

# Understanding RSV Pathogenesis and Host Immune Response: Implications for Treatment and Prevention

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## Abstract

## Original Research Article

Respiratory Syncytial Virus (RSV) is a globally prevalent pathogen and a leading cause of acute lower respiratory tract infections (LRTIs), particularly among infants, young children, the elderly, and immunocompromised individuals. Despite decades of research, RSV continues to impose a significant health and economic burden due to the absence of long-lasting immunity, the lack of a broadly effective vaccine, and limited therapeutic options. RSV pathogenesis is complex, involving not only direct viral cytopathic effects but also intricate interactions with the host immune system. The virus has evolved mechanisms to evade innate immunity, particularly by antagonizing interferon responses, which allows for sustained replication and contributes to disease severity. In infants, immature and dysregulated immune responses further complicate clinical outcomes, often leading to immunopathology. Existing treatments such as ribavirin and Palivizumab have limited effectiveness, are costly, and are reserved for specific high-risk populations. This review underscores the importance of understanding RSV's molecular pathogenesis and host immune interactions to inform the development of effective antivirals, immunomodulatory therapies, and next-generation vaccines. Bridging these gaps through interdisciplinary research is essential to reduce RSV-associated morbidity and mortality worldwide, particularly in low-resource settings.

**Keywords:** Respiratory Syncytial Virus (RSV), RSV pathogenesis, Host immune response, Innate immunity, Adaptive immunity, Cytokines, Chemokines, Viral replication, Inflammatory response.

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## 1. INTRODUCTION

### 1.1 Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) is a **non-segmented, negative-sense, single-stranded RNA virus** classified within the family *Pneumoviridae* and the genus *Orthopneumovirus*, (Collins & Graham, 2008). It is a major human pathogen responsible for acute lower respiratory tract infections (ALRTIs), particularly in infants, young children, older adults, and immunocompromised individuals, (Nair *et al.*, 2010). RSV was first isolated in 1956 from chimpanzees and shortly thereafter from human infants, with the virus named for its ability to induce **syncytium formation**—a cytopathic effect in which infected cells fuse into multinucleated giant cells, (Chanock *et al.*, 1957). The virus is primarily transmitted via respiratory droplets and direct contact with contaminated surfaces or secretions. Seasonal epidemics,

especially in temperate climates, typically occur during the fall and winter months, although tropical and subtropical regions may experience year-round circulation with seasonal peaks. The high transmissibility of RSV, combined with the lack of long-term protective immunity following natural infection, underpins its widespread endemicity and recurrent nature throughout life. The global burden of RSV infection is substantial and underscores the virus's public health significance. It is estimated that RSV is responsible for approximately 33 million episodes of acute LRTIs annually in children under the age of five, with more than 3 million cases requiring hospitalization and over 100,000 resulting in death—predominantly in low- and middle-income countries (LMICs), where healthcare infrastructure and access to supportive care remain limited, (Nair *et al.*, 2010; Shi *et al.*, 2017). This disproportionate impact on resource-poor settings highlights not only the clinical severity of RSV



infection but also the urgent need for scalable, affordable prevention strategies. In high-income countries, RSV remains the leading cause of hospitalization in infants, contributing significantly to pediatric healthcare utilization, increased parental absenteeism, and long-term respiratory morbidity. In infants and young children, RSV commonly presents with symptoms of bronchiolitis and pneumonia, ranging from mild upper respiratory tract illness to severe hypoxemia and respiratory failure requiring mechanical ventilation. Premature infants, those with congenital heart disease, neuromuscular disorders, or chronic lung disease are especially susceptible to severe RSV-associated outcomes, (Collins & Graham, 2008; Sigurs *et al.*, 2005). Importantly, beyond the acute phase, RSV infection in early life has been implicated in the development of chronic respiratory issues. Several longitudinal studies have reported an association between early RSV bronchiolitis and increased risk of recurrent wheezing or asthma later in childhood, though the causality and mechanisms underlying this relationship remain under investigation and may involve complex interactions between viral injury and host immune dysregulation. In older adults, particularly those over the age of 65 or with pre-existing cardiopulmonary conditions, RSV represents an underrecognized yet significant cause of respiratory morbidity and mortality. The clinical manifestations in this population often mirror those of influenza, including cough, dyspnea, fever, and wheezing, making accurate diagnosis challenging in the absence of routine viral testing, (Falsey *et al.*, 2005; Walsh *et al.*, 2013). RSV infection in the elderly can exacerbate chronic obstructive pulmonary disease (COPD), congestive heart failure, and asthma, frequently leading to hospitalization and increased healthcare costs. Despite its clinical importance, awareness of RSV's burden in adults remains limited, and it is often excluded from standard respiratory viral surveillance programs. The pathogenesis of RSV is multifactorial and continues to be the focus of intense investigation. RSV infection triggers a complex interplay between viral factors and host immune responses, which collectively determine disease severity. The virus employs several immune evasion strategies—most notably through its nonstructural proteins NS1 and NS2, which antagonize the host interferon response, delaying early viral recognition and clearance, (Graham, 2011; Schmidt and Varga, 2018). This immune evasion contributes to prolonged viral replication and enhances the potential for severe disease. Furthermore, RSV pathogenesis is often driven as much by host-mediated immunopathology as by direct viral cytopathic effects. In infants, the immature immune system often mounts a skewed response characterized by Th2-biased cytokine production, reduced interferon signaling, and excessive neutrophilic inflammation—all of which contribute to airway obstruction and tissue damage, (Murray *et al.*, 2014). Therapeutic and prophylactic options for RSV remain inadequate. Ribavirin, the only licensed antiviral, has shown limited effectiveness and carries concerns regarding cost, administration logistics, and teratogenic potential, thereby restricting its use to select, severe cases,

(Shafagati and Williams, 2018). The humanized monoclonal antibody Palivizumab, targeting the RSV fusion (F) protein, offers some degree of prophylaxis in high-risk infants; however, its use is constrained by the need for monthly dosing during the RSV season, high cost, and limited applicability beyond narrow risk groups, (American Academy of Pediatrics Committee on Infectious Diseases, 2014). While recent advances have brought several vaccine and long-acting monoclonal antibody candidates into late-phase clinical trials and early market approval, the absence of a universally accessible and broadly protective RSV vaccine continues to hinder effective disease control and prevention, (Anderson *et al.*, 2013). Given these challenges, a comprehensive understanding of RSV's molecular biology, immune interactions, and epidemiology is imperative for the development of next-generation therapeutics and vaccines. Current research efforts are increasingly leveraging high-throughput omics technologies, in vitro airway models, and in vivo systems to dissect host-pathogen interactions at cellular and molecular levels. These insights are being used to inform the rational design of novel antivirals, immunomodulatory agents, and both live-attenuated and subunit vaccines that aim to elicit robust, durable, and cross-protective immune responses, (Graham, 2017). Moreover, the integration of RSV surveillance into global health frameworks and the strengthening of diagnostic capacity, particularly in LMICs, are essential for guiding vaccine deployment strategies and reducing global health disparities.

The **RSV genome is approximately 15.2 kilobases (kb)** in length and encodes **11 proteins** in 10 genes arranged in the order: 3'-NS1-NS2-N-P-M-SH-G-F-M2-L-5'. These include structural and nonstructural proteins with roles in **viral replication, immune evasion, and host cell modulation**, (Collins & Graham, 2008). Among the most functionally significant are the surface glycoproteins:

- **Fusion (F) protein:** Mediates viral entry through the fusion of the viral envelope with the host cell membrane. It exists in both pre-fusion and post-fusion conformations, with the **pre-fusion form being the primary target of neutralizing antibodies** and the focus of current vaccine efforts, (McLellan *et al.*, 2013; Battles and McLellan, 2019).
- **Attachment (G) protein:** Facilitates viral attachment to the host cell, particularly to **heparan sulfate proteoglycans** on ciliated epithelial cells. The G protein also acts as a decoy by modulating the host immune response, including suppressing chemokine responses, (Tripp *et al.*, 2001).
- **Small hydrophobic (SH) protein:** Although its exact role is less well understood, the SH protein is believed to form ion channels (viroporins) and may contribute to viral persistence and modulation of host cell signaling, (Fuentes *et al.*, 2007).

