

REVIEW ARTICLE

Host Immune Response to Respiratory Syncytial Virus Infection in Children

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Received: 13 March 2024 | **Revised:** 21 August 2025 | **Accepted:** 22 August 2025

Funding: This work was supported by the Natural Science Foundation of Gansu Province (22JR5RA028), the Major Science and Technology Project of Gansu Province (22ZD6NA001), the Science and Technology Program of Department of Science and Technology of Nanjing (ZX20200009), the National Basic Research Program of China (32273019), and the National Natural Science Foundation of China (92169106).

Keywords: adaptive immune response | CD4+ T cells | CD8+ T cells | humoral immune response | innate immune response | respiratory syncytial virus

ABSTRACT

Respiratory syncytial virus (RSV) is one of the leading causes of severe respiratory diseases in children, especially in infants. The immune responses induced by RSV infection are a fairly complex process that can contribute significantly to disease severity. Despite decades of research on RSV, many immune mechanisms remain to be explored. A full exploration of these immune responses can contribute to the discovery of new therapeutic and prophylactic approaches. Despite significant advancements in vaccine development and monoclonal antibody research, effective therapeutic options remain limited. This review focuses on how the immune system reacts when children contract the respiratory syncytial virus. We describe the biological characteristics of RSV, viral-cell interactions, immune evasion, innate immunity (including pattern recognition receptors and inflammatory cells), and adaptive immunity (including CD4+ and CD8+ T cells and humoral immune response). Understanding the complicated immune response to RSV infection is essential for developing effective interventions and vaccine developments. This review aims to deepen the understanding of the impact of Respiratory Syncytial Virus (RSV) on the immune system and to contribute to the advancement of practical therapeutic strategies.

1 | Introduction

RSV was initially discovered in throat samples from a group of 20 chimpanzees suffering from symptoms including runny nose, coughing, and sneezing in 1955 [1]. RSV is a leading respiratory causative agent responsible for lower respiratory tract infections (LRTIs) in children under 5 years old worldwide [2, 3]. RSV LRTIs present with various respiratory symptoms, including fever, rhinorrhea, cough, wheezing, and shortness of breath. More severe cases may be characterized by dyspnea,

nasal flaring, grunting, intercostal and subcostal retraction during inspiration, cyanosis, and apnea. A global review of RSV burden in 2019 estimated that there were 33.0 million related LRTI episodes, 3.6 million associated LRTI hospital admissions, and approximately 26,300 linked LRTI hospital deaths, with 95% of these occurring in middle or low-income countries [4]. Infants under 6 months of age are particularly vulnerable to severe illness and mortality following RSV infection; by the age of 2 years, almost all children are universally infected [5]. Reinfection may still occur with age, but the severity of the

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disease is significantly reduced. However, in the older population, those with comorbidities, and younger children, it can still lead to serious RSV illness [5].

Premature infants, children with cardiac diseases, and immunocompromised patients are high-risk factors for severe RSV infections [6]. In addition, determining how to obtain potent RSV-specific immunity to clear viral infections without leading to exacerbation of inflammatory and immunopathological responses is critical to controlling viral infections. In recent decades, significant advances in the study of the immune response to RSV have facilitated the development of monoclonal antibodies and vaccines [6]. RSV is now a vaccine-preventable disease. For the first time in 2023, the RSV Prefusion F subunit vaccine created by Pfizer was approved by the FDA for active immunization of pregnant women for preventing RSV lower respiratory tract disease in infants from birth to 6 months [7]. It is also worth mentioning that the FDA has authorized it, along with two other vaccines, for use in the elderly with RSV infections under specific conditions [8–10]. Passive immunoprophylaxis is another important strategy for the prevention of RSV infection, especially when vaccines are not yet widely available. The introduction of long-acting RSV monoclonal antibodies has provided more effective protective measures for infants and young children, reducing the risk of RSV infection. But there are still many immune mechanisms that remain unclear, and much of the research has been done in animals and does not reflect the process of infection in humans. This review primarily focuses on the immune response of infants and young children under 5 years of age, particularly those under 6 months, who are most vulnerable to severe RSV infections. By offering current information on the immunological response to RSV infection, it will serve as the foundation for future preventative and therapeutic tactics.

2 | Biological Characteristics of RSV

RSV belongs to the Orthopneumovirus genus and is a member of the Pneumoviridae family. The RSV virion is a polymorphic

enveloped virus with spherical particles ranging from 60 to 300 nm and filamentous particles ranging from 50 nm in diameter and 1–10 µm in length. The genome, with a length of approximately 15,200 nt, contains a single-stranded nonsegmented negative-sense RNA in the order 3′ NS1-NS2-N-P-M-SH-F-G-M2-L 5′ [11], consisting of 10 genes (Figure 1A) encoding 11 proteins L [12] (Figure 1B). The proteins present in the virion consist of three surface proteins (small hydrophobic SH, attachment G, and fusion F), two nonstructural proteins (NS1 and NS2), one nucleocapsid protein N, three nucleocapsid-associated proteins L, P, and M2.1, one M2.2 protein, and one matrix protein M (as shown in Table 1). Figure 1B below is the RSV structure simulation diagram.

