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The immunological landscape of viral infections in asthma: mechanistic insights and therapeutic paradigm shifts

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Abstract

Asthma is a common chronic respiratory disease in which respiratory viral infections—particularly rhinoviruses—are closely intertwined with disease manifestations. Such infections contribute substantially to pediatric asthma episodes and to a notable proportion of adult asthma presentations, reflecting the underlying immune dysregulation characteristic of asthma. Key components of the innate antiviral response—including the airway epithelium, dendritic cells, and natural killer cells—exhibit diminished antiviral activity in asthma, a deficiency that permits greater viral replication and persistence. Concurrently, individuals with asthma frequently exhibit type 2 immunity, an immune profile that drives IgE production, eosinophilic inflammation, and airway hyperresponsiveness. Children are particularly susceptible to the immunological impacts of respiratory viral infections in the context of asthma, potentially due to immune immaturity and less robust early-life antiviral defenses. Crucially, the crosstalk between innate and adaptive immunity dictates the severity of asthma-related clinical manifestations during viral infections: a compromised antiviral innate response, when paired with a type 2-skewed adaptive immune environment, can synergistically promote severe airway inflammation and airflow obstruction. Although inhaled corticosteroids (ICS) remain a cornerstone of maintenance therapy for preventing asthma exacerbations, ICS-based therapy does not fully prevent virus-associated exacerbations, particularly in patients with type 2-low, neutrophil-predominant, or severe uncontrolled asthma. By contrast, oral or systemic corticosteroids remain the first-line treatment for acute exacerbations, highlighting the need to distinguish maintenance ICS therapy from acute systemic corticosteroid use. Future therapeutic strategies should therefore prioritize enhancing antiviral immune responses and modulating virus-induced neutrophilic inflammation to better prevent and mitigate asthma-related clinical challenges associated with viral infections.

Keywords: asthma, virus, immune response, immunotherapy

Introduction

Asthma is one of the most common chronic respiratory diseases worldwide and is characterized as a

heterogeneous disorder with variable respiratory symptoms and fluctuating airflow limitation^[1]. Epidemiological studies indicate that approximately 60%–80% of childhood asthma episodes and

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50%–70% of adult asthma exacerbations are associated with respiratory viral infections, with rhinoviruses being the predominant pathogens^[2-4]. Seasonal viruses such as influenza virus and respiratory syncytial virus are strongly linked to peaks in asthma-related hospitalizations during autumn and winter, particularly in children and individuals with uncontrolled disease^[5-6]. Viral infections not only directly impair the integrity of the airway epithelial barrier but also activate pattern recognition receptors (e.g., Toll-like receptor 3 [TLR3] and retinoic acid-inducible gene 1 [RIG-I]), triggering abnormal immune responses that disrupt the balance between type 2 inflammation and antiviral immunity (e.g., type I interferons [IFN])^[7]. Notably, although inhaled corticosteroids (ICS) remain central to asthma maintenance therapy, they do not fully prevent virus-associated exacerbations; mechanistic evidence also suggests that glucocorticoids may under certain experimental conditions attenuate type I IFN responses and potentially facilitate rhinovirus (RV) replication^[8]. These observations underscore the urgent need to elucidate the mechanisms of virus–host immune interactions.

Although the critical role of viral infections in asthma initiation and progression has been widely recognized, several unresolved questions remain. From an epidemiological perspective, do early-life viral infections directly increase asthma risk, or do they mainly reveal children with pre-existing susceptibility? Do viral infections directly precipitate acute episodes? At the immunological level, does impaired antiviral defense contribute to persistent viral infection or prolonged viral detection in subsets of asthmatic patients, and how does type 2 inflammation interact with impaired antiviral responses to create a self-perpetuating cycle of immune dysregulation? Finally, why do current therapies fail to effectively prevent virus-related disease activity?

This review aims to integrate the latest advances in understanding the role of viral infections in asthma, with a focus on dissecting the underlying immunological mechanisms at multiple levels. By doing so, we seek to provide new perspectives for the development of precision therapeutic strategies that combine both antiviral and immunomodulatory functions.

Respiratory viral infections in asthma onset and exacerbation

Rhinovirus

Rhinovirus (RV), a non-enveloped, single-stranded positive-sense RNA virus belonging to the family

Picornaviridae, plays a predominant role in acute asthma exacerbations^[9]. Based on genomic characteristics, RV is classified into three species —RV-A, RV-B, and RV-C—with distinct pathogenicity profiles. Importantly, differences in cellular receptor usage may partly explain the distinct pathogenicity of RV species. Most major-group RV-A and RV-B strains use intercellular adhesion molecule 1 (ICAM-1), whereas minor-group RV-A strains bind members of the low-density lipoprotein receptor (LDLR) family. By contrast, RV-C uses cadherin-related family member 3 (CDHR3), which is expressed on airway epithelial cells and has been genetically linked to severe childhood wheezing and asthma exacerbations. In general, RV-A and RV-C infections are more prevalent and associated with more severe symptoms, whereas RV-B tends to cause milder illness^[10].

RV infection is especially relevant to asthma development and progression in children. Cohort studies, including the high-risk Childhood Origins of Asthma (COAST) birth cohort that enrolled children with parental atopy and/or asthma, have shown that children who experience RV-induced wheezing during the first three years of life have a significantly increased risk of developing asthma during school age^[11]. Moreover, this association can persist into adolescence^[11]. However, because these findings were derived from a risk-enriched population, they should not be directly generalized to the broader pediatric population. Preschool wheeze is clinically heterogeneous, and many children with early viral wheezing do not progress to persistent asthma^[12]. This suggests that in susceptible children, allergen exposure and other environmental factors may prime a permissive airway milieu, whereas RV infection may act as an additional "hit" that disrupts immune tolerance, thereby promoting asthma onset or progression^[13]. These epidemiological observations have prompted extensive investigation into the mechanisms by which RV interacts with the asthmatic airway immune microenvironment.

Experimental studies suggest that RV can amplify type 2 inflammation in susceptible airways. In animal models, RV infection impairs immune tolerance to inhaled aeroantigens by inhibiting regulatory T-cell induction and promoting epithelial alarmin pathways involving thymic stromal lymphopoietin (TSLP), IL-33, and OX40 ligand (OX40L)^[13]. Consistently, in a human experimental RV infection model, RV induced IL-33 and type 2 cytokines in the asthmatic airway, and these responses were associated with exacerbation severity^[14]. However, clinical cohort data also indicate

that allergic sensitization may precede and increase the risk of RV-induced wheezing, rather than RV wheezing necessarily causing subsequent sensitization^[15]. Thus, RV infection may amplify pre-existing type 2-prone airway inflammation, while in selected contexts it may also contribute to impaired immune tolerance and asthma development.

Ample clinical data indicate that RV is the most common viral trigger of acute asthma exacerbations. In children with exacerbated asthma, respiratory viruses can be detected in over 60% of cases, a significantly higher rate than that observed in non-exacerbated controls^[9]. RV stands out in this context: one study detected RV in approximately 60% of nasopharyngeal swabs from children experiencing exacerbations, far exceeding the detection rate of respiratory syncytial virus (RSV), which often falls below 5%^[9]. It is important to note that RV infection is highly prevalent and sometimes asymptomatic. Follow-up studies have identified RV in asymptomatic children^[16], and RV has also been detected in bronchial tissue from adults with stable asthma who had no recent symptoms of upper respiratory infection^[17–18]. These findings suggest that ongoing asthma symptoms may not always reflect acute infection alone but may also be associated with delayed viral clearance, low-level persistent detection of viral nucleic acid, or recurrent reinfection.

Adults with asthma are also vulnerable to RV infections. Studies have shown that among hospitalized adults experiencing asthma exacerbations, RV is the most frequently detected respiratory virus. Notably, RV-A and RV-C are the predominant subtypes, whereas RV-B accounts for less than 10% of cases, demonstrating distinct molecular epidemiological patterns^[10]. RV-C infection, in particular, is often associated with more severe clinical symptoms. In asthmatic children, RV-C is more frequently detected than in the general population, and those infected with RV-C tend to have higher severity scores compared with individuals infected with RV-A or RV-B^[19]. Epidemiological and clinical studies further indicate that RV-C infections in children and adults result in a higher incidence of wheezing, lower oxygen saturation, and more severe lower respiratory tract illness, supporting the notion that RV-C contributes disproportionately to severe disease and asthma exacerbations^[20]. This phenomenon may be attributed to RV-C's unique receptor usage and structural characteristics—for example, RV-C utilizes cadherin-related family member 3 (CDHR3) as its receptor. Genetic variants in the *CDHR3* gene have been associated with

increased susceptibility to RV-C-induced asthma exacerbations^[21]. Altogether, investigating the pathogenic mechanisms of different RV genotypes may offer new avenues for the precision prevention and treatment of acute asthma exacerbations.