In addition to these surface proteins, **nonstructural proteins NS1 and NS2** play critical roles in **antagonizing host interferon responses**, particularly type I interferons,



thus facilitating immune evasion, (Spann *et al.*, 2004).

RSV is further classified into **two major antigenic subgroups—RSV-A and RSV-B**—based on variability in the G glycoprotein. Both subtypes co-circulate during annual epidemics, though the dominant circulating subtype may vary by season and geography. RSV-A strains are generally associated with more severe clinical outcomes, potentially due to higher viral loads and more robust replication kinetics, (Anderson *et al.*, 2017; Eshaghi *et al.*, 2012). RSV infects the **respiratory epithelium**, primarily targeting **nasopharyngeal and bronchiolar epithelial cells**, where it replicates and induces local inflammation.

The virus causes **cell necrosis, sloughing of epithelial cells, and mucus hypersecretion**, which collectively lead to airway obstruction—particularly in small-caliber bronchioles of infants, (Jafri *et al.*, 2004). From a public health perspective, RSV is an **immunologically complex virus**, with incomplete and short-lived immunity following natural infection. Reinfections are common throughout life, although severity tends to decline with age, (Hall *et al.*, 1991). The lack of durable immunity and the immune-modulating capabilities of the virus pose significant challenges for **vaccine development** and underscore the need for a deeper understanding of RSV molecular virology and host-pathogen interactions.

### Key Features of RSV at a Glance

Feature	Description
Genome	Non-segmented, negative-sense, ssRNA (~15.2 kb)
Family / Genus	<i>Pneumoviridae</i> / <i>Orthopneumovirus</i>
Structural Proteins	F, G, SH, M, N, P
Nonstructural Proteins	NS1, NS2
Tropism	Ciliated epithelial cells of upper and lower respiratory tract
Hallmark Pathology	Syncytium formation, epithelial sloughing, airway obstruction
Subtypes	RSV-A and RSV-B
Immune Evasion	Interferon suppression via NS1/NS2; decoy function of G protein

## 2. RSV PATHOGENESIS

The pathogenesis of respiratory syncytial virus (RSV) involves a complex interplay between viral replication, host cell damage, and immune-mediated inflammation. RSV primarily infects and damages the respiratory epithelium, initiating both direct cytopathic effects and an exaggerated immune response that contributes to clinical severity, especially in infants and vulnerable populations.

### 2.1 Viral Entry and Replication

RSV initiates infection by targeting the **apical surface of ciliated airway epithelial cells** in both the upper and lower respiratory tract. The virus exhibits a **tropism for columnar epithelial cells**, particularly in the nasopharynx and bronchioles, where it binds, fuses, and begins replicating, (Jafri *et al.*, 2004; Collins & Graham, 2008).

#### Attachment to Host Cells

Attachment of RSV to host cells is primarily mediated by the **G (glycoprotein)**, which binds to **heparan sulfate proteoglycans (HSPGs)** and **CX3CR1 receptors** on ciliated epithelial cells, (Tripp *et al.*, 2001; Johnson *et al.*, 2015). The RSV G protein mimics the CX3C chemokine motif, enabling immune evasion by modulating leukocyte chemotaxis and inflammatory signaling, (Tripp *et al.*, 2001). This mimicry reduces the

recruitment of cytotoxic immune cells and contributes to viral persistence in the respiratory tract.

#### Fusion and Entry

Following attachment, viral entry is facilitated by the **F (fusion) protein**, which undergoes a conformational change to mediate the fusion of the viral envelope with the host cell membrane (McLellan *et al.*, 2013). The F protein exists in two conformational states—**pre-fusion and post-fusion**—with the pre-fusion form being the target of most neutralizing antibodies, (Battles & McLellan, 2019). Importantly, the F protein also facilitates **cell-to-cell spread** by promoting fusion of adjacent infected and uninfected epithelial cells, leading to the formation of **syncytia**, a pathological hallmark of RSV infection, (Collins & Graham, 2008).

#### Replication Cycle

Once inside the host cell, the RSV **ribonucleoprotein (RNP) complex**, consisting of the viral RNA genome and associated nucleoproteins (N, P, and L), initiates **transcription and replication in the cytoplasm**, (Collins *et al.*, 2001). The viral RNA-dependent RNA polymerase (L protein), with the help of co-factors P and M2-1, transcribes viral mRNAs in a sequential 3' to 5' manner from the genome. These mRNAs are translated into viral proteins, and full-length positive-sense antigenomes serve as templates for the synthesis of new genomic RNA. Newly synthesized RSV genomes are encapsidated by nucleoproteins and transported to the



plasma membrane, where they assemble into virions and bud from the cell surface, often in filamentous forms, (Shingai *et al.*, 2008). However, much of RSV's spread occurs **via direct cell-to-cell transmission**, avoiding extracellular space and partially evading host antibody responses.

### Host Cell Damage and Syncytia Formation

RSV replication causes **extensive cytopathic effects**, including:

- **Destruction of ciliated epithelial cells**, impairing mucociliary clearance
- **Loss of epithelial integrity** and increased permeability
- **Formation of multinucleated syncytia**, contributing to airway obstruction, (Jafri *et al.*, 2004)

These effects are particularly severe in **narrow bronchioles of infants**, where sloughed cells and mucus plugs result in **airflow limitation, wheezing, and hypoxia**.

Furthermore, the virus disrupts tight junction proteins, such as occludin and ZO-1, enhancing epithelial permeability and facilitating viral dissemination, (Rameix-Welti *et al.*, 2014).

### Immune Evasion during Entry and Replication

RSV has evolved multiple strategies to evade innate immune detection during the entry and replication process:

- **NS1 and NS2 proteins inhibit type I interferon signaling** by degrading STAT2 and inhibiting IRF3 activation, (Spann *et al.*, 2004).
- The **G protein** inhibits **TLR signaling** and acts as a decoy for immune recognition (Stokes *et al.*, 2011).
- **Replication in cytoplasmic inclusion bodies** sequesters viral RNA from cytosolic pattern recognition receptors, (Lifland *et al.*, 2012).

These mechanisms blunt early antiviral responses, allowing RSV to replicate efficiently in the respiratory epithelium.

## 2.2 Immune Response and Immunopathology

The host immune response to **respiratory syncytial virus (RSV)** infection represents a delicate interplay between viral clearance and immunologically mediated tissue damage. While immune defenses are essential for eliminating the virus, an overactive or misdirected response—especially in infants—can exacerbate respiratory symptoms and contribute to long-term pulmonary sequelae, (Graham, 2011; Openshaw and Tregoning, 2005).

### 2.2.1 Innate Immune Response

The **innate immune system** provides the first barrier to RSV infection, sensing the virus through **pattern recognition receptors (PRRs)** such as **retinoic acid-inducible gene I (RIG-I)**, **melanoma differentiation-associated protein 5 (MDA5)**, and **Toll-like receptor 3 (TLR3)**. Upon detecting viral RNA, these PRRs activate downstream transcription factors like **IRF3**, **NF- $\kappa$ B**, and **AP-1**, which induce the expression of **type I and type III interferons (IFN- $\alpha/\beta$  and IFN- $\lambda$ )** and proinflammatory cytokines, (Liu *et al.*, 2009; Lukacs & Moore, 2007).

Despite this robust sensing system, RSV has evolved mechanisms to **subvert innate immunity**. The **NS1 and NS2 proteins** antagonize IFN pathways by targeting and degrading **STAT2**, blocking IRF3 activation, and inhibiting dendritic cell maturation, (Spann *et al.*, 2004; Lo *et al.*, 2005). This evasion results in delayed IFN production and permits extensive early viral replication.

