REVIEW ARTICLE

Respiratory Syncytial Virus Infection in Older Adults: An Update

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Abstract

Respiratory syncytial virus (RSV) infection represents one of the most common infections during childhood, with significant morbidity and mortality in newborns and in the early years of life. RSV is a common infection throughout all age groups, largely undetected and underestimated in adults, with a disproportionately high impact in older individuals. RSV infection has a wide range of clinical presentations, from asymptomatic conditions to acute pneumonia and severe life-threatening respiratory distress, including exacerbations of underlying chronic conditions. Overall, the incidence of RSV infections requiring medical attention increases with age, and it is highest among persons ≥ 70 years of age. As a consequence of a combination of an aging population, immunosenescence, and the related increased burden of comorbidities, high-income countries are at risk of developing RSV epidemics. The standard of care for RSV-infected patients remains supportive, including fluids, antipyretics, and oxygen support when needed. There is an urgent need for antivirals and preventive strategies in this population, particularly in individuals at higher risk of severe outcomes following RSV infection. In this review, we describe prevention and treatment strategies for RSV illnesses, with a deep focus on the novel data on vaccination that has become available (Arexvy, GSK, and Abrysvo, Pfizer) for older adults.

Key Points

Respiratory syncytial virus (RSV) is a common cause of infection across all ages, with different degrees of severity.

Immunosenescence is an aggravating risk factor. Older individuals and people with comorbidities are at higher risk of severe infections; RSV infection is the third most commonly identified viral cause of hospitalization.

There is no specific anti-RSV treatment. Effective active immunization is now available and suggested in adults, based on the efficacy of candidate vaccines in phase III studies. The efficacy is high in patients with chronic comorbid conditions.

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1 Epidemiology, Virology, and Immunopathology

1.1 Introduction

Respiratory syncytial virus (RSV) is a ubiquitous respiratory virus belonging to the *Pneumoviridae* family, genus *Orthopneumoviridae*. There are two subgroups (A and B), differing from each other in their molecular structure. Like other respiratory viruses, RSV infection results in annual recurring events (seasonal epidemics). RSV infection represents one of the most common infections during childhood, with significant morbidity and mortality in newborns and in the early years of life [1]. In recent decades, epidemiological data have reinforced the evidence of the many faces of RSV infection throughout all age groups, with a disproportionately high impact in elderly individuals. RSV infection has a wide range of clinical presentations, from asymptomatic infections to severe lower respiratory tract infections (LTRIs), including exacerbations of underlying chronic conditions. Overall, RSV-related acute respiratory infections (RSV-ARIs) are largely undetected in adults and substantially underestimated. Currently, two monoclonal antibodies (palivizumab and nirsevimab) are approved and available for preventing RSV infection in the high-risk infant population, whereas no such option is available for adults.

Recently, active immunization has been approved in adults based on the efficacy of candidate vaccines in phase III studies. In this article, maintaining a deep focus on elderly individuals and people with comorbidities, we discuss the latest epidemiological data about RSV, its virology and immunopathology, and the clinical characteristics and therapeutic and preventative perspectives of RSV infection.

1.2 Source and Selection Criteria

Our search sites included references in PubMed and Google Scholar between 1957 and 2023. The main search terms included "RSV" and "respiratory infections", in conjunction with "therapeutics", "vaccine", "epidemiology", "adults", "elderly", "frail", and "comorbidities". We searched for recent guidelines and consensus statements. We included observational and animal studies if clinically relevant. Finally, we searched ClinicalTrials.gov for updated clinical trial information.

1.3 Epidemiology

In 2015, the Global Burden of Disease (GBD) study estimated 1.7 million deaths caused by LTRIs, with RSV representing one of the important viral pathogens [2]. RSV has a seasonal pattern of infectivity, commonly seen in respiratory viruses, including influenza, with annual recurrence. In temperate climate countries, it spreads throughout the winter season, with a peak between December and January, whereas in tropical countries, it circulates in the summer season [3]. Either a single subgroup or both (A and B) remain each season, determining reinfection and seasonal outbreaks [3]. Reinfections are common throughout life due to a short-term, or incomplete, immunity response. Antigenic variations are considered less important, at variance with other respiratory viruses such as influenza [4]. Before the coronavirus disease 2019 (COVID-19) pandemic, RSV followed a predictable seasonal pattern of infection. During the pandemic, due to the reduced spread of infections related to generic hygiene procedures such as social distancing, wearing face masks, and hand washing/disinfecting, all respiratory viral infection rates dramatically decreased, especially the clinical manifestations of RSV and influenza. Notably, there was a rebound of viral infections following the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic season [5]. The concept of "immunity debt" has been proposed for this resurgence of cases, which caused a heavy burden on healthcare services defined as a "tridemic", a triple threat from the increasing spread of SARS-CoV-2, flu, and RSV at risk of overwhelming the healthcare systems [5]. After the SARS-CoV-2 pandemic period and the lifting of public health and social measures, a greater number of RSV cases were observed in different countries, with out-of-season epidemics and with a delayed surge of RSV, compared with the usual seasonality [6].

The highest burden of RSV infections occurs in children < 5 years old (with a global incidence of 17 per 1000 people) and older adults aged > 70 years (incidence of 6.3 per 1000 people) [5]. A global systematic analysis recently conducted in children aged < 5 years old estimated that 33.0 million RSV-LTRIs occurred in 2019, of which, 6.6 million occurred in infants 0–6 months old, with more than 95% of RSV-LRTIs occurring in low- and middle-income countries [7]. In children aged < 5 years, 3.6 million RSV hospital admissions were estimated, with 26,300 in-hospital deaths globally [7]. RSV accounts for as much as 70% of all childhood respiratory infections, with almost all children infected with RSV by the age of 3 [8, 9]. Known risk factors for severe RSV infection in younger people include prematurity, age < 2 months, underlying chronic lung or heart diseases, serious neurological or metabolic disorders, Down's syndrome, immune deficiency, crowded living conditions, and indoor smoke pollution.

Data on RSV infection in elderly individuals and in people with comorbidities are some decades behind the robustness of the paediatric evidence, although they have recently had exponential growth. The RSV burden in three European countries in both healthy older adults and adults with comorbidities is comparable to that caused by influenza [10]. RSV-ARI is the third most commonly identified viral cause of hospitalization, mostly in adults aged > 65 years old, with less than 1% of adults with RSV infection requiring hospitalization [3]. Data on adults from developing countries are scarce. No significant difference in sex or economic status has been reported in the incidence of RSV infection, even when tropical and subtropical regions were considered [11, 12].

Prospectively, in high-income countries, it is expected in 2025 that the number of RSV-ARIs in older people > 65 years could reach 10 million cases, 800,000 hospitalizations, and 74,000 in-hospital deaths [10]. A recent meta-analysis conducted by Savic et al. analysed 21 different studies regarding RSV infections in people aged 60 years and older in high-income countries, highlighting that, in 2019, the RSV-ARI attack rate was 1.62% [10]. The RSV-ARI hospitalization rate was estimated to be 0.15%, while the RSV-ARI in-hospital case fatality rate (hCFR) was 7.13% [10]. For comparison, each year influenza causes between 3 and 5 million severe cases, with 290,000–650,000 deaths globally, most of them occurring in older patients [13]. The influenza mortality rate in people aged > 70 years old is 16.4 per 100,000 people, compared to 1.9 in the general population [14]. Similarly to RSV, the population at higher risk of

severe disease or complications due to influenza infection are children under 5 years of age, older people, individuals with chronic medical conditions (i.e. cardiorespiratory, renal, or immunosuppression conditions), and pregnant women [15].

RSV infection has been increasingly identified as a cause of respiratory viral diseases in adults with comorbidities, including cardiopulmonary diseases. A meta-analysis by Shi et al. considered 20 studies on RSV-ARIs in adults with comorbidities, 18 from developed countries and two from developing countries, and ten in adults aged > 18 years and ten in older groups of > 50 years [2]. The analysis reported an incidence rate for RSV-ARI in adults with comorbidities (e.g. cystic fibrosis, chronic heart failure [CHF], chronic obstructive pulmonary disease [COPD] immunocompromised status) of 30.3 per 1000 persons per year/season [2]. The hospitalization rate in CHF or COPD adults aged > 65 years was 13.2 per 1000 persons per year, with an hCFR of 11% [16].

Indeed, it has been estimated that as a consequence of a combination of an aging population, immunosenescence, and the related increased burden of comorbidities, high-income countries are at risk of developing RSV epidemics [17]. Notably, clinicians for a long time have not been considering RSV infection as a potential cause of hospitalization and relevant morbidity in adults. This, combined with the lack of specific antiviral treatment, has discouraged physicians from performing RSV diagnostic testing and contributed to the under recognition/estimation of the real impact of RSV (particularity in at-risk populations) [10]. Indeed, to date, few ad hoc RSV surveillance systems are in place to assess the real impact of RSV infection and to raise awareness of the risks of RSV infections in sensitive populations [17]. In recent years, RSV testing has substantially increased in relation to more efficient and affordable detection methods, such as the molecular polymerase chain reaction (PCR) technique [3].

