or underlying conditions. This approach does not require identifying and targeting specific high-risk groups, making it a convenient and efficient strategy. The decision on the age threshold should balance the greatest impact on disease burden and its efficiency.⁶⁷

Table 2
Efficacy of Currently Licensed RSV Vaccines for Adults 60 Years or Older Based on Phase 3 Trial Results.^{52,55}

Endpoint	n/N, Vaccinated group	n/N, placebo group	Vaccine efficacy (CI), %
<i>RSVpreF3 protein vaccine (GSK)</i> ⁵²			
RSV acute respiratory illness: ≥ 2 respiratory symptoms/signs for ≥ 24 h OR ≥ 1 respiratory symptom/sign + 1 systemic sign for ≥ 24 h	27/12,466	95/12,494	71.7 (56.2–82.3)
RSV LRTD: ≥ 2 lower respiratory symptoms/signs for ≥ 24 h including ≥ 1 lower respiratory sign OR ≥ 3 lower respiratory symptoms for ≥ 24 h	7/12,466	40/12,494	82.6 (57.9–94.1)
RSV LRTD with ≥ 2 lower respiratory signs or assessed as 'severe' by the investigator	1/12,466	17/12,494	94.1 (62.4–99.9)
<i>Bivalent RSV prefusion F vaccine (Pfizer)</i> ⁵⁵			
RSV LRTI: ≥ 1 respiratory symptom lasting more than 1 day	22/16,306	58/16,308	62.1 (37.1–77.9)
RSV LRTI ≥ 2 symptoms: ≥ 2 lower respiratory signs/symptoms lasting more than 1 day	11/16,306	33/16,308	66.7 (28.8–85.8) ^a
RSV LRTI ≥ 3 symptoms: ≥ 3 lower respiratory signs/symptoms lasting more than 1 day	2/16,306	14/16,308	85.7 (37.9–98.4) ^a

^a 96.66% of confidence interval. CI: confidence interval; LRTD: lower respiratory tract disease; LRTI: lower respiratory tract infection; n: number of events; N: numbers of participants; RSV: respiratory syncytial virus.

Table 3
Efficacy of One Dose of Currently Licensed RSV Vaccines for Adults Aged ≥ 60 Years During the First RSV Season, the Second RSV Season and Both Seasons, 2021–2023.^{53,54}

Efficacy evaluation period	Vaccine efficacy against outcome ^h	
	RSV-associated LRTD ^a	RSV-associated medically attended LRTD ^b
<i>RSVpreF3 protein vaccine (GSK)</i> ⁵⁴		
Season 1 ^c	82.6 (57.9–94.1) ^m	87.5 (58.9–97.6) ^l
Season 2 (full) ^d	56.1 (28.2–74.4) ^l	– ^k
Combined seasons 1 and 2 (interim) ^f	74.6 (62.1–83.5) ⁿ	77.5 (57.9–89.0) ^l
<i>Bivalent RSVpreF vaccine (Pfizer)</i> ^l	RSV-associated LRTD	RSV-associated medically attended LRTD
Season 1c	88.9 (53.6–98.7) ^l	84.6 (32.0–98.3) ^l
Season 2 (interim) ^e	78.6 (23.2–96.1) ^l	– ^k
Combined seasons 1 and 2 (interim) ^f	84.4 (59.6–95.2) ^l	81.0 (43.5–95.2) ^l

CI: confidence interval; LRTD; lower respiratory tract disease; LRTI: lower respiratory tract infection; RSV: respiratory syncytial virus.

^a For RSVpreF3 (GSK), LRTD was defined as two or more lower respiratory symptoms (new or increased sputum, cough, and dyspnoea) or signs (new or increased wheezing, crackles or rhonchi detected during chest auscultation, respiratory rate ≥ 20 respirations per minute, low or decreased oxygen saturation [$<95\%$ or $\leq 90\%$ if baseline was $<95\%$], and need for oxygen supplementation) for ≥ 24 h, including one or more lower respiratory signs, or three or more lower respiratory symptoms for ≥ 24 h. For RSVpreF (Pfizer) estimates, LRTD refers to the RSVpreF trial endpoint of RSV LRTI with three or more lower respiratory signs or symptoms (see Table 2).

^b Medically attended RSV-associated LRTD defined as LRTD plus attention at one or more inpatient or outpatient health care services. Estimates were not included in per-protocol assessments.

^c Season 1 vaccine efficacy estimates reflect efficacy against first events occurring during the first complete RSV season for Northern Hemisphere participants, partial first RSV season for Southern Hemisphere participants for GSK (May 2021–April 2022; exact study-defined season dates were site-dependent) and complete RSV season Southern Hemisphere participants for Pfizer (August 2021–October 2022; exact study-defined season dates were site-dependent).