Key innate immune cell participants include:

- **Neutrophils**, which dominate bronchoalveolar lavage fluid during RSV infection. They release **myeloperoxidase, elastase, and reactive oxygen species**, contributing to **epithelial cell damage**, mucus hypersecretion, and airway obstruction, (Everard *et al.*, 1994; Welliver *et al.*, 2007).
- **Eosinophils**, more common in Th2-skewed responses, exacerbate pathology by releasing **major basic protein** and **eosinophil peroxidase**, damaging epithelial barriers.
- **Natural killer (NK) cells**, while capable of lysing infected cells, are relatively limited in RSV and may have dual roles in both protection and immune regulation, (Schmidt *et al.*, 2004).
- **Alveolar macrophages and dendritic cells (DCs)** bridge innate and adaptive immunity by releasing **IL-6, IL-8, and TNF- $\alpha$** , and by presenting antigens to naïve T cells in lymph nodes, (Shirey *et al.*, 2010).

In infants, the innate response is **skewed toward a pro-inflammatory, Th2-biased environment**, partially due to immune immaturity. This imbalance contributes to **bronchiolar inflammation, airway edema, and mucus plugging**, characteristic of severe RSV bronchiolitis.

### 2.2.2 Adaptive Immune Response

The **adaptive immune system** is essential for resolving RSV infection and establishing immunological memory, though RSV notoriously fails to elicit sterilizing immunity, allowing recurrent infections throughout life, (Hall *et al.*, 1991).

#### Humoral Immunity

- **Neutralizing antibodies**, particularly against the **pre-fusion form of the F protein**, are critical for virus neutralization and are the primary target of both natural immunity and vaccine development, (McLellan *et al.*, 2013).



- **Antibodies targeting the G glycoprotein** contribute to limiting viral spread by blocking attachment to host epithelial cells, (Collins and Graham, 2008).
- **Maternal antibodies**, transferred transplacentally or via breast milk, provide **partial and transient protection**, with significantly reduced efficacy in **preterm infants** due to lower transplacental IgG transfer, (Chu *et al.*, 2014).

Despite repeated exposure, **protective antibody responses wane rapidly**, especially in children under 2, and reinfections often occur with minimal long-term neutralizing memory, (Falsey *et al.*, 2005).

### Cell-Mediated Immunity

- **CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs)** are central to clearing RSV-infected cells. They produce **perforin, granzyme B, and IFN- $\gamma$** , but excessive CTL activity can exacerbate lung tissue injury and impair gas exchange, (Tregoning *et al.*, 2010).
- **CD4<sup>+</sup> T helper cells** play diverse roles:
  - **Th1 cells** promote viral clearance via **IFN- $\gamma$**  and **IL-2**.
  - **Th2 cells**, which dominate in infants or following inactivated RSV vaccination, secrete **IL-4, IL-5, and IL-13**, contributing to eosinophilic inflammation and mucus production, (Lukacs & Moore, 2007).
  - **Th17 cells**, which produce **IL-17A**, have been linked to **neutrophil recruitment**, airway hyperresponsiveness, and chronic inflammation, (Mukherjee *et al.*, 2011).
- **Regulatory T cells (Tregs)** maintain immune homeostasis by suppressing excessive T cell responses and limiting inflammation. However, **RSV can impair Treg function**, reducing IL-10 production and increasing Th2/Th17 skewing, (Lee *et al.*, 2010).

### 2.2.3 Immunopathology and Disease Severity

In RSV infection, clinical severity is often **disproportionate to viral load**, implicating immune-mediated damage as a central driver of disease, (Graham, 2011). Major mechanisms of immunopathology include:

#### Cytokine Storm

Elevated levels of **proinflammatory cytokines** such as **IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$**  have been detected in nasal aspirates and bronchoalveolar fluid from children with severe bronchiolitis. These cytokines drive **vascular leakage, immune cell recruitment, and mucus hypersecretion**, leading to airway narrowing and respiratory distress, (Mukherjee *et al.*, 2011).

### Airway Remodeling and Mucus Plugging

The **Th2 cytokines IL-13 and IL-5** promote **goblet cell hyperplasia and mucus production**, while eosinophil degranulation damages the epithelial lining. This contributes to **bronchial obstruction**, particularly problematic in infants with small airways.

### Post-Infectious Wheezing and Asthma

Multiple longitudinal studies have shown that **severe RSV infection in infancy** increases the risk of **recurrent wheezing and childhood asthma**, (Sigurs *et al.*, 2010). Proposed mechanisms include:

- **Immune imprinting favoring Th2 or Th17 bias**
- **Persistent airway remodeling**
- **Altered microbiota-immune interactions**

### Vaccine-Enhanced Disease (VED)

The most dramatic example of RSV-induced immunopathology was observed in the **formalin-inactivated RSV (FI-RSV) vaccine trials** during the 1960s. In this study, children immunized with the inactivated vaccine experienced **enhanced disease** upon natural RSV exposure, with **exaggerated Th2 responses, eosinophilia, and two fatalities**, (Kim *et al.*, 1969). These events led to a decades-long halt in RSV vaccine development and have influenced modern strategies that prioritize balanced immune responses and mimicry of natural infection, (Graham, 2011).

## 3. IMPLICATIONS FOR TREATMENT AND PREVENTION

The complex interplay between RSV pathogenesis and the host immune response significantly shapes strategies for treatment and prevention. A comprehensive understanding of viral entry, replication, and immune evasion mechanisms facilitates the design of targeted therapeutics, while insights into host immunity inform vaccine development and prophylaxis. The ultimate goal is to reduce disease burden, especially among vulnerable populations such as infants, the elderly, and immunocompromised individuals.

### 3.1 Current Therapeutic Approaches

At present, RSV treatment remains predominantly supportive, with limited availability of effective antiviral agents approved for routine use.

**Supportive Care:** The cornerstone of RSV management, particularly in severe cases like bronchiolitis, includes maintaining adequate oxygenation via supplemental oxygen, ensuring proper hydration, and providing ventilatory support when indicated, (Meissner, 2016). Supportive interventions aim to mitigate respiratory distress and prevent complications such as respiratory failure.

**Ribavirin:** An antiviral nucleoside analog with broad-spectrum activity, ribavirin has been approved for RSV



treatment but is infrequently used due to inconsistent clinical benefits, potential teratogenicity, and cumbersome aerosolized administration, (Shafagati & Williams, 2018). Clinical guidelines generally reserve ribavirin for severe cases in immunocompromised patients where benefits may outweigh risks.

**Palivizumab:** This humanized monoclonal antibody specifically targets the RSV F protein and is administered prophylactically to reduce hospitalization risk in high-risk infants, including those born prematurely or with congenital heart or lung disease (IMPact-RSV Study Group, 1998). Palivizumab's use is limited by its high cost, requirement for monthly intramuscular injections during the RSV season, and its indication restricted to selected populations.

**Emerging Antivirals:** Advances in understanding RSV molecular biology have led to the development of novel antiviral agents targeting critical viral proteins. For example, **Presatovir (GS-5806)** inhibits the RSV fusion protein, preventing viral entry and syncytium formation. Clinical trials demonstrated that early administration reduces viral load and symptoms in healthy adults challenged with RSV, (DeVincenzo *et al.*, 2014). Additional compounds targeting the viral RNA polymerase complex and other essential enzymes are under investigation, offering promise for more effective and timely therapeutic options.

### 3.2 Vaccine Development Challenges and Advances

The quest for a safe and effective RSV vaccine has been complicated by the virus's unique biology and historical vaccine setbacks.

**Historical Lessons:** The 1960s experience with the formalin-inactivated RSV (FI-RSV) vaccine revealed that non-neutralizing antibody responses and a Th2-skewed immune profile can exacerbate disease upon natural infection, resulting in vaccine-enhanced disease (VED) with severe immunopathology, (Kim *et al.*, 1969; Graham, 2011). This outcome set a high safety bar for subsequent vaccine candidates.