In a recent European study, almost 40% of all RSV-associated hospitalizations occurred in patients aged 65 years and older [17]. Of the 158,000 RSV-associated hospital admissions among adults older than 18 years old [17], 92% (145,000) occurred in patients older than 65 years of age (Fig. 1). Adults aged 75–84 years showed the highest annual frequency of RSV hospitalization, accounting for 75,000 cases/year, at a rate of 2.24 per 1000 adults annually, with the highest rate among elderly individuals > 85 years of age [17]. Comparable data have been reported in the United States (US), with a burden of 159,000 RSV hospitalizations in adults > 65 years of age [18]. The overall mortality for patients admitted for RSV is 6–8%, accounting for 25% of the excess winter mortality [3]. Data from Southern and Eastern Europe are still scarce. Moreover, even if data available for RSV hospital admission are likely to reflect the overall burden of the infection, to date, the estimated burden of the disease in the general population is still uncertain.

Between 10% and 31% of adults hospitalized for RSV infection require intensive care support, while 3–17% of them require mechanical ventilation. Of all high-risk patients (with cardiopulmonary disease or immunodeficiency) infected by RSV, 32% will require hospitalization and 26% will need intensive care support [19]. Data indicate that mortality rates range from 11 to 18% in hospitalized adults 65 years of age and older with RSV infection [2, 20], with an estimated 13% RSV-related case fatality for patients with cardiopulmonary disease among high-risk European adults [19].

In general, RSV infections occur more frequently in patients with underlying chronic lung diseases. In patients with obstructive lung diseases, RSV is one of the major triggers of acute exacerbations of asthma and COPD [3]. RSV is the second most common respiratory virus detected in acute exacerbations of COPD, accounting for up to 15% of exacerbations. In COPD patients, the clinical presentation, radiological findings, length of stay, hospitalization, intensive care unit (ICU) admission, and mortality rates of RSV infection are similar to those of influenza [21]. RSV is also a major risk factor for developing asthma exacerbations, particularly in patients hospitalized for RSV-ARIs in infancy [4]. Moreover, RSV can induce bronchial hyper-responsiveness, contributing to the pathogenesis of asthma in infancy [22].

1.4 Virology and Immunopathology

RSV is a respiratory virus belonging to the *Pneumoviridae* family, *Orthopneumoviridae* genus. RSV is a single-stranded negative-sense RNA virus containing an approximately 15,200-nt genome and encoding 11 proteins (Fig. 2) [23]. Proteins G and F are the two most relevant surface antigenic proteins, accounting for attachment and fusion, respectively, to host cells. RSV is categorized into two antigenic subtypes, A and B, based on the second hypervariable region of the G gene [4, 24]. RSV-A and RSV-B subtypes may cocirculate during an outbreak; RSV-A represents the predominant strain in most years [4]. Reinfection is frequent and can occur throughout life, while the severity of RSV-ARI tends to diminish after subsequent exposure [4].

RSV spreads through respiratory droplets or fomites. RSV primarily infects polarized ciliated human airway epithelial cells (hAECs) [25], reaching the upper (URT) and lower respiratory tracts (LRT). hAEC infection determines morphological alterations of infected cells, cilia loss, mucus hypersecretion, and syncytia formation (thus, the name of syncytial virus) [4]. The G protein (RSV G) is responsible for virus attachment, binding to receptors such as nucleolin,
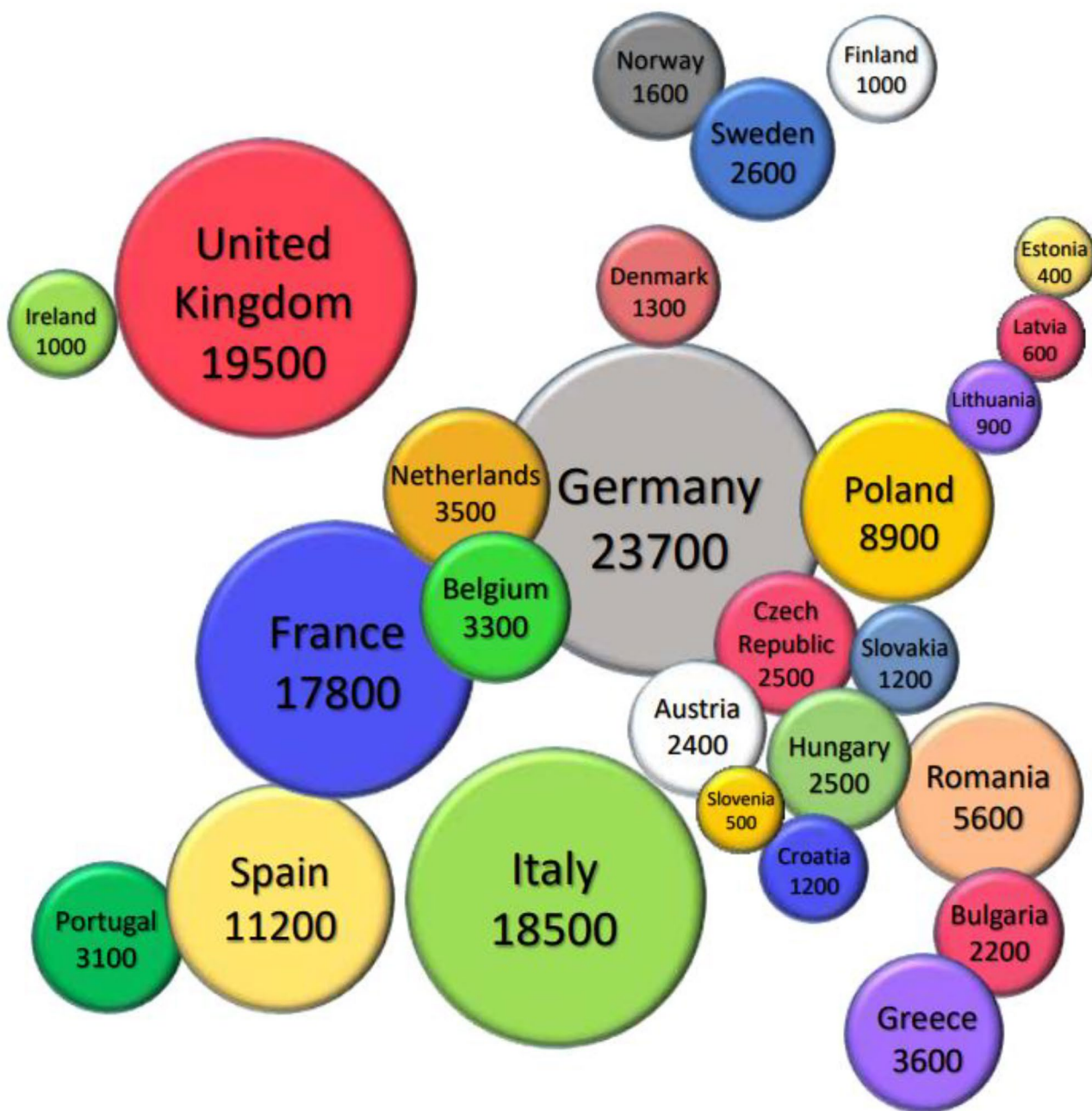
Fig. 1 Geographical distribution of the estimated annual respiratory syncytial virus-associated hospitalizations in European Union countries (including the United Kingdom) and Norway in patients aged > 65 years old (data from [17]).

CX3C motif chemokine receptor 1 (CX3CR1), Heparan Sulfate ProteoGlycans (HSPGs), and Intercellular Adhesion Molecule 1 (ICAM-1). After RSV G connects RSV to epithelial cells, RSV F protein merges with the surface membrane and enters through pores into the cytoplasm. Viral entry and infection are catalysed by the prefusion F protein after a conformational change into a post-fusion conformation, fusing the virion to host cells. Herein, viral RNA initiates transcription and viral replication [23].