Nonstructural proteins NS1 and NS2 mediate signal transduction within the innate immune response and inhibit Type 1 interferon (IFN-I) production [13]. The N protein is the major capsid component encapsulating the viral genomes that serve as an RNA production template [12, 14]. The N, L, and P proteins form the RSV ribonucleoprotein complex that facilitates the process of viral RNA transcription and replication [11]. As a polymerase component, protein P combines with N, M2-1, and L proteins to form polymerase and mediate the interaction between nucleocapsid and polymerase [7]. The polymerase subunit protein L is required for viral nucleic acid transcription and replication and is an RNA-dependent RNA polymerase participating in the replication of the viral RNA genome and the transcription of mRNA [14]. Matrix proteins (M) are endocytic proteins that are significant in forming viral particles and play an instrumental role in inhibiting the transcription process in host cells [15]. The nucleoprotein-associated protein M2-1 regulates viral transcription [16]; M2-2 regulatory protein inhibits RNA synthesis during viral particle assembly [16]. Attachment protein (G) assists viral adhesion to host cells, interferes with antibody-mediated neutralization reactions, and reduces the effective concentration of RSV-neutralizing antibodies [17]. Fusion protein (F) mediates viral particle binding to host receptors and aids viral particle entrance into host cells [18]. On the other hand, the F protein induces virus-infected cells to fuse

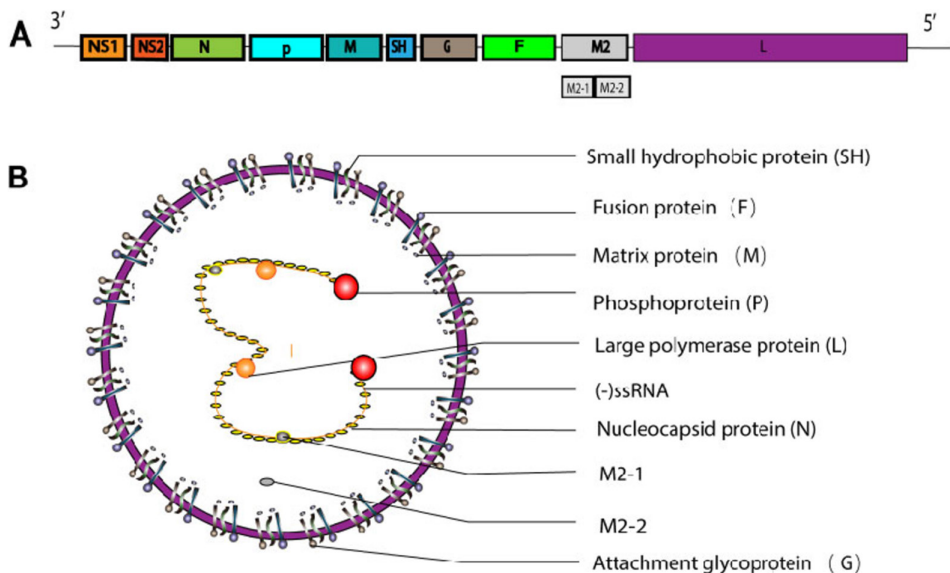


FIGURE 1 | RSV gene structure simulation map (A) and RSV structure simulation diagram (B).

TABLE 1 | Main proteins encoded by the RSV genome and their functions.

Proteins	Abbreviations	Protein length/aa	Function
Nonstructural proteins 1	NS1	139	Inhibiting the activation of the Type I interferon response [13]
Nonstructural proteins 2	NS2	124	Inhibiting the activation of the Type I interferon response [13]
Nucleocapsid protein	N	391	Regulating viral RNA transcription and replication [12, 14]
Phosphoprotein	P	214	Regulating viral RNA transcription and replication [12, 14]
Large protein	L	2165	Regulating viral RNA transcription and replication [14]
Matrix protein	M	256	Inhibiting the transcription process, mediating virion assembly [15]
The matrix protein2-1	M2-1	194	Mediating virions assembly [16]
The matrix protein2-2	M2-2	88	Mediating RNA synthesis [16]
Glycoprotein	G	298	Regulating viral adhesion to host cells, interfering with antibody-mediated neutralization reactions [17]
Fusion protein	F	574	Facilitating cellular entrance in the host cells [18]
Small hydrophobic protein	SH	64	Increasing the permeability of the host cell membrane, inhibiting apoptosis in infected cells [19]

with the surrounding cells, forming syncytia [16]. SH protein exists on the surface membrane of the virus [19]. It enhances host cell membrane permeability and prevents them from apoptosis [19]. RSV is classified into two subgroups, A and B, based primarily on the significant genetic variability and antigenic diversity of the G protein, which also serves as a key target antigen for host immune responses [19].