Respiratory syncytial virus

Respiratory syncytial virus (RSV), a single-stranded, negative-sense RNA virus with an envelope, belongs to the genus *Orthopneumovirus* of the family *Pneumoviridae*. Numerous cohort studies have confirmed a significant association between RSV infection during infancy and an increased risk of developing asthma during childhood. Although the Infant Susceptibility to Pulmonary Infections and Asthma Following Respiratory Syncytial Virus Exposure Study (INSPIRE) did not primarily stratify outcomes by hospitalization severity, previous cohort data suggest that more severe RSV disease may confer an even greater risk of later asthma, indicating a possible severity-dependent relationship^[4]. This association appears to exhibit a dose–response relationship—markers of infection severity during the acute phase, such as viral load and the need for oxygen therapy, are positively correlated with the prevalence of asthma in later years^[4].

Further long-term evidence is provided by Sigurs *et al*^[22] in a prospective cohort study conducted in Northern Europe. They reported that children hospitalized with RSV bronchiolitis in infancy had an asthma prevalence of approximately 30% by age 7, significantly higher than the 3% observed in control children. Follow-up of this cohort revealed that the elevated risk persisted into adolescence and early adulthood—by age 13, the incidence of asthma or recurrent wheezing was around 43% (versus 8% in controls), and by age 18, asthma prevalence remained as high as 39% (versus 9% in controls)^[23]. These findings suggest that severe lower respiratory tract infection with RSV during early life may contribute to the later development of wheezing and asthma. However, whether preventing RSV bronchiolitis in early infancy can prevent later asthma remains uncertain. In the MAKI randomized trial (a multicenter, double-blind, randomized, placebo-controlled trial evaluating the effect of palivizumab prophylaxis on RSV-associated respiratory morbidity in healthy preterm infants), RSV immunoprophylaxis with palivizumab during the first RSV season did not clearly improve physician-diagnosed asthma or lung function at 6 years, despite earlier reductions in wheezing outcomes^[24]. Thus, RSV prevention may reduce early respiratory morbidity, but its long-term

effect on asthma development remains unresolved. Nevertheless, RSV-associated bronchiolitis or wheezing in early life should not be equated with inevitable progression to asthma, because preschool wheeze is heterogeneous and often remits by school age^[12]. Whether RSV directly contributes to asthma pathogenesis or primarily reveals an underlying susceptible host phenotype therefore remains unresolved.

Importantly, interventional evidence from passive immunization studies provides supportive, although not definitive, evidence for a causal contribution of RSV to subsequent airway morbidity. Prophylaxis with palivizumab, a monoclonal antibody targeting the RSV fusion protein, has been associated with a significantly lower incidence of recurrent wheezing in preterm infants up to 3 years of age compared with untreated cohorts^[25]. Subsequent long-term follow-up studies have also examined the impact on later wheezing and asthma outcomes, lending further insight into how preventing severe early RSV infection may modify later respiratory outcomes^[26].

However, the causal relationship between RSV infection and subsequent asthma remains controversial. Some researchers argue that this association may be due to shared susceptibility factors rather than RSV directly causing asthma^[27]. For example, children with severe RSV infections often harbor certain genetic variants—such as polymorphisms in the IL-4/IL-13 signaling pathway or in the *TLR4* gene—which predispose them to both severe RSV lower respiratory tract infection and the development of asthma^[28]. Environmental exposures, such as air pollution or secondhand smoke, may also increase the risk of both early severe RSV infections and later asthma development^[29]. Additionally, discrepancies in asthma phenotype definitions across studies—such as varying thresholds for wheezing frequency or lung function—may introduce bias into study findings^[29]. Therefore, future studies with more rigorous designs are needed to distinguish the direct pathogenic effects of early RSV infection from the confounding influences of genetic background and environmental exposures.

Human metapneumovirus (hMPV)

hMPV, a member of the *Metapneumovirus* genus within the *Pneumoviridae* family, is an enveloped, single-stranded, negative-sense RNA virus. hMPV infection is a major cause of acute respiratory illness in children, particularly those under two years of age, and often leads to bronchiolitis. An epidemiological study conducted in Taiwan, China investigated 48

children aged 2–32 months who were hospitalized for acute lower respiratory tract infections associated with hMPV. Among these patients, 36 children (75%) were diagnosed with bronchiolitis during the acute episode. During follow-up, 13 children (27.1%) subsequently developed asthma, suggesting that early-life hMPV infection may be associated with an increased risk of later asthma development^[30].

A U.S. study further supported this association. Williams *et al*^[31] analyzed 49 children with hMPV infection and found that 59% had bronchiolitis, 18% had asthma, 8% had pneumonia, and 14% experienced acute asthma exacerbations. These findings indicate that hMPV infection not only serves as an initial trigger but may also contribute to asthma onset or exacerbation by inducing airway inflammation and immune dysregulation. Importantly, hMPV is also relevant in adults: in a multicenter prospective study of adults with asthma exacerbations, hMPV was among the commonly detected respiratory viruses, ranking after human rhinovirus (HRV)/enterovirus in that cohort^[32].

Enteroviruses

Enteroviruses, members of the *Picornaviridae* family, are small, non-enveloped, single-stranded, positive-sense RNA viruses. Unlike most enteroviruses, enterovirus D68 (EV-D68) primarily causes respiratory illness, often leading to respiratory distress and severe bronchospasm, sometimes requiring intensive care^[33–34]. Moreover, EV-D68 has been strongly linked to asthma, with multiple studies reporting a significant association between its outbreaks and asthma exacerbation rates^[35].

Mechanistic insight into this relationship has been provided by experimental studies. In a murine model, early-life enterovirus infection was shown to reprogram macrophage immunity and enhance subsequent allergen-induced airway inflammation, suggesting that early viral exposure may imprint long-term alterations in immune regulation relevant to asthma development^[36]. Additionally, Moss *et al*^[37] noted that EV-D68, similar to rhinoviruses, may contribute to asthma-like respiratory disease by inducing type 2 inflammatory responses and compromising the epithelial barrier.

Consistent with these mechanistic findings, recent clinical and epidemiological evidence indicates that EV-D68 infection is strongly associated with acute asthma exacerbations in pediatric populations, where a substantial proportion of hospitalized cases present with asthma or reactive airway disease. In September 2015, a national survey in Japan reported a surge in

pediatric hospitalizations for acute asthma exacerbations during an EV-D68 outbreak. EV-D68 was found to trigger severe asthma attacks even in children without a prior asthma diagnosis, aligning with the clinical observations of Moss *et al*[38-39]. Longitudinal follow-up studies also indicate that children with EV-D68 infection experience more severe subsequent respiratory outcomes and longer hospital stays compared with those with other enterovirus/rhinovirus infections, suggesting that EV-D68 may contribute to compromised respiratory resilience and chronic airway morbidity[40].

Human bocavirus (HBoV)

HBoV, a member of the family *Parvoviridae*, subfamily *Parvovirinae*, is a small, non-enveloped, single-stranded DNA virus. Studies have shown that HBoV infections typically result in longer hospital stays compared with RV infections, with disease severity comparable to that of RSV[41]. Further underscoring its clinical impact, in a survey of children under two years old, acute HBoV infection was detected in approximately 27% (26 of 95) of children experiencing their first episode of wheezing. Additionally, about 25% (35 of 141) of children with either first-time or recurrent wheezing tested positive for HBoV[41].

A follow-up study further reported that approximately 50% of children hospitalized with capillary bronchiolitis due to HBoV infection were later diagnosed with asthma between the ages of five and seven[42]. However, Garcia-Garcia *et al*[43] cautioned that the role of early HBoV infection in asthma development may be confounded by factors such as the high prevalence of HBoV coinfections with other respiratory viruses and its frequent detection in older children. These factors complicate efforts to isolate the true impact of early HBoV infection on asthma pathogenesis.

Influenza viruses

Influenza viruses, members of the *Orthomyxoviridae* family, are single-stranded, negative-sense RNA viruses classified into types A, B, and C. They are well-documented triggers of asthma exacerbations across all age groups[44]. During the 2009 H1N1 influenza pandemic, asthma was the most prevalent comorbidity among hospitalized patients[45]. A study of 1 520 hospitalized patients with influenza A reported that 25.3% had comorbid asthma[46]. Similarly, an analysis of hospitalized patients with asthma and influenza found that 95% of cases (38/40) were attributed to influenza A (all H1 subtype),

whereas only 5% (2/40) were linked to influenza B[47].

Epidemiological studies on influenza-induced asthma exacerbations have reported a wide range of prevalence rates, from 10.0% to 37.9%[48-51]. This variation may be influenced by factors such as baseline population characteristics, viral strain differences, surveillance methods, and seasonal influenza trends. These findings underscore the need for heightened clinical vigilance regarding the role of influenza in asthma exacerbations.

Coronaviruses

Coronaviruses, members of the *Coronaviridae* family, are enveloped, single-stranded, positive-sense RNA viruses. Common seasonal coronaviruses—such as 229E, OC43, NL63, and HKU1—can also trigger acute asthma exacerbations, but both the frequency and severity of these events are notably lower compared with those induced by rhinoviruses or influenza viruses[52].