During the first phase of infection, host cell pattern recognition receptors (PRRs) recognize RSV and initiate a signalling cascade resulting in the expression of interferon (IFN) molecules, upregulating major histocompatibility complex I (MHC-I), NLR family CARD domain containing 5 (NLRC5), and IFN-β [4]. During the later stage of RSV infection, Toll-like receptor 3 (TLR3) binds to viral RNA, activating the transcription of Nuclear factor-κB (NF-kB) and type I IFNs. The upregulation of type I IFN
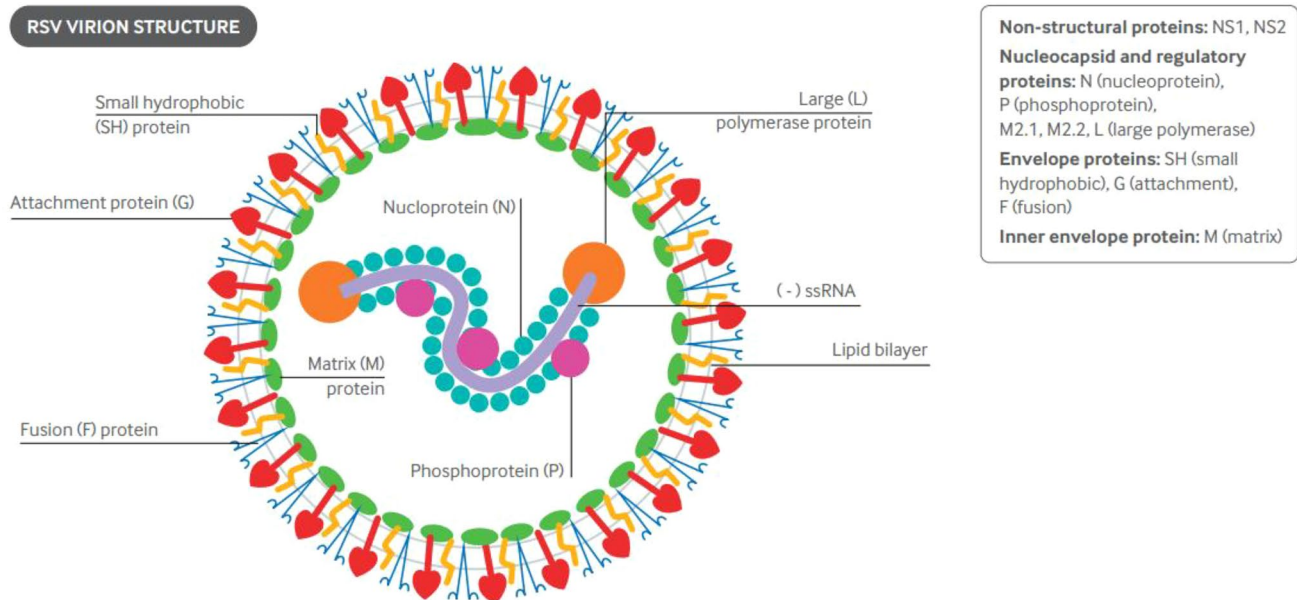
Fig. 2 Structure and genomic RNA of respiratory syncytial virus (Reproduced with permission from [3]). *ssRNA* single-stranded ribonucleic acid

predisposes cells to an "antiviral state", which restricts viral replication and warns and activates uninfected cells [4]. In mammalian models and humans, RSV proteins such as NS1, NS2, G RSV, and F RSV reduce type I responses, while several RSV proteins can interfere with type III IFNs located on hAECs, facilitating viral replication [23]. hAEC-infected cells release chemo-attractants and adhesion molecules such as tumour necrosis factor (TNFα), C-X-C motif chemokine ligand 6 (CXCL6), interleukin (IL)-1β, IL-6, IL-8, chemokine ligand 2 (CCL2), granulocyte-monocyte colony stimulating factor (GM-CSF), Macrophage inflammatory protein-1 alpha (MIP-1α), ICAM-1, and MHC-I/II, thus fully activating innate and adaptive immune responses [4]. Each different RSV protein plays a role in infection and in eliciting an immune response. NS1 and NS2 are involved in immune modulation by interacting with different immune signalling pathways, including the JAK/STAT suppressing pathway, and with the host's gene expression and activation pathways, including NF-kB. In vitro and in vivo, NS1 and NS2 induce necroptosis of hAECs, an inflammatory programmed cell death, and subsequently inhibiting the classic apoptosis pathway [26]. RSV proteins in infected hAECs not only interfere with intrinsic and classical immune pathways but also impair the activation of several genes involved in the production of cytokines and chemokines, which are critical for the recruitment of innate and adaptive immune cells [26].

Indeed, both innate and adaptive immune responses are elicited by RSV infection; they both contribute to the pathogenetic mechanisms related to the infection [23], as summarized in Fig. 3 [21]. RSV innate immune responses involve polymorphonuclear leukocytes (PMNs, such as neutrophils and eosinophils), alveolar macrophages (AMs), natural killer (NK) cells, and dendritic cells (DCs).

Neutrophils can migrate into tissues during acute viral infections and are involved in virus identification and elimination, antigen presentation, recruitment of proinflammatory cells, and cytokine production. Neutrophil activity during RSV infection consists of phagocytosis, degranulation, and NETosis, i.e. a neutrophil-death inflammation signalling pathway. Polymorphonuclear cells exhibit a bivalent role during RSV infection and could lead to more severe and symptomatic infections [4].

Eosinophils have phagocytic and antigen-presenting activity. RSV-infected in vitro hAECs secrete chemoattractant mediators such as CCL5 or MIP-1α, leading to eosinophil recruitment to the site of infection [4]. Eosinophils activate signalling cascades, resulting in increased expression of type I IFNs such as IFN-β. Eosinophils contribute to viral elimination by degranulation and secretion of RNA-degrading enzymes, such as eosinophilic cationic protein (ECP) [4]. Excessive recruitment of eosinophils may result in tissue damage and an unbalanced T cell response towards a T2-high phenotype [4, 22]. Indeed, infants with severe RSV disease have a high Th2/Th1 (T helper) ratio profile and an increased risk of developing asthma [22, 23].

NK cells are crucial to restrict viral spread in the early stages of infections, given their cytotoxic and immunological activities. In the later stages of infection, NK cells switch to a regulatory phenotype to limit immune cell-mediated lung
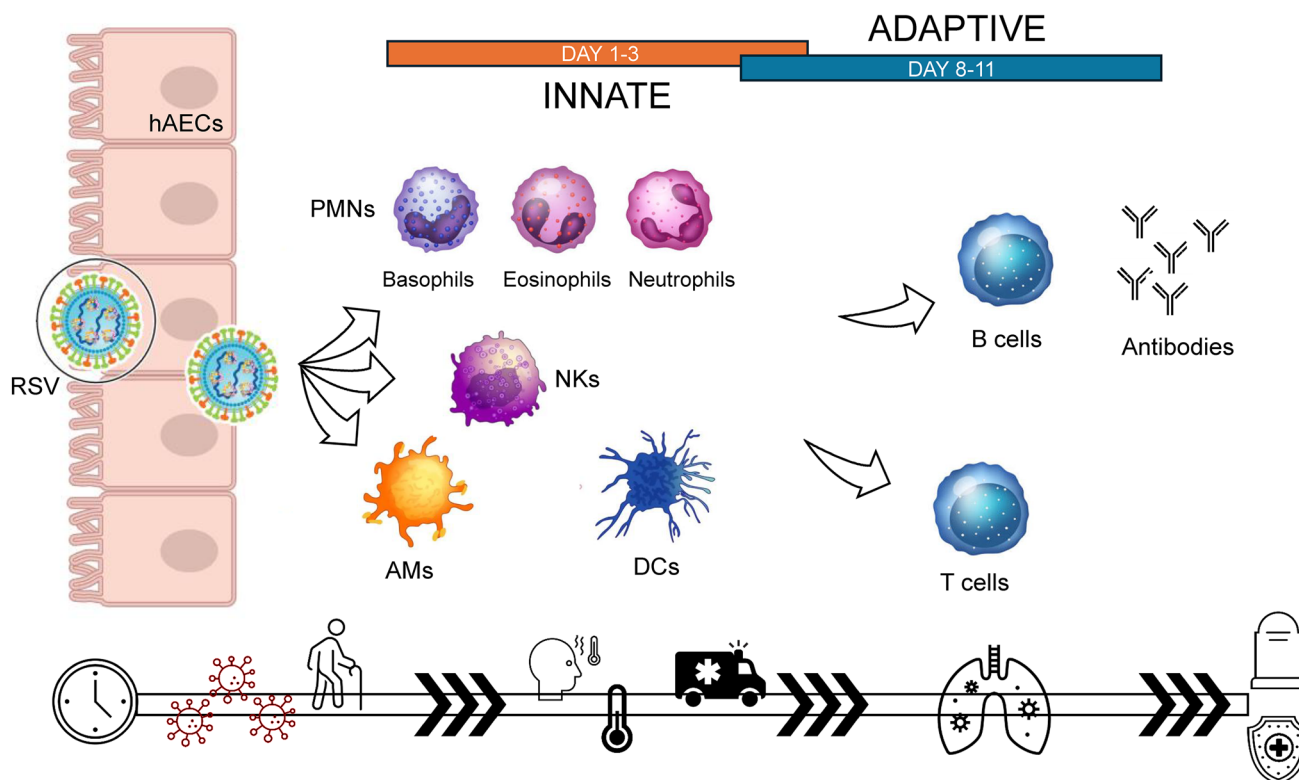
Fig. 3 Pathogenesis of RSV infections, involving the innate and adaptive immune response. *AMs* alveolar macrophages, *DCs* dendritic cells, *hAECs* human airway epithelial cells, *NKs* natural killers, *PMNs* polymorphonuclear cells, *RSV* respiratory syncytial virus

inflammation [4]. Functional monocytes migrate into the lungs during viral infections, and their role is pivotal for protection, immune regulation, and supply to the macrophage population during the acute phases of viral infection [4]. Lung DCs are professional antigen-presenting cells that are chief producers of type I IFNs and bridge innate and adaptive immune responses during viral infection. DC depletion may result in increased viral load [4, 23].

