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Landscape of respiratory syncytial virus

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Abstract

Respiratory syncytial virus (RSV) is an enveloped, negative-sense, single-stranded RNA virus of the *Orthopneumovirus* genus of the Pneumoviridae family in the order Mononegavirales. RSV can cause acute upper and lower respiratory tract infections, sometimes with extrapulmonary complications. The disease burden of RSV infection is enormous, mainly affecting infants and older adults aged 75 years or above. Currently, treatment options for RSV are largely supportive. Prevention strategies remain a critical focus, with efforts centered on vaccine development and the use of prophylactic monoclonal antibodies. To date, three RSV vaccines have been approved for active immunization among individuals aged 60 years and above. For children who are not eligible for these vaccines, passive immunization is recommended. A newly approved prophylactic monoclonal antibody, Nirsevimab, which offers enhanced neutralizing activity and an extended half-life, provides exceptional protection for high-risk infants and

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young children. This review provides a comprehensive and detailed exploration of RSV's virology, immunology, pathogenesis, epidemiology, clinical manifestations, treatment options, and prevention strategies.
Keywords: Respiratory syncytial virus; Vaccine; Lower respiratory tract infections; Niservimab; Epidemiology

Introduction

Respiratory syncytial virus (RSV) represents a significant cause of respiratory infections. It is the principal viral pathogen responsible for acute lower respiratory tract infections (ALRTIs) in children under five.[1,2] The high viral transmission rates, coupled with its propensity for severe disease, have elevated RSV to a significant public health concern.[3] Due to the lack of effective antiviral drugs, current treatments for RSV primarily involve supportive care.[4] Developing safe and effective vaccines remains an unmet need, especially for high-risk populations such as infants, young children with immunosuppression, and the elderly.[5] This review provides a comprehensive overview of RSV, covering virology, immunology, pathogenesis, epidemiology, clinical manifestations, treatment options, and prevention strategies.

Virology

RSV is an enveloped, non-segmented, negative-sense RNA virus with a spherical or filamentous shape and a helical ribonucleoprotein (RNP) core. The International Committee on Taxonomy of Viruses (ICTV) classifies it as belonging to the *Orthopneumovirus* genus of the Pneumoviridae family in the order Mononegavirales.[6–8] RSV has one serotype and two antigenic subtypes, RSV A and RSV B. Its genome is approximately 15.2 kb. RSV has 10 genes encoding 11 proteins, including three structural proteins fusion protein (F), attachment glycoprotein (G), small hydrophobic protein (SH), six nucleocapsid-associated proteins nucleoprotein (N), phosphoprotein (P), large polymerase protein (L), matrix protein (M), matrix protein 2-1 (M2-1), matrix protein 2-2 (M2-2), and non-structural proteins 1 (NS1) and 2 (NS2).[9–12] RSV's most essential surface glycoproteins are the G and F proteins, which play crucial roles in virus attachment to host cells and cell fusion and are vital transmembrane proteins on the virus surface. Antibodies against either the G or F proteins can block infection [Figure 1]. They are critical in virion entrance and antibody production as primary targets for vaccine and monoclonal antibody development.[13–16]

Variations in the G gene are the most significant among the whole genome. It contains approximately 298 amino acids and primarily comprises the cytoplasmic tail, transmembrane, and extracellular domains. It exhibits the highest nucleotide and amino acid variations among different subtypes or genotypes of RSV and the most remarkable diversity in secondary and tertiary structures.[10,17] In particular, the second-highest variable region of the G gene in its (G-HVR2) extracellular domain, with its 3′ end nucleotide sequence, exhibits high genetic variability and is widely used in the genetic variation and molecular evolution studies of RSV.[17–19] Currently, up to 22 RSV A and 37 genotypes RSV B subtypes have been identified.[20–22] The ON1 genotype of subtype A, containing a 72-nucleotide repeat insertion sequence, and the BA9 genotype of subtype B, containing a 60-nucleotide repeat insertion sequence, have become the prevalent dominant genotypes worldwide.[23–25]

Due to the significant variability of the G protein, it is challenging to induce the production of broad-spectrum neutralizing antibodies by the host. In contrast, the F gene exhibits high conservation both between and within A and B subtypes, with amino acid sequence identity exceeding 90%, demonstrating relative genetic and antigenic stability, making it the most suitable protein for vaccine and monoclonal antibody design.[26–29] F protein comprises approximately 574 amino acids. It exists in two conformations, pre-fusion and post-fusion, with a total of six antigenic sites, designated as I, II, III, IV, V, and Ø.[29,30] The antigenic sites V and Ø, present only in the pre-fusion conformation, generate antibodies that neutralize RSV more effectively than those produced against antigenic sites common to pre-fusion and post-fusion conformations. Most variations in the F protein are located on the antigenic site Ø at the apex of the pre-fusion conformation trimer, which may be the determinant site for the specificity of the F protein.[31–34] Genetic monitoring studies of RSV have observed variations in the antigenic sites of the F protein in both A and B subtypes.[30,35–43] The mutation sites observed in the RSV A subtype are mostly low-frequency.[44,45] In contrast, the amino acid mutations in the RSV B subtype genome sequence mostly show high frequency, impacting the virus's antigenicity and promoting immune evasion.[46,47] An evaluation of the conservation of Nirsevimab binding sites showed that from 2015 to 2021, the amino acid mutation rate within the nirsevimab binding sites was 0 in RSV A and 12% in RSV B. The double mutations I206M and Q209R in the RSV B subtype were observed to be very prevalent.[39,42] In many countries, consistent sequence site mutations have also been observed in RSV F gene surveillance studies.[30,35–41] In addition to the I206M and Q209R double mutations, common amino acid site mutations include R42K, I64T, L172Q, S173L, S190N, K191R, S211N, and S389P. In contrast, RSV A subtype sequences are relatively conserved, with lower frequency mutations such as I57V, K68N, T122A, L204S/I, S276N, L381I, P389S, and the double mutation A103T and T122A.[42,43,45,48,49] During the co-circulation of RSV and coronavirus disease 2019 (COVID-19), there has been an increased frequency of mutations at the S190N, S211N, and S389P sites, followed by the R42K mutation.[50] Although some mutation sites in important antigenic epitopes currently appear at low frequencies, they may gradually become prevalent or immune escape sites.[43] Related research shows that certain amino acid mutation sites in the F protein antigen epitopes can lead to reduced neutralizing activity of monoclonal antibodies.[42,44,51–54] For example, like I206M and Q209R, the S211N mutation

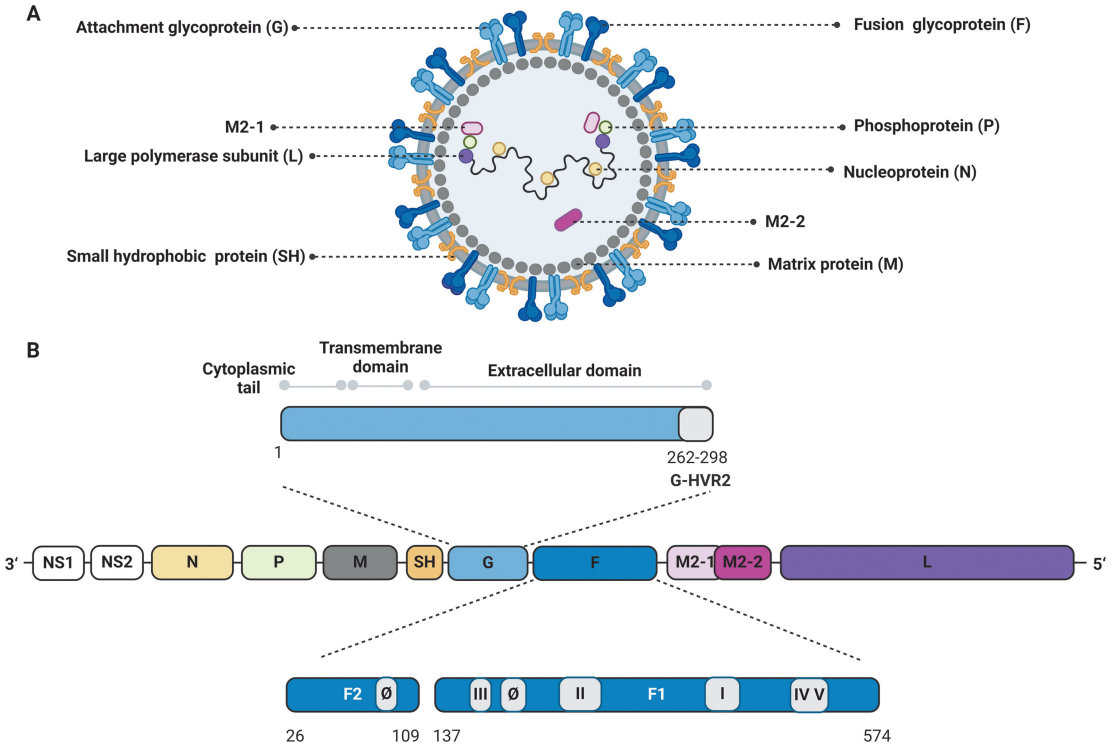

Figure 1: Structure and genome of RSV virus. (A) Structure of RSV virus. (B) Genome structure of RSV, the six major antigenic sites of the F protein, and the location of G-HVR2. RSV: Respiratory syncytial virus.

retains sensitivity to nirsevimab. In contrast, the K68E mutation in RSV A and the K68Q and N201T mutations in RSV B subtypes reduce sensitivity to nirsevimab neutralization.[42,44,51,54] Palivizumab-resistant strains with single mutations of the F protein of K272E and S275F exhibited no inhibition of cell fusion with palivizumab.[53] However, the N276S mutation, which is prevalent in circulating RSV variants, does not exhibit resistance to palivizumab,[55–57] while L258E/K, N262D, and S275H/R mutations all escape with varying degrees from palivizumab.[57,58] Specific escape mutations at two amino acid positions, L172Q and S173L, in RSV B have been identified to confer resistance to the suptavumab monoclonal antibody, leading to the failure of Regeneron's phase III clinical trial of suptavumab to meet its primary endpoint.[52] Therefore, continuous genetic surveillance and monitoring of the resistance to the monoclonal antibody and vaccines, especially for antigenic site mutations of F protein, are crucial.

Immunology and Pathogenesis

RSV entry and replication

The process of RSV entry can be divided into two major steps: (a) attachment and (b) fusion. The former primarily relies on the binding of the viral G and F glycoproteins to various cell surface receptors, including CX3C-chemokine receptor 1 (CX3CR1), intercellular adhesion molecule-1 (ICAM-1), insulin-like growth factor-1 receptor (IGF1R), nucleolin, epidermal growth factor (EGFR), CD14–Toll-like receptor 4 (TLR4), ras homolog family member A (RhoA), and cellular glycosaminoglycans (GAGs, such as heparan sulfate and chondroitin sulfate B).[3,59] RSV will adaptively select the primary receptor to infect different types of cells, mediated by the F protein.[60,61] During this process, the F protein trimer undergoes an irreversible conformational change, followed by the viral ribonucleoprotein complex (RNP) being released into the cytoplasm and carrying out replication and transcription without nuclear involvement. RSV sequentially transcribes 10 genes according to nucleic acid-based gene start (GS) and gene end (GE) signals.[62] *In vitro* experiments revealed that RSV mRNAs and proteins could reach detectable levels 4 to 8 h post-infection (hpi), and progeny virions begin to be produced at 10 hpi.[63] The dense structure in cytoplasm named "inclusion bodies" contain viral nucleic acids and their binding proteins.[64] Viral replication, transcription, and nucleocapsid assembly occur within these structures.[65] The inclusion bodies sequester specific host proteins to weaken the infection response [Figure 2].[66] The involvement of RhoA and actin promotes the formation of filamentous structures.[67] Lipid raft regions modified by F, G, SH, and M serve as specific budding sites for RSV.[68] Besides this extracellular infection route, viral particles can also utilize the F protein on the cell surface and the host cell's cytoskeletal structures to fuse with (syncytia conformation) or closely connect to neighboring cells, enabling cell-to-cell transmission and evading neutralizing antibodies.[69]

Host restriction factors against RSV replication

Host factors directly or indirectly intervene or block different stages of the RSV life cycle. Chemokine ligand 4

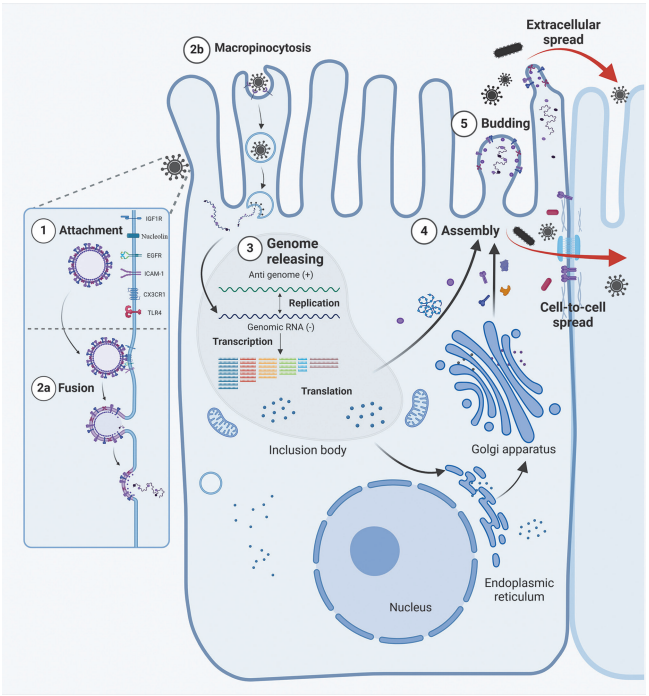

Figure 2: The life cycle of the RSV. RSV can attach to cells by binding to receptors such as CX3CR1, IGF1R, EGFR, nucleolin, ICAM-1, TLR4-CD14, and cellular GAGs, followed by membrane fusion mediated by F-glycoproteins or by the macropinocytosis to complete entry. Viral replication, transcription, and translation occur in the cytoplasm, during which dense inclusion bodies are formed. A portion of the translated viral proteins are exported with the genome directly to the vicinity of the cell apical surface and are assembled with another portion that is transported to the endoplasmic reticulum and Golgi apparatus for further processing. Afterward, the virus can be released extracellularly by budding and infecting other cells or directly spreading to neighboring cells utilizing F proteins and cytoskeleton. CX3CR1: CX3C-chemokine receptor 1; EGFR: Epidermal growth factor; GAGs: Glycosaminoglycans; IGF1R: insulin-like growth factor-1 receptor; ICAM-1: Intercellular adhesion molecule-1; RSV: Respiratory syncytial virus; TLR4: Toll-like receptor 4.

(CXCL4), a member of the chemokine family primarily involved in hematopoiesis and inflammation, has been found to inhibit viral attachment by competitively binding to heparan sulfate proteoglycan (HSPGs). Its concentration in the airway can also serve as a marker for viral load and disease severity.[70] L13a, a ribosomal protein, is released upon RSV infection and mediates the formation of respiratory syncytial virus-activated inhibitor of translation (VAIT) complexes. It binds to the untranslated regions of RSV M gene mRNA to silence its translation.[71] The other factors belong to interferon-stimulated genes (ISGs), which were previously reported to have restrictive effects on various pathogens and also found to exhibit anti-RSV activities. Knockout of interferon-inducible transmembrane (IFITM)1 and IFITM3, both members of interferon-induced transmembrane protein family, significantly aggravated RSV infection in mice.[72,73] IFI44 and IFI44L were upregulated after RSV infection and were thought to restrict RSV genome replication or transcription.[74,75] GBP5 could interact with SH protein and mediate its secretion into the extracellular space, disrupting viral components.[76] The restriction factors mentioned above are antagonistic in multiple steps of the infection process. However, the specific mechanisms of their interactions with RSV remain unclear, and their application prospects require further investigation.

Host immune responses and pathogenesis

Epithelial cells can recognize single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA) intermediates of RSV through pattern recognition receptors (PRRs), including retinoic-acid-inducible gene I (RIG-I)-like receptors (RLRs) and toll-like receptors (TLRs) family members, inducing early innate immune responses.[77] RIG-I mediates early activation of nuclear factors κB (NF-κB) and interferon response factor 3 (IRF3), while TLR3 mainly affects the late stage of infection.[78] The nuclear translocation of transcription factors NF-κB and IRF3 leads to the expression of cytokines, chemokines, and antigen-presenting receptors, triggering the recruitment of innate and adaptive immune cells and their interaction with epithelial cells.[77]

During this infection, RSV induces epithelial cell sloughing, cilia loss, sporadic syncytial body formation, and excessive mucus secretion.[79] The destruction of such epithelial cells usually manifests as discontinuity, with individual or small groups of epithelial cells infected in the respiratory tract.[80] The gain-of-function experiments with recombinant RSV NS2-expressing parainfluenza virus 3 in human airway epithelial cells (AECs) have confirmed that RSV NS2 can directly induce the cell rounding phenotype.[81] The loss of cilia may be mainly associated with microtubule damage, as the virus replicated in the apical cell surface.[82] The presence of F protein in the cilia correlated with cellular changes and reduced cilia function.[83] These detached cellular debris move down into the narrow-diameter bronchiolar airway lumen, leading to the accumulation of debris and acute obstruction in the distal airways.[77]

Cystic fibrosis transmembrane conduction regulator (CFTR) is an apical membrane chloride channel that regulates epithelial fluid, chloride ions, and bicarbonate transport.[84] Down-regulation of CFTR in airway epithelial cells in an RSV-infected mouse model has been observed. This leads to changes in bronchial secretions and impairs mucus clearance, which relates to airway inflammation.[84] The airway epithelial barrier functions as the front line of host defense against virus threats, and its integrity is essential for regulating innate immunity.[85] RSV-induced airway epithelial barrier disruption involves protein kinase D-dependent actin cytoskeletal remodeling, possibly dependent on cortactin activation.[86] The increased permeability of the airway epithelial barrier may significantly contribute to developing mucosal inflammation.[87] In addition, the interplay between the immune and nervous systems has been acknowledged in the past. Still, only several recent studies have started to unravel the cellular and molecular players of such interactions.[88] The post-viral wheezing phenotypes might be associated with the dysregulation of the nonadrenergic-noncholinergic (NANC) system via upregulation of neurotransmitters, typically Substance P.[89] This may offer future specific targets for treating RSV infection.