The COVID-19 pandemic has provided new insights into the relationship between coronaviruses and asthma. Early studies suggested that the prevalence of asthma might be higher among patients infected with SARS-CoV-2 compared with the general population[53-55]. In contrast, subsequent large-scale analyses indicated that asthma is not an independent risk factor for SARS-CoV-2 infection or for severe outcomes of COVID-19. Studies from Spain and South Korea reported no significant association between asthma and the risk of hospitalization or mortality from COVID-19 after adjusting for age, comorbidities, and other factors[53-54]. A systematic review further found that the prevalence of asthma among COVID-19 patients was similar to—or even lower than—that in the general population, suggesting no evident additional risk[56].

Interestingly, some studies observed a slightly elevated risk of poor outcomes in patients with non-allergic asthma following COVID-19 infection, whereas patients with classical allergic asthma tended to have more favorable prognoses. This discrepancy may be attributed to type 2 inflammation-mediated downregulation of the angiotensin-converting enzyme 2 (ACE2) receptor expression, which could reduce susceptibility to SARS-CoV-2 infection[57-60].

In summary, current evidence does not support a significantly increased risk of SARS-CoV-2 infection or adverse COVID-19 outcomes in patients with asthma[61-63]. However, a subset of patients with atypical asthma phenotypes or high-risk comorbid conditions may still be vulnerable, warranting further investigation and close monitoring. As research

continues to advance, our understanding of the complex interactions between coronaviruses and asthma will become more comprehensive.

Characterization of immune abnormalities in asthmatics: core mechanisms of viral susceptibility and exacerbations

Defects in the innate immune response

Impaired airway epithelial barrier function

The airway epithelium is composed of multiple cell types that collectively function as a barrier, working in coordination with the immune system to prevent the invasion of foreign particles and pathogens into the submucosa. It serves as the body's first line of defense against external pathogens. However, in asthma—a chronic inflammatory disease—the airway epithelium is prone to dysfunction and structural damage due to repeated injury. This leads to excessive recruitment of immune cells, amplified inflammation, and epithelial detachment.

Various respiratory viruses can directly or indirectly compromise the airway epithelium. For instance, RV induces epithelial cell damage and triggers an inflammatory response^[64]. RSV primarily targets ciliated airway epithelial cells and can cause epithelial dysfunction and injury in the small airways, accompanied by the release of proinflammatory cytokines and chemokines such as interleukin (IL)-8 and tumor necrosis factor- α (TNF- α)^[65]. These molecules recruit and activate neutrophils, monocytes, macrophages, and T cells, thereby amplifying the inflammatory response^[65]. In this process, ciliated cells are frequently damaged, leading to cilia shedding and dysfunction, which in turn reduces mucociliary clearance^[66]. Influenza viruses further exacerbate this damage by destroying both ciliated and non-ciliated epithelial cells, resulting in significant necrosis of the tracheal and bronchial epithelium^[67]. Biopsy and tissue-culture studies of asthmatic airways have demonstrated elevated levels of basal cell apoptosis^[68], suggesting that viral infections may further compromise epithelial integrity and disrupt local immune homeostasis.

Under normal conditions, epithelial injury initiates coordinated repair programs involving growth factor signaling, epithelial migration, proliferation, and redifferentiation. In asthma, repeated injury and dysregulated repair weaken epithelial barrier integrity, thereby increasing susceptibility to inhaled stimuli and respiratory viral infection^[69-70]. Epithelial-

mesenchymal transition (EMT)-like epithelial plasticity has been implicated in asthmatic airway remodeling, but direct evidence for complete EMT in human asthma remains limited. Recent studies using human bronchial epithelial cells and asthmatic airway samples support the involvement of EMT-related remodeling programs, including DOCK2- and WNT5A-associated pathways, characterized by loss of epithelial junctional features and acquisition of profibrotic properties^[71-72]. Thus, EMT should be interpreted cautiously as part of a broader epithelial injury–repair response rather than as a universal mechanism across all asthma phenotypes.

Notably, substantial transforming growth factor- β (TGF- β) accumulation has been observed in chronic asthma and allergy models^[69, 73], further reinforcing its critical role in epithelial barrier disruption, airway mucosal remodeling, and fibrosis. During asthma progression, viral infections may further promote EMT-related airway remodeling, thereby exacerbating extracellular matrix overproduction and subepithelial fibrosis^[74].

In conclusion, the activation of EMT beyond what is necessary for normal epithelial repair compromises the regenerative capacity of the airway barrier, significantly increasing susceptibility to external stimuli and pathogens (*Fig. 1*). This, in turn, exacerbates airway remodeling and chronic inflammation, perpetuating the pathophysiological cycle of asthma.

Dysregulated type I and type III interferon (IFN) responses

Type I IFNs (IFN- α/β) and type III IFNs (IFN- $\lambda 1-3$) form the frontline antiviral cytokine system in the airways. Following respiratory viral infection, epithelial cells, dendritic cells, and macrophages rapidly induce IFN-I/III, which signal *via* interferon- α/β receptor (IFNAR) and interferon-lambda receptor (IFNLR) to activate interferon-stimulated genes (ISGs) and curb viral replication before adaptive immunity is fully engaged. IFN- λ is particularly important at mucosal surfaces because IFNLR is enriched in epithelial cells, making it a key antiviral mediator in bronchial epithelial cells^[75-76].

Rather than a uniform "interferon deficiency", accumulating evidence supports a dysregulated kinetic model in asthma and allergic disease: low baseline and/or delayed early IFN-I/III responses allow higher early viral loads, which may then trigger a secondary exaggerated induction of interferon pathways and ISGs during respiratory illnesses^[77]. Consistent with this framework, several studies report reduced type I

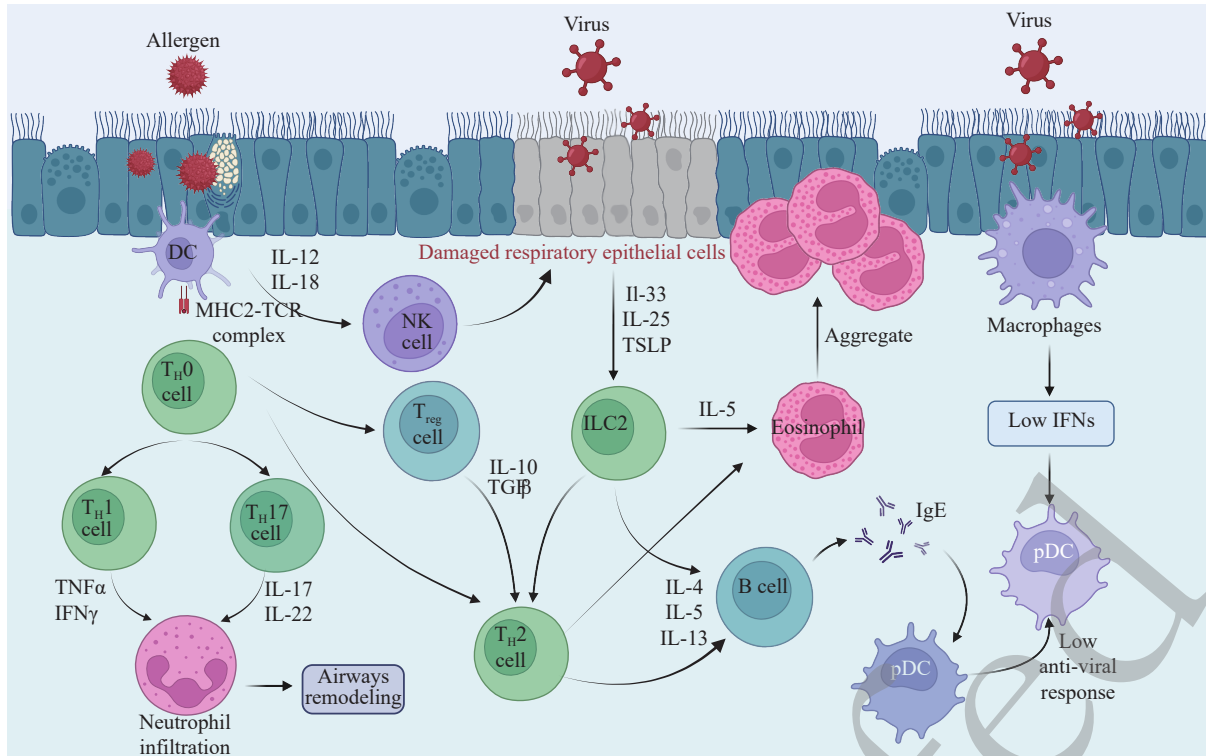


Fig. 1 Immunological dysregulation and impaired early antiviral immunity in asthma. Adaptive T-cell imbalance: Asthma is characterized by a skewed CD4⁺ T-helper cell profile. There is an overactive type 2 response with excessive IL-4, IL-5, and IL-13 production, and often an elevated Th17 response (producing IL-17 and IL-22), especially in more severe or corticosteroid-resistant cases. In contrast, Th1-mediated immunity (IFN-γ production) is relatively deficient, failing to counterbalance type 2 inflammation. Tregs, which normally suppress aberrant immune responses, are reduced in number and function in allergic asthma. These Tregs often display aberrant phenotypes, reflecting a loss of regulatory control and a bias toward T2 immunity. The net effect is a T2/Th17-dominated milieu with insufficient regulation, driving allergic inflammation. B cell activation and IgE-mediated allergy: In atopic asthma, B lymphocytes are primed by IL-4/IL-5/IL-13 and produce large amounts of IgE antibodies against environmental allergens. Chronic IgE production thus sustains an allergic inflammatory loop, contributing to ongoing airway inflammation and hyperreactivity. Allergen exposure and cross-linking of high-affinity IgE receptors impair the production of virus-induced type I and III interferons, thereby compromising the host's early antiviral immune responses. Impaired innate antiviral defenses: Upon exposure to allergens, asthma patients mount a series of specific immune responses that weaken antiviral immunity during viral clearance and re-challenge. Chronic airway inflammation compromises epithelial barrier integrity, and viral stimuli reduce IFN production by airway epithelial cells, leading to delayed viral clearance. Furthermore, IgE secreted by B cells suppresses pDC-derived IFN-α production, further impairing antiviral defenses. Abbreviations: DC, dendritic cell; IFNs, interferons; pDC, plasmacytoid dendritic cell; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