**Target Antigens:** Recent breakthroughs focus on the prefusion (pre-F) conformation of the F glycoprotein, which displays epitopes that elicit potent neutralizing antibodies not present in the postfusion form. Structural biology studies facilitated the design of stabilized pre-F immunogens, significantly improving vaccine efficacy potential, (McLellan *et al.*, 2013).

**Vaccine Platforms:** Modern RSV vaccines employ diverse technological platforms to overcome previous challenges:

- **Subunit Vaccines:** Utilizing purified, stabilized pre-F proteins to induce strong neutralizing antibody responses with favorable safety profiles. Candidates from pharmaceutical leaders such as Pfizer and GSK are in advanced clinical trials.

- **Live-Attenuated Vaccines:** Engineered to replicate minimally in the respiratory tract, these vaccines aim to mimic natural infection and induce broad immunity, including cellular responses, without causing disease. They hold particular promise for infant immunization.
- **Vector-Based Vaccines:** These use non-replicating viral vectors (e.g., adenovirus) to deliver RSV antigens, stimulating robust T cell and antibody responses. Such platforms have the advantage of strong immunogenicity and scalable manufacturing, (Anderson *et al.*, 2017).

**Maternal Immunization:** Vaccinating pregnant women to boost maternal antibody titers enables transplacental transfer of protective antibodies to neonates, offering protection during the critical early months of life when infants are most vulnerable and direct vaccination may be less effective, (Munoz *et al.*, 2019).

**Nanoparticle and mRNA Vaccines:** Inspired by the success of mRNA vaccines against SARS-CoV-2, mRNA-based RSV vaccines are being developed to induce rapid, high-magnitude immune responses. Nanoparticle formulations presenting RSV antigens also enhance immunogenicity while maintaining safety.

### 3.3 Immunoprophylaxis and Monoclonal Antibodies

Passive immunization remains an important prophylactic strategy, particularly for infants at high risk for severe RSV disease.

**Monoclonal Antibodies:** Beyond palivizumab, novel monoclonal antibodies with extended half-lives, such as **nirsevimab**, are in late-stage clinical trials. Nirsevimab can potentially provide a single intramuscular dose per RSV season, enhancing convenience and access for broader infant populations, including term infants who are currently ineligible for palivizumab, (Domachowske *et al.*, 2021). These advances promise to substantially reduce RSV-related hospitalizations and morbidity.

### 3.4 Future Directions in RSV Management

**Host-Directed Therapies:** Modulating the host immune response to mitigate immunopathology is an emerging therapeutic avenue. Approaches aimed at reducing excessive neutrophil infiltration, controlling cytokine storms, or enhancing regulatory T cell activity could complement antiviral therapies and improve clinical outcomes, (Graham *et al.*, 2015).

**Personalized Medicine:** Genetic, immunologic, and environmental factors influence RSV disease severity. Identification of biomarkers and risk profiles may enable personalized prophylactic and therapeutic interventions, optimizing resource allocation and improving efficacy in vulnerable subpopulations.

**Combination Strategies:** Integrated approaches combining vaccines, monoclonal antibodies, and antiviral agents are likely to offer the most comprehensive protection. For example, maternal immunization combined



with infant monoclonal antibody prophylaxis and antiviral treatment during breakthrough infections may synergistically reduce RSV burden.

**Table 1: Summary of Therapeutic and Preventive Strategies against RSV**

Strategy	Mechanism of Action	Target Population	Limitations	Status
<b>Supportive Care</b>	Symptom relief (oxygen, hydration, ventilation)	All symptomatic RSV patients	Does not target virus directly	Standard of care
<b>Ribavirin</b>	Broad-spectrum antiviral; inhibits viral RNA synthesis	Severely immunocompromised patients	High cost, teratogenicity, limited efficacy	FDA approved, limited use
<b>Palivizumab</b>	Monoclonal antibody against RSV F protein	High-risk infants	Monthly injections, high cost	FDA approved (prophylaxis)
<b>Nirsevimab</b>	Long-acting monoclonal antibody against prefusion F	All infants (pending indication)	Awaiting full approval in some regions	Phase 3 trials completed
<b>Presatovir (GS-5806)</b>	Fusion inhibitor; blocks viral entry	Adults (clinical trial participants)	Limited data in pediatric populations	Investigational
<b>Subunit Vaccines</b>	Prefusion F protein-based; induces neutralizing antibodies	Infants, older adults, pregnant women	No sterilizing immunity	Late-stage clinical trials
<b>Live-attenuated Vaccines</b>	Replication-competent virus with reduced virulence	Infants	Balance between attenuation and immunogenicity	Early- to mid-stage trials
<b>mRNA Vaccines</b>	Encodes RSV antigen (e.g., prefusion F) for in situ expression	Adults, pregnant women	Requires cold chain and monitoring of long-term safety	Preclinical to early trials
<b>Maternal Immunization</b>	Boosts maternal antibodies transferred via placenta	Pregnant women (benefits neonates)	Time-limited protection; maternal vaccine safety	Ongoing studies

## Figure Legend

### Figure 1: Schematic Overview of RSV Prevention and Treatment Strategies

This figure illustrates the multi-tiered approach to RSV prevention and treatment:

- **Primary prevention** through maternal vaccination, infant vaccination, and monoclonal antibody prophylaxis (e.g., palivizumab, nirsevimab).
- **Post-exposure treatment** strategies including direct-acting antivirals (e.g., fusion and polymerase inhibitors).
- **Supportive care**, encompassing oxygen therapy, hydration, and ventilation for symptomatic relief in hospitalized patients.
- **Host-modulating therapies** (under investigation) aiming to dampen harmful immune responses.

Arrows depict where each intervention interrupts the RSV disease progression—from viral entry to immune-mediated lung damage.

## 3.2 Adaptive Immunity

The adaptive immune response plays a crucial role in the control and eventual clearance of respiratory syncytial virus (RSV) infection. It involves both cellular and humoral components, which must act in a coordinated manner to eliminate the virus while minimizing host tissue damage. However, in the case of RSV, this balance is often imperfect, contributing to both viral persistence and immunopathology. The effectiveness and quality of adaptive immunity are also key considerations in the development of vaccines and monoclonal antibody-based therapeutics.

### Cellular Immunity

**CD8<sup>+</sup> Cytotoxic T Lymphocytes (CTLs):** CD8<sup>+</sup> T cells are essential for the clearance of RSV-infected cells through cytolytic mechanisms, including the release of perforin and granzymes, and through the production of antiviral cytokines such as interferon-gamma (IFN- $\gamma$ ). These cells are particularly effective during the resolution phase of RSV infection, reducing viral load and curtailing replication, (Tregoning *et al.*, 2010; Schmidt *et al.*, 2018).

However, excessive or prolonged CD8<sup>+</sup> T cell activity can exacerbate lung pathology, especially in the delicate airways of infants. Studies in animal models have demonstrated that robust CTL responses are associated with increased pulmonary inflammation and damage, suggesting that cytotoxic T cells, while beneficial for viral clearance, can also be contributors to disease severity, (Graham *et al.*, 1991; Tregoning & Schwarze, 2010).

**CD4<sup>+</sup> Helper T Cells:** CD4<sup>+</sup> T cells coordinate and shape the immune response through their differentiation into various subsets, including Th1, Th2, and Th17 cells. Each subset plays distinct roles in RSV immunity and pathogenesis:

- **Th1 cells** promote viral clearance through the production of IFN- $\gamma$  and support CTL activity and IgG2a isotype switching, typically associated with more protective immune responses, (Lukacs & Moore, 2007).
- **Th2-skewed responses** are characterized by cytokines like IL-4, IL-5, and IL-13, which promote eosinophilia, mucus hypersecretion, and airway hyperreactivity—features implicated in vaccine-enhanced disease and severe bronchiolitis (Kim *et al.*, 1969; Openshaw & Tregoning, 2005).
- **Th17 cells**, producing IL-17, have been linked to neutrophilic inflammation and may also contribute to airway pathology, although their role in RSV is still being elucidated (Mukherjee *et al.*, 2011). The balance between Th1 and Th2 responses can significantly affect the clinical outcome of RSV infection. A skewed Th2 response, often observed in young infants, is associated with more severe disease, (Welliver *et al.*, 2007).