Adaptive immune responses to RSV occur via B cell and T cell activation, and B cells prime the production of virus-specific antibodies, neutralizing the virus and thus preventing RSV cell entry. B cells produce antibodies against RSV F (to both the prefusion and post-fusion structures) that are highly neutralizing and cross-react with both RSV-A and RSV-B subtypes [27]. Unfortunately, RSV-specific B cells rapidly decrease once the infection is over, usually within months after exposure, due to an immunosuppressive effect of RSV on the generation of memory T cells [4]. CD8+ cytotoxic T cells can directly kill RSV-infected cells, while CD4+ T cells enhance B cell activation and antibody production [23]. Older adults have comparable RSV antibody responses to younger people, even if they are more susceptible to severe RSV infections, indicating that other immunological parameters, such as dysfunctional T cells, should

be considered to account for the immunological deficiencies associated with immunosenescence [4].

In childhood, the mechanisms of RSV-associated diseases are considered related to the immaturity of the defensive system; in analogy, in elderly people, immunosenescence plays a relevant role in increasing susceptibility to infection and increasing the risk of severe output of the infective event. Immunosenescence refers to the diminished efficiency of the innate and adaptive immune systems due to biological aging [28]. It is a complex condition accounting for a series of alterations in immune homeostasis and cell regulation, resulting, among others, in increased susceptibility to severe infections, poor vaccine responses, and a higher likelihood of long-term sequelae [29]. Older adults show reduced viral clearance and mucus production, which favour the occurrence of airway infections [4]. In the elderly population, B cell and antibody responses are lower in quantity and less efficient than in younger individuals. Similarly, the T cell repertoire is poorer and has low functioning, with dysregulation of cytokine production and fibrosis of lymph nodes [29]. These factors contribute to increasing susceptibility to infectious diseases. Indeed, influenza-related deaths occur in 70–90% of adults older than 65 years of age, while pneumococcal disease mortality in older adults (15–30%) is higher

than that in the younger population [29]. In addition, as a consequence of the dysregulation of immune responses due to immune senescence, elderly individuals express a lower rate of seroconversion after vaccination than younger individuals, as documented for influenza vaccines [30].

2 Clinical Presentation, Risk Factors, and Comorbidities in Adult Patients

In general, RSV-ARIs are not clinically distinguishable from those related to other respiratory viruses. There is a wide range of clinical presentations (Table 1), from asymptomatic conditions to acute pneumonia and severe life-threatening respiratory distress [31]. In adults, asymptomatic infections are less frequent than in younger patients (< 5%). The majority of adults develop signs of URT infection, such as rhinorrhoea, nasal congestion (22–78%), or pharyngodynia (16–64%), within 5 days of infection [3]. LRTIs can cause cough (85–95% of cases), wheezing (33–90%), and dyspnoea (51–93%), reflecting RSV direct/indirect damage to the lower tract [3]. Non-specific systemic symptoms are fever, asthenia, and anorexia (48–56%), which could vary in intensity and severity [3], although they occur less commonly than in influenza infection. Unlike influenza virus infections, whose clinical expression peaks at 2–3 days after the onset of the first symptom, RSV infection typically develops symptoms from 4 to 7 days after exposure, peaking between 7 and 13 days [32].

RSV LRTIs can cause pneumonia and exacerbations of chronic airway diseases such as asthma or COPD [33]. Respiratory failure has been reported in 8–13% of older adults hospitalized for RSV, with a mortality of 2–5% [34]. RSV infections can be complicated by concomitant bacterial or viral respiratory coinfection in up to 21–23% of cases, with the former pathogen coinfection being associated with an enhanced risk of death and severe RSV disease [3]. During the recent COVID-19 pandemic, significant RSV coinfection

was demonstrated in patients with SARS-CoV-2 infections. The most common coinfections were rhinovirus/enterovirus (6.9%), RSV (5.2%), and non–SARS-CoV-2 *Coronaviridae* (4.3%) [35].

Clinical manifestations of RSV infection in the elderly are hardly distinguishable from those of influenza or other respiratory viruses, but some symptoms may be more suggestive for one of the pathogens. High fever is more frequently associated with influenza. Similarly, malaise, asthenia, and myalgia, as well as gastrointestinal symptoms are less common in RSV infection than during influenza episodes [34].

Compared to influenza adults, adults hospitalized with RSV present a longer length of stay (6.0 days vs 3.6 days) [17] and increased morbidity. In a study conducted on adults in patients hospitalized for influenza-like illness during three consecutive seasons, 15% of RSV-positive patients were admitted to the ICU, and 8% died. The percentages were similar in the influenza-infected individuals. RSV patients were significantly more likely than patients with influenza or without RSV to develop pneumonia (44% vs 28% and 26%, respectively) [36].

RSV infection usually occurs more than once in life. Although our knowledge of the burden of RSV in the elderly has increased [1, 5], it is still lacking compared to the vast literature available for RSV in children [2]. Indeed, RSV was not considered a potentially serious problem in older adults until the 1970s, when outbreaks of RSV infection occurred in long-term care facilities [12, 37]. Overall, the incidence of RSV infections requiring medical attention increases with age, and it is highest (199 episodes per 10,000) among persons ≥ 70 years of age [38].

2.1 RSV Infections in Older Patients with Chronic Diseases

Many hospitalized RSV infections involve adults with chronic medical conditions. In these cases, even when the RSV infection is clinically mild, it can result in hospital admission, serious complications, and death [10]. Advanced age, pneumonia, ventilator support, and secondary bacterial infection are all associated with an increased risk of death among hospitalized patients with RSV [17].

Viral infections, particularly rhinovirus and RSV, are commonly associated with acute exacerbations of asthma [39] and have been claimed to contribute to the development of asthma in preschool children [40, 41]. A prospective study with a cohort of 206 children demonstrated that severe RSV bronchiolitis in the first year of life is followed by a diagnosis of childhood asthma by the seventh birthday in nearly half of children. High asthma rates (48% by age 7 years) have been reported after RSV bronchiolitis in childhood [42].

Table 1 Clinical symptoms in adults infected with respiratory syncytial virus

	Clinical presentation	Frequency %
Asymptomatic	None	< 5%
General symptoms	Fever, asthenia and anorexia	48–56%
Upper respiratory symptoms	Rhinorrhea	22–78%
	Pharyngodynia	16–64%
Lower respiratory symptoms	Cough	85–95%
	Wheezing	33–90%
	Dyspnea	51–93%

RSV infection is an important cause of COPD exacerbation; it has been identified with variable frequencies ranging from 0.8 to 22% of acute cases according to the different diagnostic tools [31].

A multicentre study was conducted in 28 hospitals between January 2015 and December 2018 in the Republic of South Korea in a cohort of 1177 patients hospitalized with a diagnosis of acute exacerbation of COPD. The most commonly detected viruses were rhinovirus (11%) and influenza virus A (11%), followed by RSV (4.3%) [43].

In a post hoc analysis of two longitudinal studies that examined RSV infection in high risk adults for ≤ 2 RSV seasons, an increased risk of illness with RSV among patients with COPD was associated with exposure to children and the presence of CHF [44]. The association between exposure in children and the risk of acquiring RSV illness is not surprising because respiratory secretions of infants with primary infections contain high viral titres of RSV for relatively long periods, and infectious fomites may contaminate environmental surfaces [45].

In a secondary analysis of a multicentre prospective study in hospitalized patients with acute respiratory diseases in Canada, hospitalized patients with COPD who were RSV positive had a significant morbidity compared to individuals with influenza infection. In hospitalized patients with COPD and RSV infection, 24% needed non-invasive ventilation (vs 11% with influenza) and 18% needed ICU admission. Once in the ICU, half of the patients with RSV required mechanical ventilation. A lower mortality rate (2.8%) was observed among RSV-positive versus influenza-positive individuals. However, a significantly higher proportion of patients with RSV received non-invasive ventilation (23.6% with RSV vs 11.2% with influenza), which may have affected the likelihood of survival in the context of underlying COPD [46].

The association between cardiopulmonary diseases and the severity of RSV-associated respiratory disease is likely multifactorial and includes changes in immune function, hypoxia, and fever stress and possible prothrombotic changes induced by the infection and the related inflammatory conditions. With disruption of endothelial function, the inflammatory response can lead to plaque destabilization and rupture and thus contribute to acute coronary syndrome, especially in patients already at risk. In a large multicentre review of 607 patients hospitalized with RSV in Hong Kong, 14% of patients had cardiovascular complications; likewise, 13.3% of 547 influenza virus-positive patients had cardiovascular complications. Cardiovascular complications (heart failure, atrial fibrillation, acute coronary event) occurred in 19.4% of adults (18–65 years of age) with RSV infection, as well as 21.3% of immunocompetent elderly (> 65 years of age) and 25.6% of patients with COPD [47]. In a Canadian study with 22% of patients hospitalized for RSV infection experiencing cardiovascular complications (14% CHF exacerbation, 8%

new arrhythmia, 2% stroke, and 1% myocardial infarction), 52% of patients had a past medical history of cardiac disease [48]. Acute cardiovascular events were the direct cause of mortality in 16.7% of the 72 patients with RSV who died within 60 days of hospital admission [33].