RSV is a poor inducer of interferon (IFN). It has been described that infants and neonatal mice cannot induce a robust type I IFN immune response. RSV NS1 and NS2

inhibit the expression of type I IFN, which could promote upregulation of over 300 genes that contribute to an antiviral response in infected and neighboring uninfected cells.[90] In addition, the G protein from RSV inhibits TLR3/4-mediated activation of interferon-stimulated response elements (ISREs) and blocks IFN-β production in epithelial cells.[91] Type I IFNs are essential in modulating the adaptive immune response since they activate cellular natural killer (NK) and cytotoxic T-cell responses. This leads to the up-regulation of the presentation of peptide-MHC class I complexes and the maturation of DCs. Blocking type I IFN production in AECs upon RSV infection can inhibit MHC class I expression.[92] Thus, RSV uses NS1 and NS2 proteins to avoid anti-viral response in AECs and the subsequent lysis by RSV-specific CD8 T cells via the inhibition of type I IFNs.[93] RSV F inhibits the production of interferon-λ (IFN-λ) by inducing EGFR activation, leading to a continuous increase in viral infection.[94] This inhibition of interferon can skew the immune response away from antiviral activity and towards a Th2 response, subsequently decreasing the Th1 pro-inflammatory response.[94]

Cytokines associated with a Th2-like response, such as IL-4 IL-6, IL-9, IL-10, and IL-13, are elevated in nasal washes and lungs of RSV-infected pediatric patients.[95] The innate lymphoid 2 cells (ILC2) are induced by innate cytokines (HMGB1, TSLP, IL-25, and IL-33) in RSV-infected murine and human airway epithelial cells.[96] ILC2 is thought even more effective in inducing type 2 cytokines than $CD4^+$T cells.[97] TSLPR knockout mice did not mount an IL-13-producing ILC2 response to RSV infection compared with wild-type mice.[98] ILC2s myeloid cell-derived IL-33 was required for airway inflammation, hyperresponsiveness, IL-13 production, and local and peripheral eosinophilia.[99] HMGB1 expression was localized to bronchiolar low columnar/cuboidal cells found in the small airways. Treatment with an anti-HMGB1 antibody significantly reduced HMGB1 levels and IL-4, IL-5, and IL-13 concentrations, suppressed inflammatory cell infiltration, and decreased severity scores.[100] Current research indicates that Th2 immune responses are associated with severe RSV disease, as well as various lung lesions such as asthma and airway hyperresponsiveness. Th9 secreted IL-9 during RSV infection, which has been shown to stimulate mucus production in humans and mice.[101] Human IL-9 polymorphism is associated with increased severity of RSV disease.[102] The Th17 subgroup has been shown to induce airway hyperresponsiveness during asthma.[103] Increased IL-17 levels were found in tracheal aspirates rather than nasal washes of RSV-infected infants,[104] indicating that IL-17 effect may be more important in the lower respiratory tract.[105]

Inappropriate immune responses cause the development of pathologic reactions. The immune response to RSV infection is characterized by an exacerbated inflammatory response in the lung. The inflammatory response to RSV infection acts as a "double-edged sword". It contains various antiviral properties, limiting viral replication and spread. However, it also has inappropriate or dysregulated responses that can be pathogenic, causing disease-enhancing inflammation that contributes to short- and long-term effects.

The airway epithelium is the source of over 20 pro-inflammatory cytokines, chemokines, and growth factors during RSV infection. Neutrophils are the most common cell type found in the lumen of the airways during RSV infection in infants; CXCL8 secreted from the airway epithelium is the main chemokine associated with neutrophil trafficking.[106] The influx of neutrophils in the airways and their subsequent action are thought to play a substantial role in the pathology of RSV disease.[107] Neutrophils increase the expression of neutrophil effector proteins, including releasing antimicrobial mediators that are cytotoxic to host cells[108] and disrupts the lung extracellular matrix.[109] The formation of neutrophil extracellular traps (NETs) by neutrophils can capture and inactivate viral particles but also damage healthy bystander cells.[110] Many of the NET components, including elastase and histones, are cytotoxic, leading to endothelial damage, exposure of the sub-endothelium, coagulation, and exacerbated inflammation.[111,112]

During the early phase, IL-6, IL-8, CCL2, CCL5, and macrophage inflammatory protein 1 (MIP-1)-1α derived from infected AECs and macrophages recruit monocytes to the site of infection.[113] Recruiting functional monocytes to the lungs in response to stimuli is pivotal for protection and immune regulation.[114] However, a modified cytokine expression following lung infection may shift monocyte differentiation toward an anti-inflammatory, M2-like phenotype, resulting in delayed viral clearance.[114] Expression of HLA-DR on the surface of monocytes isolated from RSV-infected infants was reduced and correlated with increased disease severity, underlining their importance in antigen presentation and the initiation of adaptive immunity [Figure 3].[115] Macrophage responses during RSV infections also follow a biphasic course. A recent study indicated RSV induces necroptosis, suggesting an enhancement of viral replication by M2-like macrophages, thus contributing to disease severity and lung pathology.[114,116]

Disease Burden and Epidemiology

Although RSV can infect populations of all ages, its disease burden is most substantial at the extremes of age. RSV-associated hospitalization and mortality rates both show a U-shaped age pattern, with infants and adults 75 years or above having the highest hospitalization and mortality rates [Figure 4].[117]

Children

RSV is the most common pathogen identified in infants and young children with acute lower respiratory infection (ALRI), accounting for about 30% of all respiratory tract pathogens. It has caused disproportionately high morbidity and mortality in low-income and middle-income countries (LMICs).[118,119] In 2019, it was estimated that there were 33.0 million RSV-associated ALRI episodes, 3.6 million RSV-associated ALRI hospital admissions, 26,300 RSV-associated ALRI in-hospital deaths, and approximately 101,000 overall deaths in children under five years globally.[119] The top five countries with the highest RSV-ALRI

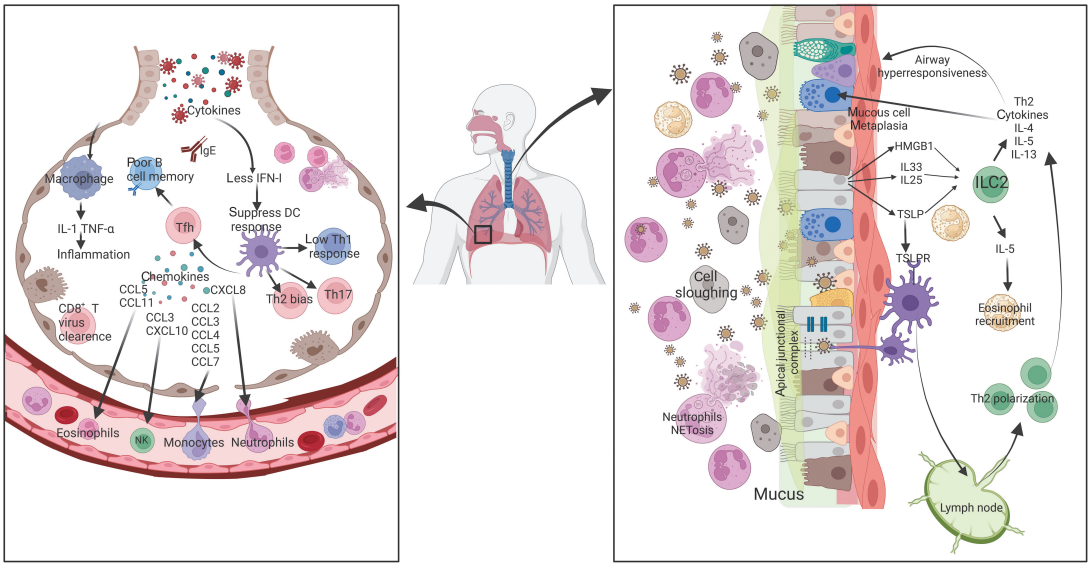

Figure 3: Pathogenesis of RSV. RSV induces rounding and shedding of ciliated cells, and neutrophils release NETs in response to RSV infection. RSV infection of epithelial cells causes the release of TSLP, IL-33, HMGB1, and IL-25, activating ILC2 to produce the type 2 cytokines. Type 2 cytokines have many immunologic and physiologic effects, including promoting airway responsiveness and mucous cell metaplasia. TSLP can induce the dendritic cells to migrate to the lymph nodes, interacting with naïve $CD4^+$ T cells, resulting in the Th2 polarization of $CD4^+$ T cells. RSV can lead to apical junctional complex disruption, allowing the pathogens to invade and activate dendritic cells. Low IFN-I can suppress the DC response, leading to a Th2/Th17 response and a low Th1 response. Impaired Tfh activation may lead to poor B cell memory and inhibition of antibody production. Alveolar macrophages express IL-1β and TNF-α to activate inflammatory responses. All these events lead to poorly protective and dysregulated immune responses in infants. Chemokines facilitate the recruitment of immune cells from the periphery to the lung (e.g., eosinophils, monocytes, neutrophils, and NK cells), where they implement pathogenic mechanisms. CCL: Chemokine (C-C motif) ligand; CXCL: C-X-C motif chemokine ligand; DC: Dendritic cell; HMGB1: High mobility group box 1 protein; IFN: Interferon; IgE: Immunoglobulin E; IL: Interleukin; ILC2: Innate lymphoid 2 cells; NK: Natural killer; RSV: Respiratory syncytial virus; Tfh: Follicular helper T cell; Th: T helper cell; TSLP: Thymic stromal lymphopoietin; TSLPR: Thymic stromal lymphopoietin receptor.

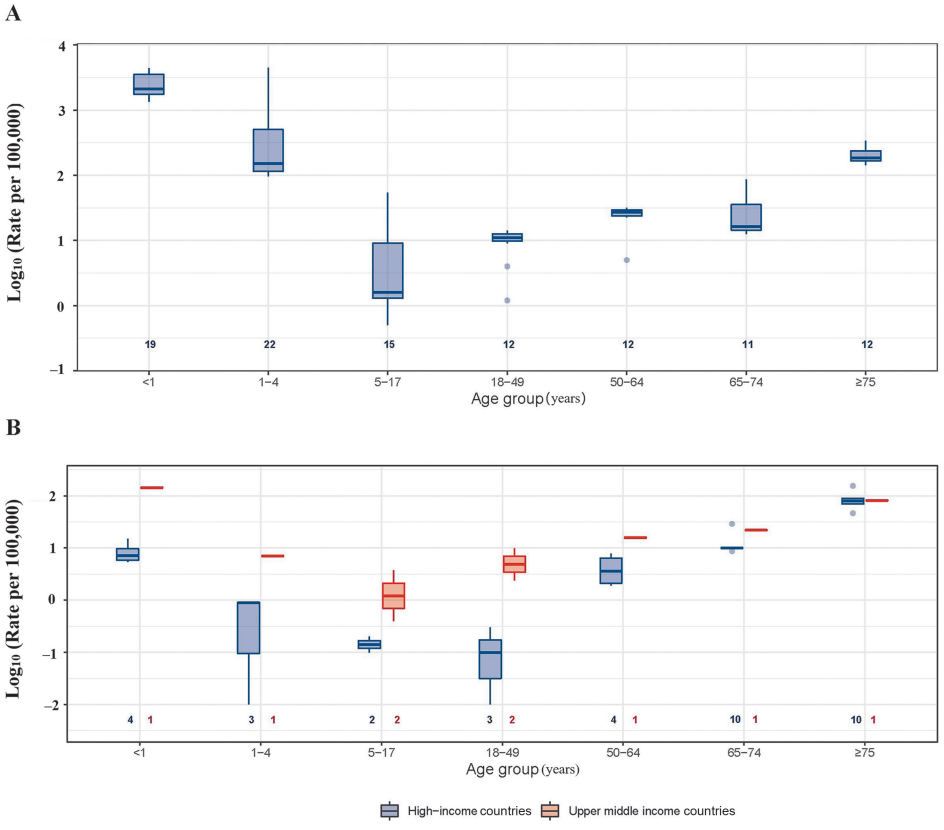

Figure 4: Reported rates estimates of RSV-associated hospitalization (A) and RSV-associated mortality (B) by age group across modeling studies.[106] The box top represents the upper IQR, the middle represents the median IQR, and the bottom represents the lower IQR. The top end of the whisker represents the highest value, excluding outliers (defined as any points with a longer distance than 1.5 times IQR from the box). The bottom end of the whisker represents the lowest value, excluding outliers. Dots represent outliers. ARI: Acute respiratory infection; IQR: Interquartile range; RSV: respiratory syncytial virus.

episodes (India, China, Nigeria, Pakistan, and Indonesia) accounted for nearly half the global RSV-ALRI burden.[120] Children with pre-existing medical conditions are generally at a higher risk for severe RSV diseases. A global-level analysis found that preterm-born infants (about 10% of live births) accounted for 25% (95% confidence interval (CI): 16–37%) of RSV-associated ALRI hospitalizations in all infants. Specifically, early preterm infants (i.e. <32 weeks of gestation) had higher rates of RSV-associated ALRI incidence and hospitalization than the general infant population (rate ratio [RR] ranging from 1.69 to 3.87); more importantly, the higher risk of hospitalization persisted into the second year of life.[121] In addition to prematurity, several systematic reviews and meta-analyses revealed that the risk of hospitalization associated with RSV was higher among children with bronchopulmonary dysplasia (OR: 2.6, 95% CI: 1.7–4.2),[122] Down syndrome (OR: 6.8, 95% CI: 5.5–8.4),[123] and congenital heart disease (OR: 2.8, 95% CI: 1.9–4.1)[124] compared to those without these conditions.

While the RSV-positive proportion in hospitalized acute respiratory infection (ARI) cases was relatively high in young children (23–29%), it declined rapidly beyond five years of age; in children and adolescents aged 5–19 years, it was estimated to be 3.9–4.5%.[119,125] A modeling study estimated that the annual global number of RSV-associated ALRI hospital admissions was 231,800 (95%CI: 142,700–373,200) among 5–19 years.[125]

Evidence regarding the RSV disease burden in China is limited, partly due to the need for robust RSV surveillance and the challenges in ascertaining the catchment population of healthcare facilities. A modeling analysis estimated that the annual incidence of RSV-associated ALRI in children under five years in China was 40 (95% CI: 30–55) per 1000 children, which was higher than that in high-income countries (24 per 1000 children; 95% CI: 14–43 per 1000 children).[119] In another modeling analysis, it was estimated that the annual RSV hospitalization rate in China was 7 to 11 per 1000 for children under five years.[126]

Adults

RSV disease burden in adults started to be appreciated just recently due to several challenges in estimating RSV disease burden in general. First, following an RSV infection, the development of symptoms and signs is less rapid in adults than in children, and it can take up to a week for an adult with RSV to seek medical care (compared to 2–4 days among children).[127,128] This leads to a potential underestimation of the RSV disease burden if RSV viral loads decline substantially when seeking healthcare. Second, adults are less likely to be ordered to do RSV testing in clinical settings than children. Third, even though RSV testing is ordered, using certain approaches of RSV testing regarding clinical specimens and diagnostic tests is associated with lower sensitivity in detecting RSV cases in adults, leading to case under-ascertainment.[129]

RSV disease burden in older adults is substantial. Globally, an estimated 336,000 (95% CI: 186,000–614,000) RSV-ARI hospitalizations for older adults aged 65 years or above occurred in 2019. However, this was likely underestimated as it did not account for the under-ascertainment related to RSV testing.[130] A recently published modeling analysis in high-income countries, adjusted for under-ascertainment, revealed that the RSV-associated ARI hospitalization rate was 347 per 100,000 after adjusting for adults 65 years or older, approximately 2.2 times the unadjusted rate. In addition to the hospitalization burden, the mortality burden of RSV among older adults is also substantial, with 6.1% (95% CI: 3.3–11.0%) of RSV hospitalized cases dying in hospital.[131] No global or regional reports were available that estimated the burden of RSV disease in younger adults.

Similar to children, adults with pre-existing conditions are at higher risk for severe RSV diseases.[132] A population-based prospective study in the US compared the hospitalization rates between adults with specific comorbidities and those without, showing that chronic obstructive pulmonary disease (COPD), asthma, diabetes, coronary artery disease, and congestive heart failure were individually associated with higher risks for RSV hospitalization; the corresponding incidence rate ratio (IRR) ranged 3–13 in 18–49 years to ≥65 years, 4–7 in 50–64 years to 18–49 years, and 4–33 in ≥80 years to 20–39 years. Notably, the RSV hospitalization rate in younger age groups (<50 years) with comorbidities was even higher than that in the older age groups (≥65 years) without comorbidities.[133] When writing the review, no reports were available to estimate the RSV disease burden in adults in China.

Seasonality

RSV seasonality is essential for healthcare services planning and recommending immunization strategies. RSV generally has a clear seasonality of circulation in most parts of the world, with more than three-quarters of the annual cases occurring within five months of a year. RSV seasonality is distinct from that of other common respiratory viruses, such as influenza, and the timing of RSV circulation does not fully overlap with that of other respiratory viruses.[134] In temperate regions, RSV typically circulates from late autumn to early spring, with a latitudinal gradient in the timing of circulation; in subtropical and tropical areas, RSV usually has a longer circulation duration, with the peak occurring during the rainy seasons [Figure 5].[134,135] RSV seasonality patterns have been demonstrated to be associated with geographical location (e.g., latitude and longitude)[134,136] and meteorological factors (e.g., temperature, relative humidity, and rainfall).[136,137] RSV seasonality was also reported to vary locally by subgroup predominance (subgroup A *vs*. B),[138] although global analyses did not yield consistent findings on the association between subgroup predominance and RSV seasonality.[139,140]

In China, RSV circulation usually occurs from November to March next year in most provinces; provinces that are on or near the Tropic of Cancer (e.g., Fujian, Guangdong, Yunnan, and Hunan) have more extensive RSV circulating duration and less clear RSV seasonality.[141] In provinces with clear RSV seasonality (duration of

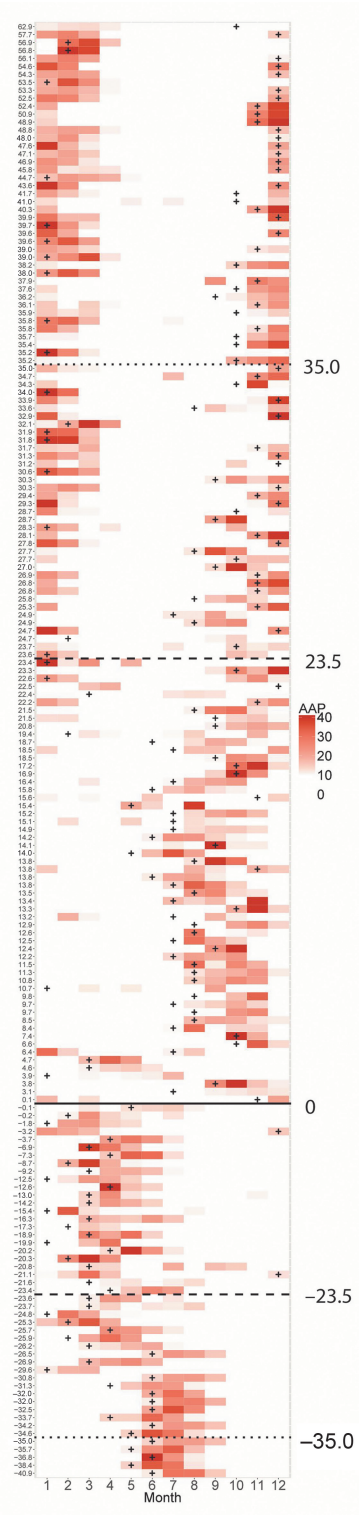

Figure 5: Heat maps of global monthly respiratory syncytial virus activity arranged by latitude.[123] "+" indicates primary season onset. AAP: Annual average percentage, as a measurement of the strength of virus activity by the formula: $AAP_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\%$, where *i* denotes the month and *n* denotes the number of cases.

RSV season ≤5 months), minor year-on-year variations and within-province variations in the season onset are observed, whereas in provinces without clear RSV seasonality, RSV activity varies substantially from year to year and within a province.[141] In provinces with clear RSV seasonality, the onset of the RSV season precedes that of the influenza season by 1–2 months.[141]

Impact of the COVID-19 pandemic on RSV epidemiology

During the COVID-19 pandemic, non-pharmacologic interventions (NPIs) implemented to mitigate SARS-CoV-2 transmission also reduced the transmission of other respiratory viruses, including RSV. This resulted in changes in RSV epidemiology in terms of seasonality, disease burden, and distribution of RSV cases by age. Due to the implementation of NPIs, most countries did not observe RSV circulation during the usual RSV season. After the relaxation of NPIs, unprecedented out-of-season resurgence and year-round circulation of RSV was observed in some countries.[142,143] A recent global-level analysis revealed that patterns of RSV activity have generally returned to normal following successive waves in the post-pandemic era.[144]

In 2020, the annual rate of RSV-associated ALRI hospitalization in children under five decreased by 14–80% in different country income strata compared to 2019.[145] However, after the relaxation of NPIs, the hospitalization rate increased at varied levels according to the country's income strata. In high-income countries, the annualized RSV-associated ALRI hospitalization rate returned to a level similar to the pre-pandemic period. In contrast, in middle-income countries, the hospitalization rate remained lower than that of the pre-pandemic period, suggesting a persistent negative impact of the pandemic on healthcare systems and healthcare access in the middle-income region.[145] Notably, some countries such as Denmark and the US reported even more RSV cases and hospital admissions during the out-of-season RSV epidemics than during the typical winter peaks, which could not be solely explained by changes in RSV testing activity.[146,147]

During the COVID-19 pandemic, there were also changes in the distribution by age among RSV hospitalized cases in young children. While infants continued to have the highest RSV hospitalization rate, a significantly increased proportion of children beyond one year were hospitalized compared to the pre-pandemic period.[145,148,149] The changes in the age distribution could be explained by the "immunity debt".[150] Further monitoring of RSV epidemiology is essential to examine whether it will return to the pre-pandemic pattern as RSV immunization products targeting young children are implemented in many countries.