**Regulatory T Cells (Tregs):** Tregs help maintain immune homeostasis by suppressing excessive immune activation and inflammation. Their presence in the lungs during RSV infection has been shown to limit immunopathology and prevent airway hyperreactivity, (Lee *et al.*, 2010). Impaired Treg function or numbers may contribute to severe RSV-induced inflammation, highlighting their protective role.

## HUMORAL IMMUNITY

**Neutralizing Antibodies:** Humoral immunity, particularly through the production of neutralizing antibodies, is a critical component of the adaptive response to RSV. These antibodies target key viral surface glycoproteins, especially the fusion (F) and attachment (G) proteins, neutralizing the virus and preventing entry into host cells, (Collins & Graham, 2008).

- **F Protein:** The prefusion form of the F protein contains several antigenic sites, such as site Ø that are recognized by potent neutralizing antibodies. Antibodies against this form are especially effective and form the basis for several monoclonal therapies and vaccine candidates, (McLellan *et al.*, 2013; Gilman *et al.*, 2016).
- **G Protein:** While antibodies against the G protein also contribute to virus neutralization, the

protein's high variability and glycosylation may limit its effectiveness as a sole antigenic target.

Despite generating neutralizing antibodies, natural RSV infection does not induce long-lasting sterilizing immunity. Reinfections are common, even within the same season, though typically less severe (Hall *et al.*, 1991). This suggests that while humoral immunity reduces disease severity, it does not fully prevent reinfection, likely due to incomplete memory B cell responses or antigenic drift in RSV strains.

**Maternal Antibodies:** Maternal IgG antibodies transferred transplacentally offer temporary protection in early infancy. However, their levels decline rapidly postnatally, especially in preterm infants, which may explain their increased susceptibility to severe RSV disease, (Chu *et al.*, 2014).

## Implications for Vaccine Development

An effective RSV vaccine must elicit balanced adaptive responses—strong enough to confer protection but regulated to avoid immunopathology. This includes:

- Inducing **high-affinity neutralizing antibodies**, especially against prefusion F protein.
- Promoting **Th1-biased CD4<sup>+</sup> T cell responses** over Th2 or Th17 polarization.
- Stimulating **CD8<sup>+</sup> T cells** for viral clearance without excessive inflammation.
- Preserving or enhancing **Treg function** to control immunopathology.

These goals are now central to modern RSV vaccine design, especially in light of past failures where inappropriate adaptive immune responses led to worsened outcomes.

## 4. IMMUNOPATHOLOGY AND DISEASE SEVERITY

The clinical severity of respiratory syncytial virus (RSV) infection is not merely a consequence of viral replication but reflects a dynamic and, at times, maladaptive host immune response. Several factors—including the immaturity of the infant immune system, interference by maternal antibodies, a Th2-skewed T cell response, and the host's age and comorbidities—play key roles in shaping disease outcomes. Understanding these immunopathogenic mechanisms is vital for guiding treatment decisions and improving vaccine safety.

### 4.1 Infant Immune Immaturity and Maternal Antibody Interference

Infants, especially those under six months, are the most vulnerable group affected by RSV. Their innate and adaptive immune systems are not fully developed, resulting in an inadequate initial response to infection. Neonatal dendritic cells exhibit reduced antigen presentation and cytokine production, especially type I interferons (IFN- $\alpha/\beta$ ), which impairs the orchestration of antiviral immunity, (Ruckwardt *et al.*, 2019). Moreover, the presence of maternally derived immunoglobulin G (IgG), although partially protective, can paradoxically inhibit the development of infant immune memory. High

titers of maternal antibodies may neutralize live-virus vaccine components or sequester viral antigens during natural infection, limiting endogenous B cell activation and affinity maturation, (Munoz *et al.*, 2019). This phenomenon has posed challenges for infant vaccine development, prompting consideration of maternal immunization strategies to bridge the early-life immunity gap.

## 4.2 Th2-Biased Responses and Vaccine-Enhanced Disease

A central feature of RSV immunopathology is the **Th2-biased adaptive immune response**, especially in infants. This skewing is characterized by elevated levels of IL-4, IL-5, and IL-13, cytokines that promote eosinophilic infiltration, mucus production, and airway hyperreactivity—hallmarks of severe bronchiolitis (Openshaw & Tregoning, 2005). This Th2 dominance gained historical significance following the **formalin-inactivated RSV (FI-RSV)** vaccine trial failure in the 1960s. Vaccinated children experienced heightened disease severity upon subsequent natural RSV exposure, with two deaths attributed to **vaccine-enhanced respiratory disease (ERD)**. Lung biopsies revealed extensive eosinophil recruitment and mononuclear infiltration, signifying an aberrant, non-protective immune response, (Kim *et al.*, 1969; Graham, 2011). Crucially, the FI-RSV vaccine failed to generate high-affinity neutralizing antibodies or effective cytotoxic T cell responses, leaving vaccinated individuals unprotected and immunopathologically primed. In both vaccine-enhanced and natural RSV disease, **IL-4** and **IL-13** are implicated in pathogenesis. IL-4 drives IgE class switching and Th2 polarization, while IL-13 promotes goblet cell hyperplasia and mucus hypersecretion, further contributing to airway obstruction and respiratory distress (Lukacs & Moore, 2007). These findings have steered modern RSV vaccine development toward eliciting Th1-skewed responses, favoring IFN- $\gamma$  production and cytotoxic immunity.

## 4.3 Age- and Comorbidity-Dependent Immunopathogenesis

The immunopathology response to RSV infection is influenced by the host's age, baseline immune status, and presence of comorbidities:

- **Infants and toddlers:** Their Th2-biased and cytotoxic T cell-deficient responses predispose them to bronchiolitis, hypoxemia, and severe airway inflammation, (Welliver *et al.*, 2007). Preterm infants, in particular, have reduced surfactant levels and immature lung architecture, compounding disease severity.
- **Older adults:** Immunosenescence impairs both innate (e.g., diminished interferon production, slower neutrophil recruitment) and adaptive (e.g., reduced T cell function) arms of the immune system. RSV can exacerbate chronic cardiopulmonary diseases like chronic obstructive pulmonary disease (COPD) and heart

failure, increasing morbidity and mortality in this group, (Falsey *et al.*, 2005).

- **Immunocompromised patients:** Individuals undergoing hematopoietic stem cell or organ transplantation, or those receiving chemotherapy, exhibit deficient T and B cell responses, leading to prolonged RSV shedding and risk of disseminated infection, (Hall *et al.*, 2013). Mortality rates in these groups are substantially higher, warranting aggressive prophylaxis and early intervention. These age- and condition-specific patterns highlight the necessity for **tailored preventive and therapeutic strategies**, including **extended half-life monoclonal antibodies** for high-risk infants and **vaccines or antivirals** adapted for the elderly and immunocompromised.

## 4.4 Long-Term Sequelae: Asthma and Recurrent Wheezing

Beyond acute illness, **severe RSV infection during infancy has been linked to an increased risk of chronic respiratory conditions**, particularly recurrent wheezing and asthma in later childhood. While causality remains debated, longitudinal cohort studies suggest that RSV may trigger lasting alterations in airway structure and immune programming.

Potential mechanisms include:

- **Immune imprinting** toward a Th2 phenotype, enhancing susceptibility to allergic airway inflammation, (Sigurs *et al.*, 2010).
- **Disruption of epithelial integrity**, enabling greater allergen penetration and sustained inflammation, (Holt *et al.*, 2014).
- **Dysregulated Treg responses**, reducing immunologic tolerance and amplifying inflammatory cascades.

Although the extent to which RSV directly causes asthma versus unmasks a predisposition is unclear, the strong association underlines the importance of **early-life RSV prevention** to potentially mitigate long-term pulmonary morbidity.