A number of high-risk factors for RSV infection have been identified in haematopoietic stem cell transplantation, such as male sex, type of transplant (i.e. allogeneic), cytomegalovirus seropositivity, and engraftment status [4, 37]. Infection with RSV is also of special concern in lung transplant recipients [26]. The estimated incidence of community-acquired respiratory virus infections in lung transplant recipients is 15–50 cases per 100 patient-years, and RSV accounts for 19% of these infections (i.e. 2–10 per 100 patient-years) [49].

3 Diagnostic Tools and Innovation

Four principal methods of diagnosing RSV acute infection are currently available: viral culture; antigen detection by immunofluorescence assay (IFA) or enzyme immunoassay (EIA); RNA detection by reverse transcription-PCR (RT-PCR); and serological assessment of RSV-specific Immunoglobulin M (IgM) antibodies or a significant rise in RSV-specific IgG antibodies between acute- and convalescent-phase sera. The latter method provides only a retrospective diagnosis [50]. Molecular techniques, such as nucleic acid amplification tests, which can detect very low viral titres, have high diagnostic accuracy in adults and provide rapid results. Reverse transcriptase real-time PCR (RT-PCR) has become the reference diagnostic method for RSV detection [51, 52].

Nearly all recent RSV incidence estimates have been obtained by RT-PCR testing of nasal or nasopharyngeal (NP) swabs [53]. The advantages of adding multiple tools for detection are questionable [54]. NP swabs have become a common self-administered tool for detecting viral infection during the COVID-19 pandemic; thus, currently, obtaining accurate epidemiological/diagnostic data has become simpler.

In the case of respiratory symptoms appearing in an elderly individual, early detection of RSV would allow a more effective containment of virus spread and prevention of outbreaks, as we learned from the recent COVID-19 pandemic. Additionally, the opportunity to use swabs to simultaneously identify multiple respiratory pathogens would enable a faster and more targeted management approach. Therefore, considering the simplicity of (and familiarity with) NP swab collection in the general population (particularly among healthcare professionals and caregivers), the use of tools such as nasal and NP swabs

should be encouraged, particularly in nursing homes and long-term care facilities, where the most vulnerable individuals reside and are at higher risk of severe clinical manifestations.

Radiological findings associated with RSV infection are usually nonspecific and nondiagnostic, particularly on chest X-ray.

In an observational and retrospective study, hospitalized adults with laboratory-confirmed RSV infection underwent chest radiography at admission. The chest radiography was abnormal in 50% of patients, with consolidation (48%) and ground glass opacity (GGO) in a single unilateral lower zone (40%) being the most frequent findings. [55].

Computed tomography may reveal pulmonary nodules and GGOs [56]. In general, imaging studies should be considered in most severe cases for differential diagnosis. In children with RSV infection (1 day to 10 years [median 7 months]), chest X-ray demonstrates radiological findings of central pneumonia and peribronchitis or the absence of abnormalities in equal proportions [57]. In an observational study in adults, lung bilateral involvement was less frequently reported in RSV cases than in other non-RSV viral infections [58].

The diagnosis of RSV infection in immunocompromised individuals is also associated with findings such as GGOs, nodular lesions, and signs of organizing pneumonia. In contrast to RSV, tree-in-bud opacities are frequently reported in influenza infections [59].

4 Management and Prevention

The standard of care for RSV-infected patients remains supportive, including fluids, antipyretics, and oxygen support when needed [60]. In children, only short-term clinical benefits are achieved with the use of available drugs and antivirals, with little or no effect from pharmacotherapy-based bronchodilators and glucocorticoids. There is no recommendation for the routine use of 3% nebulized hypertonic solution in children experiencing acute bronchiolitis [61]. Two antibody drugs, palivizumab and nirsevimab, have been approved for preventing RSV infection in infants. No such option is currently available for the treatment of RSV infection in adults. Therefore, there is an urgent need for antivirals and preventive strategies in this population, particularly in individuals at higher risk of severe outcomes following RSV infection. In the next sections, we will analyse some of the molecules currently under investigation for the treatment of RSV infection, as well as novel data for the prevention of RSV infection in adults/elderly people.

4.1 Pharmacological Treatment

A number of treatments (mainly antivirals) have been developed and tested in RSV acute infections. They have been recently reviewed in detail [62]. Here, we summarized only some of the relevant data and antiviral drugs currently in clinical development.

4.1.1 Ribavirin

The only antiviral treatment for RSV approved by the Food and Drug Administration (FDA) in infants is ribavirin. It inhibits replication of both RNA and DNA viruses. Ribavirin can be administered intravenously, orally, and by aerosolization and has often been given in combination with intravenous immunoglobulin.

Compared to the original inhaled formulation, the oral formulation is equally effective and cheaper; thus, it is the preferred route of administration. The efficacy data are controversial, and use is restricted to life-threatening RSV LRTIs and lung transplant recipients [63].

4.1.2 Presatovir (GS-5806)

GS-5806 is an oral small molecule that inhibits RSV entry at low nanomolar concentrations by blocking viral-envelope fusion with the host cell membrane. A phase I study in humans showed no adverse events. The study was conducted in healthy adults experimentally infected with a clinical strain of RSV and showed a significant reduction in the viral load, along with a reduction in mucus production and the total symptom score [64]. A phase IIb study conducted in patients undergoing lung transplantation found no efficacy in reducing the viral load, symptom improvement, or prevention of lung function deterioration in lung transplant recipients infected with RSV [49].

4.1.3 Sisunatovir (RV521)

RV521 is an orally bioavailable inhibitor of RSV fusion to host cells. Oral bioavailability in preclinical species ranged from 42 to > 100%, with evidence of highly efficient penetration into lung tissue. In healthy adult human volunteers experimentally infected with RSV, a potent antiviral effect was observed with a significant reduction in both viral load and symptoms [65].

4.1.4 Ziresovir (AK0529)

Ziresovir is an RSV fusion inhibitor that reduces cytopathic effects in HEp-2 cell cultures [66] infected with both RSV A and B strains [67]. In a phase II study, AK0529 was well

tolerated in hospitalized RSV-infected infant patients, and treatment with AK0529 2 mg/kg bid reduced viral load [68].

4.2 Prevention

4.2.1 Hygiene Measures

As for other respiratory viruses, RSV is classically spread through inhalation of aerosolized droplets and, especially in children, by contact with fomites. Good hygiene practices therefore have a fundamental role in limiting the transmission of this infection. Multiple strategies could be applied, such as careful and periodic hand washing, social distancing, especially outside the house and with non-family members, home isolation of people presenting respiratory symptoms, covering coughs and sneezes with a single-use tissue or the elbow, using easily cleanable toys if working with children, cleaning frequently touched surfaces with bleach solution or disinfectants, and wearing a facial mask in public situations when social distancing is not feasible. Furthermore, structural and procedural measures should be implemented for the frailest population, such as those living in long-term care facilities. During the COVID-19 pandemic, the broad application of these rules deeply impacted the circulation of all respiratory viruses, including RSV, as reported by the Centers for Disease Control and Prevention (CDC). In the 4 years before the COVID-19 pandemic, the weekly percentage of positivity of RSV detection tests in the US usually rose from 3% to 12.5–16.7% between October and December. In contrast, from January to April 2020, it fell from 15.3% to 1.4% and persisted < 1% weekly during the next year. From October 2020 to April 2021, the cumulative incidence of hospitalization related to RSV disease decreased to 0.3 cases per 100,000 people, starting from 27.1 and 33.4 in the preceding two seasons (Fig. 4) [69]. In addition, COVID-19 spread in nursing homes and long-term care facilities was deeply reduced by procedural and structural measures, such as protected zones for family visits, entry restrictions, and COVID-19 isolation areas [70].

Preventive hygiene measures should therefore be performed, especially in older people, those with social contact with children and frail patients.

4.2.2 Passive Immunization

The main purpose of passive immunization consists of reducing the spread of RSV from the URT to the LRT using anti-RSV antibodies, limiting the severity of the infection to an URT infection. Currently, passive immunization is an option exclusively for high-risk infants [71]. Studies are needed to evaluate the efficacy and cost-effectiveness of these drugs in adult patients to provide more preventive opportunities, especially for those with a contraindication to vaccination.

4.2.2.1 Palivizumab Palivizumab, an RSV-specific monoclonal antibody approved for the prevention of RSV infection, is effective in reducing RSV hospitalization rates by approximately 60%. The use is indicated in infants at risk (overall in 3% of the total infant population), e.g. those who are born prematurely or have underlying conditions (chronic lung disease, congenital heart disease, immunodeficiencies, or other severe chronic illnesses). This antibody protects against severe disease; it is expensive and therefore, it is only used in high-income countries of high-risk preterm infants. Palivizumab exhibits no efficacy in the treatment of RSV infection [72].