interferon production after viral infection in asthmatic airway epithelial cells and in immune cells such as dendritic cells and macrophages^[78-79], leading to an attenuated early antiviral response, uncontrolled viral replication, and exacerbation^[80]; however, other studies observe no significant differences between asthmatics and controls^[81-82], likely reflecting heterogeneity in disease severity, sampling time points across infection kinetics, and *in vitro* culture conditions (e.g., air-liquid interface). Despite extensive investigation, the mechanisms by which otherwise innocuous mucosal viruses cause disproportionate clinical severity in asthma remain incompletely understood.

Pritchard *et al.*^[83] co-cultured peripheral blood mononuclear cells (PBMCs) from patients with allergic asthma and healthy donors with RV and found

that PBMCs from asthmatics exhibited reduced expression of key interferon regulatory factors (IRF1, IRF7) and STAT1, which are essential for innate antiviral signaling against RV. Additionally, they observed a concurrent reduction in TLR7/8 activation. Some investigators have hypothesized that defective type I interferon signaling in asthmatics is linked to abnormalities in pattern recognition receptors (PRRs)^[84], which include TLR3, melanoma differentiation-associated protein 5 (MDA5), and RIG-I. These receptors are critical for recognizing viral RNA and initiating interferon signaling. However, studies indicate that the interferon deficiency observed in bronchial epithelial cells is not necessarily associated with impaired PRR expression. In fact, *in vivo* analyses of asthmatic patients have shown that baseline epithelial expression of TLR3,

MDA5, and RIG-I is not defective, and that TLR3 and MDA5 expression levels increase following rhinovirus infection^[85]. Notably, because PRR activation feeds into both type I and type III interferon pathways, intact PRR expression does not preclude impaired downstream signaling; dysregulation of IFN- λ -mediated epithelial antiviral responses (often alongside IFN- β) has been reported in asthma, suggesting that defects may reside in signal transduction, transcriptional competence, or enhanced negative regulation rather than PRR abundance alone^[77].

Importantly, IgE-mediated allergic inflammation can suppress antiviral interferon responses, providing a mechanistic bridge between atopy and virus-driven wheezing/exacerbations. In particular, IgE-Fc ϵ RI crosslinking on plasmacytoid dendritic cells (pDCs) can impair TLR7/9-mediated IFN- α production, thereby weakening early antiviral defense, as discussed further in the dendritic cell section. Clinical and mechanistic data from anti-IgE intervention studies show that omalizumab reduces the duration of rhinovirus infection, viral shedding, and the risk of rhinovirus illnesses in children with allergic asthma, supporting the concept that IgE pathways increase susceptibility to viral infection partly by constraining antiviral interferon programs^[86].

Additionally, allergen exposure can contribute to the overexpression of negative regulators in the interferon signaling pathway. In a mouse model of influenza virus-induced asthma exacerbation, the asthma-associated cytokine TSLP was shown to upregulate CUL5 expression. CUL5 negatively regulates IFN- β expression by inhibiting O-GlcNAc glycosylation of mitochondrial antiviral signaling protein (MAVS), thereby suppressing antiviral immunity^[87].

Collectively, available evidence supports a model in which early insufficiency of type I/III interferon responses—modulated by allergic/IgE signals and context-dependent regulatory circuits—allows increased viral replication, which then contributes to later heightened interferon/ISG activation and amplified immunopathology (**Fig. 1**). This "early-low, late-high" interferon dysregulation framework helps reconcile prior conflicting reports and provides a rationale for precision strategies that restore timely mucosal IFN-I/III responses in high-risk asthma endotypes.

Natural killer (NK) cell dysregulation

NK cells are critically involved in antiviral defense and are increasingly recognized as key determinants

of susceptibility to virus-triggered asthma exacerbations (**Fig. 1**). Human NK cells are classically divided into CD56^{bright} (cytokine-producing, immunoregulatory) and CD56^{dim} (cytotoxic) subsets^[88-89]. In healthy airways, NK-cell compartmentalization supports efficient antiviral surveillance; however, in severe asthma this balance is disrupted, with reduced airway NK cell abundance and an altered CD56^{bright}/CD56^{dim} profile^[90].

This phenotypic shift is accompanied by functional impairment. Although peripheral NK cells from patients with asthma may display increased activation signatures, their ability to eliminate virus-infected airway epithelial targets is reduced *in vitro*^[90]. During rhinovirus challenge, NK cells from patients with severe asthma show defective activation and lower IFN- γ output, resulting in less effective viral control^[91]. These findings support a model in which NK cell dysfunction contributes to delayed viral clearance and prolonged airway inflammation during exacerbations.

A type 2-skewed immune milieu further aggravates this defect. Severe asthma has been associated with expansion of IL-4⁺ NK-like responses and reduced IFN- γ -dominant antiviral NK activity^[91-92], which may increase vulnerability to respiratory viral infection and amplify post-infectious wheeze. In addition, persistent corticosteroid exposure may reshape NK cell subsets and attenuate antiviral cytotoxic function^[90], potentially contributing to incomplete inflammatory resolution in steroid-treated severe disease.

Overall, NK cell dysregulation in asthma is best interpreted in the context of viral exacerbation biology: impaired antiviral effector function, reduced IFN- γ competence, and type 2-biased reprogramming together create a permissive environment for impaired viral clearance, prolonged viral detection, and exacerbation progression^[90-91, 93].

Dendritic cells (DCs) and their role in asthma and viral susceptibility

DCs play a central role in initiating adaptive immune responses in the airways by capturing antigens, migrating to draining lymph nodes, activating CD4⁺ and CD8⁺ T cells, and shaping innate lymphoid cell responses^[94-95]. In the pathogenesis of asthma, DC dysfunction disrupts immune homeostasis through multiple mechanisms, acting as a key driver of type 2 inflammation and increased susceptibility to viral infections (**Fig. 1**).

In patients with atopic asthma, local allergen exposure recruits DCs to the airway epithelium^[96], and the initiation of atopic asthma is generally considered

to involve DC-mediated antigen presentation to T lymphocytes^[97]. Notably, during viral infections, DC migration to the draining lymph nodes is enhanced, a process that not only facilitates the presentation of viral antigens but also amplifies the immune response to co-exposed allergens such as house dust mites. Atopic DCs from patients with asthma, upon stimulation with allergens (*e.g.*, *Dermatophagoides pteronyssinus* group 1 allergen [Der p 1]), aberrantly upregulate type 2-promoting receptors such as G protein alpha inhibitory subunit 2 (GNAI2), FGD1-related F-actin-binding protein (frabin), and cathepsin D, alongside reduced expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and increased endocytic capacity^[98-99]. These DCs produce elevated levels of IL-6 while secreting less IL-12p70, thereby promoting type 2 polarization and suppressing the generation of IL-10⁺ regulatory T cells^[100].

Meanwhile, interactions between DCs and bronchial epithelial cells are indispensable in the initiation and progression of allergic diseases^[101-102]. Certain allergens not only disrupt epithelial tight junctions—facilitating direct access to DCs—but also trigger the release of IL-1 α , which activates inflammasomes and promotes the secretion of IL-33 and GM-CSF. These signals collectively drive type 2-skewed inflammation and exacerbate allergic airway inflammation^[103-104].