# 5. IMPLICATIONS FOR TREATMENT

## 5.1 Antiviral Therapies

Small-molecule antivirals directed at RSV-specific viral targets have emerged as promising therapeutic candidates. These compounds aim to attenuate viral replication, reduce symptom severity, and mitigate complications—especially when administered early during infection.

### 5.1.1 Ribavirin

- **Mechanism of Action:** Ribavirin is a guanosine analog that interferes with viral RNA synthesis and modulates nucleotide pools, producing broad-spectrum antiviral effects (ribavirin entry mechanism descriptions)..



- **Clinical Use:** Although approved for RSV treatment, its clinical utility is limited to severely ill infants or immunocompromised patients due to cumbersome aerosolized administration, teratogenic risk, and modest efficacy (RKI statement). Controlled trials have not reliably demonstrated robust clinical benefit, leading many guidelines to no longer recommend its routine use.
- **Limitations:** Adverse effects include hemolytic anemia, high cost, complexity of delivery, and teratogenic potential—all of which constrain its clinical adoption.

### 5.1.2 Fusion Inhibitors

Orally bioavailable fusion inhibitors disrupt RSV entry and syncytium formation via binding to the viral F protein:

- **Presatovir (GS-5806):**

Shown to inhibit RSV-A and RSV-B with EC<sub>50</sub> values around 0.4 nM. In healthy adult challenge studies, presatovir significantly reduced viral load and symptom burden; phase 2 trials in transplant recipients also assessed its safety and antiviral effects.

- **Additional Candidates:**

- **Ziresovir (AK-0529):** Oral fusion inhibitor in phase 2 trials, demonstrating oral bioavailability, safety, and antiviral activity in preclinical models.

- **JNJ-53718678, MDT-637, TP0591816:** These inhibitors, some targeting the pre-fusion conformation of F protein, exhibit antiviral activity in early-phase studies and against resistant RSV strains in preclinical settings.

While fusion inhibitors show promise as orally administered therapies, pediatric efficacy and safety data are still forthcoming.

### 5.1.3 N-Protein Inhibitors (Replication Inhibitors)

- **EDP-938:** A novel small-molecule targeting the RSV nucleoprotein (N), essential for viral replication. In vitro potency (EC<sub>50</sub> ≈ 21–64 nM) extends across RSV-A and RSV-B strains, with efficacy preserved in resistant variants. In a Phase 2a human challenge study involving healthy adult volunteers, EDP-938 achieved statistically significant reductions in RSV viral load AUC and total symptom scores (both p < 0.001), as well as reduced mucus output. The drug was well-tolerated with mild adverse effects and no discontinuations. EDP-938 has received FDA fast track designation, and a Phase 2b trial is underway in high-risk adults (e.g., elderly, COPD, CHF) to assess clinical efficacy and progression of RSV disease.

**5.1.4 Summary Table: Antiviral Agents in Development**

Agent	Target / Mechanism	Key Findings	Clinical Status
Ribavirin	RdRp analog, broad-spectrum	Modest efficacy, toxicity, complex aerosol dosing	FDA-approved; rarely used
Presatovir (GS-5806)	F protein fusion inhibitor	EC <sub>50</sub> ≈ 0.4 nM; significant viral load and symptom reduction	Phase 2 trials completed
Ziresovir (AK-0529)	F fusion inhibitor	Oral availability; reduced lung titers in animal models	Phase 2 in adults/infants
JNJ-53718678 <i>et al.</i>	Pre-fusion F blockers	Activity in early trials; effective against resistant strains	Phase 2 / preclinical
EDP-938	N protein replication inhibitor	~90% viral load reduction; robust symptom relief; excellent safety	Phase 2a human challenge; 2b ongoing

### 5.1.5 Clinical Considerations and Implications

- **Timing Matters:** Antiviral agents show greatest efficacy when administered early, ideally before viral peak replication.
- **Resistance Potential:** Fusion inhibitors may select for F protein mutations, whereas EDP-938 exhibits a higher genetic barrier to resistance in vitro and in vivo
- **Target Populations:** High-risk individuals such as infants, the elderly, and immunocompromised patients stand to benefit most.

- **Combination Therapy:** Leveraging agents with complementary mechanisms (e.g., fusion + replication inhibitors) may enhance efficacy and reduce resistance risk.

## 5.2 MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) targeting the respiratory syncytial virus (RSV) fusion (F) glycoprotein represent a significant advancement in passive immunization strategies. These antibodies are engineered to specifically bind to the prefusion conformation of the F protein, a critical viral surface protein responsible for mediating membrane fusion and viral entry into host cells.



By targeting this conserved region, mAbs effectively neutralize the virus and prevent infection, (Anderson *et al.*, 2017).

- This form of immunoprophylaxis is particularly beneficial for populations at elevated risk of severe RSV disease, including neonates, preterm infants, and those with underlying cardiopulmonary or immunocompromising conditions. Unlike active immunization, which requires time to elicit an adaptive immune response, passive immunization with mAbs provides immediate protection. This rapid onset of immunity is crucial during peak RSV seasons or in outbreak settings, (Munoz *et al.*, 2019).
- Currently, **nirsevimab** and **palivizumab** are two notable mAbs used for RSV prevention. Palivizumab, a humanized monoclonal antibody, has been in clinical use for years and is administered monthly during RSV season. More recently, nirsevimab—an extended half-life monoclonal antibody—has demonstrated efficacy in protecting infants with a single dose, offering a more convenient and potentially more cost-effective alternative, (Munoz *et al.*, 2019).

Ongoing research is focused on improving the breadth and duration of protection offered by mAbs, as well as expanding their use in broader pediatric and adult populations. The integration of mAbs into RSV prevention strategies represents a promising complement to vaccines, particularly for those who cannot mount an effective immune response to vaccination.

### 5.2.1 Palivizumab (Synagis)

**Target and Mechanism of Action:** Palivizumab is a humanized IgG1 monoclonal antibody directed against antigenic site A of the RSV fusion (F) protein, thereby neutralizing RSV and preventing viral entry into host cells.

**Clinical Efficacy:** In two pivotal randomized controlled trials (IMPact-RSV and Feltes), palivizumab reduced ospitalization rates by **55% to 78%** among preterm infants and those with bronchopulmonary dysplasia (BPD) or congenital heart disease (CHD) [synagishcp.com](http://synagishcp.com). Observational studies confirm ~50–70% risk reduction for RSV hospitalization in high-risk children.

**Eligibility and Guidelines:** The American Academy of Pediatrics recommends monthly prophylaxis during RSV season for infants born at  $\leq 28$  weeks gestational age, those below 12 months with BPD or CHD, and selected high-risk groups (e.g. cystic fibrosis, neuromuscular disease).

**Safety & Limitations:** Palivizumab has a favorable safety profile; most common side effects are injection-site reactions and rash. It requires monthly intramuscular dosing during RSV season, incurs high costs, and may promote rare emergence of resistant viral variants.

**Long-Term Effects:** Prophylaxis with palivizumab has also been associated with reductions in recurrent wheezing and asthma-like symptoms in preterm infants through age 2–3 years, although data primarily come from observational studies, [Wikipedia+6PMC+6NCBI+6](#).

### 5.2.2 Nirsevimab (Beyfortus)

**Target and Design:** Nirsevimab is an Fc-engineered human monoclonal antibody with enhanced half-life and high-affinity binding to a conserved epitope of the RSV F protein, providing potent neutralization across RSV subtypes A and B, [synagishcp.com+15Dove Medical Press+15PMC+15](http://synagishcp.com+15Dove Medical Press+15PMC+15).

**Clinical Effectiveness:** In pooled data from Phase 2b (MEDLEY) and Phase 3 (MELODY) trials involving term and preterm infants, nirsevimab reduced medically attended RSV lower respiratory tract infections (RSV LRTI) by **~71–80%**, RSV-associated hospitalizations by **77%**, and very severe RSV by **86%**, [Verywell Health+8PMC+8Dove Medical Press+8](http://Verywell Health+8PMC+8Dove Medical Press+8).