Some evidence has shown a safe and well-tolerated profile of this drug in immunocompromised adults [73–76], although it has been tested in small studies and there is no approved indication.
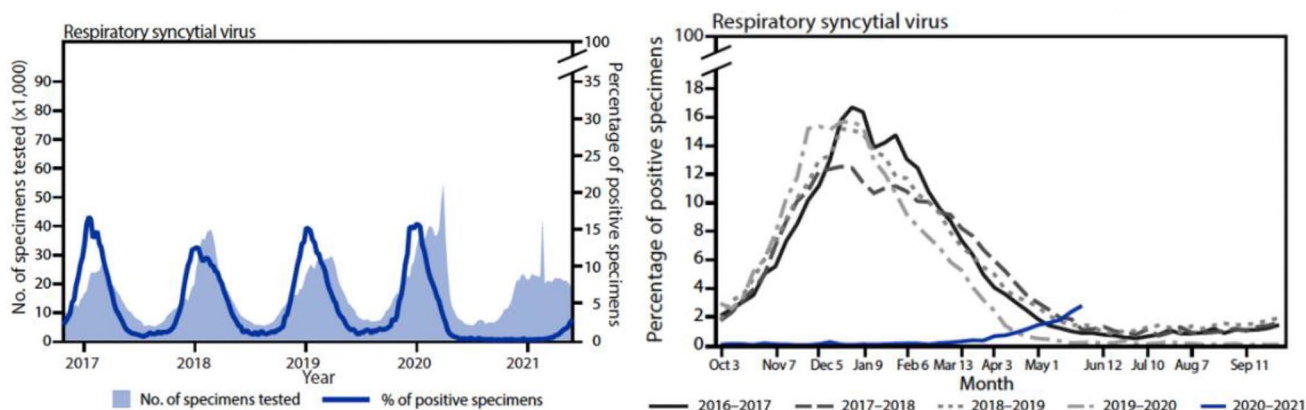

Fig. 4 Evolution of RSV epidemiology during the COVID-19 pandemic. Reproduced from Ref. [69] (Content source: Centers for Disease Control and Prevention). *COVID-19* coronavirus disease 2019, *RSV* respiratory syncytial virus

4.2.2.2 Nirsevimab Nirsevimab is a derivative antibody from a precursor of the prefusion F protein; it has been engineered to increase efficacy and prolong the antibody half-life. In a recent efficacy trial in infants, nirsevimab achieved the primary endpoint of reduction of medically attended LRTIs and the secondary endpoint of reduction of hospitalizations and was granted prime eligibility status by the European Medicines Agency (EMA) and breakthrough status by the US FDA. This monoclonal antibody was 100 times more potent than palivizumab. Thanks to the increased antibody efficacy and the extended half-life via engineering technology, a single dose administration at birth provides protection for the entire RSV first season [77]. Nirsevimab is currently recommended only in infants [78].

4.2.2.3 Clesrovimab (MK-1654) Clesrovimab is a monoclonal antibody similar to nirsevimab, and it targets site IV of the RSV prefusion F protein and the same YTE mutation. Studies in children are ongoing to evaluate whether clesrovimab reduces the incidence of RSV-associated medically attended LTRI from day 1 through day 150 post-dose and to assess its safety profile [79].

4.2.3 Active Immunization

In the last decade, there have been multiple efforts to develop RSV vaccines, with variable results. Several approaches have been developed, such as live attenuated vaccines (LAVs) for infants, stabilized pre-F subunit vaccines for pregnant women, and subunit, vector-based and nucleic acid vaccines for older adults (Fig. 5) [80].

LAVs, attenuated through various techniques to reduce virulence [81], mimic natural RSV infection and are able to induce both a potent humoral mucosal and cellular immune response. Several LAV candidates have been developed and are currently being tested in phase I or II trials, with promising results. Among the others, MV-012-968 was reported to be safe and able to induce a mucosal IgA response in seropositive patients [82].

Chimeric live virus vaccines consist of related attenuated viral particles expressing RSV-specific proteins. They are reported to have more effective antigen presentation than vectored vaccines, leading to the activation of an intense specific adaptive immune response with a good safety profile [83, 84]. Among the two chimeric vaccines that are being studied, the rBCG-N-hRSV vaccine, an attenuated recombinant BCG (Bacillus Calmette-Guérin) vaccine producing RSV nucleoprotein, was proven to be well tolerated in a phase I trial [85].

Subunit and inactivated virus vaccine development has been abandoned since a formalin-inactivated RSV vaccine was reported to have enhanced the severity of the RSV disease of the first natural RSV infection subsequent to vaccination in RSV-naive children [86].

In adults, the Adult Respiratory Syncytial Virus (AReSVi-006) study was the first positive trial with a subunit RSV vaccine. It is an ongoing, randomized, multicentric, placebo-controlled trial evaluating the efficacy of the RSVPreF3 OA vaccine (Arexvy, GSK) in adults aged 60 years old or older. This vaccine includes a stabilized RSV F protein, which stimulates the development of specific neutralizing antibodies, and the AS01E adjuvant system. The primary outcome consisted of evaluating the efficacy of this vaccine in preventing RSV-lower respiratory tract disease (LRTD) in older patients during the first season after vaccination. The definition of RSV-LRTD relied on the presence of at least three LRT symptoms or two LRT symptoms or signs (with at least one sign) for at least 1 day. Approximately 25,000 patients were included in this study and randomized 1:1 to receive either placebo or a single dose of vaccine (treatment arm) before the commencement of the RSV season. This vaccination reduced the number of patients who had an RSV-LRTD, with vaccine efficacy detected: 82.6% (96.95% confidence interval [CI] 57.9–94.1) for a median follow-up of 6.7 months (Fig. 6). A similar result was achieved in terms of severe RSV-LRTD, with a vaccine efficacy of 94.1% (95% CI 62.4–99.9). The numbers of patients who reported at least one acute respiratory infection (ARI) due to RSV, defined as at least one systemic plus one respiratory sign or symptom or no less than two respiratory signs or symptoms for at least 1 day, were 95 and 27 in the two groups, respectively (vaccine efficacy of 71.7% [95% CI 56.2–82.3]). An equivalent efficacy was reported according to viral subtype (A or B), and it remained high in the two major age groups (60–69 and 70–79) and in frail adults. The responses were specifically evaluated in subgroups according to the presence of specific comorbidities known to be associated with a higher risk of severe disease (described as "conditions of interest" [COI]), such as cardiopulmonary, endocrine, and metabolic comorbidities, where vaccine efficacy was similarly obtained. In addition, the investigational vaccine had a good safety profile [87].

For the second season, the initial cohort of patients was divided into three subgroups (placebo, annual vaccination, and single dose) evaluating the vaccine efficacies over two seasons of annual revaccination and single dose. The annual revaccination group showed a vaccine efficacy over two seasons of 67.1% (97.5% CI 48.1–80.0), similar to that of the single dose of vaccine (67.2%, 97.5% CI 48.2–80.0). A sustained vaccine efficacy over two seasons was also reported against RSV-ARI, severe RSV-LRTD, and RSV-LRTD in the groups 60–69 years old and 70–79 years old, patients with at least one COI, and in the prefrail subgroup [88].

The preventive efficacy on RSV-LRTD and ARI was elevated in patients with at least one COI (94.6% and 81.0%,
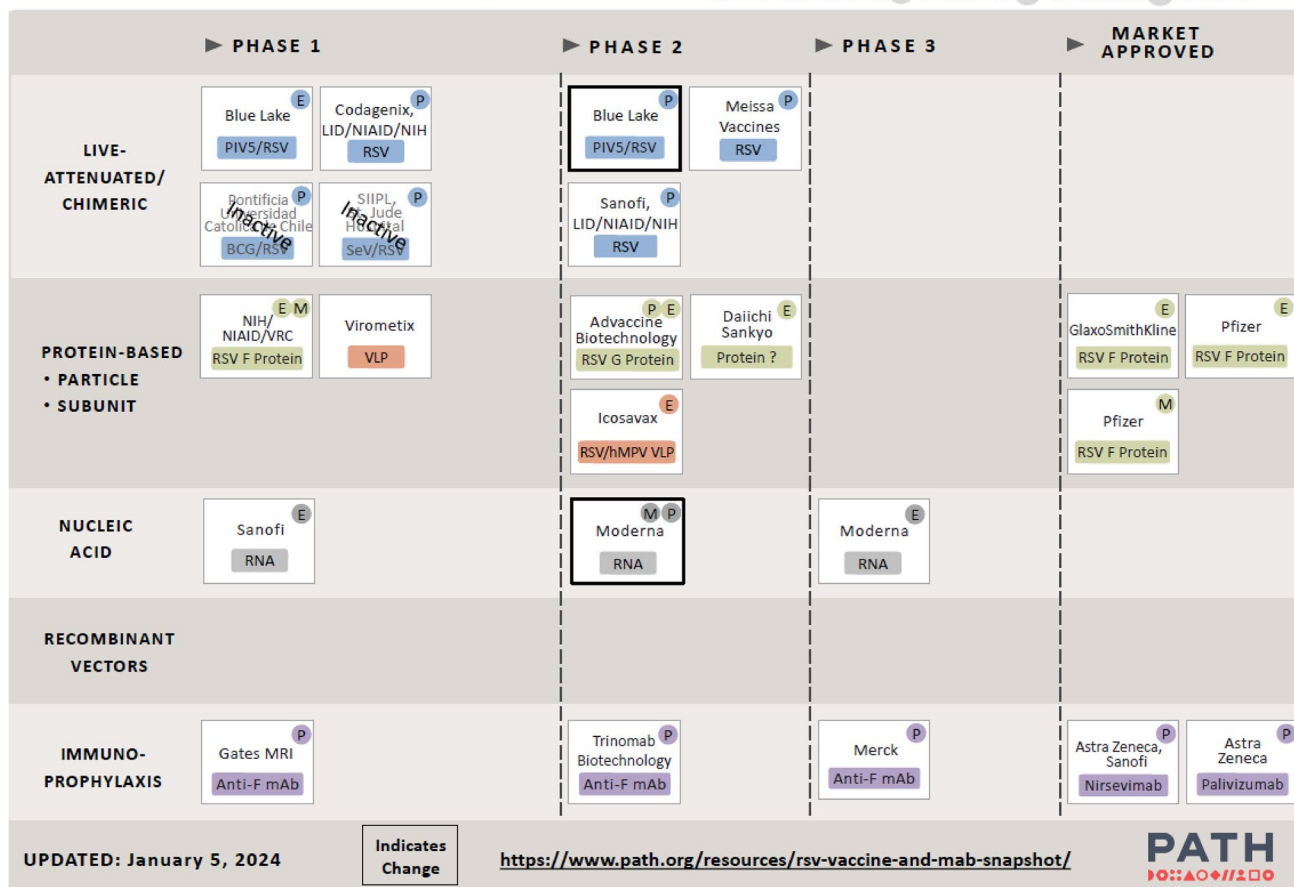
RSV Vaccine and mAb Snapshot