Recent studies have also highlighted the role of pDCs in promoting immune tolerance and preventing allergic asthma^[105]. Unlike conventional DCs (cDCs), pDCs secrete large amounts of type I interferons and present antigens to both naïve and memory CD4⁺ and CD8⁺ cytotoxic T lymphocytes, thus bridging innate and adaptive immunity^[106]. However, pDCs are significantly reduced in patients with allergic asthma^[107]. Additionally, IgE-Fc ϵ RI crosslinking negatively regulates the TLR7/9 signaling pathways in pDCs, suppressing IFN- α production^[108]. This impairment facilitates viral evasion from early immune surveillance and contributes to wheezing and acute exacerbations^[108]. Clinical studies have confirmed that anti-IgE monoclonal antibody therapy (*e.g.*, omalizumab) significantly reduces the risk of virus-induced asthma exacerbations in children^[109], suggesting that blocking IgE signaling may restore the antiviral functions of pDCs.

Moreover, respiratory viruses can target DCs and establish a vicious cycle of allergy-infection interactions. For instance, RSV nucleoprotein (N protein) aberrantly localizes to the surface of infected DCs and interferes with immunological synapse

formation, thus impairing T cell activation^[110]. DCs infected by influenza virus exhibit dysregulated cytokine secretion and accelerated apoptosis, resulting in impaired antigen presentation^[111]. Thus, DCs are thought to reside at a critical immunological crossroads—coordinating antiviral immunity for effective viral clearance while simultaneously regulating tolerance to self and non-self antigens^[112].

Dysregulation of adaptive immunity

Imbalance of T cell subpopulations

In asthma, CD4⁺ T-cell disequilibrium is most clinically relevant during virus-triggered exacerbations, when insufficient early antiviral control biases adaptive immunity toward pathogenic effector programs^[113-114]. A relative reduction in Th1-type antiviral activity, together with exaggerated type 2 signaling, is associated with poorer viral containment and greater risk of acute worsening in allergic asthma^[115]. In this context, IgE-Fc ϵ RI-dependent amplification of type 2 immunity can further suppress antiviral pathways, facilitating infection-driven wheeze and exacerbation^[115-116].

A Th17-skewed response represents another major exacerbation-prone pattern, particularly in severe or difficult-to-control disease^[117]. Increased IL-17 signaling is linked to neutrophilic airway inflammation, lower lung function, and higher exacerbation frequency^[118-119]. Although transient neutrophil recruitment may contribute to early host defense^[120], persistent IL-17–neutrophil activation promotes non-resolving inflammation; consistent with this, IL-17 blockade attenuates virus-induced airway hyperresponsiveness in experimental models^[121]. This is aligned with broader evidence that sustained neutrophilic inflammation contributes to chronic tissue injury and remodeling in severe inflammatory disease^[120, 122].

Treg dysfunction is a key failure point in exacerbation resolution. In asthma, reduced Treg number and/or suppressive function weakens control of Th2/Th17 effector activity, allowing prolonged post-viral inflammation^[123-124]. Severe disease is associated with reduced FOXP3⁺ Tregs and impaired tolerance-associated phenotypes, including altered trafficking and suppressive signatures^[125]. Experimental data further support a causal role: impaired inducible Treg programs favor mucosal type 2 inflammation and asthma-like pathology^[126]. Mechanistically, inflammatory reprogramming pathways (*e.g.*, NOTCH4–Hippo/YAP/TAZ and IL4R α R576-linked signaling) can destabilize Treg

identity and promote Th17-like conversion, thereby amplifying exacerbation susceptibility^[127-129].

Single-cell studies reinforce this framework by identifying interferon-responsive TH/Treg states associated with better immune restraint, whereas loss of these states is linked to exacerbation-prone inflammation^[130]. TRAIL-related programs may contribute to suppression of excessive T-cell activation and type 2 inflammation, suggesting a potential regulatory axis in virus-associated attacks^[130]. Overall, virus-induced exacerbations are best interpreted as a combined failure of antiviral Th1-linked control, expansion of Th2/Th17 inflammation, and insufficient Treg-mediated resolution.

B cells and abnormal antibody responses in asthma

B cells play a critical role in the pathophysiology of asthma, traditionally recognized for their function as producers of IgE in type 2 immune responses, particularly in allergic asthma^[131]. However, recent studies have highlighted their broader immunoregulatory functions, especially the role of regulatory B cells in modulating allergic airway inflammation and promoting allergen tolerance^[132]. Emerging evidence suggests that IgA⁺ memory B cells may also contribute to asthma pathology. Recent studies have observed a significant increase in IgA⁺ memory B cells in asthma patients, with the frequency of CD27⁺IgA⁺ memory B cells positively correlating with lung function impairment, particularly in individuals with small airway dysfunction^[133]. This finding suggests that IgA⁺ memory B cells may play a previously underappreciated role in small airway pathology in asthma.

In patients with allergic asthma, the synergistic effect of IgE-dependent sensitization and viral infections significantly increases the risk of asthma exacerbation. Studies have shown that allergen exposure and cross-linking of high-affinity IgE receptors impair virus-induced type I and type III interferon production, particularly in peripheral blood cells^[134]. This leads to a weakened early immune response against viral infections. A clinical study by Bergroth *et al*^[135] found that infants and young children with IgE-dependent sensitization and wheezing during RV-C infection had the highest risk of developing asthma. This may be due to viral infections altering host immune responses, airway inflammation, and repair mechanisms, which simultaneously increase the production of pro-inflammatory cytokines and chemokines, exacerbating airway damage.

In addition, several studies have identified impaired

expression of the polymeric immunoglobulin receptor (pIgR) and reduced levels of secretory immunoglobulin A (sIgA) in the bronchial epithelium of asthmatic patients, suggesting that pIgR-sIgA axis may play an important role in asthma development^[136]. Furthermore, increased IgA levels have been shown to exert a protective effect in allergic diseases such as asthma^[137].

Imbalance of cytokines and chemokines

Respiratory viral infections frequently induce a surge in host-derived pro-inflammatory cytokines and chemokines, resulting in aggravated airway inflammation. Influenza virus infection significantly increases the levels of IL-2, IL-6, and TNF- α , with IL-6 concentrations rising up to 39-fold and correlating with disease severity^[138]. In patients with asthma, this virus-induced inflammation is superimposed upon preexisting type 2 inflammation, amplifying the overall immune response. Allergen exposure prompts airway epithelial cells to secrete epithelial-derived cytokines such as IL-25, IL-33, and TSLP^[139-140], which further activate type 2 innate lymphoid cells (ILC2s), enhancing eosinophil-mediated type 2 inflammatory cascades^[141]. Although ILC2s are outnumbered by CD4⁺ Th2 cells, they possess a much greater capacity to produce type 2 cytokines^[141-142]. Additionally, IL-33 activates mast cells, further intensifying the inflammatory response^[143].

Viral infection also exacerbates inflammation by compromising the airway epithelial barrier. Influenza A virus suppresses the expression of tight junction proteins such as occludin and zonula occludens-1 (ZO-1), increasing epithelial permeability and thereby magnifying local inflammation; however, short-chain fatty acids (*e.g.*, acetate) can partially restore barrier integrity *via* the GPR43 receptor and reduce production of TNF- α , IL-6, and IL-1 β ^[144]. Moreover, rhinovirus-induced upregulation of C-X-C motif chemokine ligand 8 (CXCL8)/IL-8 leads to neutrophil recruitment to the airways, worsening inflammation and airway obstruction^[145].

In summary, respiratory viral infections exacerbate the imbalance of adaptive immunity in asthma patients through multiple mechanisms (**Fig. 1**). Virus-induced epithelial injury and defects in innate immunity drive dysregulated T cell polarization, resulting in overactivation of type 2 and Th17 responses and suppression of Treg function. This impairs type 1 antiviral immunity and leads to uncontrolled inflammation. Concurrently, allergen sensitization mediated by IgE synergizes with viral infection to suppress interferon production, enhance type 2

inflammation, and impair mucosal antiviral defenses due to sIgA deficiency. Furthermore, the cytokine storm triggered by viral infection (*e.g.*, IL-6, IL-33, and TSLP) interacts with preexisting type 2 inflammation, amplifying the recruitment of ILC2s, eosinophils, and neutrophils, creating a positive feedback loop between viruses, allergens, and inflammation. This cascading immune imbalance exacerbates airway hyperresponsiveness and tissue remodeling while also fostering a microenvironment favorable for impaired viral clearance and prolonged viral detection by compromising epithelial integrity and activating inflammasomes. Therefore, targeting critical host-virus interaction nodes—such as blocking IgE-FcεRI signaling, inhibiting the IL-4Rα/TSLP pathway, and enhancing sIgA secretion—may offer promising immunomodulatory strategies for restoring the Th/Treg balance, suppressing cytokine storms, and

repairing mucosal barriers, thereby enabling precision intervention for asthma management.