In a recent large-scale trial covering the 2022–2023 RSV season, the antibody reduced hospitalization for RSV-associated LRTI by **83.2%** (95% CI 67.8–92.0%) and very severe RSV by **75.7%**, demonstrating consistent efficacy across countries and subgroups, [New England Journal of Medicine](http://New England Journal of Medicine).

**Real-World Data:** Meta-analysis of real-world cohort studies across multiple countries confirmed significantly lower odds of RSV hospitalization (OR 0.17), ICU admission (OR 0.19), and medically attended LRTI (OR 0.25) among infants receiving nirsevimab, [PubMed+1PMC+1](http://PubMed+1PMC+1).

**Regulatory Status & Indications:** Approved in the EU and UK in late 2022, Canada in April 2023, and the US by the FDA in July 2023. Recommended for infants entering their first RSV season and children up to 24 months at high risk during a second season, [publications.aap.org+5Wikipedia+5parents.com+5](http://publications.aap.org+5Wikipedia+5parents.com+5).

**Advantages Over Palivizumab:** A single intramuscular dose provides seasonal protection (~5 months), associated with improved compliance and less healthcare burden. Has ~50-fold greater in vitro potency and a longer half-life (~150 days) compared to palivizumab, [Wikipedia+5Dove Medical Press+5PMC+5](http://Wikipedia+5Dove Medical Press+5PMC+5).

**Safety Profile:** Well tolerated with similar adverse event rates compared to placebo; common effects include local injection symptoms and mild rash, [Verywell Health+15PMC+15PMC+15](http://Verywell Health+15PMC+15PMC+15).

### 5.2.3 Summary Table: Monoclonal Antibody Prophylactics

Agent	Target	Dosing Regimen	Efficacy in Trials	Approved Population
Palivizumab	RSV	F Monthly	↓ RSV hospitalization: 55–78%	High-risk infants (preterm,



Agent	Target	Dosing Regimen	Efficacy in Trials	Approved Population
	glycoprotein	intramuscular		BPD, CHD)
Nirsevimab	RSV F (prefusion epitope)	Single seasonal dose	↓ RSV LRTI by ~71–80%; hospitalization by 77–83%	All infants <8 months; high-risk infants up to 24 mo

### 5.2.4 Clinical and Public Health Considerations

- **Target Populations:** Palivizumab remains standard for select high-risk infants; nirsevimab expands protection to healthy term infants and broader high-risk cohorts, offering greater reach and convenience.
- **Implementation Challenges:** Nirsevimab supply shortages have led to prioritization of infants under six months and those with comorbidities, while palivizumab continues to be used for eligible infants.
- **Cost-Effectiveness:** Single-dose regimens and broad efficacy make nirsevimab potentially more cost-effective compared to multi-dose palivizumab, particularly when extended prophylaxis is considered for longer RSV seasons.
- **Future Directions:** Next-generation mAbs such as clesrovimab, with even longer half-lives and equal efficacy, are under development. Ongoing research focuses on integrating monoclonal prophylaxis with vaccine and antiviral strategies for comprehensive RSV control,

*NCBI+15Dove* *Medical Press+15Wikipedia+15TIME+2parents.com+2Wikipedia+2TIME.*

## 6. IMPLICATIONS FOR PREVENTION

### 6.1 Vaccine Development

Respiratory syncytial virus (RSV) continues to pose a significant global health challenge, especially affecting vulnerable populations such as infants, older adults, and immunocompromised individuals, (Anderson *et al.*, 2013). Despite decades of research, an effective and safe RSV vaccine remains elusive, largely due to the virus's unique biology and the complexities of the host immune response. The development of vaccines against RSV has been hindered by the potential for vaccine-enhanced disease (VED), where vaccination paradoxically exacerbates subsequent natural infection. However, recent advances in molecular virology, immunology, and novel vaccine technologies have rejuvenated vaccine development efforts, leading to several promising candidates that aim to induce durable and protective immunity without triggering harmful immunopathology.

### 6.1.1 Challenges in RSV Vaccine Development

A critical historical hurdle in RSV vaccine development was the experience with the formalin-inactivated RSV (FI-RSV) vaccine in the 1960s. Clinical trials of the FI-RSV vaccine demonstrated that vaccinated infants developed an exacerbated form of RSV disease upon natural infection, characterized by severe pulmonary inflammation and increased hospitalizations and mortality, (Kim *et al.*, 1969). Subsequent immunological investigations revealed that the FI-RSV vaccine failed to elicit potent neutralizing antibodies and instead induced a skewed CD4+ T-helper cell response biased toward a Th2 phenotype, promoting eosinophilic inflammation and immune complex deposition in the lungs, (Graham, 2011; Openshaw and Tregoning, 2005). This immunopathologic response underscored the necessity for RSV vaccines to stimulate a balanced immune response combining effective neutralizing antibodies with a non-pathogenic cellular immunity profile.

#### Further challenges complicating RSV vaccine development include:

- **Immature Infant Immune System:** The neonatal immune system exhibits functional immaturity in antigen-presenting cells and reduced production of interferons, leading to suboptimal vaccine-induced responses. This immunological immaturity reduces the efficacy of certain vaccine platforms in young infants, the group most at risk for severe RSV infection, (Ruckwardt *et al.*, 2019).
- **Maternal Antibody Interference:** Passively acquired maternal antibodies can neutralize vaccine antigens, diminishing the infant's ability to mount an active immune response. This presents a challenge to early life vaccination strategies, necessitating consideration of timing and vaccine design to circumvent interference, (Munoz *et al.*, 2019).
- **RSV Antigenic Diversity and Genetic Drift:** RSV circulates as two major antigenic subgroups, A and B, with continual antigenic drift. Effective vaccines must provide broad cross-protection against these variants to achieve sustained population immunity, (Hall *et al.*, 1991).

### 6.1.2 Promising Vaccine Approaches

To address these challenges, diverse vaccine platforms are under evaluation, many leveraging novel



antigen designs and delivery methods to enhance immunogenicity and safety.

**Live-Attenuated Vaccines:** These vaccines utilize genetically modified RSV strains attenuated to reduce pathogenicity while retaining immunogenicity. They mimic natural infection, stimulating mucosal immunity in the respiratory tract and generating balanced humoral and cellular responses without causing disease symptoms, (Karron *et al.*, 2017). This makes them particularly suited for administration in infants. Several candidates are currently undergoing Phase I and II clinical trials, demonstrating promising safety and immunogenicity profiles.

**Vector-Based Vaccines:** Recombinant viral vectors such as adenoviruses and measles virus vectors have been engineered to express RSV antigens. These vectors efficiently stimulate innate immunity and prime both B and T cell responses. Adenovirus vectors are advantageous due to their ability to be administered via intramuscular or intranasal routes and their manufacturing scalability. Vector vaccines are progressing through clinical trials and have shown encouraging immunogenicity results, (Anderson *et al.*, 2017).

**Subunit Vaccines:** Subunit vaccines focus on purified or recombinant RSV proteins, primarily the prefusion-stabilized fusion (F) glycoprotein. The prefusion conformation of the F protein exposes neutralization-sensitive epitopes not present in the postfusion form, resulting in significantly enhanced induction of potent neutralizing antibodies, (McLellan *et al.*, 2013). Such vaccines generally require adjuvants to boost immune responses and are particularly targeted for older children, adults, and maternal immunization programs. This approach balances safety with strong immunogenic potential, (Nunes & Madhi, 2018).

**mRNA Vaccines:** The success of mRNA vaccines against SARS-CoV-2 has opened new avenues for RSV vaccine development. mRNA vaccines encoding stabilized prefusion F protein can be rapidly developed and modified, producing high levels of neutralizing antibodies and robust T cell responses. Early phase clinical trials are underway, with promising expectations based on the COVID-19 mRNA vaccine platform's safety and efficacy profile, (Pardi *et al.*, 2018; ClinicalTrials.gov, 2023).