Fig. 5 Picture of the effort to track the development of RSV vaccine and mAb candidates worldwide. (Reproduced from the PATH website at www.path.org, April 2024). *mAb* monoclonal antibody, *RSV* respiratory syncytial virus, *BCG* Bacillus Calmette-Guérin, *hMPV* human metapneumovirus, *NIAID* National Institute of Allergy and Infectious Diseases, *NIH* National Institutes of Health, *PIV5* Parainfluenza virus 5, *SeV* Sendai virus, *VLP* virus-like particle, *VRC* Vaccine Research Center

respectively), at least one cardiopulmonary comorbidity (92.1% and 88.1%, respectively), at least one endocrine/metabolic comorbidity (100% and 79.4%, respectively), and at least two COI (92.0% and 88.0%, respectively). Similarly, the antibody responses to the vaccine were not influenced by the presence of at least one COI [89].

The RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR) trial was a randomized 1:1, multicentre, placebo-control, phase III study evaluating a bivalent vaccine containing an RSV prefusion F protein (RSVpreF vaccine [Abrysvo, Pfizer]) from the two major viral subgroups (RSV-A and B) in older adults 60 years old or older. This formulation did not include an adjuvant system. At the time of this publication, this study was ongoing [90]. The two primary outcomes of the prespecified interim analysis were the evaluation of the efficacy of the investigational vaccine in the prevention of RSV-LRTD with either two or three symptoms or signs

with a duration of at least 24 h in older patients with an RSV infection confirmed by an RT-PCR assay or equivalent test. Approximately 34,000 patients were randomized to receive either the RSVpreF vaccine (treatment arm) or placebo before the beginning of the RSV season, and the mean follow-up was 7 months. The reported RSV-LRTDs with at least two signs/symptoms were 1.19 per 1000 person-years of follow-up in the treatment arm and 3.58 per 1000 person-years of follow-up in the placebo arm (the vaccine efficacy was 66.7%, 96.66% CI 28.8–85.8). RSV-LRTDs with at least three signs/symptoms were 0.22 per 1000 person-years of follow-up in the treatment group and 1.52 per 1000 person-years of follow-up in the other one (the vaccine efficacy was 85.7%, 96.66% CI 32.0–98.7). In addition, the vaccine efficacy did not significantly differ according to viral subtype (A or B), age group (60–69, 70–79, or ≥ 80), and presence of high-risk conditions for adverse outcomes. The cases of RSV-ARI with at least one sign or symptom
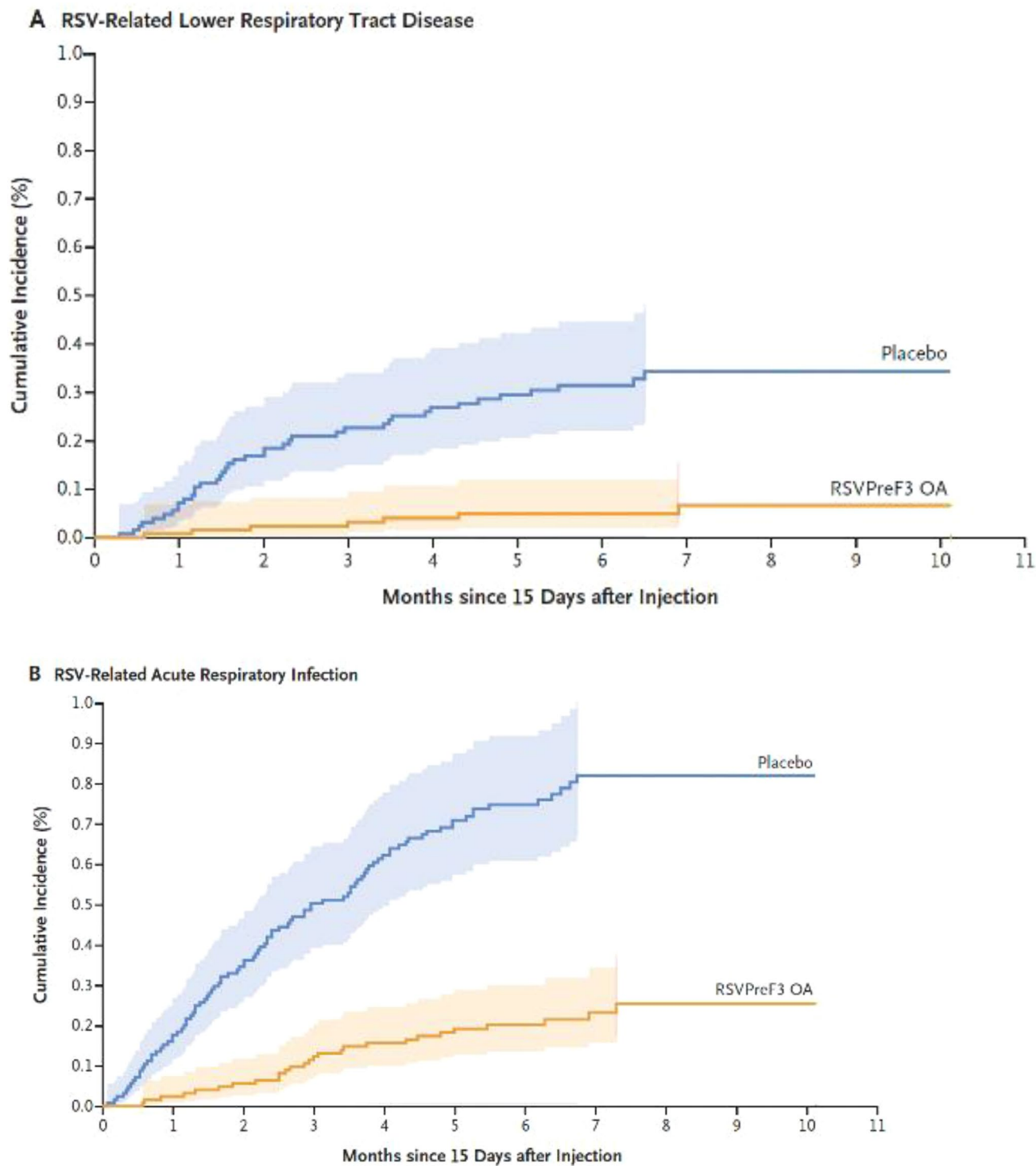
A RSV-Related Lower Respiratory Tract Disease

B RSV-Related Acute Respiratory Infection

Fig. 6 RSVPreF3 OA vaccine efficacy in reducing incidence of RSV-LRTD and acute respiratory infections. (Reproduced with permission from [87]). *LRTD* lower respiratory tract disease, *RSV* respiratory syncytial virus

and a confirmed infection (RT-PCR assay) were 2.38 per 1000 person-years and 6.30 per 1000 person-years in the two study arms, respectively (vaccine efficacy was 62.1%, 95% CI 37.1–77.9). Interestingly, the vaccine efficacy increased with increasing severity of RSV-LRTD, in concordance with the available evidence for other vaccines (e.g. SARS-CoV-2 or influenza virus) [90–93].