^d Season 2 vaccine efficacy estimates (GSK) reflect efficacy against first events occurring during the second complete Northern Hemisphere RSV season for Northern Hemisphere participants (August 2022–March 2023; exact study-defined season dates were site-dependent). In addition to Northern Hemisphere participants, Southern Hemisphere participants were also included in these analyses, but this time span reflects an interseason period with low RSV incidence in the Southern Hemisphere.

^e Season 2 (interim) vaccine efficacy estimates (Pfizer) reflect efficacy against first events occurring during the second complete RSV season for Northern Hemisphere participants only (July 2022–January 2023; Southern Hemisphere data not yet available).

^f Combined season 1 and 2 (interim) vaccine efficacy estimates reflect efficacy against first events occurring any time during Season 1 or Season 2. The mean time from start to end of efficacy surveillance was approximately 15 months (GSK) or 12 months (Pfizer) per participant.

^g Interim analysis underpowered to estimate efficacy.

^h Manufacturer-calculated efficacy. Includes events > 14 days after injection and person-time available from the manufacturer's pivotal Phase 3 trial.

ⁱ Estimates adjusted for participant age and region.

^j Estimates are unadjusted.

^k Interim analysis underpowered to estimate efficacy.

^l 95% CI.

^m 96.95% CI; the CI for the primary trial endpoint was adjusted for multiplicity.

ⁿ 97.5% CI; the CI for the primary trial endpoint was adjusted for multiplicity.

High-risk Groups Targeting Strategy

The strategy of targeting high-risk groups involves prioritising RSV vaccination for populations at higher risk of severe RSV infection or its complications (Table 4). The main justifications for a strategy of targeting high-risk groups would be: (1) high-risk groups, such as older adults, people with chronic respiratory diseases, immunocompromised individuals and healthcare workers, are more likely to experience severe RSV infection or transmit the virus to vulnerable populations^{68,69}; (2) limited vaccine supply or higher vaccine costs may necessitate prioritising high-risk groups to achieve the greatest public health impact; and (3) targeting high-risk groups allows for a more targeted approach,

ensuring that those most susceptible to severe RSV illness are protected.⁷⁰

Timing and Scheduling of RSV Vaccination

Timing of RSV Vaccination: Maximising Protection

To ensure maximum protection, it is important to consider the following:

- Seasonal outbreaks: RSV infection typically occurs in seasonal outbreaks, with the highest incidence in temperate regions occurring during the autumn and winter months. However, RSV

Table 4
High-risk Groups for RSV Vaccination Recommendations Irrespective of Age.

High-risk group	Rationale
Chronic respiratory disease (COPD/asthma)	Higher risk of severe respiratory complications
Chronic cardiovascular disease	Greater vulnerability to RSV-related morbidity
Immunocompromised individuals (including solid organ transplant recipients, HIV)	Heightened risk of severe RSV infection, Impaired immune function and susceptibility to RSV
Chronic hepatic or renal disease	Impaired immune function, greater susceptibility to RSV
Diabetes	Increased risk of RSV-related illness
Neurological impairment	Increased risk of RSV-related illness
Adults living in nursing homes or long-term care facilities	Increase risk of RSV disease

COPD: chronic obstructive pulmonary disease; HIV; human immunodeficiency virus; RSV: respiratory syncytial virus.

activity can vary geographically. Therefore, local surveillance data should be considered when determining the optimal timing of vaccination.

- **Ideal timing:** Vaccination should ideally be administered before the onset of the RSV season to provide the highest level of protection. However, considering that the currently available vaccines induce protection for at least two seasons,^{53,54} timing should be as early as possible for those eligible, irrespective of RSV activity.

Schedule of RSV Vaccination: Tailoring to Vaccine Type and Individual Factors

- **Vaccine type:** The schedule may vary depending on the specific vaccine. This includes the number of doses required and the interval between doses. Both currently approved RSV vaccines are recommended for administration as a single dose.
- **Booster doses:** Evidence to determine the need for revaccination is not currently available.