3 | Viral-Cell Interactions

The airway epithelial cells (AECs) and their overlying mucus layer form the primary physicochemical defense against RSV invasion. RSV exhibits a pronounced tropism for Type I alveolar pneumocytes and ciliated columnar epithelial cells, which also serve as the primary sites for RSV replication [20]. Notably, the differentiation status of AECs critically modulates viral susceptibility: Polarized AECs demonstrate significantly higher infection rates compared to their undifferentiated counterparts [21]. The process of viral entry into cells involves two critical glycoprotein interactions: First, the G protein contributes to RSV's attachment to the host cells. Then, G and F proteins interact with unique viral receptors on the cell membrane. The interaction facilitates the viral envelope and host cell membrane convergence by inducing a fusion form transition, thereby enabling the virus to enter the host cells. These receptors include Toll-like receptor 4 (TLR-4), heparan sulfate membrane proteoglycan receptors (HSPGs), intercellular adhesion molecule-1 (ICAM-1), epidermal growth factor receptor (EGFR), nucleolin protein, annexin II, chemokine CX3 receptor 1 (CX3CR1), and insulin growth factor 1 receptor (IGF1R) [22, 23]. Heparan sulfate proteoglycans (HSPGs) are ubiquitously expressed on the basement membranes of most mammalian cell types and in the extracellular

matrix and can serve as attachment factors for some viruses [22]. However, HSPGs are barely expressed on the apical surface of AECs in vivo, suggesting that other receptors are likely necessary for RSV infection [24]. Upon viral entrance, intracellular and extracellular pattern recognition receptors (PRRs) recognize the pathogen and initiate innate immune responses. Infection of AECs with RSV consequently induces the secretion of adhesion molecules, chemokines, and proinflammatory cytokines, including IFN-I (IFN- α/β), IFN-III (IFN- λ), IL-1 β , IL-6, IL-8, tumor necrosis factor (TNF)- α , CXCL6, CXCL10, regulated upon activation normal T cell expressed and secreted factor (RANTES), and macrophage inflammatory protein-1 α (MIP-1 α) [22, 23, 25, 26]. Chemokines and cytokines secreted by AECs, in turn, recruit a host of effector molecules, the innate and adaptive immune cells, which come into direct contact with RSV and resist viral invasion, ultimately leading to inflammatory responses. These inflammatory responses include the destruction of bronchial ciliated epithelial cells, peribronchial lymphocytic infiltration, and epithelial cell proliferation and necrosis [27].

4 | Immune Evasion

Although the body acquires innate and adaptive immune responses to its infection, RSV employs various strategies to evade immune defenses, delay viral clearance, and induce immune tolerance. The ability of RSV to be repeatedly infected without extensive mutation may be due to the ability of its structure and metabolites to evade immunity. The most intensively studied immunomodulatory mechanism is the inhibitory effect of the RSV nonstructural protein NS1/NS2 on TYPE I interferons (IFN I). Still, other RSV proteins, such as surface fusion protein F,

surface attachment protein G, and nucleoprotein N, have also shown significant immunomodulatory effects.

NS1 and NS2 proteins prevent the production of IFN and inhibit the downstream signaling pathway of IFN- α/β [28]. Research has demonstrated that the NS1 protein colocalizes with essential components of the IFN I pathway, such as the CREB binding protein (CBP), IRF-3, and mitochondrial signaling protein (MAVS), inhibiting the signaling pathway [29]. Similarly, NS2 binds to the N-terminal caspase recruitment domain (N-CARD) of RIG-I, inhibiting its ability to interact with MAVS [30]. Additionally, research has shown that NS1 and NS2 mediate the proteasome degradation mentioned above, thereby decreasing the signal transducer and activator of Transcription 2 (STAT2) [31]. Another essential protein that affects innate immune evasion is G protein. G protein is structurally similar to CX3CL1. CX3CL1 combines with the CX3CR1 receptor on the surface of Natural Killer (NK) cells, Cytotoxic T Lymphocytes (CTL), and $\gamma\delta$ T cells to exert cytotoxicity and clear the virus, thus inhibiting the killing of the virus. G protein inhibits such effects [32, 33]. RSV-infected Dendritic Cells (DCs) display impaired assembly of immune synapses, which may be regulated by protein N. Expression of protein N in DCs and epithelial cells is associated with a decrease in major histocompatibility complex (MHC) antigenic determinants on the cell surface [34].

5 | Innate Immune Response

Upon RSV entry into the airways, the host's innate immune response is rapidly initiated through coordinated cellular interactions. Following viral invasion of AECs, resident alveolar macrophages and Plasmacytoid DC (pDC) are activated with recruitment of neutrophils to the infection site (Figure 2). This cascade triggers a robust production of proinflammatory mediators

that serve dual antiviral functions: directly suppressing viral replication and orchestrating the recruitment and activation of immune cells. IFN-I (IFN- α/β) and IFN-III (IFN- λ) establish an antiviral state by upregulating interferon-stimulated genes (ISGs) [35, 36], whereas TNF- α and IL-6 synergistically enhance epithelial barrier integrity [25, 26]. The chemokines CCL5/RANTES and CXCL10/IP-10 serve as critical chemokines, mediating the infiltration of CD8+ T cells and NK cells to eliminate virus-infected cells [25, 37]. At the molecular level, ISG-encoded effectors execute stage-specific antiviral functions: ISG15 conjugates to viral nucleocapsid proteins, disrupting RSV assembly [38]; OAS/RNase L degrades viral RNA through 2'-5' oligoadenylate-mediated ribonuclease activation [39]; PKR phosphorylates eIF2 α to block viral translation initiation, selectively halting RSV protein synthesis [40]. The innate immune response, initiated by PRR-PAMP interactions, establishes both immediate viral containment and immune microenvironment remodeling, as detailed in the following section on PRRs and inflammatory cells.

5.1 | Pattern Recognition Receptors

The host immune cells harbor various PRRs on cell membranes and in endosomal membranes, lysosomal membranes, and cytoplasm. PRRs have been classified into three types: toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) (Figure 3) [26]. Among them, TLR2, TLR3, TLR4, TLR6, TLR7, RIG-I, and NOD2 can recognize RSV PAMPs.