Complications

RSV has a wide range of pathological impacts that extend beyond the respiratory system, potentially affecting multiple organs and leading to various complications. In terms of respiratory complications, potential issues include respiratory failure, acute respiratory distress syndrome (ARDS), pulmonary consolidation, and atelectasis. Additionally, RSV can impact the cardiovascular system, causing myocardial damage and heart failure, among other severe conditions. Some cases may also present with

rashes, conjunctivitis, and immunocompromising. The occurrence of these complications further underscores the complexity and severity of RSV infections. Reports indicate that the primary complications of RSV in adults, the elderly, and individuals with compromised immune systems include pneumonia, respiratory failure, exacerbations of chronic obstructive pulmonary disease (COPD), exacerbations of congestive heart failure, exacerbations of asthma, and hypoxemia.[151] We conducted a review of the relevant literature, identifying the following complications with high incidence rates as shown in the Table 1.

RSV and the respiratory system

Within the respiratory system, an increase in intrathoracic negative pressure combined with hypoxia/hypercapnia may be a common factor leading to various clinical manifestations such as respiratory failure, pulmonary edema, and pneumothorax. Changes in intrathoracic pressure induced by hypoxia and damage to the capillary endothelium can lead to pulmonary edema.[159] The primary mechanisms for pneumothorax may include (1) destructive parenchymal lung disease and (2) alveolar rupture secondary to obstruction of the proximal airways. In RSV bronchiolitis, inflammatory responses followed by bronchial mucosal edema, secretion accumulation, inflammatory cell infiltration, and epithelial cell necrosis may cause partial bronchial airway obstruction, where intrathoracic negative pressure can lead to bronchial rupture and pneumothorax.[202] Additionally, the severity of pulmonary dysfunction is associated with severe hyponatremia, which is related to elevated levels of antidiuretic hormone.[159] Numerous clinical and cohort studies have demonstrated that severe RSV infections in infancy are associated with an increased risk of recurrent wheezing in childhood. The relationship between RSV and childhood wheezing is complex, and the specific causal mechanisms remain unclear.[96,203–204]

Table 1: Respiratory syncytial virus infection-associated complications.

System category	Complications
Respiratory system	Respiratory failure[152–162]
	Acute respiratory distress syndrome [153,163–165]
	Lung consolidation[156,166]
	Pulmonary atelectasis[156,166–168]
Cardiovascular system	Sinus bradycardia [169,170]
	Increased myocardial enzyme spectrum[152,169,171–174]
	Atrial premature beats[169,174]
	Heart failure[5,16,23,27,30–32]
Digestive system	Vomiting[172]
	Diarrhea[167,172]
	Liver damage[153,175–178]
	Elevated liver enzymes (ALT, AST)[172,178]
Nervous system	Toxic encephalopathy[153,165,167,179–184]
	Febrile convulsion[157,182,185,186]
Others	Secondary thrombocytosis[166,172,175,187]
	Otitis media[158,172,188–200]
	Conjunctivitis[158,189,201]
	Immunocompromised[153,163]
	Hyponatremia[160,161,175,179–181]
	Low pH[172]

ALT: Alanine aminotransferase; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase.

RSV and the cardiovascular system

The mechanisms of cardiovascular complications following RSV infection include: (1) Genetic factors predispose the host to an excessive immune response, leading to extrapulmonary tissue damage. (2) Severe pulmonary parenchymal pathology causes hypoxia or pulmonary arterial hypertension, which leads to right ventricular decompensation. Sufficient data indicate that cardiovascular involvement is significant during severe episodes of RSV bronchiolitis.

RSV and the digestive system

The mechanisms by which RSV infection causes liver injury remain unclear. Liver damage induced by infectious diseases is primarily a result of direct assault by toxins from pathogens such as viruses and bacteria or indirectly through inflammatory mediators such as tumor necrosis factor and interleukins, which impair liver function by affecting the uptake and excretion of bile in the capillaries.

RSV and the central nervous system

RSV has been demonstrated to release several neurotoxic mediators, both directly and indirectly, and to induce encephalopathy associated with respiratory diseases.[205] RSV can spread from the lungs to the central nervous system (CNS) via the hematogenous route, altering local homeostasis. For instance, elevated levels of IL-6, IL-8, CCL2, CCL4, and brain-derived neurotrophic factor (BDNF) have been found in infected children's cerebrospinal fluid (CSF).

Others

The pathogenesis of RSV complications varies across different systems. For example, platelet increase may be associated with releasing a series of inflammatory factors and mediators, such as platelet-derived growth factor, following airway inflammation caused by RSV infection.[175] RSV-associated otitis media is more common in infants than in older children,[194] likely due to the ease with which local infections in the nasopharynx can spread to adjacent organs. RSV causes nasopharynx and Eustachian tube inflammation, triggering host immune and inflammatory responses.[191]

Treatment for RSV Infection

Currently, no specific antiviral drugs are available for RSV infection. The treatment is mainly symptomatic and supportive, including hydration, supplemental oxygen, suctioning of airways, and adequate liquid and

nutrition.[205,206] However, antiviral therapy with ribavirin is beneficial for RSV-infected patients with immunodeficiency. Some new and promising anti-RSV drugs are undergoing clinical trials. Approved and in clinical development anti-RSV drugs are listed in Table 2.

Current antiviral therapy for RSV infection

Ribavirin

Ribavirin is a nucleotide analog with broad-spectrum antiviral activity against various viruses.[207,208] Aerosolized ribavirin is the only licensed antiviral therapy available for RSV disease, by FDA in 1985.[209] However, its clinical use is limited by its uncertain efficacy, potential side effects, and high cost. Ribavirin is currently limited to life-threatening RSV infections in immunocompromised patients.

Ribavirin does not yield significant clinical benefits in immunopotent children with RSV infection. A meta-analysis reviewed several randomized controlled trials and concluded that there is insufficient evidence to support a substantial benefit of ribavirin in reducing mortality or the need for mechanical ventilation in children with RSV bronchiolitis.[210] Another systematic review found that while ribavirin may have some benefits in reducing RSV viral load, its overall impact on clinical outcomes, such as duration of mechanical ventilation and length of hospital stay, remains uncertain.[211]

However, ribavirin shows reasonable efficacy against RSV for patients in immunosuppression conditions (such as hematopoietic cell transplant recipients). In a multicenter prospective trial, RSV-infected hematopoietic cell transplant recipients were randomized to receive either ribavirin aerosol (2 g at 60 mg/mL) three times daily or supportive care only for 10 d. After 10 d of treatment, the average viral load in ribavirin recipients decreased by 0.75 log10 copies/mL, whereas untreated patients experienced a viral load increase of 1.26 log10 copies/mL. A meta-analysis and systemic review demonstrated that ribavirin could significantly reduce the mortality of RSV-LRTIs in hematological patients.[212] Thus, ribavirin may be an alternative option for treating RSV-LRTIs in hematological patients.[213]

Interferons

Interferons (IFNs) produce broad-spectrum antiviral effects by upregulating interferon-stimulated genes (ISGs).[214] Some studies have investigated the therapeutic value of IFNs against RSV infection. A multicenter, randomized, prospective study evaluated the therapeutic effects and safety of IFNα1b nebulization in infants with bronchiolitis, primarily caused by RSV, and found that IFNα1b nebulization effectively alleviated coughing and wheezing symptoms and shortened their duration. The study reported significant improvements in coughing severity between days one and three and in wheezing severity between days three and five for the nebulization groups compared to the control group. No severe complications were observed during the treatment period, indicating the safety of IFNα1b nebulization.[215] A retrospective study evaluated the efficacy and safety of IFNα1b in treating neonates with RSV LRTIs. The results showed that the treatment group experienced significantly shorter remission times for significant symptoms such as cough, tachypnea, choking on milk, prebilabial cyanosis, moist rales, and reduced oxygen inhalation time. There were minimal adverse effects, with only two cases of mild fever following IFNα1b administration.[216]

Palivizumab

Palivizumab is the first FDA-approved humanized monoclonal antibody targeting a conserved epitope in the antigenic site II of the RSV F protein.[217] While it could protect in the prophylactic context, several studies have investigated

Table 2: Approved and in clinical-development anti-RSV drugs.

Compounds	Target	Mode of action	Clinical trial phase	References
Entry				
Palivizumab	Site II of F protein	Neutralizing the virus	Approved by FDA in 1998	[217–219]
Nirsevimab	Site Ø of F protein	Blocking the conformational change of F protein necessary for viral entry into host cells	Approved by FDA in 2023	[40, 220]
Ziresovir (RO-0529, AK0529)	F protein	Targeting the RSV F protein by binding to its HRC region	NDA in China in 2022	[221–223]
Sisunatovir (RV521)	F protein	Targeting a central region created by the trimeric structure of the F protein	Phase 2a	[224, 225]
Post-entry				
Ribavirin	RdRp	Incorporating into the viral RNA chain and causing premature termination of RNA synthesis	Approved by FDA in 1985	[207, 208, 210–215]
PC786	L protein	Inhibiting the RSV polymerase function	Phase 1b/2a	[226–228]
EDP-323	L protein	Inhibiting the RSV L protein by binding to the capping domain of the L protein	Phase 2a	[229,230]
EDP-938	N protein	Inhibiting RSV primary transcription and processes before the onset of primary transcription	Phase 2b	[233–235]

FDA: Food and drug administration; HRC: Heptad repeat C; NDA: New Drug Application; RdRp: RNA-dependent RNA polymerase; RSV: Respiratory syncytial virus.

its potential role in treating RSV infection. However, these studies yielded disappointing results.[218,219]

Nirsevimab

Nirsevimab, a highly potent monoclonal antibody, was developed by MedImmune/AstraZeneca (Gaithersburg, USA) as a potential RSV vaccine surrogate. It targets a highly conserved epitope on the pre-fusion form of the RSV F protein of both subtypes A and B.[42] The binding involves extensive interactions with the F1 and F2 subunits, blocking the conformational change necessary for viral entry into host cells.

FDA approved Beyfortus (Nirsevimab-clip, Sanofi/AstraZeneca) in July 2023 for preventing lower respiratory tract disease caused by RSV in neonates and infants who are either born during or entering their first RSV season. Additionally, this approval extends to children up to 24 months old who are still at risk for severe RSV disease during their second RSV season.[220] Given its cheering prophylactic effects against RSV, further studies are warranted to explore its potential role in treating RSV infection.

New anti-RSV drug candidates in clinical development

Fusion inhibitor

Ziresovir

Ziresovir (RO-0529, AK0529, Shanghai Ark Biopharmaceutical, China), an RSV F protein inhibitor, targets the RSV F protein to prevent the fusion of viruses and cell membranes by binding to the heptad repeat C (HRC) region. Ziresovir showed high potency with EC_{50} of 0.02–0.04 μmol/L in the CPE assay against both laboratory strains of RSV (Long, A2, and B18537) and clinical RSV strains.[233]

In a randomized, double-blind, placebo-controlled, two-part phase 2 proof-of-concept trial (VICTOR Study, ClinicalTrials.gov Identifier: NCT02654171),[234] 72 hospitalized infants aged 1–24 months with RSV infection were randomly assigned to receive either single or multiple doses of AK0529 or placebo. In Part 1, 24 patients received a single dose of up to 4 mg/kg of AK0529 or placebo. The results indicated that the reductions in viral load at 24 h post-dose were less than 1 log10 PFUe/mL compared to placebo. In Part 2, 48 patients received up to 2 mg/kg of AK0529 twice daily or placebo for 5 d. The results for viral load demonstrated a 1.25 log10 PFUe/mL and 1.73 log10 PFUe/mL more significant reduction at 72 h and 96 h post-dose, respectively, for the 2 mg/kg twice daily dose compared to placebo. The latest phase 3 trial of Ziresovir (AIRFLO Study, ClinicalTrials.gov Identifier: NCT04231968) in China has been completed, but its results have yet to be officially announced. In December 2022, China's National Medical Products Administration (NMPA) accepted and granted Priority Review to the New Drug Application (NDA) for the clinical use of Ziresovir in treating RSV infection.[223]

Sisunatovir (RV521)

RV521 (Pfizer, NY, USA) targets a central region created by the trimeric structure of the F protein. Fundamental interactions include π-bonding with phenylalanine residues (Phe140 and Phe488) from two different monomers and a hydrogen bond with the backbone carbonyl of threonine 397 from the third monomer. *In vitro*, RV521 showed a mean IC_{50} of 1.2 nmol/L against a range of RSV A and B laboratory strains and clinical isolates.[224] In a randomized, double-blind, placebo-controlled phase 2a trial (ClinicalTrials.gov Identifier: NCT03258502),[225] and 66 healthy adults were inoculated with RSV-A Memphis-37b and randomly assigned to receive either 200 mg or 350 mg of RV521 or a placebo twice daily for five days. The viral load results demonstrated a 63.05% and 55.25% reduction for the 350 mg and 200 mg doses, respectively. In addition, RV521 significantly reduced total symptom scores and nasal mucus weight compared to placebo. No treatment-related serious adverse events were reported. Pharmacokinetic assessments revealed that RV521 plasma concentrations achieved the target trough levels necessary for efficacy. However, a multicenter, 3-part, phase 2 study in infants hospitalized due to RSV LRTIs (REVIRAL 1, ClinicalTrials.gov Identifier: NCT04225897) was terminated due to strategic consideration. Another phase 2 study (ClinicalTrials.gov Identifier: NCT04267822) in the treatment of adult subjects who have undergone hematopoietic cell transplantation with RSV-related URTIs has been withdrawn for unknown reasons.

Replication inhibitor

PC786

PC786 (Pulmocide Ltd, Boston, USA) a potent non-nucleoside inhibitor of the RSV L protein,[226] PC786 inhibits RSV RNA-dependent RNA polymerase (RdRp) activity and exhibits potent antiviral activity against both RSV-A and RSV-B, with IC_{50} values ranging from 0.09 to 0.71 nmol/L for RSV-A and 1.3 to 50.6 nmol/L for RSV-B. PC786 primarily inhibits the replication and transcription activities of the RSV polymerase. It showed high potency for late therapeutic intervention in a human airway epithelium model.[227] The administration of PC786 (700 nmol/L), initiated on day three post-inoculation, reduced the viral load to below detectable limits by day six. In a randomized, double-blind, placebo-controlled phase 1b/2a trial (ClinicalTrials.gov Identifier: NCT03382431),[228] nebulized PC786 was found to be safe and effective in reducing RSV viral load by 32–34% and alleviating symptoms compared to the placebo group.

EDP-323

EDP-323 (Enanta Pharmaceuticals, Inc, MA, USA) is a small molecule that inhibits the RSV L protein by binding to the capping domain of the L protein.[229] EDP-323 demonstrated potent antiviral activity with EC_{50} values ranging from 0.11 to 0.44 nmol/L across different RSV strains and cell lines. A randomized, double-blind,

placebo-controlled phase 1 study has been completed (ClinicalTrials.gov Identifier: NCT05587478).[230] The results indicated that EDP-323 was well-tolerated at doses up to 800 mg once daily for seven days. Pharmacokinetic analysis showed that EDP-323 was rapidly absorbed and supported once-daily dosing. Enanta Pharmaceuticals is currently recruiting for a randomized, phase 2a (ClinicalTrials.gov Identifier: NCT06170242), double-blind, placebo-controlled study to evaluate the safety, pharmacokinetics, and antiviral activity of multiple doses of orally administered EDP-323 against respiratory syncytial virus infection.

EDP-938

EDP-938 (Enanta Pharmaceuticals) was identified through a series of chemical optimizations based on 1,4-benzodiazepine inhibitors of RSV.[233] EDP-938 was effective against multiple RSV-A and RSV-B strains, with EC_{50} values ranging from 28–72 nmol/L for CPE inhibition and 54–110 nmol/L for viral load reduction in various cell lines, including HEp-2, A549, Vero, and BHK cells.[233] A phase 2a, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03691623)[234] evaluated the efficacy and safety of EDP-938. In part 1, 115 participants received 600 mg once daily, 300 mg twice daily after a 500 mg loading dose, or placebo. In part 2, 63 participants received 300 mg once daily after a 600 mg loading dose, 200 mg twice daily after a 400 mg loading dose, or placebo. Both parts showed significant reductions in RSV viral load (72.5–80.2%) and total symptom score (62.0–79.3%) with EDP-938 compared to placebo. In another phase 2a trial (ClinicalTrials.gov Identifier: NCT04196101),[235] participants receiving 800 mg once daily for 5 d demonstrated a significant reduction in RSV viral load and symptoms. The mean viral load AUC was 37.00 d × log10 copies/mL for the EDP-938 group compared to 46.96 for placebo. Symptom severity was also lower, with a higher percentage of participants achieving undetectable viral loads by Day 5 (16.7% for EDP-938 *vs*. 6.3% for placebo). Currently, a phase 2 trial (ClinicalTrials.gov Identifier: NCT04816721) and a phase 2b trial (ClinicalTrials.gov Identifier: NCT05568706) are recruiting.

Prevention

The preventative strategy for RSV encompasses a multifaceted approach that incorporates NPIs as the most readily accessible modalities,[231] alongside potential pharmacological prevention candidates such as monoclonal antibodies (mAbs) and vaccines.

Research progress and immunization strategy for RSV prevention candidates

RSV vaccine development began in the 1960s with an unsuccessful formalin-inactivated RSV (FI-RSV) vaccine that induced a severe and, in two cases, lethal-lung inflammatory response during the first natural RSV infection after vaccination of RSV-naive infants. This adverse reaction to natural RSV infection has been designated as vaccine-associated enhanced respiratory disease (ERD). The concerns over the FI-RSV vaccine hindered the development of alternative RSV vaccines for many years.[232] However, recently, a more profound comprehension of RSV biology and concomitant technological advancements have propelled the inclusion of numerous vaccine candidates in clinical development, particularly RSV vaccines tailored for older adults and maternal populations, along with RSV mAbs intended for infants and young children.

RSV vaccines

The primary target populations for RSV vaccination comprise children, maternal populations, and elderly individuals. Currently, three vaccines for older adults (RSV prefusion F3, RSVPreF, and mRNA-1345) and one for maternal populations (RSVPreF) have been authorized for use in select regions. Furthermore, as of May 31, 2024, over 36 RSV prevention candidates are undergoing clinical development, many of which are grounded in cutting-edge technologies, including intranasal administration and combined vaccine formulations [Table 3].