Feed-forward loop linking respiratory viral infections to epigenetic reprogramming

Viral infections exacerbate airway inflammation and immune imbalance through epigenetic reprogramming^[146]. Meanwhile, asthma-related epigenetic modifications can weaken antiviral responses or amplify inflammatory signaling^[147], fostering persistent inflammatory responses and recurrent viral susceptibility and creating a vicious cycle of viral infection and asthma-associated epigenetic abnormalities (**Fig. 2A**). On the one hand, respiratory viruses can induce epigenetic alterations, such as DNA methylation and histone acetylation, in host airway epithelial and immune cells, leading to interferon pathway suppression or upregulation of

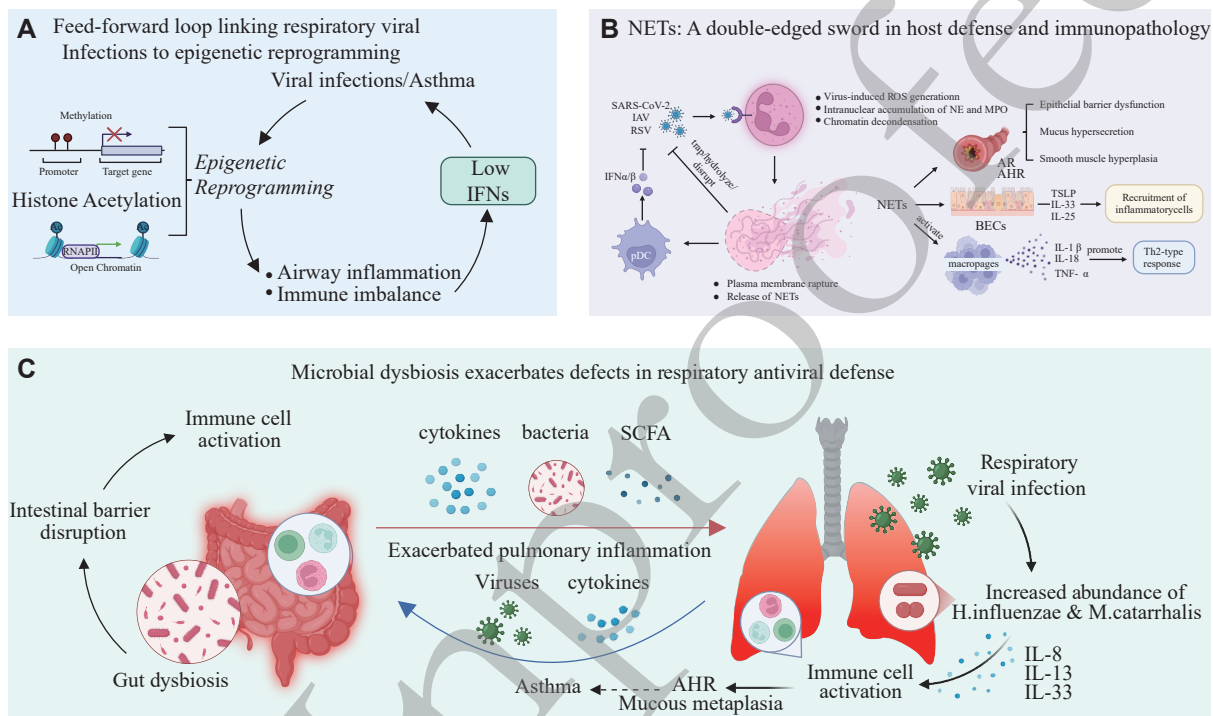


Fig. 2 Specific mechanisms of virus-asthma host interactions. A: Respiratory viruses induce epigenetic modifications, including promoter methylation and histone acetylation, which suppress interferon and promote airway inflammation. Reduced IFN levels exacerbate immune imbalance, perpetuating viral persistence and asthma pathogenesis. B: This schematic depicts mechanisms by which respiratory viruses trigger NET release *via* ROS generation, chromatin decondensation, and intranuclear accumulation of NE/MPO. NETs exhibit dual roles. Host defense: NETs directly act on viral particles, inhibiting their replication, or activate pDCs to produce IFNα/β and promote antiviral T2 responses. Immunopathology: NETs drive epithelial barrier dysfunction, mucus hypersecretion, smooth muscle hyperplasia, and recruitment of inflammatory cells that release cytokines, amplifying T2 responses and asthma exacerbations. C: This schematic delineates the cascade of events initiated by respiratory viral infections and their interplay with gut microbiota in driving asthma pathogenesis. Key pathways are summarized below. Viral infection of the respiratory tract: Viral infection disrupts airway microbial homeostasis, increasing the abundance of *Haemophilus influenzae* and *Moraxella catarrhalis*. These bacteria further exacerbate inflammation *via* IL-8, IL-13, and IL-33 production, promoting T2 activation, AHR, and mucus metaplasia. Gut dysbiosis and barrier disruption: Respiratory viruses indirectly induce gut dysbiosis, disrupting intestinal barrier integrity. This facilitates bacterial translocation and systemic dissemination of microbial metabolites (*e.g.*, SCFAs) and inflammatory mediators. Dysbiosis-derived SCFAs and cytokines circulate systemically, reaching the lungs where they modulate immune responses. Abbreviations: AHR, airway hyperresponsiveness; AR, airway remodeling; BECs, bronchial epithelial cells; IAV, Influenza A virus; MPO, myeloperoxidase; NE, neutrophil elastase; NETs, neutrophil extracellular traps; ROS, reactive oxygen species; SCFA, short-chain fatty acids.

pro-inflammatory genes. For instance, RSV infection triggers extensive histone acetylation in the promoter region of the *ORMDL3* gene, inducing its overexpression and promoting downstream activation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes^[148], thereby exacerbating airway inflammation.

On the other hand, asthmatics exhibit pre-existing epigenetic abnormalities. Findings from the Isle of Wight whole-population birth cohort revealed distinct DNA methylation profiles in asthmatic individuals, directly influencing the expression of coronavirus-associated genes and the clinical outcomes of coronavirus disease 2019 (COVID-19)^[149]. The increasing prevalence of asthma in recent decades also reflects, to some extent, the modulation of immune responses and inflammatory genes by environmental stimuli through epigenetic pathways^[150]. In asthmatic airways, histone modifications play a crucial role in sensitization and persistent inflammation^[151]. In allergic states, these modifications regulate the activation of key immune cells, such as T cells and macrophages^[152]. Notably, histone H3 lysine 18 acetylation (H3K18ac) and its interaction with the acetyltransferase p300 in asthmatic airway smooth muscle cells drive CXCL8 overexpression, contributing to steroid-resistant neutrophilic inflammation. However, bromodomain inhibitors can downregulate CXCL8 expression by disrupting bromodomain-containing protein 4 (BRD4) binding to RNA polymerase II^[153]. Additionally, chromatin modifications, such as cAMP response element-binding protein (CREB)/CREB-binding protein (CBP)-mediated chromatin acetylation, are closely linked to the persistent inflammatory phenotype^[154], further underscoring the critical role of virus-host epigenetic interactions in asthma exacerbation. Future therapeutic strategies may focus on targeting epigenetic regulatory nodes, paving the way for precision therapies based on epigenetic markers.

Neutrophil extracellular traps (NETs): a double-edged sword in host defense and immunopathology

During virus-induced acute asthma exacerbations, there is a marked increase in airway neutrophils, which release NETs. NETs consist of an extracellular DNA scaffold decorated with various antimicrobial proteins such as myeloperoxidase (MPO) and neutrophil elastase (NE), contributing to both host defense and pathological inflammation. Viral infections can induce NET formation *via* multiple mechanisms. For instance, the F protein of RSV activates inflammatory signaling through the TLR4

pathway, promoting NET generation^[155]. RV stimulates type 2 cytokines such as IL-5 and IL-13, which enhance type 2 immune responses and NET release^[156]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces massive production of reactive oxygen species, triggering NET formation^[157-158]. Influenza A virus (IAV) promotes NET release through the interaction of antimicrobial peptide LL-37 with neutrophil receptor FPRL-1^[159].

NETs exert dual effects in virus-induced asthma. On one hand, they can trap and neutralize viral particles, preventing viral entry into host cells^[155, 160]. The DNA scaffold of NETs physically entraps viruses, while MPO and α -defensins exhibit direct virucidal activity and suppress viral replication^[161]. Moreover, NETs can activate pDCs, enhancing type I interferon production and bolstering antiviral immunity^[162-163]. However, current evidence is insufficient to confirm that these protective effects translate into clinically meaningful reductions in acute asthma exacerbations.

On the other hand, excessive NET release exacerbates airway inflammation and tissue damage^[164]. NETs stimulate bronchial epithelial cells to release pro-inflammatory cytokines such as TSLP, IL-33, and IL-25, activate inflammasomes, and induce monocyte secretion of IL-1 β , thereby amplifying local inflammation and epithelial injury^[159, 165-167]. NET formation also increases airway mucus production and viscosity, contributing to airway obstruction^[168-169]. Post-rhinovirus infection, extracellular double-stranded DNA levels—indicative of NET activity—are significantly elevated and strongly associated with IL-5 and IL-13 levels^[156]. Animal studies have further demonstrated that inhibiting NET formation, either through NE inhibition or DNase treatment, can attenuate virus-induced type 2 inflammation^[156]. Recent evidence suggests that IL-33 can directly induce NET release, and blockade of IL-33 signaling reduces NET formation and alleviates asthma exacerbations^[170]. Additionally, IgE-dependent mechanisms may potentiate NET formation, promoting chronic airway inflammation. Clinically, NET-associated markers such as MPO, matrix metalloproteinase-9 (MMP-9), and CXCL8 are significantly elevated in patients with severe asthma^[162].