TLRs can be found in various cells, such as macrophages, DCs, epithelial cells, neutrophils, and eosinophils. TLR's activation is

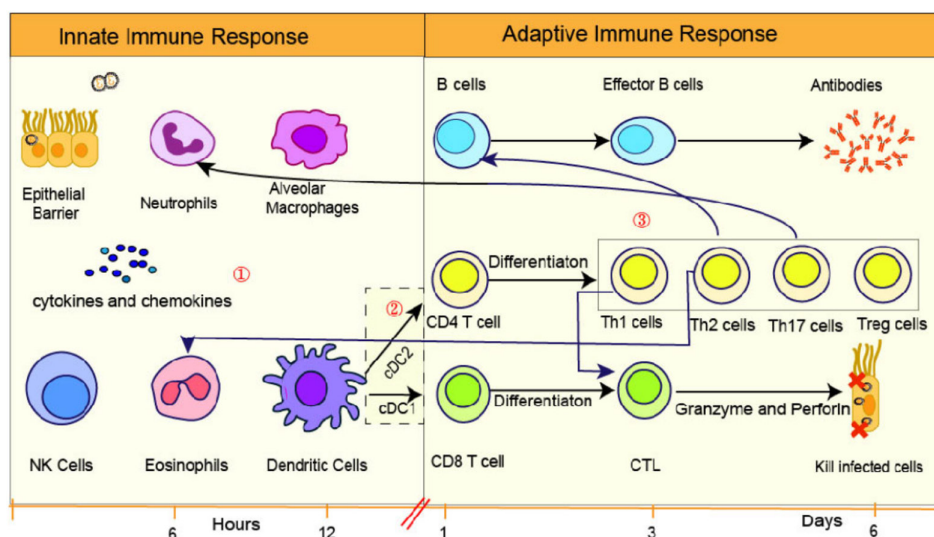


FIGURE 2 | Overview of innate and adaptive response during RSV infection. The following procedures are included in the immune response's schematic diagram: ① The innate immune response: host cell infection recruit neutrophils, macrophages, NK cells, and other immune defense cells. It also releases various cytokines and chemokines and initiates an immunological defensive response. This swiftly starting process aids in the early elimination of the virus during the illness and prepares for the adaptive immune response. ② The dotted box shows antigen presentation: cDC1 activates CD8+ T cells and mediates pathogen clearance; cDC2 stimulates CD4+ T cells and helps polarize helper T cells. ③ The adaptive immune response includes humoral and cellular immune responses. Abbreviations: cDC1, conventional DC1; cDC2, conventional DC2; CTL, cytotoxic T lymphocyte.

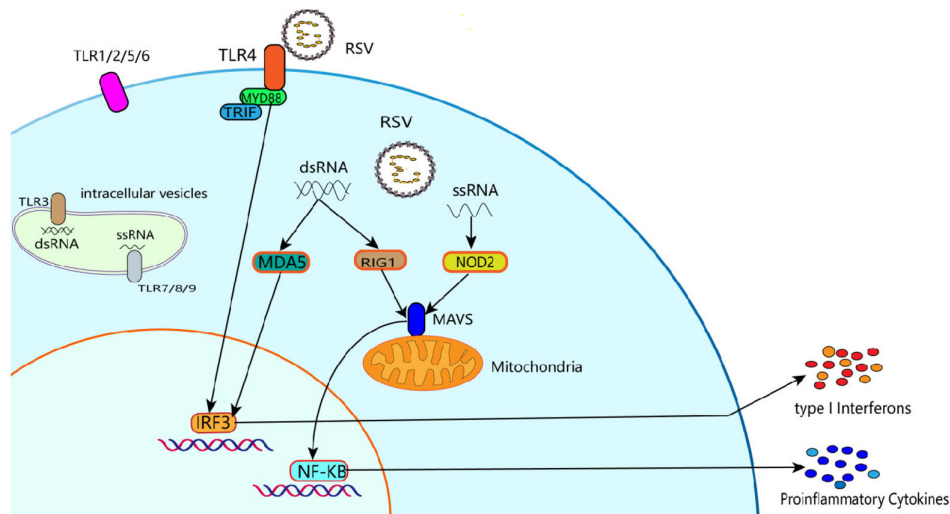


FIGURE 3 | The major well-known pattern recognition receptors (PRRs) and signal pathways in innate immune response. Abbreviations: dsRNA, double-stranded RNA; IRF3, interferon regulatory factor 3; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary response protein MyD88; NF- κ B, nuclear factor kappa-B; NOD2, nucleotide-binding oligomerization domain 2; RIG-I, retinoic acid-inducible gene I; RSV, respiratory syncytial virus; ssRNA, single-stranded RNA; TLR, toll-like receptor; TRIF, TIR domain-containing adaptor molecule.

essential for innate immune defense initiation. Currently, there are 11 well-known human TLRs. TLR1, TLR2, TLR4, TLR5, and TLR6 are involved in RSV recognition when they come into contact with hRSV molecules and products (e.g., LPS or RSV fusion [F] proteins) on the cell surface. TLR3, TLR7, TLR8, and TLR9 are expressed in intracellular vesicles and recognize viral nucleic acids. TLR4, the most studied and significant PRR, recruits myeloid differentiation factor (MyD88) and TIR domain-containing adaptor molecule (TRIF), which allows interferon regulatory factor (IRF) or nuclear factor kappa-B (NF- κ B) into the nucleus, regulating proinflammatory cytokines, IFN, and TNF's production and release, thus producing the corresponding inflammation [41]. TLR4 polymorphisms were linked to RSV infection susceptibility [42], and RSV virus clearance was retarded in TLR4-deficient animals [43].