### 6.1.3 Maternal Immunization

Maternal immunization presents a promising strategy to protect neonates by boosting transplacental transfer of RSV-specific neutralizing antibodies, thus providing passive immunity during the first months of life when infants are most vulnerable. Clinical studies have demonstrated that vaccinating pregnant women can significantly raise infant antibody levels at birth and reduce RSV-related hospitalizations during early infancy, (Munoz *et al.*, 2019; Madhi *et al.*, 2020). Subunit vaccines based on the prefusion F protein are leading candidates for maternal vaccination, with phase III clinical trials currently evaluating their safety and effectiveness, (PATH, 2023). This approach circumvents the challenges of direct infant vaccination, such as immune immaturity and maternal antibody interference.

### 6.1.4 Future Directions and Considerations

The path to a licensed and effective RSV vaccine will likely involve:

- **Advanced Antigen Design:** Continued optimization of prefusion F protein stabilization to elicit maximal neutralizing antibody titers.
- **Adjuvant Innovation:** Selecting adjuvants that enhance vaccine immunogenicity without inducing a harmful Th2-biased immune response or immunopathology.
- **Population-Specific Strategies:** Tailoring vaccine formulations and schedules to different demographics—infants, pregnant women, and the elderly—to optimize protection.
- **Post-Licensure Surveillance:** Rigorous monitoring for safety signals, especially VED, is critical once vaccines enter widespread use.

**Systems Biology Approaches:** Integrating immunoprofiling, genomics, and bioinformatics can inform rational vaccine design, allowing fine-tuning of immune responses toward protective immunity, (Anderson *et al.*, 2017).

## 6.2 Maternal Immunization

Maternal immunization against respiratory syncytial virus (RSV) is a promising preventative strategy that leverages the natural process of transplacental antibody transfer to provide passive immunity to newborns. Since infants younger than six months are at the highest risk of severe RSV disease but have underdeveloped immune systems that limit their ability to respond effectively to vaccines, maternal vaccination aims to protect infants during this critical early-life period by boosting maternal antibody levels and facilitating their transfer to the fetus, (Munoz *et al.*, 2019).

### 6.2.1 Mechanism and Rationale

During the third trimester of pregnancy, maternal immunoglobulin G (IgG) antibodies are actively transported across the placenta to the developing fetus via the neonatal Fc receptor (FcRn), which selectively binds IgG and facilitates its transfer, (Simister, 2003). This process results in the accumulation of maternal antibodies in the fetal circulation, providing passive immunity at birth. The efficiency of this transfer increases significantly after 28 weeks of gestation, making timing critical for vaccination, (Heath *et al.*, 2017). Vaccinating pregnant women with RSV vaccines, particularly those targeting the prefusion (pre-F) conformation of the RSV fusion protein, substantially increases the levels of neutralizing antibodies in maternal serum. This increase translates into higher concentrations of protective antibodies transferred to the fetus, which can neutralize RSV infection during the first few months of life before infants can mount their own immune response, (McLellan *et al.*, 2013; Munoz *et al.*, 2019).



## Key reasons why maternal immunization is particularly important for RSV include:

- **Early-life vulnerability:** RSV is a leading cause of severe lower respiratory tract infections in infants, with the highest rates of hospitalization occurring within the first 2-3 months of life, a period when infant vaccination is not yet feasible, (Nunes & Madhi, 2018).
- **Immature infant immune system:** Neonates have reduced functional capacity in both humoral and cellular arms of the immune system, limiting their responses to direct immunization, (Ruckwardt *et al.*, 2019).
- **Maternal antibody interference with infant vaccination:** While maternal antibodies may inhibit active infant immune responses to some vaccines, the passive protection they provide is a critical bridge against early RSV exposure, (Munoz *et al.*, 2019).

## 6.2.2 Clinical Trials and Evidence

Several RSV vaccine candidates designed for maternal immunization have advanced through clinical development, most notably subunit vaccines based on the stabilized prefusion RSV F protein, which is known to elicit highly potent neutralizing antibodies, (McLellan *et al.*, 2013). Among these, **Pfizer's RSVpreF vaccine** has demonstrated promising results. The PREPARE Phase II/III trial showed that vaccination during pregnancy induced robust maternal neutralizing antibody responses and efficient transplacental antibody transfer to neonates. Infants born to vaccinated mothers exhibited reduced incidence of medically significant RSV lower respiratory tract infections and hospitalizations in their first 90 days of life, (Pfizer, 2023; Madhi *et al.*, 2020). Similarly, vaccine candidates from **GlaxoSmithKline (GSK)** and **Novavax** have reported positive safety and immunogenicity data in early-phase maternal immunization trials. These vaccines are generally administered during the late second or early third trimester (approximately 28–36 weeks gestation) to optimize antibody transfer before delivery (PATH, 2023).

## 6.2.3 Safety and Implementation Considerations

Safety profiles from maternal RSV vaccine studies are reassuring, with no significant increases in adverse maternal or neonatal outcomes reported. Ongoing monitoring in large-scale trials and post-marketing surveillance remains essential to confirm long-term safety, (Munoz *et al.*, 2019).

## Challenges and considerations in implementing maternal RSV vaccination include:

- **Optimal timing:** Vaccination between 28 and 36 weeks gestation maximizes transplacental antibody

transfer but requires coordination with prenatal care schedules, (Nunes & Madhi, 2018).

- **Vaccine coverage and accessibility:** Successful implementation depends on widespread access to antenatal care and effective communication to improve maternal vaccine acceptance.
- **Integration with other maternal vaccines:** Combining RSV vaccines with routine maternal immunizations (e.g., influenza, Tdap) can improve adherence and optimize healthcare resource utilization.

## 6.2.4 Future Perspectives

Maternal immunization against RSV represents a feasible and effective intervention to reduce RSV-associated infant morbidity and mortality globally. As large phase III trials progress and regulatory approvals are sought, integrating maternal RSV vaccines into standard prenatal care could become a cornerstone of RSV prevention strategies. Additionally, continued research on optimal antigen design, vaccine dosing, and timing will refine this approach. Complementary strategies, such as infant vaccination and monoclonal antibody prophylaxis, may be used synergistically with maternal immunization to broaden protection across different age groups and risk categories.

## 7. CONCLUSION

Respiratory syncytial virus (RSV) remains a significant global health threat, particularly for infants, the elderly, and immunocompromised populations. A comprehensive understanding of RSV pathogenesis and the intricacies of the host immune response is fundamental for the development of effective therapeutic and preventive interventions. RSV's complex interplay with the immune system—including its capacity for immune evasion, the delicate balance between protective immunity and immunopathology, and challenges related to vaccine-enhanced disease—continues to inform current research priorities, (Graham, 2011; Ruckwardt *et al.*, 2019).

## 7.1 Future Research Directions

To fully realize effective RSV prevention and treatment, future research should prioritize several key areas. First, further elucidation of immune correlates of protection is essential to guide rational vaccine design and identify biomarkers predictive of long-term immunity, (Ruckwardt *et al.*, 2019). Next, optimizing combination strategies—such as maternal immunization paired with infant vaccination or monoclonal antibody prophylaxis—could provide layered protection tailored to different risk groups, (Munoz *et al.*, 2019; Domachowske *et al.*, 2021). Additionally, expanding vaccine access and coverage in low- and middle-income countries will require implementation science research focused on health system integration and overcoming socioeconomic barriers, (PATH, 2023). Investigating the impact of emerging viral variants on vaccine efficacy is also critical, as genetic drift may affect antigenic targets, (Hall *et al.*, 1991). Lastly, long-term safety and effectiveness studies, including post-



marketing surveillance, will ensure sustained public confidence and adapt immunization policies as needed.

## 7.2 Summary

In summary, the evolving landscape of RSV research—fueled by advances in virology, immunology, and innovative vaccine technologies—offers unprecedented opportunities to reduce the substantial morbidity and mortality caused by RSV globally. Continued interdisciplinary collaboration, coupled with robust clinical evaluation and equitable implementation strategies, will be essential to translate scientific progress into tangible public health benefits, ultimately safeguarding vulnerable populations from this pervasive respiratory pathogen.

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