Of note, the efficacy of the RSVpreF vaccine evaluated in the RENOIR study (adults) was tested in pregnancy for the reduction of RSV-LRTD in infants in the Maternal Immunization Study for Safety and Efficacy (MATISSE) study. The trial showed a significant reduction in medical attended severe RSV-LRTD within 90 and 180 days after delivery and no significant difference for the total cases of RSV-LRTD analysis [94].

mRNA vaccines consist of messenger RNA coding for specific viral antigens that are able to induce a specific immune response (this vaccination platform was used with COVID-19). The mRNA-1345 vaccine (Moderna) consists of an mRNA encoding a stabilized RSV pre-F protein and a lipid formulation that is able to induce and augment the humoral and cellular immune response to this protein. The ConquerRSV study was a randomized 1:1, multicentre, placebo-controlled, phase III trial evaluating the mRNA-1345 vaccine in a population of approximately 37,000 adults of at least 60 years of age. The two primary outcomes were the prevention of RSV-LRTD with at least two or three symptoms. An interim analysis showed a vaccine efficacy of 83.7% (95.88% CI 66.0–92.2%, $p < 0.0001$) in reducing RSV-LRTD defined as at least two signs or symptoms, with 55 and nine cases reported in the placebo arm and vaccine arm, respectively. In addition, RSV-LRTDs with at least three signs or symptoms were reduced from 17 in the placebo arm to three in the vaccine arm, corresponding to a vaccine efficacy of 82.4% (96.36% CI 34.8–95.3%, $p = 0.0078$). The investigational vaccine was reported to have a good safety profile and was well tolerated [95]. The company announced that marketing authorization applications for this investigational vaccine had been submitted to EMA, Swissmedic, and the Therapeutic Goods Administration (TGA) in Australia, along with a rolling submission of a Biologics License Application to the FDA [96].

Other different vaccine strategies of RSV vaccination already tested and/or currently in development for adults have been recently reviewed in detail [62]. Here, we summarized only some of the relevant data.

The particle-based vaccines are based on the presentation of multiple antigens via assembled particles inducing a highly effective immune response. These investigational vaccines are currently in early development but with promising results. Icosavax's IVX-121 consists of a synthetic virus-like particle that delivers multiple copies of stabilized trimeric pre-F proteins and was reported to induce a persistent humoral response at 12 months after the first administration in the interim analysis of the phase Ib extension trial [97].

The IVX-A12, a combination of the RSV vaccine IVX-121 and the human metapneumovirus (hMPV) vaccine IVX-241, is currently being evaluated in adults in an ongoing phase II clinical study. [98]

Recombinant vector vaccines consist of modified replication-defective viruses that contain RSV genes codifying for specific antigens stimulating a specific cellular and antibody response. In this field, the MVA-BN-RSV vaccine (Modified vaccinia Ankara-Bavarian Nordic) consists of a poxvirus acting as a vector to express RSV intracellular proteins, such as N and M2, and surface proteins F and G [99]. MVA-BN-RSV vaccination was associated with a depletion of viral load, a 79% reduction in RSV disease, and a high title humoral response lasting at least 6 months after administration [100, 101]. The phase III VANIR study evaluated the efficacy of this vaccine in more than 20,000 participants aged over 60 years. A recent press release reported the preliminary results with a 59% vaccine efficacy in the prevention of LRTD with at least two symptoms. A 42.9% efficacy was reported in the prevention of LRTD with at least three symptoms, which failed to meet one of the co-primary outcomes of the trial, resulting in the discontinuation of Bavarian Nordic's RSV vaccine development programme [102].

The Ad26-RSV-pre-F vaccine (Janssen) consists of an adenoviral vector that leads to the expression of the RSV pre-F protein in combination with a recombinant pre-F protein. Ad26-RSV-pre-F was evaluated in the CYPRESS study, a phase IIb, proof-of-concept trial. The primary endpoint was the first occurrence of RSV-LRTD, showing an efficacy of 80% for the most severe disease, defined as three or more LRTD symptoms (94.2% CI 52.2–92.9, $p < 0.001$) and 69.8% for all RSV-ARIs (94.2% CI 43.7–84.7, $p < 0.001$). The vaccine reduced the severity of symptoms with a faster recovery compared to placebo [103]. The EVERGREEN study, a phase III trial evaluating this vaccine in older adults, was finally discontinued following a company's assessment of the RSV vaccine landscape [104, 105].

Based on evidence and decisions of regulatory agencies, Arexvy and Abrysvo have been approved and are currently available in the US and Europe. To date, both the FDA and EMA, together with the 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, recommend RSV vaccination in patients older than 60 years old and/or with chronic heart and lung comorbidities. The CDC suggests a single dose of the RSV vaccine for those older than 60 years old, preferably administered a few months before the viral seasonal peak, such as in late summer or early fall. The CDC suggests a shared clinical decision-making (SDM) approach for RSV vaccination. In other words, the decision to proceed with vaccination should be based on an informed patient's preference reached through an active discussion with the healthcare provider (HCP). This discussion should cover various topics, including available evidence, the patient's health status, risk factors for severe RSV disease, HCP's suggestions, and the safety profile of the vaccine, among others [106–111].

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) suggests RSV vaccination for adults aged at least 75 years old [112].

In Spain, the Spanish NeumoExperts Prevention Group (NEP) recommends this vaccination among adults over 60 years old, prioritizing those with chronic comorbidities deemed at high risk of severe RSV illness, as well as healthcare workers, who are at elevated risk of both acquiring and transmitting RSV [113].

Both vaccines should be administered via intramuscular route into the deltoid muscle, and Abrysvo is the only vaccine approved in pregnancy [114–116].

5 Discussion

Not considered a disease of the youngest anymore, RSV burden remains to date an underestimated cause of morbidity and hospitalization globally in the elderly and immunocompromised population. RSV is an insidious respiratory infection, partly due to nonspecific symptoms, often similar to other viral respiratory tract infections, along with a seasonal pattern of transmission during the wintertime in epidemic outbreaks that recurs annually [3]. Early diagnosis is challenging, particularly in elderly or fragile patients, where the virus can lead to more severe clinical presentations such as pneumonia, respiratory failure, and Acute Respiratory Distress Syndrome (ARDS). Among the elderly older than 65 years, the European Union is facing 145,000 RSV-associated hospitalizations each year, and the US, 159,000. The mortality rate in elderly hospitalized RSV patients is significant, up to 18% [1, 20]. The documented coinfection with other respiratory pathogens, which further complicates the clinical presentation, should not be overlooked. Several studies have demonstrated an increased risk of exacerbation of chronic respiratory diseases (such as asthma and COPD) and an elevated cardiovascular risk in both immunocompetent elderly individuals and those with multiple comorbidities, adding to the overall burden on public health costs. Currently, the most accurate and rapid diagnostic investigation for detecting RSV is RT-PCR amplification on nasal or NP swabs. During the recent COVID-19 pandemic, these tests have become readily available and easy to perform, even by the patients' caregivers themselves. At present, instrumental radiological examinations do not allow the specific detection of pleuro-parenchymal alterations caused by this pathogen. Due to the absence of effective therapies against RSV disease, prophylaxis has rapidly become the most efficient measure to reduce RSV diffusion and clinical impact in the population, especially among the most vulnerable patients such as older adults, polymorbid patients, or those living in nursing facilities. Hygiene measures, such as procedural or structural interventions, have significantly lowered respiratory virus transmission [70], but active prophylaxis remains essential and should be pursued, targeting those at higher risk of severe disease. Several clinical trials have been conducted and published that show a significant reduction in the incidence of RSV disease, especially in its most severe form. In addition, vaccination was proven to be highly effective regardless of the presence of specific comorbidities and persisted as effective across different seasons [87–90]. As a result, regulatory agencies such as the EMA and the FDA have now included RSVPreF3 (Arexvy, GSK) and RSVpreF (Abrysvo, Pfizer) in the suggested vaccinations for individuals over 60 years of age. While Arexvy contains the AS01E adjuvant system, the latter does not contain any adjuvant. Both vaccines protect against the two major RSV subtypes (A and B); Abrysvo is bivalent, containing an RSV prefusion F protein from both RSV-A and B, while Arexvy, even though it is not technically bivalent, demonstrated an optimal efficacy for both subtypes in clinical trials [87, 90]. Both Arexvy and Abrysvo can be administered on the same occasion of the influenza vaccination, and national health authorities may approve the simultaneous administration of RSV vaccines with the others [111, 117].

In the last decades, significant economic resources have been invested in influenza vaccination. Now it is the time to invest also in RSV vaccination, leading to wider protection against seasonal respiratory viruses in frail and older patients.

6 Conclusions

RSV is a ubiquitous respiratory virus with a seasonal pattern of infection. While RSV represents one of the most common infections during childhood, epidemiological data indicate a substantial impact throughout all ages, with a disproportionately high impact in elderly individuals. RSV carries a serious burden affecting older adults with comorbidities, i.e. the frailest population. No therapeutic option is available for adults. Active immunisation has been recently approved in older adults aged > 60 years old based on the results of multiple phase III studies, such as the RENOIR and AReSVi-006 studies, showing a substantial reduction of RSV-related LTRD and severe LTRD [87, 90]. In addition, a single dose of Arexvy has been shown to be as effective as annual revaccination, simplifying the vaccination schedule [88]. To date, vaccinations represent the best protection from developing severe disease and serious adverse events related to RSV infection, especially for the elderly population with multimorbidities

(in particular, cardiopulmonary and metabolic) and immunocompromised individuals.

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