The RLRs, including MDA5 and RIG-I, were found in the cytoplasm. They interact with MAVS [44], recognize ssRNAs and short dsRNAs of pathogenic origin, trigger downstream signaling pathways, and promote the production of proinflammatory cytokines and type I IFN [45, 46]. According to a clinical study about RSV-infected infants with bronchiolitis, RSV viral load is significantly and positively linked to RIG-I mRNA levels [47]. Vissers et al. [48] demonstrated that RIG-I expression was up-regulated in healthy volunteers after RSV infection. According to these findings, RIG-I seems to be especially critical for the host immune response against RSV infection.

The NLRs are cytoplasmic sensors that detect ssRNA. They participate in various intracellular functions, including inflammasome formation, transcriptional activation, signal transmission, and autophagy [13]. After the infection of RSV, NOD2, a subfamily member of the NLRs, could recognize ssRNA and activate the production of IRF3 and IFN through NF- κ B signaling pathways [49]. It has been shown that NOD2-deficient mice have reduced IRF3 activation and IFN-I production and increased susceptibility to RSV and lung disease compared to control mice

[50]. NLRP3 (NOD leucine-rich repeat [LRR]-containing protein 3) is another NLR family member. It has been shown that NLRP3-mediated excessive inflammation causes lung tissue destruction; NLRP3 is considered a viable therapeutic target for RSV infection protection [51].

5.2 | Inflammatory Cells

5.2.1 | Neutrophils

Neutrophils are among the first immune cells to arrive at the infection site. High numbers of neutrophils were found in autopsy lung tissue from a deceased case of RSV-induced ALRI, emphasizing the possible significant involvement of neutrophils in the development of RSV illness [52]. They promote RSV killing by releasing neutrophil extracellular traps (NETs) [53]. Severely ill patients with viral respiratory infections exhibit a considerable deficiency of neutrophils in their bloodstream [54, 55]. Neutrophils have antimicrobial effects, mainly via phagocytosis, degranulation, and NET formation [56]. In addition, by presenting CD8+ T cells with viral antigens, neutrophils can modulate the adaptive immune response and exert an indirect antiviral effect [57, 58]. The equilibrium between pulmonary immunopathology and neutrophil-induced antimicrobial effects may determine the outcome of RSV infection [59]. This equilibrium is inverted in patients with extensive RSV infection in favor of a pathologic response [59].

5.2.2 | Alveolar Macrophages

Alveolar macrophages (AMs) are located in the walls of the alveolar space. They are imperative components of the innate immune barrier of the respiratory tract and serve pivotal functions in the phagocytosis of pathogens and antigen presentation [60]. According to a mouse study, RSV infection triggers alveolar

macrophage necroptosis, a process that relies on the participation of receptor-interacting protein kinase 1, receptor-interacting protein kinase 3, and the pseudokinase mixed-lineage kinase domain-like, and is mediated by autocrine tumor necrosis factor (TNF), which may drive RSV disease pathogenesis [61]. AMs undergo polarization upon infection with RSV, forming two distinct phenotypes: M1-like and M2-like macrophages. Polarized AMs regulate the differentiation of T lymphocytes and the inflammatory response [62], strongly correlated with chronic airway hyperresponsiveness (AHR). Thus, anti-AM immunotherapy is being investigated as a potential preventative measure against the asthma associated with RSV infection [62].

5.2.3 | Dendritic Cells

Dendritic cells (DCs), as the most prominent antigen-presenting cells in the body, stimulate the initial T-cell response, secrete cytokines and chemokines, and further participate in immune regulation, which contributes significantly to the pathogenesis of infectious and immune-related diseases. The DCs can be categorized into pDC, conventional DC1 (cDC1), and cDC2 [63]. Several studies revealed that cDC1 is the first subtype to activate CD8+ T cells that mediate pathogen elimination [64, 65]. Compared with adult mice, neonatal mice infected with RSV are functionally defective in lung cDC1 populations [66]. Through antigen presentation, cDC2 stimulates CD4+ T cells, aiding in the polarization of helper T cells and their subsequent development into Th2, Th17, and T follicular helper cells [67–69]. IFN-1 is primarily produced by pDCs and is necessary for RSV-specific CTL to protect the host from severe RSV illness [70, 71]. When RSV-infected neonatal mice were administered TLR agonists, RSV-specific CD8+ T cells increased due to an elevation of CD86 expression in DCs [72]. This study sheds light on anti-RSV treatment and vaccine development tactics [73].