RSVPre-F3 (GSK, London, UK), a vaccine designed for intramuscular administration, is intended for active immunization in individuals aged 60 and above. It is aimed at preventing RSV-associated lower respiratory tract disease (RSV-LRTD).[236,237] An ongoing Phase 3 clinical study conducted in 17 countries showed that, compared with a placebo, RSVPre-F3 significantly reduced the risk of developing RSV-LRTD in participants 60 years of age and older.[238] On May 3, 2023, RSVPre-F3 obtained FDA authorization for RSV-LRTD prevention in adults over 60, marking it as the first registered RSV vaccine.[239] Subsequently, it garnered approval from the European Medicines Agency (EMA) on June 6, 2023,[240] the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) on July 10, 2023,[241] Canada in August 2023,[242] the Japanese Ministry of Health, Labour, and Welfare (MHLW) in September 2023,[243] and Australia in January 2024.[244] Another authorized product designed for intramuscular administration, the RSVPreF (PF-06928316; Pfizer, New York, US) vaccine, is intended for active immunization in individuals aged 60 and above and pregnant women between 32 and 36 weeks of gestation.[237,245] Interim results from an ongoing Phase 3 clinical study assessing the efficacy and safety of RSVPreF in preventing RSV-LRTD among individuals aged 60 and older have demonstrated that the study met pre-set criteria for establishing the vaccine's efficacy in preventing RSV-LRTD with ≥2 symptoms and RSV-LRTD with ≥3 symptoms.[245] The vaccine was approved for people aged 60 years and older in Canada, the United States, the European Union, the United Kingdom (UK), Japan, and Australia on January 4, 2023,[246] May 31, 2023,[247] August 23, 2023,[248] November 23, 2023,[241] 18 January 2024,[249] and March 20, 2024,[250] respectively. Additionally, interim results from a Phase III clinical study evaluating maternal vaccination with RSVPreF in 18 countries have shown its effectiveness in preventing severe RSV-LRTD in infants with favorable safety profiles.[251] Consequently, in 2023, RSVPreF received FDA approval

Table 3: Overview of RSV vaccines and mAbs in clinical development. (Searched from the ClinicalTrials.gov, 31 May 2024).

Prevention candidates	Route of administration	Clinical phase and time	Target population	Clinical results
Monoclonal antibodies				
Palivizumab	Intramuscular	Phase 3: Commencing on July 23, 2019, and concluding on March 21, 2023, with the ClinicalTrials.gov identifier NCT03979313	A total of 1502 children with prematurity (≤35 weeks) or bronchopulmonary dysplasia (BPD)	The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (12.8% placebo *vs.* 7.9% palivizumab) and patients enrolled with a diagnosis of prematurity without BPD (8.1% placebo *vs.* 1.8% palivizumab).
Nirsevimab	Intramuscular	Phase 3: Commencing on July 23, 2019, and concluding on March 21, 2023, with the ClinicalTrials.gov identifier NCT03979313	A total of 1490 infants	75% efficacy against medically attended RSV-LRTI.
Clesrovimab (MK1654)	Intramuscular	Phase 1: Commencing in June 2017 and concluding in February 2019	A total of 152 healthy adults	The antibody displayed a half-life of 73 to 88 days and an estimated bioavailability of 69% at the 300-mg dose. The overall safety profile of MK-1654 was similar to that of the placebo, and treatment-emergent antidrug antibodies were low (2.6%) with no associated adverse events.
		Phase 2b/3: Commencing on April 7, 2021, and concluding on August 15, 2024, with the ClinicalTrials.gov identifier NCT04767373	A total of 3300 healthy pre-term and full-term infants	Clesrovimab met its primary safety and efficacy endpoints, including reducing medically attended lower respiratory infections (MALRI) caused by RSV through Day 150.
		Phase 3: Commencing on November 30, 2021, and concluding on October 27, 2025, with the ClinicalTrials.gov identifier NCT04938830	A total of 1000 infants	No results published
TNM001	Intramuscular	Phase 2b/3: Commencing on 31 October 2023 and concluding on August 31, 2026, with the ClinicalTrials.gov identifier NCT06083623	A total of 2250 infants	No results published
Narsy	Intranasal	Phase 1 and 2b trial: Commencing on January 14, 2019, and concluding on January 28, 2021, with the ClinicalTrials.gov identifier NTR7378 and NTR7403	A total of 268 infants	Any RSV infection was similar in infants in both groups (38.3%) palivizumab arm versus (23.4%) placebo arm.
		Phase 2: Commencing on November 2018 and concluding on April 2020, with the ClinicalTrials.gov identifier NTR7403	A total of 408 late preterm infants 32–35 weeks gestational age with at least one sibling who is less than six months of age at the onset of the RSV season.	No results published
RB0026	Intramuscular	Phase 1 and 2: Commencing on June 2022 and concluding on September 2023, with the ClinicalTrials.gov identifier CTR20232147	Healthy adults	No results published
RSM0	Intramuscular	Phase 1: Commencing on November 2021 and concluding on February 2022, with the ClinicalTrials.gov identifier NCT05118386	A total of 56 healthy adults	No results published
GR210	Intramuscular	Phase 1: Commencing on March 2024 and concluding on December 6, 2025, with the ClinicalTrials.gov identifier CTR20240608	A total of 132 healthy adults aged 18 to 45 years old	No results published
MB05	Intramuscular	Phase 1: Commencing on December 2021 and concluding on September 2023, with the ClinicalTrials.gov identifier NCT05121246.	A total of 141 healthy adults	No results published
Vaccine				

(*continued*)

Table 3

(Continued)

Prevention candidates	Route of administration	Clinical phase and time	Target population	Clinical results
Subunit vaccine				
RSVPre-F3 (GSK3844766A)	Intramuscular	Phase 3: Commencing on May 25, 2021, and concluding on June 18, 2024, with the ClinicalTrials.gov identifier NCT04886596	A total of 26,668 adults aged ≥60 years old	Efficacy over 2 seasons of 1 RSVPreF3 OA dose was 67.2% against RSV-LRTD and 78.8% against severe RSV-LRTD. Efficacy over two seasons of a first dose followed by revaccination was 67.1% against RSV-LRTD and 78.8% against severe RSV-LRTD. The reactogenicity/safety of the revaccination dose was similar to that of dose 1.
RSVPreF	Intramuscular	Phase 3: Commencing on August 31, 2021, and concluding on June 12, 2026, with the ClinicalTrials.gov identifier NCT05035212	A total of 34,284 adults ≥ 60 years of age	RSVpreF vaccine prevented RSV-LRTD and RSV-associated acute respiratory illness in adults without evident safety concerns.
VN-0200	Intramuscular	Phase 1: Commencing on June 2021 and concluding on January 2022 with the ClinicalTrials.gov identifier NCT04914520.	A total of 48 healthy adults and older adults	No results published
	Intramuscular	Phase 2: Commencing on October 13, 2022, and concluding on February 15, 2024, with the ClinicalTrials.gov identifier NCT05547087	A total of 342 healthy adults aged 60 to 80 years old	No results published
DS-Cav1	Intramuscular	Phase 1: Commencing in February 2017 and concluding in October 2019, with the ClinicalTrials.gov identifier NCT03049488	A total of 95 healthy adults	No results published
DPX-RSV	Intramuscular	Phase 1: Commence in May 2015 and conclude in June 2017, with the ClinicalTrials.gov identifier NCT02472548.	A total of 40 healthy adults aged ≥ 50–64 years old	No results published
BARS13	Intramuscular	Phase 2: Commencing on May 2021 and concluding on June 2023, with the ClinicalTrials.gov identifier NCT04681833	A total of 120 older adults	No results published
SCB-1019	Intramuscular	Phase 1: Commencing on December 13, 2023, and concluding on May 2025, with the ClinicalTrials.gov identifier NCT06194318	A total of 60 healthy adults aged 18 to 85 years old	No results published
Particle-based vaccine				
V306-SVL	Intramuscular with skin patch boosters	Phase 1: Commencing on September 2020 and concluding on March 2022, with the ClinicalTrials.gov identifier NCT04519073	A total of 60 healthy adult women aged 18 to 45 years old	No results published
IVX-A12	Intramuscular	Phase 1/1b: Commencing on September 21, 2022, and concluding on January 24, 2024, with the ClinicalTrials.gov identifier NCT05664334	A total of 90 healthy young adults aged 18 to 45 years old; A total of 130 healthy older adults aged 60 to 75 years old	IVX-121 was generally well-tolerated across all dosage groups and induced a robust immune response.
		Phase 2: Commencing on May 15, 2023, and concluding on September 30, 2025, with the ClinicalTrials.gov identifier NCT05903183	A total of 264 older adults aged 60 to 85 years old	No results published
Nucleic acid vaccine				
mRNA-1345	Intramuscular	Phase 2 and 3: Commencing on November 17, 2021, and concluding on August 25, 2025, with the ClinicalTrials.gov identifier NCT05127434	A total of 35,541 adults aged ≥60 years old	Vaccine efficacy was 83.7% against RSV-LRTD with at least two signs or symptoms and 82.4% against the disease with at least three signs or symptoms. Vaccine efficacy was 68.4% against RSV- LRTD.

(*continued*)

Table 3

(Continued)

Prevention candidates	Route of administration	Clinical phase and time	Target population	Clinical results
STR-V003	Intramuscular	Phase 1/2: Commencing on May 2024 and concluding on May 2025, with the ClinicalTrials.gov identifier NCT06344975	A total of 48 healthy adults aged 18 years and older	No results published
IN006	Intramuscular	Phase 1: Commencing on August 2024 and concluding on October 2026, with the ClinicalTrials.gov identifier NCT06287450	A total of 200 healthy adults aged 18 to 79 years old	No results published
RSV mRNA LNP CL-0059 and RSV mRNA LNP CL-0137	Intramuscular	Phase 1/2: Commencing on November 17, 2022, and concluding on April 29, 2025, with the ClinicalTrials.gov identifier NCT05639894	A total of 865 adults aged 18 years and older	No results published
RSV/hMPV mRNA Vaccine	Intramuscular	Phase 1/2a: Commencing on November 1, 2023, and concluding on March 10, 2026, with the ClinicalTrials.gov identifier NCT06134648	A total of 210 older adults aged 60 years and older	No results published
Recombinant vectors vaccine				
AD26.RSV.PreF	Intramuscular	Phase 2: Commencing on July 6, 2018, and concluding on May 16, 2022, with the ClinicalTrials.gov identifier NCT03502707		A combination regimen comprising Ad26.RSV.preF elicited strong humoral and cellular responses, and RSV preF protein increased humoral responses.
		Phase 3: Commencing on July 2021 and concluding on January 2024, with the ClinicalTrials.gov identifier NCT04908683		No results published
AD26.RSV.PreF	Intramuscular	Phase 1 and 2: Commencing on November 8, 2016, and concluding on January 29, 2019, with the ClinicalTrials.gov identifier NCT02926430; Commencing on November 29, 2017, and concluding on April 21, 2020, with the ClinicalTrials.gov identifier NCT03303625	A total of 73 adults aged ≥60 years old; A total of 48 participants aged 12 months to 50 years old	Well-tolerated and elicited both humoral and cellular immune responses.
		Phase 3: Commencing on July 2021 and concluding on January 2024, with the ClinicalTrials.gov identifier NCT04908683	A total of 23000 adults aged ≥60 years old	No results published
MVA-BN RSV	Intramuscular	Phase 2: Commencing on September 2016 and concluding on December 2018, with the ClinicalTrials.gov identifier NCT02873286	Adults aged ≥55 years old	A single dose increased the neutralizing and total antibodies (1.6 to 3.4-fold increase from baseline) and induced a broad Th1-biased cellular immune response to all five vaccine inserts (5.4 to 9.7-fold increases).
		Phase 3: Commencing on February 28, 2022, with the ClinicalTrials.gov identifier NCT05238025	A total of 21656 adults aged ≥60 years old	No results published
RSV/Flu-01E	Intranasal	Phase 1: Commencing on May 10, 2023, and concluding on September 18, 2023, with the ClinicalTrials.gov identifier NCT05970744	A total of 60 healthy adults aged ≥18 years old	No results published
Chimeric vaccine				
SeV/RSV	Intranasal	Phase 1: Commencing on May 2018 and concluding on February 2019, with the ClinicalTrials.gov identifier NCT03473002	A total of 21 healthy adults	No results published
rBCG-N-hRSV	Intranasal	Phase 1: Commencing on June 27, 2017, and concluding on June 1, 2018, with the ClinicalTrials.gov identifier NCT03213405	Healthy males aged 18–50 years old	The rBCG-N-RSV vaccine was safe and well-tolerated, and no serious adverse events related to the vaccine were recorded.

(*continued*)

Table 3

(Continued)

Prevention candidates	Route of administration	Clinical phase and time	Target population	Clinical results
Live-attenuated vaccine				
RSV-MinL4.0	Intranasal	Phase 1: Commencing on July 2020 and concluding on May 2021, with the ClinicalTrials.gov identifier NCT04295070	A total of 36 healthy adults aged 50 to 75 years old	No results published
		Phase 1: Commencing on March 2022 and concluding on February 2023, with the ClinicalTrials.gov identifier NCT04919109	A total of 18 children aged two to five years and 33 children aged six months to less than two years old	No results published
CodaVax-RSV	Intranasal	Phase 1: Commencing on March 28, 2023, and concluding on June 5, 2024, with the ClinicalTrials.gov identifier NCT04919109	51 healthy children aged six months to five years old.	No results published
IT-RSVΔG	Intranasal	Phase 1: ClinicalTrials.gov identifier NTR7173	Healthy adults aged 18 to 50 years old	RSVΔG was well tolerated with no findings of clinical concern. No infectious virus was detected in nasal wash samples.
MV-012-968	Intranasal	Phase 2: Commencing on December 29, 2020, and concluding on September 9, 2021, with the ClinicalTrials.gov identifier NCT04690335	A total of 60 healthy adults aged 18 to 45 years old	No results published
RSV ΔNS2/ Δ1313 / I1314	Intranasal	Phase 2: Commencing on May 2019 and concluding on April 2023, with the ClinicalTrials.gov identifier NCT03916185	A total of 160 children six to 24 months of age	No results published
RSV LID/ΔM2–2/1030s	Intranasal	Phase 1: Commencing on September 2020 and concluding on April 2022, with the ClinicalTrials.gov identifier NCT04520659	A total of 81 infants and children six to 24 months of age	No results published
RSV 6120/ΔNS2/1030s	Intranasal	Phase 1: Commencing on May 2019 and concluding on April 2023, with the ClinicalTrials.gov identifier NCT03916185	A total of 160 children six to 24 months of age	No results published
RSV 6120/F1/G2/ΔNS1	Intranasal	Phase 1: Commencing on June 2018 and concluding on December 2023, with the ClinicalTrials.gov identifier NCT03596801	A total of 75 children 12 to 59 months of age and infants and children six to 24 months of age	No results published
VAD00001(SP0125)	Intranasal	Phase 1 and 2: Commencing on September 2020 and concluding on April 2023, with the ClinicalTrials.gov identifier NCT04491877	A total of 300 infants and toddlers	No results published
BLB-201	Intranasal	Phase 1: Commencing on March 9, 2023, and concluding on December 23, 2024, with the ClinicalTrials.gov identifier NCT05655182	A total of 137 healthy children aged eight months to five years	No results published
		Phase 1: Commencing on July 20, 2022, and concluding on May 3, 2023, with the ClinicalTrials.gov identifier NCT05281263	A total of 30 healthy adults aged 18 to 75 years old	No results published
rBCG-N-hRSV	Intradermal	Phase 1: Commencing on June 27, 2017, and concluding on June 1, 2018, with the ClinicalTrials.gov identifier NCT03213405	A total of 24 adults aged 18 to 50 years old	No results published

hMPV: Human metapneumovirus; mAbs: Monoclonal antibodies; RSV: Respiratory syncytial virus; RSV-LRTD: RSV-associated lower respiratory tract disease.

for use in pregnant women between 32 and 36 weeks of gestation to prevent acute LRTI and severe LRTI caused by RSV in infants up to 6 months of age.[252] On May 31, 2024, the FDA approved mRNA-1345 (Moderna, Massachusetts, US), marking the first authorization of an mRNA vaccine to prevent RSV-LRTD in adults aged 60 years and older. Several clinical trials are underway for combined vaccines utilizing nucleic acid technology. These include mRNA-1230, aimed at preventing influenza, COVID-19, and RSV, and mRNA-1365, designed to avoid RSV and human metapneumovirus (hMPV). These endeavors represent a promising direction in developing multifaceted vaccines with broader protective capabilities.

RSV monoclonal antibodies

Using mAbs as a means of passive immunization for high-risk populations has exhibited noteworthy success, mainly when RSV vaccines for children are unavailable. Two mAbs, nirsevimab, which gained authorization in China in January 2024, and palivizumab, have secured regulatory approval in select regions. Seven mAbs are currently undergoing clinical investigation [Table 3]. The first licensed mAb for RSV prevention is palivizumab, which the FDA approved in 1998. Real-world evidence has confirmed that palivizumab immunoprophylaxis is associated with a low incidence of severe RSV infection.[253,254] However, due to its half-life of 28 days, monthly administration throughout the RSV season is necessary. Palivizumab is recommended for monthly dosing by intramuscular injection during the RSV season for the prevention of severe RSV disease in specific high-risk children, including those born very prematurely or those with moderate to severe bronchopulmonary dysplasia or hemodynamically significant congenital heart disease.[255,256] Palivizumab is used in most countries in a restricted manner among very high-risk infants, in part due to its high cost. As of late 2019, it is registered in no low-income countries, three lower-middle-income countries, 18 upper-middle-income countries, and 44 high-income countries.[257]

Because of its YTE amino acid substitutions, nirsevimab has high neutralizing activity and an extended half-life compared to palivizumab. Phase I studies have shown that the half-life of nirsevimab in healthy adults is 85 to 117 days, about three times longer than palivizumab. This provides the possibility of long-term prevention after a single vaccination (a single intramuscular injection protects infants for an entire season).[258] Multicenter clinical trials have validated the safety and efficacy of nirsevimab.[259–262] Real-world data further suggests that nirsevimab effectively mitigates the risk of RSV-associated hospitalizations among infants during their first RSV season.[263] Notably, the most salient advantages of nirsevimab over palivizumab are its single-dose administration and reduced costs, which enable its administration to all infants, not just high-risk children.[16] In October 2022, April 2023, July 2023, March 2024, and April 2024, nirsevimab received regulatory approval from the European Union, Canada, the United States, Japan, and South Korea, respectively. And it is the first licensed human monoclonal antibody (mAb) to prevent RSV disease in infants and young children in China.[264] The target population for nirsevimab encompasses newborns and infants approaching or born during their first RSV infection season, including healthy full-term infants, late and preterm infants, and infants with specific health conditions predisposing them to severe RSV infections.