Integrating RSV Vaccination With Other Vaccines: Optimising Immunisation Coverage

- **Recommended timing and schedules:** RSV vaccination in adults can be seamlessly integrated into routine immunisation schedules by considering the recommended timing and schedules of other vaccines. This allows for efficient and convenient administration of multiple vaccines.
- **Co-administration with other vaccines:** By combining vaccines, individuals can receive multiple vaccinations during a single healthcare visit, reducing the need for additional appointments and associated costs. Both RSVpreF3 (Arexvy, GSK) and RSVpreF (Abrysvo, Pfizer) can be administered concurrently with the seasonal influenza vaccine. RSVpreF3 shows non-inferior immune responses in adults aged 60 and older, but co-administration resulted in numerically lower RSV A and B neutralising titres and influenza A and B hemagglutination inhibition titres, with unknown clinical relevance. RSVpreF, studied in adults aged 65 and older, also demonstrated non-inferior immune responses, but co-administration with adjuvanted influenza vaccine showed similar reductions. RSVpreF requires a two-week interval before tetanus, diphtheria, and acellular pertussis vaccine, and is associated with lower immune responses to pertussis components in co-administration; the clinical relevance remains unknown.^{50,51} Despite the lack of specific studies, public health authorities can decide to authorise the co-administration of RSV with other vaccines, favouring the opportunity of vaccination against the eventual immunological interference.^{53,54}

NEP Positioning and RSV Prophylaxis Recommendations in Adults

The Spanish Neumoexperts Prevention Group (NEP; www.neumoexpertos.org) publishes updated immunisation

recommendations to prevent community-acquired pneumonia in adults.⁷⁰ The proposed vaccine schedule prioritises individual protection to effectively prevent CAP in adults. This schedule is designed to assist healthcare professionals in daily practice by offering the most optimal vaccination recommendations based on the latest evidence. Fig. 1 illustrates the most recent NEP recommendations, including those for RSV vaccination.

Concerning RSV prevention, NEP recommends the following measures:

1. Implement infection control measures in healthcare facilities and long-term care settings.⁷¹
2. Promote public awareness and education regarding RSV transmission and preventive measures.⁷¹
3. Develop and reinforce surveillance systems to monitor community RSV activity and promptly identify outbreaks.⁷¹
4. Recommendations for vaccination.

From an individual protection perspective, the NEP in Spain recommends RSV vaccination for older adults aged ≥ 60 , especially those with chronic pulmonary disease, chronic cardiovascular disease, and other diagnoses or conditions that cause impaired lung function or poor cough strength and stagnation of secretions (extreme obesity or neurological impairments),⁷² kidney disease, diabetes, immunosuppression, or institutionalised status. Although there are currently two approved vaccines for adults, RSVpreF (Abrysvo, Pfizer) and RSVpreF3 (Arexvy, GSK) that are difficult to compare, given their different clinical studies, varying case definitions, and analysis criteria, both vaccines have demonstrated their efficacy and safety and are recommended in this age group.

From a public health perspective, we believe that an aged-based indication is the most recommendable strategy, although the concrete age threshold should be determined balancing the burden of disease prevented and the associated costs of the intervention. The Centres for Disease Control and Prevention (CDC) recommends RSV vaccination for individuals aged ≥ 60 based on shared clinical decision-making between the healthcare provider and the vaccine (Table 5) using either available vaccine.⁵⁴ In the United Kingdom, the Joint Committee on Vaccination and Immunisation (JCVI) used their modelling to establish the indication for RSV vaccination among older adults aged ≥ 75 (Table 5).⁷³

Irrespective of the age indication, any adult aged over 60 years with specific risk factors for severe RSV disease (Table 4) should be prioritised for vaccination. This strategy likely constitutes a good starting point for any RSV vaccination policy and should be warranted to protect the most vulnerable (Table 6). Also, healthcare workers should be offered RSV vaccination because they are at a higher risk of contracting RSV and to the increased risk of transmitting RSV to their patients.^{14–16}