5.2.4 | Eosinophils

Evidence shows eosinophils are active during the RSV LRTI acute phase. In research involving infants older than 2 months, researchers observed a considerable suppression of eosinophil counts in children with RSV-caused upper respiratory tract infections (URI). Oppositely, infants with bronchiolitis had higher eosinophil counts than those with URI alone, albeit not as high as the same-aged healthy children, suggesting that a subset of infants maintain (or are unable to suppress) peripheral blood eosinophilia [74]. Another animal study demonstrated that RSV infection in neonates enhanced lung eosinophil numbers and heightened allergen stimulation in allergic asthma [75]. Levels of the eosinophil chemokines CCL-5 (RANTES), ECP, and esotaxin have been shown to correlate with the number of eosinophils in the respiratory tract and to increase with the transition from acute to convalescent illness in patients with RSV LRTI [76, 77].

5.2.5 | Natural Killer (NK) Cells

NK cells comprise 10%–20% of the resident lymphocytes of the human lung [78]. Upon RSV infection, NK cells kill

pathogen-infected cells primarily by activating extracellular death receptors and the exocrine release of cytosolic particles. At the same time, NK cells mediated by NKG2D produce excessive IFN- γ , causing lung immune injury [79, 80]. As IFN- γ gradually accumulates, activated NK cells can drive CD8+ T cell responses, contributing to lung immune injury. NK cells perform different roles at different infection stages, contributing to early-stage viral clearance and causing late-stage lung injury [81]. Evidence suggests severely RSV-infected infants have fewer NK cells than mildly infected or healthy ones [82, 83]. An in vitro study showed that antibody-enhanced RSV infection of NK cells triggers a range of proinflammatory responses, including increased viral load, NK cells, and IFN γ expression, which may lead to immunopathology [84]. Experiments have demonstrated that in vitro RSV-specific maternal antibodies stimulate NK cells, and antibody-mediated activation and glycosylation of NK cells can protect against severe RSV illness [85].

6 | Adaptive Immune Response

Upon hRSV infection, innate immune response activation can initiate a targeted acquired immune response (i.e., the adaptive immune response) consisting of cellular and humoral immune responses (Figure 2). The cellular immune response comprises CD8+ and CD4+ T cells. CD8+ T cells are essential killer effector cells that kill target cells upon differentiation, whereas CD4+ T cells can assist other lymphocytes by promoting the differentiation of B cells into plasma cells and memory B cells and activating CTLs [86]. The humoral immune response comprises B cells and antibodies, and adaptive immunity is essential to eradicate RSV and create long-term memory to stave off infections in the future [64].

6.1 | CD4+ T Cells

The impact of CD4 T cells on disease severity is substantial, as they are instrumental in both immune response induction and regulation [87]. CD4 T cells can be classified into various functional subpopulations according to their expressed cytokines, including Th1 (T helper 1), Th2 (T helper 2), Th17 (T helper 17), Treg (T regulatory), and Tfh (T follicular helper) cells.

Th1 cells are proinflammatory and essential to the body's anti-intracellular pathogen infection. It secretes proinflammatory products including IFN- γ , IL-1, IL-12, IL-2, IL-18, and TNF- α [76]. These substances mediate cytotoxic immune responses, assist in antibody generation, and delay hypersensitivity reactions. The quantities of IFN- γ and the soluble interleukin-2 receptor (sCD25), indicators of the Th1 response, rise in response to RSV infection [88, 89]. In infants with RSV LRTI, circulating IL-12 and IFN- γ have lower levels in severe disease than in those with mild infections [90, 91]. CXCR3 is a crucial chemokine receptor expressed by Th1 cells and is widely used to identify human Th1 cells.

Th2 cells primarily contribute to host protection against large extracellular pathogens, and parasites are the typical targets. Th2 cells promote the release of proinflammatory cytokines such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, leading to IgE

production and allergic reactions [92]. In children with RSV LRTI, IL-6 and IL-10 levels in serum are elevated and correlate with disease severity [93]. In addition, Th1 and Th2 cells can inhibit and reduce each other's activation levels [94]. These data show an imbalance in Th1/Th2 in children with hRSV LRTI, which relates to the severity of infection.

Th17 cells primarily refer to type III immune responses against extracellular pathogen invasion and various autoimmune diseases [95]. Furthermore, they have been linked to allergic inflammation, such as asthma [96]. They are distinguished by the production of IL-17A, IL-17F, and other similar cytokines [97]. A study shows that IL-17 stimulates the release of cytokines that induce neutrophil migration and further recruit neutrophils to sites of inflammation in the lungs, thereby clearing the virus and acting as a defense against RSV infection [98]. In RSV infection-induced asthma experiments, studies showed that RSV enhances IL-17A protein production [99] and mucus-associated protein expression [100]. Nevertheless, the allergic airway inflammation was attenuated in IL-17 receptor knock-down mice compared to the control group [101].

Treg cells are a specific subset of lymphocyte populations that perform immune regulatory functions and maintain immune homeostasis. It has been demonstrated that infants with RSV infection have significantly reduced peripheral blood Treg counts and poorly regulated host immune responses, leading to the development of severe RSV infections [102]. Treg knockdown mice showed higher airway constriction, increased morbidity, and delayed viral clearance. Their illness severity also increased [103]. In animal studies, RSV affects the host lung microenvironment and impairs Treg cell function, which is related to increased susceptibility to asthma after RSV infection [104]. Recent *in vivo* experiments suggest that RSV infection promotes asthma susceptibility by increasing the Th17/Treg ratio rather than the imbalance of Th1/Th2 [96].