In conclusion, while NETs play a protective role in pathogen trapping and clearance, their excessive accumulation leads to heightened airway inflammation and structural damage, making them a true "double-edged sword" (*Fig. 2B*). Modulating the formation and clearance of NETs to maintain a

dynamic equilibrium may represent a novel therapeutic approach for virus-induced asthma. Potential strategies include targeting key NET components (e.g., MPO, NE, peptidylarginine deiminase 4 [PAD4]) or enhancing DNase-mediated NET degradation to restore epithelial barrier function—though caution is warranted, as excessive suppression may compromise antiviral defense. Given the potential heterogeneity of NET-mediated pathology across asthma endotypes, biomarker-guided and endotype-stratified studies are essential to elucidate their precise role.

Microbiota dysbiosis exacerbates defects in respiratory antiviral defense

From birth, the gut and lung microbiota are tightly interconnected through the gut–lung axis^[171]. Viral infections can both directly drive asthma-related inflammation and disrupt microbial homeostasis: for example, during RSV-associated acute respiratory infection, the abundance and gene expression of *Haemophilus influenzae* increase in the respiratory tract^[172], and overgrowth of *Haemophilus influenzae* can exacerbate allergic airway inflammation^[173]. In mice, influenza infection reshapes the gut microbiota—expanding *Enterobacteriaceae* while reducing *Lactobacillus/Lactococcus*^[174–175]. Conversely, the gut microbiota critically modulate antiviral immunity^[176]: ecological disruption in the gut disturbs the balance and recruitment of pulmonary immune cells, potentially heightening susceptibility to respiratory viral infection^[177]. An intact gut community preserves macrophage responsiveness to type I/II interferons and constrains viral replication^[178–179]. After antibiotic-induced depletion of the microbiota, mice with influenza exhibit higher morbidity/mortality, blunted antibody responses, reduced Th1 (IFN- γ) activity, and fewer virus-specific CD8⁺ T cells^[179–180].

Mechanistically, multi-omics studies indicate extensive gut microbe–metabolite–cytokine interrelationships in COVID-19 and its complications^[181]. Gut dysbiosis and barrier damage facilitate translocation of bacteria and bacterial products, driving lung inflammation *via* TLR4/NF- κ B signaling^[182]. Dysbiosis-associated pro-inflammatory mediators and microbial products may translocate into the circulation when intestinal barrier integrity is compromised^[183], whereas protective microbial functions—particularly short-chain fatty acid (SCFA) production—are often reduced in functional output^[184]. SCFAs exert anti-inflammatory and immunoregulatory effects through G-protein-coupled receptors and histone deacetylase inhibition^[185].

Influenza infection can also induce gut dysbiosis by increasing *Enterobacteriaceae* and decreasing *Lactobacillus/Lactococcus*. Such alterations influence adaptive immunity—including Tregs and Th17—by disturbing pulmonary immune cell balance and recruitment, thereby modulating lung inflammation^[186] and potentially increasing asthma risk.

In summary, microbial dysbiosis compromises mucosal antiviral defenses and amplifies type 2 inflammation through the gut–lung axis, thereby increasing viral susceptibility and aggravating asthma manifestations; reciprocally, respiratory viruses further destabilize the microbial ecosystem, establishing a positive feedback loop^[177] (**Fig. 2C**). These insights support microbiota-based interventions—using commensals or their derivatives to remodel the ecosystem and recalibrate innate antiviral thresholds and adaptive immunity—as potential strategies for virus-related asthma^[179].

Precision therapeutic strategies for virus-induced asthma

Given the central role of viral infections in acute asthma exacerbations, researchers have increasingly focused on developing targeted strategies for virus-induced asthma. These approaches aim to enhance antiviral immunity—such as boosting interferon responses—while suppressing virus-induced aberrant inflammation, without compromising host defense. Conventional treatments like ICS can partially control airway inflammation, but their efficacy during virus-triggered exacerbations remains limited. Virus-associated exacerbations may still occur despite guideline-based controller therapy, highlighting the need for targeted antiviral and immunomodulatory strategies.

Driven by recent mechanistic insights, several novel therapeutic pathways are under investigation. These include modulation of interferon signaling, inhibition of type 2 inflammatory pathways, restoration of epithelial barrier function, and the development of direct antiviral and prophylactic measures (**Fig. 3**).

Targeting IFN pathway

Interferons are central to early antiviral innate immunity, and deficient airway interferon responses in asthma are thought to increase susceptibility to virus-triggered exacerbations^[187]. This provides a rationale for therapeutic interferon augmentation.

Early proof-of-concept data suggested potential benefit in selected patients: in corticosteroid-resistant asthma, low-dose IFN- α was associated with

improvement in symptoms/lung function and reduced oral corticosteroid requirement^[188]. Subsequent studies focused on inhaled IFN- β to enhance local antiviral defense. In a randomized trial, inhaled IFN- β did not significantly reduce the overall rate of virus-associated

worsening, but subgroup analyses showed clinically relevant benefit in patients with more severe disease, including improved asthma control (ACQ) and lung function^[189]. A later phase 2 trial (INEXAS) also did not meet its primary efficacy endpoint^[190]. Taken