VACCINATION GUIDE AGAINST COMMUNITY ACQUIRED PNEUMONIA IN ADULTS 2024

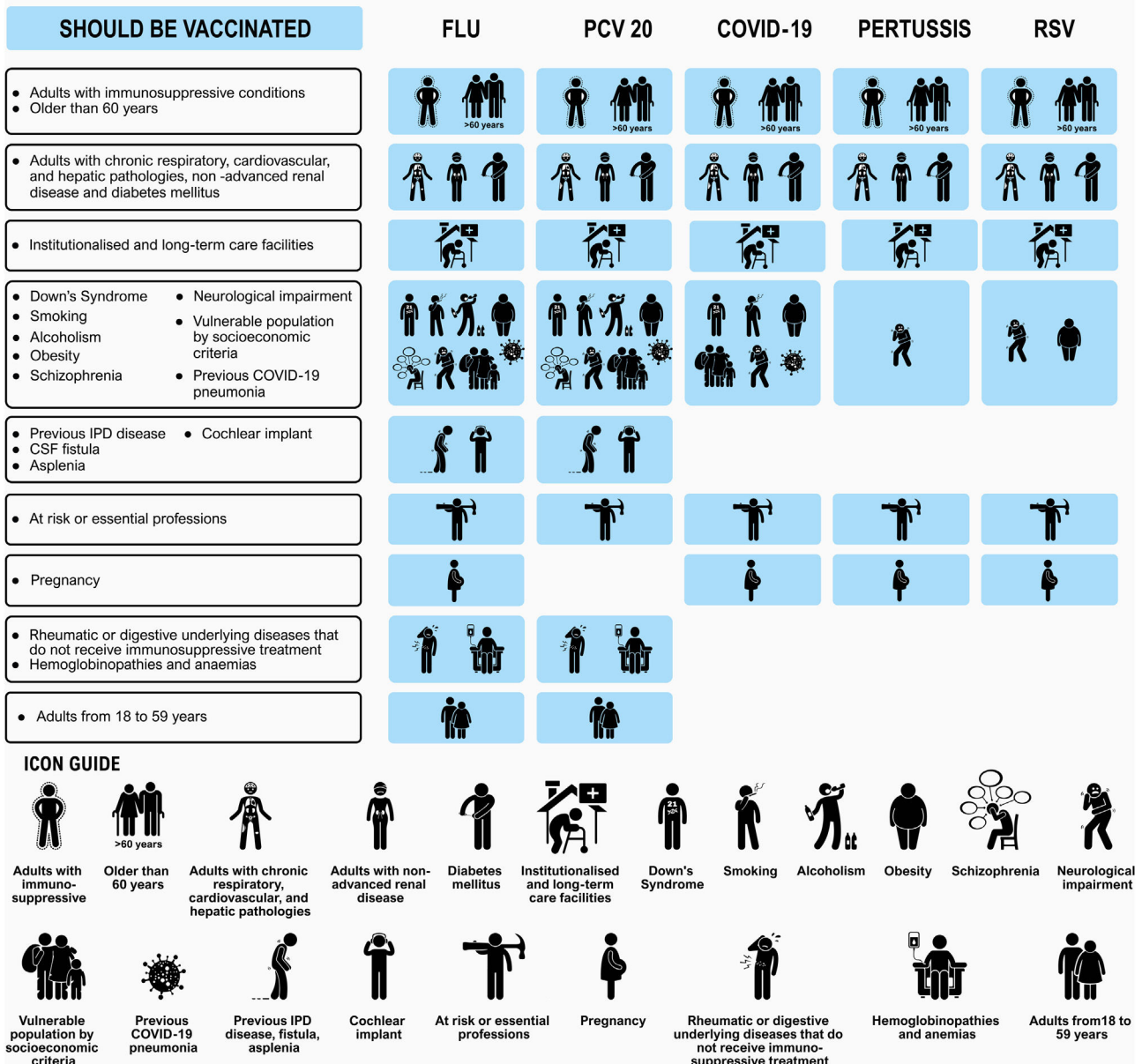


Fig. 1. Vaccination guide against community-acquired pneumonia in adults caused by vaccine-preventable diseases. CSF: cerebrospinal fluid; IPD: invasive pneumococcal disease.

Adapted from Redondo et al.⁷⁰

Table 5
Official Recommendations on the Use of Licensed RSV Vaccines for Older Adults.

Agency/society	Age (years)	Risk groups	Vaccine implementation practice
CDC (US) ⁵⁴	≥ 60	Pulmonary/Heart Disease, Immunosuppression, Institutionalised	Arexvy (GSK) and Abrysvo (Pfizer), Shared Clinical Decision-Making
JCVI (UK) ⁷³	≥ 75	No specified risk groups	Arexvy (GSK) and Abrysvo (Pfizer), Vaccination Programme
NEP (SP)	≥ 60	Pulmonary/Heart Disease, Cardiac Disease, Hepatic Insufficiency, Kidney Disease, Diabetes, Immunosuppression, Institutionalised, Neurological Diseases	Arexvy (GSK) and Abrysvo (Pfizer), Individual recommendation ≥ 60 Vaccination Programme: at least risk group

CDC: Centres for Disease Control and Prevention; JCVI: Joint Committee on Vaccination and Immunisation.

Table 6
Summary of NEP Group Positioning on RSV Vaccination in Older Adults.