Immunization strategy for RSV prevention candidates

Currently, the three registered RSV vaccines are indicated for active immunization to prevent LRTD caused by RSV in individuals 60 years of age and older. As of the June 26, 2024, Advisory Committee on Immunization Practices (ACIP) meeting, the work group issued a transition from shared clinical decision-making (SCDM) to a universal recommendation among adults 75 years and older and a risk-based recommendation among adults aged 60 to 74 years to be vaccinated by RSV vaccines: (1) All adults aged 75 years and older should receive a single dose of RSV vaccination. (2) All adults aged 60 to 74 years with certain chronic medical conditions or other factors that increase the risk of severe RSV disease should receive a single dose of RSV vaccination. These recommendations replace the SCDM recommendation, meaning that adults aged 60 to 74 without risk factors for severe RSV disease are no longer recommended to receive RSV vaccination. The meeting concluded that insufficient evidence exists to recommend RSV vaccination in adults 50 to 59. RSV vaccination will have the most benefit if given in late summer or early fall. Adults who have already received an RSV vaccine dose do not need another dose in the same year. Per General Best Practice Guidelines for Immunization, co-administration of RSV vaccines with other adult vaccines is acceptable. This includes giving RSV vaccines simultaneously with seasonal influenza, COVID-19, pneumococcal, Td/Tdap, and recombinant zoster (Shingrix, GSK) vaccines.[237]

For infants, WHO documented two preventive strategies in 2017: (1) the development of vaccines for pediatric immunization to prevent RSV disease in infants and young children and (2) the development of vaccines for maternal immunization during pregnancy, leading to trans-placental antibody transfer and the prevention of severe RSV disease in neonates and young infants.[257] Due to the lingering concerns over the safety of pediatric vaccination, the existing RSV vaccines employing current technical approaches are primarily administered to adults. In recent years, based on the active-passive immunization approach, a breakthrough has been made in the maternal vaccine and the long-acting mAb. In 2021, the WHO updated the preventive strategies and pointed out that public health needs should be prioritized. The ideal mAb product would be a high-quality, safe, and effective RSV immunoprophylaxis product that could be used to prevent severe RSV illness and death in infants under 12 months of age and to reduce morbidity in children under five years of age. It should be affordable, accessible, and could be used globally, including in low-and middle-income countries.[265] As of March 2024, more than 10 countries have endorsed using RSV long-acting mAbs for RSV prevention in infants and young children through their respective national ACIP. These countries are gradually evaluating the inclusion of these mAbs in

their immunization programs, aiming to ensure accessibility for healthy infants and young children.[266–275]

The ACIP documented that most infants do not need to receive both maternal vaccine and mAb, and recommends that one of the two strategies be selected for immunization.[276] In 2023, the British Society of Maternal and Infant Medicine's clinical instructions stated that administering both the vaccine to the pregnant woman and the mAb to the infant is not recommended. All infants should be protected against RSV using one of these strategies.[277] The RSVpreF maternal vaccine to be administered seasonally to pregnant women between 32–36 weeks of gestation and the nirsevimab are recommended in the following scenarios: (a) infants whose pregnant parent either did not receive the RSV preF vaccine or whose vaccine history is not known; (b) pregnant patients vaccinated within 14 days of delivery; (c) infants and children aged 8 to 19 months at increased risk for severe RSV disease and entering their second RSV season, irrespective of the vaccine status of the pregnant person. Nirsevimab may also be considered for infants when there is a potential incremental benefit despite vaccination, including (1) maternal conditions resulting in inadequate immune response and/or decrease in transplacental transfer (i.e., infants born to pregnant people with chronic immunosuppression with anticipated diminished immune responses to vaccination [e.g., those with an organ transplant or for chronic steroid use]); (2) infants with loss of maternal antibodies (i.e., those who have undergone cardiopulmonary bypass or extracorporeal membrane oxygenation); (3) infants with substantially increased risk for severe RSV disease (i.e., hemodynamically significant congenital heart disease).[277]

In the wake of the approval of nirsevimab and the advancing development of other RSV prevention candidates, it is imperative to conduct clinical trials and real-world studies to complement the assessment of their safety and efficacy in the Chinese population. There is a need to standardize immunization strategies; currently, there is a lack of official documentation outlining vaccination schedules for diverse demographic groups. To this end, efforts should prioritize enhancing the RSV surveillance system, providing scientific evidence to guide the implementation of immunization strategies tailored to different populations and prevention candidates during the applicable seasons. Concurrently, emphasis should be placed on elevating the awareness of professionals and the public regarding RSV infection and the value of vaccination. The formulation and introduction of national policies, laws, and regulations governing the management and application of RSV prevention candidates, particularly long-acting mAbs, must be expedited to ensure standardized market management and oversight. While effective RSV prevention candidates exist, their global promotion and utilization remain limited. Future efforts should continuously promote evidence-based studies, encompassing clinical trials and real-world research related to RSV prevention candidates. Developing scientifically feasible policy initiatives while raising public awareness of RSV infection and prevention candidates will facilitate the integration of RSV prevention candidates into public health programs across all regions, ultimately alleviating the RSV disease burden in the population.

NPI

NPIs, colloquially referred to as public health and social measures, encompass a range of behaviors with a preventive impact on transmitting infectious diseases. These encompass personal protective measures, environmental measures, social distancing measures, and travel restrictions, all aimed at reducing the infection rate, mitigating the epidemic peak, and securing crucial vaccine development and treatment preparation time.[278] During the COVID-19 pandemic, NPIs effectively slowed down and suppressed the spread of the epidemic.[279] These measures reduced the number of patients infected with other respiratory pathogens, such as RSV.[280,281]

At the personal level[282–284]

1. Utilization of facial masks is especially advised during the RSV outbreak season. Masks are recommended in regions with confirmed or suspected respiratory virus transmission, particularly in poorly ventilated areas or where maintaining a one-meter social distance is not feasible.[285]

2. Maintaining optimal respiratory hygiene and proper cough etiquette is crucial. When coughing or sneezing, individuals must cover their mouth and nose with a tissue or elbow to prevent the spread of respiratory droplets and facilitate immediate disposal.

3. Ensuring air cleanliness through measures such as outdoor air intake and indoor air purification is critical. Natural ventilation, weather permitting, should occur two to three times daily for at least 30 minutes; air-conditioned spaces should be ventilated at least twice hourly.

4. Frequent hand washing or sanitization is crucial, as is avoiding touching the eyes, nose, or mouth with unclean hands. Additionally, regular disinfection of frequently touched surfaces is advised.

5. Maintaining appropriate physical distances is recommended to minimize the risk of transmission. It is also advised to avoid proximity with individuals exhibiting symptoms of illness and to self-isolate and avoid contact with others when ill.

6. Healthcare professionals must adhere to the prescribed guidelines for personal protective equipment (PPE) and engage in hand disinfection practices before and after interactions with patients confirmed to be infected with RSV.

At the community level[282–284]

1. Relevant information regarding public health and social interventions for RSV and other respiratory viral infections must be disseminated through systematic health education.

2. In medical institutions, where feasible, dedicated infection control units and wards are recommended to facilitate the isolation of patients, individually or in centralized settings, mitigating the spread of infectious agents.

3. In the advent of an outbreak or epidemic involving RSV and other respiratory infectious diseases, a prompt and comprehensive assessment should be conducted to evaluate the necessity of implementing measures such as school closures, curtailment of social gatherings, and imposition of movement restrictions to curb the transmission dynamics.

References

1. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946–958. doi: 10.1016/S0140-6736(17)30938-8.
2. Bénet T, Sánchez Picot V, Messaoudi M, Chou M, Eap T, Wang J, *et al*. Microorganisms associated with pneumonia in children <5 years of age in developing and emerging countries: The GABRIEL pneumonia multicenter, prospective, case-control study. Clin Infect Dis 2017;65:604–612. doi: 10.1093/cid/cix378.
3. Langedijk AC, Bont LJ. Respiratory syncytial virus infection and novel interventions. Nat Rev Microbiol 2023;21:734–749. doi: 10.1038/s41579-023-00919-w.
4. Zhang XL, Zhang X, Hua W, Xie ZD, Liu HM, Zhang HL, *et al*. Expert consensus on the diagnosis, treatment, and prevention of respiratory syncytial virus infections in children. World J Pediatr 2024;20:11–25. doi: 10.1007/s12519-023-00777-9.
5. Ruckwardt TJ. The road to approved vaccines for respiratory syncytial virus. NPJ Vaccines 2023;8:138. doi: 10.1038/s41541-023-00734-7.
6. Blount RE Jr., Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med 1956;92:544–549. doi: 10.3181/00379727-92-22538.
7. Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. Am J Hyg 1957;66:281–290. doi: 10.1093/oxfordjournals.aje.a119901.
8. Rima B, Collins P, Easton A, Fouchier R, Kurath G, Lamb RA, *et al*. ICTV virus taxonomy profile: Pneumoviridae. J Gen Virol 2017;98:2912–2913. doi: 10.1099/jgv.0.000959.
9. Mufson MA, Orvell C, Rafnar B, Norrby E. Two distinct subtypes of human respiratory syncytial virus. J Gen Virol 1985;66(Pt 10):2111–2124. doi: 10.1099/0022-1317-66-10-2111.
10. Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it. Nat Rev Microbiol 2019;17:233–245. doi: 10.1038/s41579-019-0149-x.
11. Drysdale SB, Barr RS, Rollier CS, Green CA, Pollard AJ, Sande CJ. Priorities for developing respiratory syncytial virus vaccines in different target populations. Sci Transl Med 2020;12:eaax2466. doi: 10.1126/scitranslmed.aax2466.
12. Sanz-Muñoz I, Sánchez-de Prada L, Castrodeza-Sanz J, Eiros JM. Microbiological and epidemiological features of respiratory syncytial virus. Rev Esp Quimioter 2024;37:209–220. doi: 10.37201/req/006.2024.
13. Melero JA, Mas V, McLellan JS. Structural, antigenic and immunogenic features of respiratory syncytial virus glycoproteins relevant for vaccine development. Vaccine 2017;35:461–468. doi: 10.1016/j.vaccine.2016.09.045.
14. Mazur NI, Higgins D, Nunes MC, Melero JA, Langedijk AC, Horsley N, *et al*. The respiratory syncytial virus vaccine landscape: Lessons from the graveyard and promising candidates. Lancet Infect Dis 2018;18:e295–e311. doi: 10.1016/S1473-3099(18)30292-5.
15. Ruckwardt TJ, Morabito KM, Graham BS. Immunological lessons from respiratory syncytial virus vaccine development. Immunity 2019;51:429–442. doi: 10.1016/j.immuni.2019.08.007.
16. Mazur NI, Terstappen J, Baral R, Bardají A, Beutels P, Buchholz UJ, *et al*. Respiratory syncytial virus prevention within reach: The vaccine and monoclonal antibody landscape. Lancet Infect Dis 2023;23:e2–e21. doi: 10.1016/S1473-3099(22)00291-2.
17. Ramaekers K, Rector A, Cuypers L, Lemey P, Keyaerts E, Van Ranst M. Towards a unified classification for human respiratory syncytial virus genotypes. Virus Evol 2020;6:veaa052. doi: 10.1093/ve/veaa052.
18. Cui A, Xie Z, Xu J, Hu K, Zhu R, Li Z, *et al*. Comparative analysis of the clinical and epidemiological characteristics of human influenza virus versus human respiratory syncytial virus versus human metapneumovirus infection in nine provinces of China during 2009-2021. J Med Virol 2022;94:5894–5903. doi: 10.1002/jmv.28073.
19. Song J, Zhu Z, Song J, Mao N, Cui A, Xu W, *et al*. Circulation pattern and genetic variation of human respiratory syncytial virus in China during 2008-2021. J Med Virol 2023;95:e28611. doi: 10.1002/jmv.28611.
20. Muñoz-Escalante JC, Comas-García A, Bernal-Silva S, Robles-Espinoza CD, Gómez-Leal G, Noyola DE. Respiratory syncytial virus A genotype classification based on systematic intergenotypic and intragenotypic sequence analysis. Sci Rep 2019;9:20097. doi: 10.1038/s41598-019-56552-2.
21. Muñoz-Escalante JC, Comas-García A, Bernal-Silva S, Noyola DE. Respiratory syncytial virus B sequence analysis reveals a novel early genotype. Sci Rep 2021;11:3452. doi: 10.1038/s41598-021-83079-2.
22. Madi N, Safar HA, Al-Adwani A, Sadeq M, Al-Turab M. Genomic characterization of circulating human respiratory syncytial viruses A and B in Kuwait using whole-genome sequencing. Microbiol Spectr 2024;12:e0015924. doi: 10.1128/spectrum.00159-24.
23. Trento A, Galiano M, Videla C, Carballal G, García-Barreno B, Melero JA, *et al*. Major changes in the G protein of human respiratory syncytial virus isolates introduced by a duplication of 60 nucleotides. J Gen Virol 2003;84(Pt 11):3115–3120. doi: 10.1099/vir.0.19357-0.
24. Eshaghi A, Duvvuri VR, Lai R, Nadarajah JT, Li A, Patel SN, *et al*. Genetic variability of human respiratory syncytial virus A strains circulating in Ontario: A novel genotype with a 72 nucleotide G gene duplication. PLoS One 2012;7:e32807. doi: 10.1371/journal.pone.0032807.
25. Langedijk AC, Vrancken B, Lebbink RJ, Wilkins D, Kelly EJ, Baraldi E, *et al*. The genomic evolutionary dynamics and global circulation patterns of respiratory syncytial virus. Nat Commun 2024;15:3083. doi: 10.1038/s41467-024-47118-6.
26. McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, *et al*. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science 2013;340:1113–1117. doi: 10.1126/science.1234914.
27. Chen X, Xu B, Guo J, Li C, An S, Zhou Y, *et al*. Genetic variations in the fusion protein of respiratory syncytial virus isolated from children hospitalized with community-acquired pneumonia in China. Sci Rep 2018;8:4491. doi: 10.1038/s41598-018-22826-4.
28. McGinnes Cullen L, Luo B, Wen Z, Zhang L, Durr E, Morrison TG. The Respiratory Syncytial Virus (RSV) G Protein Enhances the Immune Responses to the RSV F Protein in an Enveloped Virus-Like Particle Vaccine Candidate. J Virol. 2023;97:e0190022. doi: 10.1128/jvi.01900-22.
29. Liljeroos L, Krzyzaniak MA, Helenius A, Butcher SJ. Architecture of respiratory syncytial virus revealed by electron cryotomography. Proc Natl Acad Sci U S A 2013;110:11133–11138. doi: 10.1073/pnas.1309070110.
30. Sun YP, Lei SY, Wang YB, Wang YZ, Qiang HS, Yin YF, *et al*. Molecular evolution of attachment glycoprotein (G) and fusion protein (F) genes of respiratory syncytial virus ON1 and BA9 strains in Xiamen, China. Microbiol Spectr 2022;10:e0208321. doi: 10.1128/spectrum.02083-21.
31. McLellan JS, Ray WC, Peeples ME. Structure and function of respiratory syncytial virus surface glycoproteins. Curr Top Microbiol Immunol 2013;372:83–104. doi: 10.1007/978-3-642-38919-1_4.
32. Crank MC, Ruckwardt TJ, Chen M, Morabito KM, Phung E, Costner PJ, *et al*. A proof of concept for structure-based vaccine design targeting RSV in humans. Science 2019;365:505–509. doi: 10.1126/science.aav9033.
33. Mejias A, Rodríguez-Fernández R, Oliva S, Peeples ME, Ramilo O. The journey to a respiratory syncytial virus vaccine. Ann Allergy Asthma Immunol 2020;125:36–46. doi: 10.1016/j.anai.2020.03.017.
34. Rios-Guzman E, Simons LM, Dean TJ, Agnes F, Pawlowski A, Alisoltanidehkordi A, *et al*. Deviations in RSV epidemiological patterns and population structures in the United States following the COVID-19 pandemic. Nat Commun 2024;15:3374. doi: 10.1038/s41467-024-47757-9.
35. Redlberger-Fritz M, Springer DN, Aberle SW, Camp JV, Aberle JH. Respiratory syncytial virus surge in 2022 caused by lineages