Tfh cells aid B lymphocyte maturation, germinal center formation, and high-affinity antibody production [105]. Although Tfh cells were first identified in the tonsils, they are also present in peripheral blood, where they are referred to as circulating Tfh cells. Severe RSV infections had fewer circulating Tfh cells and lower plasma IL-21 levels than moderate cases [106]. IL-21 therapy restores Tfh cell function and enhances the production of neutralizing antibodies in the context of RSV infection [107].

6.2 | CD8+ T Cells

Following exposure to RSV, naive CD8 T lymphocytes are activated by DCs through antigen presentation, inducing the apoptosis of the target cell by the secretion of perforin and granzymes, which are vital for virus clearance, preventing RSV secondary infection, and inducing immunopathology after RSV infection. Several animal experimentations have demonstrated that the peak of CD8 T cell growth in the lungs corresponds to the complete clearance of the virus from the lungs [108, 109]. Infants with severe RSV pneumonia who need mechanical ventilation had fewer systemic effector CD8+ T cells at the peak of their illness, but with time, their CD8+ T cell numbers gradually increased [110]. After the recovery phase of RSV infection, most

CD8 T cells experience apoptosis, and less stable memory T cells remain; these virus-specific memory CD8 T cells are mainly enriched in the lungs and respiratory tracts and protect against secondary RSV exposure [111, 112].

Additionally, CD8 T cells induce immunopathological damage by excreting IFN- γ and TNF following a primary or secondary RSV infection [113]. A clinical trial study about severe RSV-infected infants suggested an increase in Tc2 cells (CD8+T cells that express IL-4), a decrease in Tc1 cells (CD8+T cells that express IFN γ), and a decrease in IL-17 concentrations in nasal aspirates. This experiment allows the assumption that Tc1 and Tc17 (CD8+T cells that express IL-17) are associated with a shorter duration of hospitalization and perform a protective role, whereas Tc2 cells may be implicated in pathological mechanisms [114].

Tissue-resident memory CD8+ T (Trm) cells are a critical component of the immune response to RSV, providing immediate defense at the site of infection in the respiratory tract [115]. These cells are long-lived and do not recirculate, allowing for rapid response upon reexposure to the virus. RSV-specific CD8+ Trm cells have been shown to accumulate in the airways and lung parenchyma, and their presence correlates with reduced disease severity and viral loads [115]. This implies that these cells could play a significant role in early viral clearance and disease amelioration. The functionality of RSV-specific CD8+ T cells in the blood is limited, with modest frequencies of cytokine-producing cells and a tendency to produce only a single cytokine. In contrast, Trm cells in the airways may exhibit innate-like sensing functions and could potentially have a more robust effector capacity [116].

6.3 | Humoral Immune Response

Humoral immune response is characterized by the production of antibodies by B cells. Upon activation by antigens, naive or memory B cells proliferate and develop into effector B cells and then release antibodies. B cells are activated in lymph nodes and the spleen. During viral infections, B lymphocytes produce antibodies that are tailored to the specific virus, which neutralize the pathogen and impede its entry into cells by obstructing the viral attachment sites. Consequently, B lymphocytes and the antibodies they generate are crucial for the immune response, as they initiate protective mechanisms against the virus. RSV-infected infants were found to have increased levels of circulating B cells [77, 117]. Studies also indicate that these B cell counts quickly decline once the virus is eradicated [118]. In infants with fatal RSV bronchiolitis, plasma cells secreting IgM, IgG, and IgA and CD20+B cells were markedly elevated in the lung tissues [75]. B cell-activating factor (BAFF) derived from infected epithelial cells is a major determinant of mucosal IgA immunity in infants after RSV infection [118]. In infants with severe RSV LRTI, pulmonary BAFF levels are elevated [117]; animal experiments showed similar results [119]; lung tissue showed elevated production of B cell homeostatic chemokines, including CXCL12, CXCL13, CCL19, and CCL21, as well as BAFF [120].

Neutralizing antibodies against RSV primarily target F proteins and G proteins [121]. These antibodies, mainly in the form of

IgA and IgG, mediate viral clearance and offer durable protection against RSV attacks based on various mechanisms, including antibody-dependent cellular phagocytosis (ADCC), the induction of virus-specific antibodies, and the neutralization of viral particles [121]. RSV-specific neutralizing antibodies can be identified in humans within 2 days following infection, primarily targeting the RSV G protein and F protein (both prefusion and postfusion conformations) [122, 123]. G-protein-induced antibodies protect only against patients with the same subtype of RSV, whereas F-protein-induced IgG antibodies are cross-protective against different virus subtypes [122, 123]. The RSV F protein, which is the predominant antigenic target for developing neutralizing antibodies or vaccines, has six major antigenic sites, known as sites Ø, I, II, III, IV, and V [124]. Sites I–IV are conserved in both the prefusion and postfusion conformations of the F protein, whereas sites Ø and V are exclusively exposed in the prefusion state [124]. Notably, Site Ø, which serves as the epitope for the long-acting monoclonal antibody nirsevimab, is the major contributor to neutralizing activity [125].