1. RSV is a significant cause of respiratory pathology in adults, with a potentially underestimated burden and a significant mortality rate.
2. There are currently two approved vaccines for adults, RSVpreF (Abrysvo, Pfizer) and RSVpreF3 (Arexvy, GSK) that are difficult to compare, given their different clinical studies, varying case definitions, and analysis criteria. Nevertheless, both vaccines have demonstrated their efficacy and safety.
3. The opportunity of co-administration of any available RSV vaccines with other vaccines should be highly considered even in the absence of specific studies.
4. From an individual protection perspective, any individual aged 60 years and older can benefit from vaccination.
5. From a public health perspective, determining the most efficient age recommendation for RSV vaccination in Spain will depend on the applied pharmaco-economic models/studies. However, it seems reasonable and advisable to at least include it in the adult vaccination schedule for adults aged 60 years and older in the following risk groups: institutionalised individuals, those with chronic cardiovascular, pulmonary or renal diseases, individuals with diabetes mellitus, individuals with immunosuppression and those with neurological impairments.

RSV: respiratory syncytial virus.

Conclusion

Severe RSV disease can have significant consequences in individuals aged ≥ 60 years, particularly those with chronic medical conditions or other risk factors. Vaccination effectively reduces the risk of disease, lessens the severity of illness, and protects vulnerable populations. It is imperative for individuals aged ≥ 60 years to prioritise their health by considering vaccination against RSV as part of their healthy lifestyle and ideal immunisation schedule against pneumonia. Ongoing research, including studies on new vaccine candidates and antiviral therapies, offers hope for the development of even more effective interventions. As vaccines reach the population, implementing positioning strategies, such as improved infection control measures in healthcare facilities and targeted education campaigns, and promoting preventive measures, such as hand hygiene and respiratory etiquette, can help mitigate the impact of RSV on adult health. However, RSV vaccination constitutes a key pillar in the prevention strategy. Continued research, collaboration between scientists, vaccine manufacturers, healthcare professionals and policymakers, and investment in RSV surveillance systems are indispensable to advance our understanding of RSV epidemiology, risk factors, and clinical outcomes in adults and to develop evidence-based interventions to safeguard this vulnerable population.

Authors' Contributions

All authors have significantly contributed to the conceptualization and performance of the study. The literature analysis workload has been equally divided among the authors. The elaboration of recommendations has been discussed and agreed among the members, including the multidisciplinary perspective of the NeumoExpert group. All authors have contributed to the critical review of the manuscript.

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Conflicts of Interest

FM-T has acted as principal investigator in randomised controlled trials of Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Sanofi Pasteur, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK, with honoraria paid to his institution. FM-T reports a relationship with GSK Vaccines SRL that includes consulting or advisory. FM-T reports a relationship with Pfizer Inc that includes consulting or advisory. FM-T reports a relationship with Sanofi Pasteur Inc that includes consulting or advisory. FM-T reports a relationship with Janssen Pharmaceuticals Inc that includes consulting or advisory. FM-T reports a relationship with MSD that includes consulting or advisory. FM-T reports a relationship with Seqirus Pty Ltd that includes consulting or advisory. ER has participated in advisory boards, conferences, courses and lectures organised by Sanofi Pasteur, MSD, GSK, Seqirus, Pfizer and AstraZeneca. IRC has participated in advisory boards organised by MSD, GSK, Sanofi and Pfizer. IRC has been involved in clinical trials funded by Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK, although the funds were paid to the institution. EM has participated in advisory boards by Astra-Zeneca, Boehringer Ingelheim, Esteve, GSK, MSD, Menarini, Mundifarma, Novartis, Orion, Pfizer, Roche, Rovi, Takeda and TEVA. DO has participated in advisory boards from Lilly, Boehringer Ingelheim, Novartis, Pfizer, Takeda, Esteve, Almirall, GlaxoSmithKline, Astra-Zeneca, Chiesi, Mundipharma, Teva, Solvay Pharma, Rovi, Gebro Pharma, Janssen, MSD, Novo Nordisk and Menarini. IJ has participated in advisory boards from Pfizer, Sanofi Pasteur, and conference attendance scholarships paid by Menarini, Esteve. AG has participated in advisory boards by Pfizer, GlaxoSmithKline, Janssen, MSD and Sanofi Pasteur. ML has participated in advisory boards and research projects organised by Pfizer. FGR has participated in advisory boards, conferences, courses and lectures organised by Sanofi Pasteur, MSD, GSK, Pfizer and Moderna. JY received grants from MSD-USA (Merck Investigator Studies Programme), and Pfizer, outside of this work and the funds were awarded to the Institution. JY participated in advisory boards organized by MSD and Pfizer. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.arbres.2024.01.004](https://doi.org/10.1016/j.arbres.2024.01.004).

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