already present before the COVID-19 pandemic. J Med Virol 2023;95:e28830. doi: 10.1002/jmv.28830.
36. Fang YP, Chang CC, Lai W, Lee CY. Genetic characterization of respiratory syncytial virus surface glycoproteins F and G in Taiwan, 2017-2021. J Microbiol Immunol Infect 2024;57:564-572. doi: 10.1016/j.jmii.2024.06.003.
37. Mabilo P, Mthiyane H, Simane A, Subramoney K, Treurnicht FK. Characterisation of RSV Fusion Proteins from South African Patients with RSV Disease, 2019 to 2020. Viruses 2022;14(11):2321. doi: 10.3390/v14112321. PMID: 36366419; PMCID: PMC9698603.
38. Zhou X, Jiang M, Wang F, Qian Y, Song Q, Sun Y, *et al*. Immune escaping of the novel genotypes of human respiratory syncytial virus based on gene sequence variation. Front Immunol. 2023;13:1084139. doi: 10.3389/fimmu.2022.1084139.
39. Haider SA, Jamal Z, Tahir F, Salman M, Umair M. Genomic characterization of human respiratory syncytial virus circulating in Islamabad, Pakistan, during an outbreak in 2022-2023. Arch Virol. 2024;169:106. doi: 10.1007/s00705-024-06036-0.
40. Piñana M, González-Sánchez A, Andrés C, Vila J, Creus-Costa A, Prats-Méndez I, *et al*. Genomic evolution of human respiratory syncytial virus during a decade (2013–2023): bridging the path to monoclonal antibody surveillance. J Infect. 2024;88:106153. doi: 10.1016/j.jinf.2024.106153.
41. Tramuto F, Maida CM, Randazzo G, Guzzetta V, Santino A, Li Muli R, *et al*. Whole-Genome Sequencing and Genetic Diversity of Human Respiratory Syncytial Virus in Patients with Influenza-like Illness in Sicily (Italy) from 2017 to 2023. Viruses 2024;16:851. doi: 10.3390/v16060851.
42. Wilkins D, Langedijk AC, Lebbink RJ, Morehouse C, Abram ME, Ahani B, *et al*. Nirsevimab binding-site conservation in respiratory syncytial virus fusion glycoprotein worldwide between 1956 and 2021: An analysis of observational study sequencing data. Lancet Infect Dis 2023;23:856–866. doi: 10.1016/S1473-3099(23)00062-2.
43. Tabor DE, Fernandes F, Langedijk AC, Wilkins D, Lebbink RJ, Tovchigrechko A, *et al*. Global molecular epidemiology of respiratory syncytial virus from the 2017-2018 INFORM-RSV Study. J Clin Microbiol 2020;59:e01828–20. doi: 10.1128/JCM.01828-20.
44. Ahani B, Tuffy KM, Aksyuk AA, Wilkins D, Abram ME, Dagan R, *et al*. Molecular and phenotypic characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. Nat Commun 2023;14:4347. doi: 10.1038/s41467-023-40057-8.
45. Holland LA, Holland SC, Smith MF, Leonard VR, Murugan V, Nordstrom L, *et al*. Genomic Sequencing Surveillance to Identify Respiratory Syncytial Virus Mutations, Arizona, USA. Emerg Infect Dis. 2023;29:2380–2382. doi: 10.3201/eid2911.230836.
46. Anderson LJ, Dormitzer PR, Nokes DJ, Rappuoli R, Roca A, Graham BS. Strategic priorities for respiratory syncytial virus (RSV) vaccine development. Vaccine. 2013;31 Suppl 2(Suppl 2):B209-B215. doi: 10.1016/j.vaccine.2012.11.106.
47. Langedijk AC, Harding ER, Konya B, Vrancken B, Lebbink RJ, Evers A, *et al*. A systematic review on global RSV genetic data: Identification of knowledge gaps. Rev Med Virol 2022;32:e2284. doi: 10.1002/rmv.2284.
48. Adhikari B, Hassan F, Harrison CJ, Dien Bard J, Dunn J, Kehl S, *et al*. A multi-center study to determine genetic variations in the fusion gene of respiratory syncytial virus (RSV) from children <2 years of age in the U.S. J Clin Virol. 2022;154:105223. doi: 10.1016/j.jcv.2022.105223.
49. Goya S, Sereewit J, Pfalmer D, Nguyen TV, Bakhash SAKM, Sobolik EB, *et al*. Genomic Characterization of Respiratory Syncytial Virus during 2022-23 Outbreak, Washington, USA. Emerg Infect Dis. 2023;29:865–868. doi: 10.3201/eid2904.221834.
50. Mazela J, Jackowska T, Czech M, Helwich E, Martyn O, Aleksiejuk P, *et al*. Epidemiology of respiratory syncytial virus hospitalizations in Poland: An analysis from 2015 to 2023 covering the entire polish population of children aged under five years. Viruses 2024;16:704. doi: 10.3390/v16050704.
51. Ahani B, Tuffy KM, Aksyuk AA, Wilkins D, Abram ME, Dagan R, *et al*. Author Correction: Molecular and phenotypic characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. Nat Commun 2024;15:3026. doi: 10.1038/s41467-024-47421-2.
52. Simões EAF, Forleo-Neto E, Geba GP, Kamal M, Yang F, Cicirello H, *et al*. Suptavumab for the prevention of medically attended respiratory syncytial virus infection in preterm infants. Clin Infect Dis 2021;73:e4400–e4408. doi: 10.1093/cid/ciaa951.
53. Jo WK, Schadenhofer A, Habierski A, Kaiser FK, Saletti G, Ganzenmueller T, *et al*. Reverse genetics systems for contemporary isolates of respiratory syncytial virus enable rapid evaluation of antibody escape mutants. Proc Natl Acad Sci U S A 2021;118:e2026558118. doi: 10.1073/pnas.2026558118.
54. Christopher A Morehouse, Bahar Ahani, Anastasia A Aksyuk, Tyler Brady, Kevin M Tuffy, Hong Ji, *et al*. Nirsevimab binding-site conservation in RSV F protein between 2015 and 2022: The US OUTSMART-RSV surveillance study. Open Forum Infectious Disease 2023; 10 Suppl _2: ofad500.2253. https://doi.org/10.1093/ofid/ofad500.2253.
55. Zhu Q, Patel NK, McAuliffe JM, Zhu W, Wachter L, McCarthy MP, *et al*. Natural polymorphisms and resistance-associated mutations in the fusion protein of respiratory syncytial virus (RSV): Effects on RSV susceptibility to palivizumab. J Infect Dis 2012;205:635–638. doi: 10.1093/infdis/jir790.
56. Yasui Y, Yamaji Y, Sawada A, Ito T, Nakayama T. Cell fusion assay by expression of respiratory syncytial virus (RSV) fusion protein to analyze the mutation of palivizumab-resistant strains. J Virol Methods 2016;231:48–55. doi: 10.1016/j.jviromet.2016.01.003.
57. Hashimoto K, Hosoya M. Neutralizing epitopes of RSV and palivizumab resistance in Japan. Fukushima J Med Sci 2017;63:127–134. doi: 10.5387/fms.2017-09.
58. Jallow MM, Diagne MM, Sagne SN, Tall F, Diouf JBN, Boiro D, *et al*. Respiratory syncytial virus in pediatric patients with severe acute respiratory infections in Senegal: Findings from the 2022 sentinel surveillance season. Sci Rep 2023;13:20404. doi: 10.1038/s41598-023-47015-w.
59. Feng Z, Xu L, Xie Z. Receptors for respiratory syncytial virus infection and host factors regulating the life cycle of respiratory syncytial virus. Front Cell Infect Microbiol 2022;12:858629. doi: 10.3389/fcimb.2022.858629.
60. King T, Mejias A, Ramilo O, Peeples ME. The larger attachment glycoprotein of respiratory syncytial virus produced in primary human bronchial epithelial cultures reduces infectivity for cell lines. PLoS Pathog 2021;17:e1009469. doi: 10.1371/journal.ppat.1009469.
61. Zhang L, Bukreyev A, Thompson CI, Watson B, Peeples ME, Collins PL, *et al*. Infection of ciliated cells by human parainfluenza virus type 3 in an in vitro model of human airway epithelium. J Virol 2005;79:1113–1124. doi: 10.1128/JVI.79.2.1113-1124.2005.
62. Fields BN. Fields' virology. Amsterdam: Lippincott Williams & Wilkins, 2007.
63. Kuo L, Fearns R, Collins PL. Analysis of the gene start and gene end signals of human respiratory syncytial virus: Quasi-templated initiation at position 1 of the encoded mRNA. J Virol 1997;71:4944–4953. doi: 10.1128/jvi.71.7.4944-4953.1997.
64. Galloux M, Risso-Ballester J, Richard CA, Fix J, Rameix-Welti MA, Eléouët JF. Minimal elements required for the formation of respiratory syncytial virus cytoplasmic inclusion bodies in vivo and in vitro. mBio 2020;11:e01202–20. doi: 10.1128/mBio.01202-20.
65. Cervantes-Ortiz SL, Zamorano Cuervo N, Grandvaux N. Respiratory syncytial virus and cellular stress responses: Impact on replication and physiopathology. Viruses 2016;8:124. doi: 10.3390/v8050124.
66. Jobe F, Simpson J, Hawes P, Guzman E, Bailey D. Respiratory syncytial virus sequesters NF-κB subunit 65 to cytoplasmic inclusion bodies to inhibit innate immune signaling. J Virol 2020;94:e01380–20. doi: 10.1128/JVI.01380-20.
67. Gower TL, Pastey MK, Peeples ME, Collins PL, McCurdy LH, Hart TK, *et al*. RhoA signaling is required for respiratory syncytial virus-induced syncytium formation and filamentous virion morphology. J Virol 2005;79:5326–5336. doi: 10.1128/JVI.79.9.5326-5336.2005.
68. Yeo DS, Chan R, Brown G, Ying L, Sutejo R, Aitken J, *et al*. Evidence that selective changes in the lipid composition of raft-membranes occur during respiratory syncytial virus infection. Virology 2009;386:168–182. doi: 10.1016/j.virol.2008.12.017.
69. Tsutsumi H, Kojima T, Hirakawa S, Masaki T, Okabayashi T, Yokota S, *et al*. Respiratory syncytial virus infection and the tight junctions of nasal epithelial cells. Adv Otorhinolaryngol 2011;72:153–156. doi: 10.1159/000324777.
70. Han Z, Rao J, Xie Z, Wang C, Xu B, Qian S, *et al*. Chemokine (CXC motif) ligand 4 is a restrictor of respiratory syncytial virus infection and an indicator of clinical severity. Am J Respir Crit Care Med 2020;202:717–729. doi: 10.1164/rccm.201908-1567OC.
71. Mazumder B, Poddar D, Basu A, Kour R, Verbovetskaya V, Barik S. Extraribosomal l13a is a specific innate immune factor

for antiviral defense. J Virol 2014;88:9100–9110. doi: 10.1128/JVI.01129-14.
72. Smith SE, Busse DC, Binter S, Weston S, Diaz Soria C, Laksono BM, *et al*. Interferon-induced transmembrane protein 1 restricts replication of viruses that enter cells via the plasma membrane. J Virol 2019;93:e02003–18. doi: 10.1128/JVI.02003-18.
73. Everitt AR, Clare S, McDonald JU, Kane L, Harcourt K, Ahras M, *et al*. Defining the range of pathogens susceptible to Ifitm3 restriction using a knockout mouse model. PLoS One 2013;8:e80723. doi: 10.1371/journal.pone.0080723.
74. Li L, Ni YA, Song Z, Yi Z, Wang F. Identification of pathogenic genes and transcription factors in respiratory syncytial virus. BMC Pediatr 2021;21:27. doi: 10.1186/s12887-020-02480-4.
75. Busse DC, Habgood-Coote D, Clare S, Brandt C, Bassano I, Kaforou M, *et al*. Interferon-induced protein 44 and interferon-induced protein 44-like restrict replication of respiratory syncytial virus. J Virol 2020;94:e00297–20. doi: 10.1128/JVI.00297-20.
76. Li Z, Qu X, Liu X, Huan C, Wang H, Zhao Z, *et al*. GBP5 is an interferon-induced inhibitor of respiratory syncytial virus. J Virol 2020;94:e01407–20. doi: 10.1128/JVI.01407-20.
77. Lay MK, Bueno SM, Gálvez N, Riedel CA, Kalergis AM. New insights on the viral and host factors contributing to the airway pathogenesis caused by the respiratory syncytial virus. Crit Rev Microbiol 2016;42:800–812. doi: 10.3109/1040841X.2015.1055711.
78. Liu P, Jamaluddin M, Li K, Garofalo RP, Casola A, Brasier AR. Retinoic acid-inducible gene I mediates early antiviral response and toll-like receptor 3 expression in respiratory syncytial virus-infected airway epithelial cells. J Virol 2007;81:1401–1411. doi: 10.1128/JVI.01740-06.
79. Neilson KA, Yunis EJ. Demonstration of respiratory syncytial virus in an autopsy series. Pediatr Pathol 1990;10:491–502. doi: 10.3109/15513819009067138.
80. Johnson JE, Gonzales RA, Olson SJ, Wright PF, Graham BS. The histopathology of fatal untreated human respiratory syncytial virus infection. Mod Pathol 2007;20:108–119. doi: 10.1038/modpathol.3800725.
81. Liesman RM, Buchholz UJ, Luongo CL, Yang L, Proia AD, DeVincenzo JP, *et al*. RSV-encoded NS2 promotes epithelial cell shedding and distal airway obstruction. J Clin Invest 2014;124:2219–2233. doi: 10.1172/JCI72948.
82. Wong J, Rutman A, O'Callaghan C. Recovery of the ciliated epithelium following acute bronchiolitis in infancy. Thorax 2005;60:582–587. doi: 10.1136/thx.2004.024638.
83. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 2009;9:799–809. doi: 10.1038/nri2653.
84. Long C, Qi M, Wang J, Luo J, Qin X, Gao G, *et al*. Respiratory syncytial virus persistent infection causes acquired CFTR dysfunction in human bronchial epithelial cells. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2021;46:949–957. doi: 10.11817/j.issn.1672-7347.2021.210210.
85. Linfield DT, Raduka A, Aghapour M, Rezaee F. Airway tight junctions as targets of viral infections: Tight junctions and viral infections. Tissue Barriers 2021;9:1883965. doi: 10.1080/21688370.2021.1883965.
86. Rezaee F, DeSando SA, Ivanov AI, Chapman TJ, Knowlden SA, Beck LA, *et al*. Sustained protein kinase D activation mediates respiratory syncytial virus-induced airway barrier disruption. J Virol 2013;87:11088–11095. doi: 10.1128/JVI.01573-13.
87. Rezaee F, Harford TJ, Linfield DT, Altawallbeh G, Midura RJ, Ivanov AI, *et al*. cAMP-dependent activation of protein kinase A attenuates respiratory syncytial virus-induced human airway epithelial barrier disruption. PLoS One 2017;12:e0181876. doi: 10.1371/journal.pone.0181876.
88. Godinho-Silva C, Cardoso F, Veiga-Fernandes H. Neuro-immune cell units: A new paradigm in physiology. Annu Rev Immunol 2019;37:19–46. doi: 10.1146/annurev-immunol-042718-041812.
89. Wang B, Cardenas M, Bedoya M, Colin AA, Rossi GA. Upregulation of neuropeptides and obstructive airway disorder in infancy: A review with focus on post-RSV wheezing and NEHI. Pediatr Pulmonol 2021;56:1297–1306. doi: 10.1002/ppul.25292.
90. Shang Z, Tan S, Ma D. Respiratory syncytial virus: From pathogenesis to potential therapeutic strategies. Int J Biol Sci 2021;17:4073–4091. doi: 10.7150/ijbs.64762.
91. Shingai M, Azuma M, Ebihara T, Sasai M, Funami K, Ayata M, *et al*. Soluble G protein of respiratory syncytial virus inhibits toll-like receptor 3/4-mediated IFN-beta induction. Int Immunol 2008;20:1169–1180. doi: 10.1093/intimm/dxn074.
92. Garofalo R, Mei F, Espejo R, Ye G, Haeberle H, Baron S, *et al*. Respiratory syncytial virus infection of human respiratory epithelial cells up-regulates class I MHC expression through the induction of IFN-beta and IL-1 alpha. J Immunol 1996;157:2506–2513.
93. González PA, Bueno SM, Carreño LJ, Riedel CA, Kalergis AM. Respiratory syncytial virus infection and immunity. Rev Med Virol 2012;22:230–244. doi: 10.1002/rmv.1704.
94. Kalinowski A, Galen BT, Ueki IF, Sun Y, Mulenos A, Osafo-Addo A, *et al*. Respiratory syncytial virus activates epidermal growth factor receptor to suppress interferon regulatory factor 1-dependent interferon-lambda and antiviral defense in airway epithelium. Mucosal Immunol 2018;11:958–967. doi: 10.1038/mi.2017.120.
95. Bermejo-Martin JF, Bernardo D, Dominguez-Gil M, Alonso A, Garcia-Arevalo MC, Pino M, *et al*. Interleukin (IL)-1β, IL-6 and IL-8 in nasal secretions: A common role for innate immunity in viral bronchial infection in infants? Br J Biomed Sci 2006;63:173–175. doi: 10.1080/09674845.2006.11978093.
96. Rossi GA, Ballarini S, Salvati P, Sacco O, Colin AA. Alarmins and innate lymphoid cells 2 activation: A common pathogenetic link connecting respiratory syncytial virus bronchiolitis and later wheezing/asthma? Pediatr Allergy Immunol 2022;33:e13803. doi: 10.1111/pai.13803.
97. Herbert DR, Douglas B, Zullo K. Group 2 innate lymphoid cells (ILC2): Type 2 immunity and helminth immunity. Int J Mol Sci 2019;20:2276. doi: 10.3390/ijms20092276.
98. Stier MT, Bloodworth MH, Toki S, Newcomb DC, Goleniewska K, Boyd KL, *et al*. Respiratory syncytial virus infection activates IL-13-producing group 2 innate lymphoid cells through thymic stromal lymphopoietin. J Allergy ClinImmunol 2016;138:814–824.e11. doi: 10.1016/j.jaci.2016.01.050.
99. Wu YH, Lai AC, Chi PY, Thio CL, Chen WY, Tsai CH, *et al*. Pulmonary IL-33 orchestrates innate immune cells to mediate respiratory syncytial virus-evoked airway hyperreactivity and eosinophilia. Allergy 2020;75:818–830. doi: 10.1111/all.14091.
100. Chen S, Yu G, Xie J, Tang W, Gao L, Long X, *et al*. High-mobility group box-1 protein from CC10+ club cells promotes type 2 response in the later stage of respiratory syncytial virus infection. Am J Physiol Lung Cell Mol Physiol 2019;316(1):L280–L290. doi: 10.1152/ajplung.00552.2017.
101. Soroosh P, Doherty TA. Th9 and allergic disease. Immunology 2009;127:450–458. doi: 10.1111/j.1365-2567.2009.03114.x.
102. Schuurhof A, Bont L, Siezen CL, Hodemaekers H, van Houwelingen HC, Kimman TG, *et al*. Interleukin-9 polymorphism in infants with respiratory syncytial virus infection: An opposite effect in boys and girls. Pediatr Pulmonol 2010;45:608–613. doi: 10.1002/ppul.21229.
103. Oboki K, Ohno T, Saito H, Nakae S. Th17 and allergy. Allergol Int 2008;57:121–134. doi: 10.2332/allergolint.R-07-160.
104. Mukherjee S, Lindell DM, Berlin AA, Morris SB, Shanley TP, Hershenson MB, *et al*. IL-17-induced pulmonary pathogenesis during respiratory viral infection and exacerbation of allergic disease. Am J Pathol 2011;179:248–258. doi: 10.1016/j.ajpath.2011.03.003.
105. Christiaansen AF, Knudson CJ, Weiss KA, Varga SM. The CD4 T cell response to respiratory syncytial virus infection. Immunol Res 2014;59:109–117. doi: 10.1007/s12026-014-8540-1.
106. Rajarathnam K, Schnoor M, Richardson RM, Rajagopal S. How do chemokines navigate neutrophils to the target site: Dissecting the structural mechanisms and signaling pathways. Cell Signal 2019;54:69–80. doi: 10.1016/j.cellsig.2018.11.004.
107. Geerdink RJ, Pillay J, Meyaard L, Bont L. Neutrophils in respiratory syncytial virus infection: A target for asthma prevention. J Allergy ClinImmunol 2015;136:838–847. doi: 10.1016/j.jaci.2015.06.034.
108. Mejias A, Dimo B, Suarez NM, Garcia C, Suarez-Arrabal MC, Jartti T, *et al*. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. PLoS Med 2013;10:e1001549. doi: 10.1371/journal.pmed.1001549.
109. Cavarra E, Martorana PA, Gambelli F, de Santi M, Van Even P, Lungarella G. Neutrophil recruitment into the lungs is associated with increased lung elastase burden, decreased lung elastin, and emphysema in alpha 1 proteinase inhibitor-deficient mice. Lab Invest 1996;75:273–280.
110. Jenne CN, Kubes P. Virus-induced NETs–Critical component of host defense or pathogenic mediator? PLoS Pathog 2015;11:e1004546. doi: 10.1371/journal.ppat.1004546.

111. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD Jr., *et al*. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A 2010;107:15880–15885. doi: 10.1073/pnas.1005743107.
112. Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, *et al*. Extracellular histones are major mediators of death in sepsis. Nat Med 2009;15:1318–1321. doi: 10.1038/nm.2053.
113. Goritzka M, Makris S, Kausar F, Durant LR, Pereira C, Kumagai Y, *et al*. Alveolar macrophage-derived type I interferons orchestrate innate immunity to RSV through recruitment of antiviral monocytes. J Exp Med 2015;212:699–714. doi: 10.1084/jem.20140825.
114. Glaser L, Coulter PJ, Shields M, Touzelet O, Power UF, Broadbent L. Airway epithelial derived cytokines and chemokines and their role in the immune response to respiratory syncytial virus infection. Pathogens 2019;8:106. doi: 10.3390/pathogens8030106.
115. Ahout IM, Jans J, Haroutiounian L, Simonetti ER, van der Gaast-de Jongh C, Diavatopoulos DA, *et al*. Reduced expression of HLA-DR on monocytes during severe respiratory syncytial virus infections. Pediatr Infect Dis J 2016;35:e89–e96. doi: 10.1097/INF.0000000000001007.
116. Santos LD, Antunes KH, Muraro SP, de Souza GF, da Silva AG, Felipe JS, *et al*. TNF-mediated alveolar macrophage necroptosis drives disease pathogenesis during respiratory syncytial virus infection. Eur Respir J 2021;57:2003764. doi: 10.1183/13993003.03764-2020.
117. Cong B, Dighero I, Zhang T, Chung A, Nair H, Li Y. Understanding the age spectrum of respiratory syncytial virus associated hospitalisation and mortality burden based on statistical modelling methods: A systematic analysis. BMC Med 2023;21:224. doi: 10.1186/s12916-023-02932-5.
118. Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. J Glob Health 2015;5:010408. doi: 10.7189/jogh.05.010408.
119. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, *et al*. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: A systematic analysis. Lancet 2022;399:2047–2064. doi: 10.1016/S0140-6736(22)00478-0.
120. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, *et al*. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: A systematic review and modelling study. Lancet 2017;390:946–958. doi: 10.1016/S0140-6736(17)30938-8.
121. Wang X, Li Y, Shi T, Bont LJ, Chu HY, Zar HJ, *et al*. Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: A systematic review and meta-analysis of aggregated and individual participant data. Lancet 2024;403:1241–1253. doi: 10.1016/S0140-6736(24)00138-7.
122. Chaw PS, Hua L, Cunningham S, Campbell H, Mikolajczyk R, Nair H, *et al*. Respiratory syncytial virus-associated acute lower respiratory infections in children with bronchopulmonary dysplasia: Systematic review and meta-analysis. J Infect Dis 2020;222(Suppl 7):S620–S627. doi: 10.1093/infdis/jiz492.
123. Chan M, Park JJ, Shi T, Martinón-Torres F, Bont L, Nair H, *et al*. The burden of respiratory syncytial virus (RSV) associated acute lower respiratory infections in children with down syndrome: A systematic review and meta-analysis. J Glob Health 2017;7:020413. doi: 10.7189/jogh.07.020413.
124. Chaw PS, Wong SWL, Cunningham S, Campbell H, Mikolajczyk R, Nair H, *et al*. Acute lower respiratory infections associated with respiratory syncytial virus in children with underlying congenital heart disease: Systematic review and meta-analysis. J Infect Dis 2020;222(Suppl 7):S613–S619. doi: 10.1093/infdis/jiz150.
125. Wang X, Li Y, Mei X, Bushe E, Campbell H, Nair H. Global hospital admissions and in-hospital mortality associated with all-cause and virus-specific acute lower respiratory infections in children and adolescents aged 5-19 years between 1995 and 2019: A systematic review and modelling study. BMJ Glob Health 2021;6:e006014. doi: 10.1136/bmjgh-2021-006014.
126. Li Y, Johnson EK, Shi T, Campbell H, Chaves SS, Commaille-Chapus C, *et al*. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: A modelling study. Lancet Respir Med 2021;9:175–185. doi: 10.1016/S2213-2600(20)30322-2.
127. Walsh EE, Peterson DR, Kalkanoglu AE, Lee FE, Falsey AR. Viral shedding and immune responses to respiratory syncytial virus infection in older adults. J Infect Dis 2013;207:1424–1432. doi: 10.1093/infdis/jit038.
128. Meissner HC. Viral bronchiolitis in children. N Engl J Med 2016;374:62–72. doi: 10.1056/NEJMra1413456.
129. Onwuchekwa C, Moreo LM, Menon S, Machado B, Curcio D, Kalina W, *et al*. Underascertainment of respiratory syncytial virus infection in adults due to diagnostic testing limitations: A systematic literature review and meta-analysis. J Infect Dis 2023;228:173–184. doi: 10.1093/infdis/jiad012.
130. Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, *et al*. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: A systematic review and meta-analysis. J Infect Dis 2020;222(Suppl 7):S577–S583. doi: 10.1093/infdis/jiz059.
131. Li Y, Kulkarni D, Begier E, Wahi-Singh P, Wahi-Singh B, Gessner B, *et al*. Adjusting for case under-ascertainment in estimating RSV hospitalisation burden of older adults in high-income countries: A systematic review and modelling study. Infect Dis Ther 2023;12:1137–1149. doi: 10.1007/s40121-023-00792-3.
132. Shi T, Vennard S, Jasiewicz F, Brogden R, Nair H; RESCEU Investigators. Disease burden estimates of respiratory syncytial virus related acute respiratory infections in adults with comorbidity: A systematic review and meta-analysis. J Infect Dis 2022;226(Suppl 1):S17–S21. doi: 10.1093/infdis/jiab040.
133. Branche AR, Saiman L, Walsh EE, Falsey AR, Sieling WD, Greendyke W, *et al*. Incidence of respiratory syncytial virus infection among hospitalized adults, 2017-2020. Clin Infect Dis 2022;74:1004–1011. doi: 10.1093/cid/ciab595.
134. Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, *et al*. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: A systematic analysis. Lancet Glob Health 2019;7:e1031–e1045. doi: 10.1016/S2214-109X(19)30264-5.
135. Chadha M, Hirve S, Bancej C, Barr I, Baumeister E, Caetano B, *et al*. Human respiratory syncytial virus and influenza seasonality patterns—Early findings from the WHO global respiratory syncytial virus surveillance. Influenza Other Respir Viruses 2020;14:638–646. doi: 10.1111/irv.12726.
136. Li Y, Wang X, Broberg EK, Campbell H, Nair H; European RSV Surveillance Network. Seasonality of respiratory syncytial virus and its association with meteorological factors in 13 European countries, week 40 2010 to week 39 2019. Euro Surveill 2022;27:2100619. doi: 10.2807/1560-7917.ES.2022.27.16.2100619.
137. Thongpan I, Vongpunsawad S, Poovorawan Y. Respiratory syncytial virus infection trend is associated with meteorological factors. Sci Rep 2020;10:10931. doi: 10.1038/s41598-020-67969-5.
138. Yu J, Liu C, Xiao Y, Xiang Z, Zhou H, Chen L, *et al*. Respiratory syncytial virus seasonality, Beijing, China, 2007–2015. Emerg Infect Dis 2019;25:1127–1135. doi: 10.3201/eid2506.180532.
139. Deng S, Guo L, Cohen C, Meijer A, Moyes J, Pasittungkul S, *et al*. Impact of subgroup distribution on seasonality of human respiratory syncytial virus: A global systematic analysis. J Infect Dis 2024;229(Suppl 1):S25–S33. doi: 10.1093/infdis/jiad192.
140. Staadegaard L, Meijer A, Rodrigues AP, Huang S, Cohen C, Demont C, *et al*. Temporal variations in respiratory syncytial virus epidemics, by virus subtype, 4 countries. Emerg Infect Dis 2021;27:1537–1540. doi: 10.3201/eid2705.204615.
141. Guo L, Deng S, Sun S, Wang X, Li Y. Respiratory syncytial virus seasonality, transmission zones, and implications for seasonal prevention strategy in China: A systematic analysis. Lancet Glob Health 2024;12:e1005–e1016. doi: 10.1016/S2214-109X(24)00090-1.
142. Li M, Cong B, Wei X, Wang Y, Kang L, Gong C, *et al*. Characterising the changes in RSV epidemiology in Beijing, China during 2015-2023: Results from a prospective, multi-centre, hospital-based surveillance and serology study. Lancet Reg Health West Pac 2024;45:101050. doi: 10.1016/j.lanwpc.2024.101050.
143. Löwensteyn YN, Zheng Z, Rave N, Bannier MAGE, Billard MN, Casalegno JS, *et al*. Year-round respiratory syncytial virus transmission in The Netherlands following the COVID-19 pandemic: A prospective nationwide observational and modeling study. J Infect Dis 2023;228:1394–1399. doi: 10.1093/infdis/jiad282.
144. Thindwa D, Li K, Cooper-Wootton D, Zheng Z, Pitzer VE, Weinberger DM. Global patterns of rebound to normal RSV dynamics

following COVID-19 suppression. BMC Infect Dis 2024;24:635. doi: 10.1186/s12879-024-09509-4.
145. Cong B, Koç U, Bandeira T, Bassat Q, Bont L, Chakhunashvili G, *et al*. Changes in the global hospitalisation burden of respiratory syncytial virus in young children during the COVID-19 pandemic: A systematic analysis. Lancet Infect Dis 2024;24:361–374. doi: 10.1016/S1473-3099(23)00630-8.
146. Munkstrup C, Lomholt FK, Emborg HD, Møller KL, Krog JS, Trebbien R, *et al*. Early and intense epidemic of respiratory syncytial virus (RSV) in Denmark, August to December 2022. Euro Surveill 2023;28:2200937. doi: 10.2807/1560-7917.ES.2023.28.1.2200937.
147. Suss RJ, Simões EAF. Respiratory syncytial virus hospital-based burden of disease in children younger than 5 years, 2015-2022. JAMA Netw Open 2024;7:e247125. doi: 10.1001/jamanetworkopen.2024.7125.
148. Alrayes T, Wait A, Spencer P, Merolla DM, Lampe K, Salimnia H, *et al*. Features of an atypical RSV surge during the COVID-19 pandemic. Clin Pediatr (Phila) 2023;62:265–268. doi: 10.1177/00099228221124677.
149. Jiang W, Chen S, Lv M, Zhang Z, Wang Z, Shao X, *et al*. Are we ready to face the next wave of RSV surge after the COVID-19 Omicron pandemic in China? Front Cell Infect Microbiol 2023;13:1216536. doi: 10.3389/fcimb.2023.1216536.
150. Hatter L, Eathorne A, Hills T, Bruce P, Beasley R. Respiratory syncytial virus: Paying the immunity debt with interest. Lancet Child Adolesc Health 2021;5:e44–e45. doi: 10.1016/S2352-4642(21)00333-3.
151. Kaler J, Hussain A, Patel K, Hernandez T, Ray S. Respiratory syncytial virus: A comprehensive review of transmission, pathophysiology, and manifestation. Cureus 2023;15:e36342. doi: 10.7759/cureus.36342.
152. Gu Y, Yao ZZ. Analysis of serum myocardial enzyme in 231 infants with respiratory syncytial virus pneumonia. Zhejiang Pract Med 2007;12:28–29.
153. Li P, Lang YM, Shi YX. Clinical characteristics of adenovirus and syncytial virus pneumonia in hospitalized children from 2015 to 2018 (in Chinese). Chin Med Rec J 2019;20:93–96.
154. Cai Y. Comparison of clinical features and complications of pneumonia children infected with two viruses(in Chinese). Harbin Med 2016;36:643–644.
155. Chen H, Fu JH. Research progress on neonatal respiratory syncytial virus infection (in Chinese). Chin Pediatr Emerg Med 2020;27:754–757. doi: 10.3760/cma.j.issn.1673-4912.2020.10.009.
156. Savić N, Janković B, Minić P, Vasiljević Z, Sovtić A, Pejić K, *et al*. Clinical characteristics of respiratory syncytial virus infection in neonates and young infants. Vojnosanit Pregl 2011;68:220–224. doi: 10.2298/VSP1103220S.
157. Lee SH, Hon KL, Chiu WK, Ting YW, Lam SY. Epidemiology of respiratory syncytial virus infection and its effect on children with heart disease in Hong Kong: A multicentre review. Hong Kong Med J 2019;25:363–371. doi: 10.12809/hkmj197903.
158. Kuczborska K, Rustecka A, Wawrzyniak A, Będzichowska A, Kalicki B. Manifestations and risk factors in children hospitalized with respiratory syncytial virus infection. Arch Pediatr Infect Dis 2021;9:e108723. doi: 10.5812/pedinfect.108723.
159. Piastra M, Caresta E, Tempera A, Langer A, Zorzi G, Pulitanò S, *et al*. Sharing features of uncommon respiratory syncytial virus complications in infants. Pediatr Emerg Care 2006;22:574–578. doi: 10.1097/01.pec.0000230704.74022.3e.
160. Hanna S, Tibby SM, Durward A, Murdoch IA. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr 2003;92:430–434. doi: 10.1111/j.1651-2227.2003.tb00573.x.
161. Zhang DW, Lu G. Progress in diagnosis and treatment of critically ill children caused by respiratory virus infection (in Chinese). Chin J Appl Pediatr 2019;34.
162. Yu J, Xie Z, Zhang T, Lu Y, Fan H, Yang D, *et al*. Comparison of the prevalence of respiratory viruses in patients with acute respiratory infections at different hospital s ettings in North China, 2012-2015. BMC Infect Dis 2018;18:72. doi: 10.1186/s12879-018-2982-3.
163. Zheng JB, Tao JP, Zhang JH, *et al*. Comparison of clinical features between adenovirus and syncytial virus pneumonia in children (in Chinese). GuangDong Med J 2015:569–571.
164. Subissi L, Bossuyt N, Reynders M, Gérard M, Dauby N, Bourgeois M, *et al*. Capturing respiratory syncytial virus season in Belgium using the influenza severe acute respiratory infection surveillance network, season 2018/19. Euro Surveill 2020;25:1900627. doi: 10.2807/1560-7917.ES.2020.25.39.1900627.
165. Watabe S. Examination of clinical characteristics of severe RSV infection. Paediatr Respir Rev 2010;11:S86. doi: 10.1016/S1526-0542(10)70100-7.
166. Li W, Liu LY, Li J, *et al*. Clinical characteristics and significance of secondary thrombocytosis in children with bronchial pneumonia caused by respiratory syncytial virus infection (in Chinese). Chongqing Med 2020;49:3216–3219.
167. Zhou HX. Study on renal damage in children with respiratory syncytial virus bronchiolitis (in Chinese). Chin J Mod Pediatr 2004;1.
168. Frankel LR, Lewiston NJ, Smith DW, Stevenson DK. Clinical observations on mechanical ventilation for respiratory failure in bronchiolitis. Pediatr Pulmonol 1986;2:307–311. doi: 10.1002/ppul.1950020511.
169. Wang BZ, Ge LX, Zhang YH, *et al*. Early intervention analysis of 640 cases of bronchiolitis complicated with cardiovascular system damage caused by respiratory syncytial virus (in Chinese). Shaanxi Med J 2011;40:1243–1244.
170. Karatza AA, Kiaffas M, Rammos S. Complete heart block complicating the acute phase of respiratory syncytial virus bronchiolitis (in Chinese). Pediatr Pulmonol 2017;52:E61–E63. doi: 10.1002/ppul.23714.
171. Zhu QY, Sun YG. Analysis of 7 cases of respiratory syncytial virus pneumonia complicated with myocarditis (in Chinese). Chin J Misdiagnosis 2008;28:1490–1491.
172. Zhou WF, Ji W. Clinical analysis of 220 cases of respiratory syncytial virus pneumonia (in Chinese). J Suzhou Univ (Medical Edition) 2008:159–160. doi: 10.3969/j.issn.1673-0399.2008.01.059.
173. Qiao CL, Yang N. Detection of myocardial enzymes in 96 infants with bronchiolitis and its clinical significance (in Chinese). Shaanxi Med J 2010;39:1236–1238.
174. Hou W, Wang L. Respiratory syncytial pneumonia with myocardial damage (analysis of 35 cases) (in Chinese). Shaanxi Med J 1996;025:685.
175. Ye JL. Clinical symptoms and therapeutic effect of 40 children with respiratory syncytial virus pneumonia (in Chinese). J Navy Med 2013;34:32–34.
176. Chen J. Pathogenic study of 260 cases of bronchiolitis virus. Shandong University, 2012.
177. Yuan SF. Clinical analysis of respiratory syncytial virus infection complicated with abnormal liver function (in Chinese). J Clin Exp Med 2006;5.
178. Zheng JY, Li HF, Tang HF. Liver damage caused by respiratory syncytial virus infection in children (in Chinese). Zhejiang Preventive Med 2005;17.
179. Millichap JJ, Wainwright MS. Neurological complications of respiratory syncytial virus infection: Case series and review of literature. J Child Neurol 2009;24:1499–1503. doi: 10.1177/0883073808331362.
180. Bohmwald K, Espinoza JA, González PA, Bueno SM, Riedel CA, Kalergis AM. Central nervous system alterations caused by infection with the human respiratory syncytial virus. Rev Med Virol 2014;24:407–419. doi: 10.1002/rmv.1813.
181. Uda K, Kitazawa K. Febrile status epilepticus due to respiratory syncytial virus infection. Pediatr Int 2017;59:878–884. doi: 10.1111/ped.13300.
182. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci 2018;12:386. doi: 10.3389/fncel.2018.00386.
183. Miyamoto K, Fujisawa M, Hozumi H, Tsuboi T, Kuwashima S, Hirao J, *et al*. Systemic inflammatory response syndrome and prolonged hypoperfusion lesions in an infant with respiratory syncytial virus encephalopathy. J Infect Chemother 2013;19:978–982. doi: 10.1007/s10156-013-0558-0.
184. Kakimoto Y, Seto Y, Ochiai E, Satoh F, Osawa M. Cytokine elevation in sudden death with respiratory syncytial virus: A case report of 2 children. Pediatrics 2016;138:e20161293. doi: 10.1542/peds.2016-1293.
185. Cha T, Choi YJ, Oh JW, Kim CR, Park DW, Seol IJ, *et al*. Respiratory syncytial virus-associated seizures in Korean children, 2011–2016. Korean J Pediatr 2019;62:131–137. doi: 10.3345/kjp.2018.07066.
186. Sweetman LL, Ng YT, Butler IJ, Bodensteiner JB. Neurologic complications associated with respiratory syncytial virus.

Pediatr Neurol 2005;32:307–310. doi: 10.1016/j.pediatrneurol.2005.01.010.
187. Zheng SY, Xiao QY, Xie XH, Deng Y, Ren L, Tian DY, *et al*. Association between secondary thrombocytosis and viral respiratory tract infections in children. Sci Rep 2016;6:22964. doi: 10.1038/srep22964.
188. Baker KA, Ryan ME. RSV infection in infants and young children. What's new in diagnosis, treatment, and prevention? Postgrad Med 1999;106:97–9, 103–4, 7–8 passim. doi: 10.3810/pgm.1999.12.803.
189. Díez-Domingo J, Pérez-Yarza EG, Melero JA, Sánchez-Luna M, Aguilar MD, Blasco AJ, *et al*. Social, economic, and health impact of the respiratory syncytial virus: A systematic search. BMC Infect Dis 2014;14:544. doi: 10.1186/s12879-014-0544-x.
190. Stockmann C, Ampofo K, Hersh AL, Carleton ST, Korgenski K, Sheng X, *et al*. Seasonality of acute otitis media and the role of respiratory viral activity in children. Pediatr Infect Dis J 2013;32:314–319. doi: 10.1097/INF.0b013e31827d104e.
191. Nokso-Koivisto J, Marom T, Chonmaitree T. Importance of viruses in acute otitis media. Curr Opin Pediatr 2015;27:110–115. doi: 10.1097/MOP.0000000000000184.
192. Andrade MA, Hoberman A, Glustein J, Paradise JL, Wald ER. Acute otitis media in children with bronchiolitis. Pediatrics 1998;101(4 pt 1):617–619. doi: 10.1542/peds.101.4.617.
193. Alper CM, Winther B, Hendley JO, Doyle WJ. Cytokine polymorphisms predict the frequency of otitis media as a complication of rhinovirus and RSV infections in children. Eur Arch Otorhinolaryngol 2009;266:199–205. doi: 10.1007/s00405-008-0729-2.
194. Qian J. Bacterial complications in hospitalized children with respiratory syncytial virus infection (in Chinese). Foreign Med (Pediatrics) 1990:272–273.
195. Thomas E, Mattila JM, Lehtinen P, Vuorinen T, Waris M, Heikkinen T. Burden of respiratory syncytial virus infection during the first year of life. J Infect Dis 2021;223:811–817. doi: 10.1093/infdis/jiaa754.
196. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel JA, Nair S, *et al*. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis 2008;46:815–823. doi: 10.1086/528685.
197. Kaskinen A, Alexandersson A, Andersson S, Saxén H, Peltola V, Kolho KL, *et al*. Decreased airway epithelial ion transport was associated with the severity of the respiratory syncytial virus infection and complications in infants. Acta Paediatr 2020;109:2313–2315. doi: 10.1111/apa.15311.
198. Diaz A, Bunsow E, Mertz S, *et al*. Nasopharyngeal bacterial colonization and acute otitis media in children with RSV respiratory infection. J Pediatric Infect Dis Soc 2018;7:S90.
199. Marom T, Nokso-Koivisto J, Chonmaitree T. Viral-bacterial interactions in acute otitis media. Curr Allergy Asthma Rep 2012;12:551–558. doi: 10.1007/s11882-012-0303-2.
200. Yano H, Okitsu N, Hori T, Watanabe O, Kisu T, Hatagishi E, *et al*. Detection of respiratory viruses in nasopharyngeal secretions and middle ear fluid from children with acute otitis media. Acta Otolaryngol 2009;129:19–24. doi: 10.1080/00016480802032777.
201. Tao QQ, Li XR, Zhang XM. Research progress on ocular tendency of respiratory viruses (in Chinese). Chin J Exp Ophthalmol 2020;38.
202. Kambouri K, Gardikis S, Tsalkidis A, Cassimos D, Deftereos S, Chatzimichael A. Late onset of spontaneous pneumothorax complicating acute bronchiolitis in a 5-month-old infant: Case report and literature review. Pediatr Emerg Care 2007;23:889–891. doi: 10.1097/pec.0b013e31815c9d95.
203. Rosas-Salazar C, Chirkova T, Gebretsadik T, Chappell JD, Peebles RS Jr., Dupont WD, *et al*. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): A population-based, prospective birth cohort study. Lancet 2023;401:1669–1680. doi: 10.1016/S0140-6736(23)00811-5.
204. Makrinioti H, Hasegawa K, Lakoumentas J, Xepapadaki P, Tsolia M, Castro-Rodriguez JA, *et al*. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma-A systematic review and meta-analysis. Pediatr Allergy Immunol 2022;33:e13741. doi: 10.1111/pai.13741.
205. Ralston SL, Lieberthal AS, Meissner HC. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatrics 2015;136:782. doi: 10.1542/peds.2015-2862.
206. Turner TL, Kopp BT, Paul G, Landgrave LC, Hayes D Jr., Thompson R. Respiratory syncytial virus: Current and emerging treatment options. Clinicoecon Outcomes Res 2014;6:217–225. doi: 10.2147/CEOR.S60710.
207. Beaucourt S, Vignuzzi M. Ribavirin: A drug active against many viruses with multiple effects on virus replication and propagation. Molecular basis of ribavirin resistance. Curr Opin Virol 2014;8:10–15. doi: 10.1016/j.coviro.2014.04.011.
208. Parker WB. Metabolism and antiviral activity of ribavirin. Virus Res 2005;107:165–171. doi: 10.1016/j.virusres.2004.11.006.
209. Ribavirin therapy of respiratory syncytial virus. AAP News 1986;2:7–8. doi: 10.1542/2.12.7.
210. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2007:CD000181. doi: 10.1002/14651858.CD000181.pub3.
211. Randolph AG, Wang EE. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract. Cochrane Database Syst Rev 2000:CD000181. doi: 10.1002/14651858.CD000181.
212. Boeckh M, Englund J, Li Y, Miller C, Cross A, Fernandez H, *et al*. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. Clin Infect Dis 2007;44:245–249. doi: 10.1086/509930.
213. Tejada S, Martinez-Reviejo R, Karakoc HN, Peña-López Y, Manuel O, Rello J. Ribavirin for treatment of subjects with respiratory syncytial virus-related infection: A systematic review and meta-analysis. Adv Ther 2022;39:4037–4051. doi: 10.1007/s12325-022-02256-5.
214. Randall RE, Goodbourn S. Interferons and viruses: An interplay between induction, signalling, antiviral responses and virus countermeasures. J Gen Virol 2008;89(Pt 1):1–47. doi: 10.1099/vir.0.83391-0.
215. Chen L, Shi M, Deng Q, Liu W, Li Q, Ye P, *et al*. A multi-center randomized prospective study on the treatment of infant bronchiolitis with interferon alpha1b nebulization. PLoS One 2020;15:e0228391. doi: 10.1371/journal.pone.0228391.
216. He L, Yang L, Zhang H, Luo Q. Efficacy and safety of interferon on neonates with respiratory syncytial virus pneumonia. Exp Ther Med 2020;20:220. doi: 10.3892/etm.2020.9350.
217. Johnson S, Oliver C, Prince GA, Hemming VG, Pfarr DS, Wang SC, *et al*. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997;176:1215–1224. doi: 10.1086/514115.
218. Alansari K, Toaimah FH, Almatar DH, El Tatawy LA, Davidson BL, Qusad MIM. Monoclonal antibody treatment of RSV bronchiolitis in young infants: A randomized trial. Pediatrics 2019;143:e20182308. doi: 10.1542/peds.2018-2308.
219. Sáez-Llorens X, Moreno MT, Ramilo O, Sánchez PJ, Top FH Jr., Connor EM, *et al*. Safety and pharmacokinetics of palivizumab therapy in children hospitalized with respiratory syncytial virus infection. Pediatr Infect Dis J 2004;23:707–712. doi: 10.1097/01.inf.0000133165.85909.08.
220. Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks O, Sánchez PJ, *et al*. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: Recommendations of the Advisory Committee on Immunization Practices–United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920–925. doi: 10.15585/mmwr.mm7234a4.
221. Zheng X, Gao L, Wang L, Liang C, Wang B, Liu Y, *et al*. Discovery of ziresovir as a potent, selective, and orally bioavailable respiratory syncytial virus fusion protein inhibitor. J Med Chem 2019;62:6003–6014. doi: 10.1021/acs.jmedchem.9b00654.
222. Huang LM, Schibler A, Huang YC, Tai A, Chi H, Chieng CH, *et al*. Safety and efficacy of AK0529 in respiratory syncytial virus-infected infant patients: A phase 2 proof-of-concept trial. Influenza Other Respir Viruses 2023;17:e13176. doi: 10.1111/irv.13176.
223. Ark biopharmaceutical announces NMPA acceptance and priority review of new drug application for ziresovir for treatment of RSV infection. Ark Biopharmaceutical. 2022. Available from: https://www.arkbiosciences.com/en_2022n/114. [Last accessed on June 2, 2024].
224. Cockerill GS, Angell RM, Bedernjak A, Chuckowree I, Fraser I, Gascon-Simorte J, *et al*. Discovery of sisunatovir (RV521), an inhibitor of respiratory syncytial virus fusion. J Med Chem 2021;64:3658–3676. doi: 10.1021/acs.jmedchem.0c01882.
225. DeVincenzo J, Tait D, Efthimiou J, Mori J, Kim YI, Thomas E, *et al*. A randomized, placebo-controlled, respiratory syncytial