Infants' antibodies specific to the RSV F protein exhibit low affinity and neutralization capacity due to limited somatic hypermutation, which may contribute to the immaturity of their immune response [126]. However, as children grow older, their levels of RSV-specific antibodies gradually increase. Specifically, children under the age of 2 have relatively low levels of IgG antibodies against the pre-F protein of RSV. But between the ages of 2 and 5, these antibody levels rise significantly and remain stable into adulthood [127]. Maternal IgG antibodies, which are transferred transplacentally to the fetus, confer essential protection during the first few months after birth [128]. Studies have shown that higher levels of maternal antibodies are associated with a lower risk of RSV infection and hospitalization in infants [128]. However, these maternal IgG antibodies reduce the IgG response of host cells to the RSV G protein and modulate local IFN production, as demonstrated in both murine models and human cohorts [32, 129]. Significantly, antiprotein F antibodies in young children's adenoids demonstrate higher binding affinity and stronger RSV neutralization than in blood circulation [130]. This suggests that local mucosal immunity may play a more significant role in controlling RSV infection than systemic immunity. Furthermore, for infants under the age of 6 months, secretory IgA obtained from maternal breastfeeding plays a vital protective role, providing dual defense against both primary infection and reinfection in the upper respiratory tract through specific viral neutralization mechanisms [131]. It is possible that the IgE reaction to RSV F and G glycoproteins is harmful. Compared to patients without RSV bronchiolitis and infants who were not infected, infants with RSV bronchiolitis had a higher percentage of CD23 (IgE receptor) B cells in their peripheral blood [132]. Elevated serum IgE levels were linked to the severity of RSV bronchiolitis or pneumonia in children, and it has been experimentally shown that IgE concentrations are related to wheezing during RSV LRTI [133, 134]. Maternal vaccination effectively stimulates the maternal immune system to generate high concentrations of RSV-specific neutralizing antibodies. These antibodies are efficiently transferred to the infant through the placenta. Notably, they not only achieve higher levels in the infant but also retain their efficacy for an extended duration, offering robust and durable protection against RSV infection [135]. These maternally derived antibodies offer

robust protection for infants for up to 6–12 months after birth, bridging the critical “window period” when maternal antibodies decline and the infant's own adaptive immune system is still maturing [135]. This highlights their remarkable long-term protective potential. Similarly, the long-acting monoclonal antibody nirsevimab, which targets site Ø on the RSV F protein, has been shown to provide effective protection against severe RSV infection during an infant's first RSV season [125]. The success of nirsevimab underscores the importance of targeting specific antigenic sites on the F protein to elicit potent neutralizing responses.

7 | Conclusions

RSV infection remains a dramatic global health and economic burden, especially in low- and middle-income countries. RSV infection-induced immune responses are complicated and can contribute significantly to disease severity. Despite decades of research on RSV, many immune mechanisms remain to be explored. Currently, mainstream therapeutic modalities remain supportive of care. Exploring the host immune response during RSV infection contributes to the development of novel RSV vaccines and RSV-specific therapies. Researchers have had repeated failures in pursuing a successful hRSV vaccine, beginning with creating the first formalin-inactivated vaccine, FI-RSV, in the 1960s. Fortunately, research on RSV vaccinations and monoclonal antibodies that target the prefusion F protein conformation has advanced significantly in recent years. On August 21, 2023, the RSV Prefusion F Vaccine (RSVpreF; ABRYSVO) became the first approved maternal vaccine to protect infants against RSV illness in America [7]. Maternal vaccination is an excellent and possibly the best strategy for prevention of severe RSV infection in infants residing in low-resource countries where access to advanced medical care may be limited. The landscape of RSV prophylaxis has been further enhanced by monoclonal antibodies like palivizumab [136], which has been instrumental in high-risk infant populations. Nirsevimab and clesrovimab are long-acting monoclonal antibodies mainly used to prevent RSV infections in infants during their first RSV season [137, 138]. This progress underscores the evolution of RSV prevention strategies, optimizing both efficacy and patient compliance. However, the scalable deployment of these interventions in low-income settings is impeded by affordability constraints and the intricacies of integrating novel prophylactics into existing healthcare frameworks. Future endeavors must address these disparities to realize the global health potential of RSV immunoprophylaxis, particularly in regions with the most pronounced disease burden [139]. Gaining insights into the complex interplay between RSV and the immature immune system of children is crucial for advancing our comprehension of the pathophysiology underpinning RSV-associated disease severity. It provides a foundation for the development of prophylactic and therapeutic strategies, including the design of vaccines that can safely and effectively induce protective immunity without enhancing disease, as historically observed with early vaccine candidates. By translating these findings into clinical practice, we can potentially reduce the substantial morbidity and mortality attributed to RSV in infants and young children worldwide, ultimately informing public health policies and medical guidelines aimed at mitigating the impact of RSV infections.

Author Contributions

Gang Chen: writing – original draft, conceptualization. **Xiuchang Ma:** supervision. **Jinhuan Wu:** supervision. **Yi Yan:** writing – original draft. **Wenxian Qian:** methodology. **Apeng Chen:** conceptualization, writing – review and editing. **Changhua Yi:** conceptualization, project administration, funding acquisition. **Man Tian:** conceptualization, writing – review and editing.

Acknowledgments

This work was supported by the Natural Science Foundation of China (92169106), the Science and Technology Program of the Department of Science and Technology of Nanjing (ZX20200009), the National Basic Research Program of China (32273019), the Natural Science Foundation of Gansu Province (22JR5RA028), and the Major Science and Technology Project of Gansu Province (22ZD6NA001). All figures were created with Adobe Illustrator.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Peer Review

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/irv.70156>.

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