virus human challenge study of the antiviral efficacy, safety, and pharmacokinetics of RV521, an inhibitor of the RSV-F protein. Antimicrob Agents Chemother 2020;64:e01884–19. doi: 10.1128/AAC.01884-19.
226. Coates M, Brookes D, Kim YI, Allen H, Fordyce EAF, Meals EA, *et al*. Preclinical characterization of C786, an inhaled small-molecule respiratory syncytial virus L protein polymerase inhibitor. Antimicrob Agents Chemother 2017;61:e00737–17. doi: 10.1128/AAC.00737-17.
227. Brookes DW, Coates M, Allen H, Daly L, Constant S, Huang S, *et al*. Late therapeutic intervention with a respiratory syncytial virus L-protein polymerase inhibitor, PC786, on respiratory syncytial virus infection in human airway epithelium. Br J Pharmacol 2018;175:2520–2534. doi: 10.1111/bph.14221.
228. DeVincenzo J, Cass L, Murray A, Woodward K, Meals E, Coates M, *et al*. Safety and antiviral effects of nebulized PC786 in a respiratory syncytial virus challenge study. J Infect Dis 2022;225:2087–2096. doi: 10.1093/infdis/jiaa716.
229. EDP-323, a small molecule L-protein inhibitor in development against respiratory syncytial virus. Enanta Pharmaceutical. 2022. Available from: https://www.enanta.com/wp-content/uploads/2022/10/EDP-323-Discovery-on-Target-presentation-Final-1.pdf. [Last accessed on June 2, 2024].
230. EDP-323, a first-in-class, once-daily, oral L-protein inhibitor for the treatment of RSV: Results from a phase 1 study in healthy subjects and correlation with in vitro antiviral activity. Enanta Pharmaceutical. 2023. Available from: https://www.enanta.com/wp-content/uploads/2023/09/EDP-323-001-ESWI-Poster-presentation_FINAL.pdf. [Last accessed on June 2, 2024].
231. World Health Organization. Global influenza strategy 2019-2030 [EB/OL]. 2019. Available from: https://iris.who.int/handle/10665/311184. [Last accessed on June 2, 2024].
232. World Health Organization. Respiratory syncytial virus (RSV) disease [EB/OL]. Available from: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/respiratory-syncytial-virus-disease. [Last accessed on June 2, 2024].
233. Rhodin MHJ, McAllister NV, Castillo J, Noton SL, Fearns R, Kim IJ, *et al*. EDP-938, a novel nucleoprotein inhibitor of respiratory syncytial virus, demonstrates potent antiviral activities in vitro and in a non-human primate model. PLoS Pathog 2021;17:e1009428. doi: 10.1371/journal.ppat.1009428.
234. Ahmad A, Eze K, Noulin N, Horvathova V, Murray B, Baillet M, *et al*. EDP-938, a respiratory syncytial virus inhibitor, in a human virus challenge. N Engl J Med 2022;386:655–666. doi: 10.1056/NEJMoa2108903.
235. A study to assess EDP-938 for the treatment of acute upper respiratory tract infection with respiratory syncytial virus in adult subjects (RSVP). ClinicalTrials.gov. 2023. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT04196101. [Last accessed on June 2, 2024].
236. GlaxoSmithKline Biologicals. Arexvy (Respiratory syncytial virus vaccine, adjuvanted) suspension for intramuscular injection [EB/OL]. 2023. Available from: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Arexvy/pdf/AREXVY.PDF. [Last accessed on June 2, 2024].
237. U.S. Centers for Disease Control and Prevention. RSV vaccine to protect adults ages 60 and older [EB/OL]. Available from: https://www.cdc.gov/rsv/about/prevention.html. [Last accessed on June 2, 2024].
238. Glaxosmithkline. Efficacy study of GSK's investigational respiratory syncytial virus (RSV) vaccine in adults aged 60 years and above [EB/OL]. Available from: https://clinicaltrials.gov/study/NCT04886596. [Last accessed on April 16, 2024].
239. BLA Approval [EB/OL]. 2023. Available from: https://www.fda.gov/media/167806/download?attachment. [Last accessed on May 23, 2023].
240. European Medicines Agency. Arexvy recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with AS01E [EB/OL]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy. [Last accessed on June 2, 2024].
241. Immunisation T J C o V a. Respiratory syncytial virus (RSV) immunisation programme: JCVI advice [EB/OL]. 2023. Available from: https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-jcvi-advice-7-june-2023. [Last accessed on September 11, 2023].
242. Gsk. Help protect yourself against RSV disease with Arexvy [EB/OL]. Available from: https://arexvy.ca/en-ca/. [Last accessed on June 2, 2024].
243. Xinjingbao. The GlaxoSmithKline vaccine against respiratory syncytial virus in the elderly has been approved in Japan [EB/OL]. 2023. Available from: https://new.qq.com/rain/a/20230925A08VUE00. [Last accessed on September 25, 2023].
244. Asia B. GSK Australia announces regulatory approval of respiratory syncytial virus vaccine Arexvy [EB/OL]. 2024. Available from: https://www.biospectrumasia.com/news/37/23600/gsk-australia-announces-regulatory-approval-of-respiratory-syncytial-virus-vaccine-arexvy.html. [Last accessed on January 19, 2024].
245. Inc P. ABRYSVO® (Respiratory syncytial virus vaccine) for injection, for intramuscular use [EB/OL]. 2023. Available from: https://www.fda.gov/media/168889/download. [Last accessed on June 2, 2024].
246. Canada P. Health Canada approves Pfizer's bivalent respiratory syncytial virus (RSV) Vaccine for older adults and infants through maternal immunization [EB/OL]. 2024. Available from: https://www.biospace.com/article/releases/health-canada-approves-pfizer-s-bivalent-respiratory-syncytial-virus-rsv-vaccine-for-older-adults-and-infants-through-maternal-immunization/. [Last accessed on January 04, 2024].
247. Pfizer Inc. U.S. FDA Approves ABRYSVO™, Pfizer's vaccine for the prevention of respiratory syncytial virus (RSV) in older adults [EB/OL]. 2023. Available from: https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-abrysvotm-pfizers-vaccine-prevention. [Last accessed on May 31, 2023].
248. Pfizer Inc. European Commission Approves Pfizer's ABRYSVO™ to help protect infants through maternal immunization and older adults from RSV [EB/OL]. 2023. Available from: https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-pfizers-abrysvotm-help-protect. [Last accessed on August 24, 2023].
249. Japan P. Japan approves Piasky, Beyfortus, broader use for Abrysvo, and lot more [EB/OL]. 2024. Available from: https://pj.jiho.jp/article/250675. [Last accessed on March 27, 2024].
250. The Department of Health and Aged Care. ABRYSVO (Pfizer Australia Pty Ltd) [EB/OL]. Available from: https://www.tga.gov.au/resources/prescription-medicines-registrations/abrysvo-pfizer-australia-pty-ltd. [Last accessed on May 20, 2024].
251. Buonsenso D. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;389:1053. doi: 10.1056/NEJMc2307729.
252. Harris E. FDA approves maternal RSV vaccine. JAMA 2023;330:1029. doi: 10.1001/jama.2023.16106.
253. Gonzales T, Bergamasco A, Cristarella T, Goyer C, Wojdyla M, Oladapo A, *et al*. Effectiveness and safety of palivizumab for the prevention of serious lower respiratory tract infection caused by respiratory syncytial virus: A systematic review. Am J Perinatol 2024;41(S 01):e1107–e1115. doi: 10.1055/a-1990-2633.
254. Fitzpatrick T, McNally JD, Stukel TA, Kwong JC, Wilton AS, Fisman D, *et al*. Palivizumab's real-world effectiveness: A population-based study in Ontario, Canada, 1993–2017. Arch Dis Child 2021;106:173–179. doi: 10.1136/archdischild-2020-319472.
255. U.S. Food and Drugs. Approved drug products [EB/OL]. Available from: www.accessdata.fda.gov/scripts/cder/daf/index.cfm. [Last accessed on June 2, 2024].
256. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134:415–420. doi: 10.1542/peds.2014-1665.
257. World Health Organization. WHO preferred product characteristics for respiratory syncytial virus (RSV) vaccines [EB/OL]. 2017. Available from: http://www.who.int/immunization/documents/en/. [Last accessed on June 2, 2024].
258. Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK, *et al*. Safety, tolerability, and pharmacokinetics of MEDI8897, the respiratory syncytial virus prefusion F-targeting monoclonal antibody with an extended half-life, in healthy adults. Antimicrob Agents Chemother 2017;61:e01714–16. doi: 10.1128/AAC.01714-16.
259. Domachowske J, Madhi SA, Simões EAF, Atanasova V, Cabañas F, Furuno K, *et al*. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. N Engl J Med 2022;386:892–894. doi: 10.1056/NEJMc2112186.

260. Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, *et al*. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med 2022;386:837–846. doi: 10.1056/NEJMoa2110275.
261. Muller WJ, Madhi SA, Seoane Nuñez B, Baca Cots M, Bosheva M, Dagan R, *et al*. Nirsevimab for prevention of RSV in term and late-preterm infants. N Engl J Med 2023;388:1533–1534. doi: 10.1056/NEJMc2214773.
262. Drysdale SB, Cathie K, Flamein F, Knuf M, Collins AM, Hill HC, *et al*. Nirsevimab for prevention of hospitalizations due to RSV in infants. N Engl J Med 2023;389:2425–2435. doi: 10.1056/NEJMoa2309189.
263. Moline HL, Tannis A, Toepfer AP, Williams JV, Boom JA, Englund JA, *et al*. Early estimate of nirsevimab effectiveness for prevention of respiratory syncytial virus-associated hospitalization among infants entering their first respiratory syncytial virus season–New vaccine surveillance network, October 2023-February 2024. MMWR Morb Mortal Wkly Rep 2024;73:209–214. doi: 10.15585/mmwr.mm7309a4.
264. Astrazeneca. Lovichu® is approved in China for the prevention of respiratory syncytial virus infection in infants [EB/OL]. 2024. Available from: https://www.astrazeneca.com.cn/zh/media/press-releases/2024/01-02-01.html. [Last accessed on June 2, 2024].
265. World Health Organization. WHO preferred product characteristics of monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) disease [EB/OL]. 2021. Available from: https://www.who.int/publications-detail-redirect/9789240021853. [Last accessed on June 2, 2024].
266. CDC. CDC recommends a powerful new tool to protect infants from the leading cause of hospitalization [EB/OL]. Available from: https://www.cdc.gov/media/releases/2023/p-0803-new-tool-prevent-infant-hospitalization-.html. [Last accessed on August 03, 2023].
267. Salud C I N D. Recomendaciones de utilización de nirsevimab para la temporada 2024-2025 en España [EB/OL]. 2024. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/comoTrabajamos/docs/Nirsevimab.pdf. [Last accessed on March 14, 2024].
268. Gov.Uk. RSV immunisation programme: JCVI advice [EB/OL]. 2023. Available from: https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023. [Last accessed on September 11, 2023].
269. Infectieuses C S D M. Recommandations du Conseil supérieur des maladies infectieuses concernant l'immunisation passive contre le RSV par des nouveaux anticorps monoclonaux Juillet 2023 [EB/OL]. 2023. Available from: https://sante.public.lu/dam-assets/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/Infection-a-virus-respiratoire-syncitial-_RSV_/17072023-recommandation-csmi-rsv-immunisation-vf.pdf. [Last accessed on June 2, 2024].
270. Salud M d. Ministerio de Salud intensifica inmunización contra virus respiratorios [EB/OL]. 2024. Available from: https://vacunas.minsal.cl/campana-de-invierno-2024-ministerio-de-salud-intensifica-inmunizacion-contra-virus-respiratorios/. [Last accessed on April 01, 2024]
271. Agency S M P. Läkemedelsprofylax mot allvarlig RSVinfektion hos barn inför säsongen 2023/2024–rekommendation från Läkemedelsverket [EB/OL]. 2023. Available from: https://www.lakemedelsverket.se/4a71a6/globalassets/dokument/behandling-och-forskrivning/behandlingsrekommendationer/behandlingsrekommendation/rekommendation-rsv-barn-sasong-2023-2024.pdf. [Last accessed on September 22, 2023].
272. Ireland R C O P O. Recommendations for passive immunisation and vaccination against respiratory syncytial virus in infants, children and older adults [EB/OL]. 2023. Available from: https://rcpi.access.preservica.com/uncategorized/IO_9275434a-99ff-44e5-b19c-04771ba2b1c0/. [Last accessed on October 12, 2023].
273. Environment H F c s. Preventive strategies against RSV disease in children [EB/OL]. 2023. Available from: https://www.health.belgium.be/en/report-9760-prevention-against-rsv-disease-children. [Last accessed on December 2023]
274. Health Council of the Netherlands. Protect all children against RSV through national vaccination programme [EB/OL]. 2023. Available from: https://www.healthcouncil.nl/latest/news/2024/02/14/protect-all-children-against-rsv-through-national-vaccination-programme. [Last accessed on February 14, 2024].
275. FOPH. Consensus statement/recommendation on the prevention of respiratory syncytial virus (RSV) infections with the monoclonal antibody Nirsevimab. 2024. Available from: https://www.bag.admin.ch/bag/fr/home/krankheiten/krankheiten-im-ueberblick/rsv.html. [Last accessed on May 4, 2024].
276. Fleming-Dutra KE, Jones JM, Roper LE, Prill MM, Ortega-Sanchez IR, Moulia DL, *et al*. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants: Recommendations of the Advisory Committee on Immunization Practices–United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:1115–1122. doi: 10.15585/mmwr.mm7241e1.
277. Society for Maternal-Fetal Medicine. Society for maternal-fetal medicine statement: Clinical considerations for the prevention of respiratory syncytial virus disease in infants. Am J Obstet Gynecol 2024;230:B41–B49. doi: 10.1016/j.ajog.2023.10.046.
278. World Health Organization. Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza [EB/OL]. 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329438/9789241516839-eng.pdf?ua=1. [Last accessed on January 07, 2024].
279. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, *et al*. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA 2020;323:1915–1923. doi: 10.1001/jama.2020.6130.
280. Rodgers L, Sheppard M, Smith A, Dietz S, Jayanthi P, Yuan Y, *et al*. Changes in seasonal respiratory illnesses in the united states during the coronavirus disease 2019 (COVID-19) pandemic. Clin Infect Dis 2021;73(Suppl 1):S110–S117. doi: 10.1093/cid/ciab311.
281. Rybak A, Levy C, Angoulvant F, Auvrignon A, Gembara P, Danis K, *et al*. Association of nonpharmaceutical interventions during the COVID-19 pandemic with invasive pneumococcal disease, pneumococcal carriage, and respiratory viral infections among children in France. JAMA Netw Open 2022;5:e2218959. doi: 10.1001/jamanetworkopen.2022.18959.
282. European Centre for Disease Prevention and Control. Respiratory syncytial virus (RSV) [EB/OL]. Available from: https://www.ecdc.europa.eu/en/respiratory-syncytial-virus-rsv. [Last accessed on June 2, 2024].
283. U.S. Centers for Disease Control and Prevention. Prevention actions to limit the spread of RSV [EB/OL]. Available from: https://www.cdc.gov/rsv/about/prevention.html. [Last accessed on June 2, 2024].
284. World Health Organization. Global influenza strategy 2019–2030 [EB/OL]. 2019. Available from: https://www.who.int/publications/i/item/9789241515320. [Last accessed on June 2, 2024].
285. World Health Organization. Infection prevention and control in the context of COVID-19: A guideline [EB/OL]. 2023. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-guideline-2023.4. [Last accessed on June 2, 2024].

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