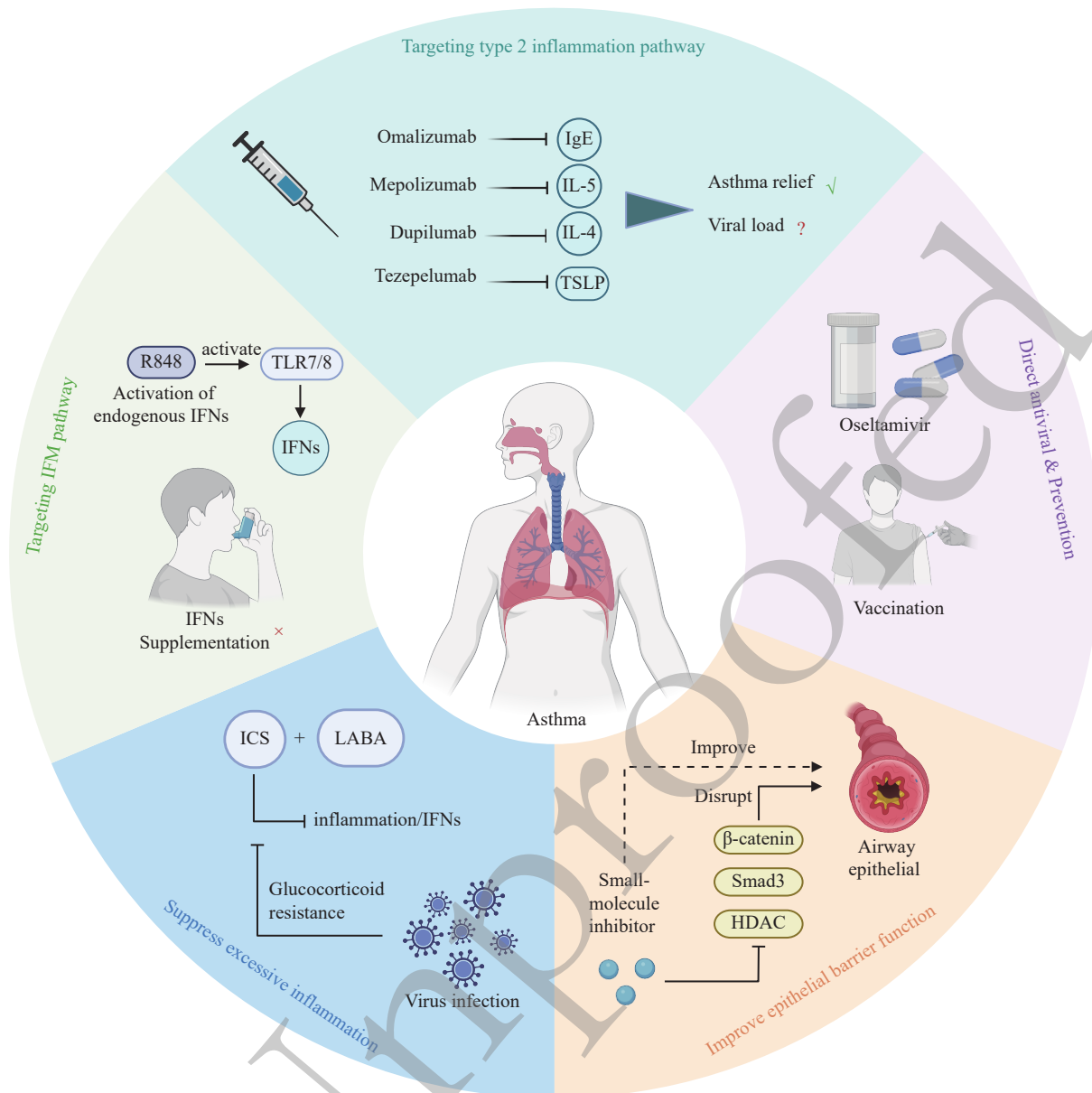


Fig. 3 Precision therapeutic strategies for virus-induced asthma. Precision therapeutic strategies for virus-induced asthma interferon pathway modulation (left, green). Agonists of endosomal TLR7/8 (e.g., R848) enhance innate antiviral immunity by inducing endogenous type I interferons. Direct interferon supplementation (inhaled or systemic) has shown limited efficacy and tolerability in clinical trials. Type 2 inflammation blockade (top, teal). Approved biologics—omalizumab (IgE), mepolizumab/reslizumab/benralizumab (IL-5/IL-5R), dupilumab (IL-4R α /IL-13), and tezepelumab (TSLP)—reduce exacerbation frequency across multiple asthma phenotypes. However, these biologics markedly alleviate asthmatic symptoms, yet their impacts on viral load remain unclear. Direct antiviral and preventive measures (right, purple). Influenza vaccination and neuraminidase inhibitors (e.g., oseltamivir) reduce infection-associated exacerbations. Recent advances include RSV vaccines (Arexvy, Abrysvo) for older adults and maternal immunization, as well as long-acting monoclonal antibodies (nirsevimab) for infant prophylaxis. Epithelial barrier restoration (bottom right, orange). Emerging strategies target structural abnormalities in the airway epithelium. Pharmacological modulation of β -catenin/CBP, SMAD3, or histone deacetylases (HDACs) can restore junctional protein expression and barrier integrity. Most remain at the preclinical or early translational stage. Broad anti-inflammatory control (bottom left, blue). Inhaled corticosteroids combined with long-acting β_2 -agonists (ICS/LABA) remain the cornerstone of maintenance therapy. Nevertheless, concurrent suppression of interferon responses limits their ability to fully prevent viral exacerbations. Abbreviations: HDAC, histone deacetylases; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; TLR7/8, toll-like Receptor 7/8.

together, these studies suggest that the key limitation may be timing of administration (treatment initiated too late in the cold/exacerbation trajectory), rather than a major safety barrier per se^[189-190].

Given these constraints, current strategies increasingly emphasize upstream induction of endogenous interferon pathways. In this context, intranasal TLR7/8 agonism (R848) increased nasal mucosal antiviral/immune mediators (including IFN- α 2a, IFN- γ , and chemokine responses) in asthma/allergic rhinitis, with transient eosinophil reduction and no evidence of problematic systemic inflammatory activation in that study^[191].

This prevention-oriented concept is now being extended to prophylactic mucosal IFN- λ priming: an ongoing Phase IIa trial in asthma is evaluating intranasal ETH47 (an IFN- λ 1 mRNA candidate) to test whether pre-emptive dosing can attenuate rhinovirus-associated symptom worsening (ClinicalTrials.gov: NCT07059767)^[192].

In parallel, RIG-I01 (a RIG-I agonist interferon booster) has shown preclinical antiviral activity (including influenza models) and has been publicly presented as progressing toward clinical development, further supporting upstream innate-interferon amplification as a preventive strategy^[193].

Suppressing excessive inflammatory responses

ICS remain the cornerstone of anti-inflammatory therapy in asthma. By inhibiting pro-inflammatory signaling pathways such as NF- κ B and reducing eosinophilic infiltration, ICS significantly lowers the risk of exacerbations and improves lung function in most patients. Numerous studies have demonstrated that combining ICS with long-acting β 2-agonists (LABAs) further enhances clinical efficacy. For example, in a 26-week randomized controlled trial, the addition of formoterol to ongoing ICS therapy reduced the risk of the first severe exacerbation requiring systemic corticosteroids by approximately 14%^[194]. As a result, ICS/LABA combination therapy is now recommended in national and international guidelines as standard maintenance treatment for patients with moderate-to-severe asthma due to its superior performance in symptom control and exacerbation prevention.

However, traditional broad-spectrum anti-inflammatory strategies do not fully prevent virus-associated asthma exacerbations. This limitation may be particularly relevant in patients with type 2-low, neutrophil-predominant, or severe uncontrolled asthma phenotypes, in which corticosteroid responsiveness is often reduced. In addition,

mechanistic evidence suggests that glucocorticoids may attenuate epithelial antiviral interferon signaling, which may partly explain why virus-associated exacerbations can still occur despite regular ICS/LABA therapy^[195]. Clinically, many patients experience worsening of symptoms during seasonal peaks of respiratory viral infections.

Therefore, relying solely on broad-spectrum anti-inflammatory agents is insufficient to block virus-triggered asthma attacks. Additional targeted interventions are necessary. With advancing understanding of asthma immunopathology, biologics targeting specific inflammatory mediators offer a novel perspective for the management of virus-induced asthma (see next section).

Biologics targeting type 2 inflammatory pathways

Virus-induced asthma exacerbations are frequently accompanied by robust type 2 inflammatory responses in the airways. Biologic agents targeting the type 2 axis have increasingly demonstrated their value in the prevention and management of virus-related asthma.

The anti-IgE monoclonal antibody omalizumab has been shown to reduce both overall and virus-induced exacerbation rates in allergic asthma. In the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study on pediatric asthma, omalizumab was found to shorten the duration of RV infection (11.2 days vs. 12.4 days, $P = 0.03$), significantly reduce viral load, and decrease the risk of RV-associated exacerbations by 36%^[86]. This study demonstrated that blocking the IgE pathway may enhance host viral clearance and reduces the likelihood of virus-triggered asthma exacerbations. In a preseasonal randomized trial in inner-city children with asthma, omalizumab reduced fall exacerbations compared with placebo, whereas the comparison between omalizumab and an ICS boost was more nuanced and appeared most evident in children with an exacerbation during the run-in phase^[196].

Anti-IL-5/IL-5R monoclonal antibodies, such as mepolizumab, reslizumab, and benralizumab, have shown strong efficacy in reducing exacerbation rates in patients with severe eosinophilic asthma^[197]. Because eosinophils can participate in antiviral host defense, IL-5/IL-5R blockade has raised questions about whether eosinophil depletion could influence viral clearance in selected contexts. In a placebo-controlled rhinovirus type 16 (RV16) challenge study in mild asthma, mepolizumab increased nasal RV16 load but did not worsen symptoms or lung function, indicating that its effects on antiviral responses may be context-dependent^[198]. The prospective MEX study

(the inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab) further showed that residual exacerbations during mepolizumab treatment are heterogeneous: approximately half were eosinophilic, whereas the remaining events were non-eosinophilic, neutrophil-high, and infection-associated^[199]. Therefore, these findings should not be interpreted as evidence of a generalized impairment of antiviral immunity by anti-IL-5 therapy, but rather as support for phenotype-guided assessment of residual exacerbations during biologic treatment.

Biologics targeting the IL-4/IL-13 axis also appear to influence virus-induced exacerbations. Dupilumab, a monoclonal antibody against IL-4 receptor alpha (IL-4R α), has been shown to significantly reduce exacerbation rates in moderate-to-severe asthma. In Phase III clinical trials, dupilumab reduced annualized severe exacerbation rates by approximately 47.7% (200 mg biweekly dose), and by as much as 65.8% in patients with high eosinophil counts, while also improving forced expiratory volume in 1 second (FEV₁) and asthma control scores^[200]. Since IL-4 and IL-13 can suppress innate antiviral responses (e.g., reducing interferon production by airway epithelial cells), blockade of this pathway may theoretically relieve suppression on antiviral signaling^[201]. Although no clinical trials have directly assessed dupilumab in the context of active viral infection, its substantial efficacy in preventing exacerbations suggests the possibility of indirectly improving antiviral immune competence through modulation of type 2 modulation. Observational data support this hypothesis: dupilumab has not been associated with an increased risk of viral infections. In fact, a post hoc analysis of major dupilumab trials reported a significantly lower incidence of respiratory infections in the dupilumab group compared to placebo (approximately 22% relative reduction in asthma patients, $P < 0.0001$), along with a reduced need for anti-infective medications^[202]. This contrasts with the observations for anti-IL-5 therapies, suggesting that IL-4/IL-13 blockade may indirectly strengthen host antiviral defense while mitigating type 2 inflammation.

Finally, biologics targeting epithelial-derived cytokines, particularly TSLP, have recently emerged as promising candidates^[203]. Tezepelumab, a monoclonal antibody that blocks TSLP, has demonstrated efficacy in reducing exacerbation risks in severe uncontrolled asthma due to its upstream mechanism of action. In the Phase III study to evaluate tezepelumab in adults and adolescents with

severe uncontrolled asthma (NAVIGATOR) trial, tezepelumab reduced annualized exacerbation rates by approximately 60%, with consistent benefits observed across both high and low eosinophil subgroups^[204]. Further analysis indicated that tezepelumab effectively reduced exacerbations throughout the year, including during autumn and winter viral seasons and spring allergen peaks^[205]. In other words, whether exacerbations are triggered by seasonal allergens or respiratory viral infections, TSLP blockade confers broad protective effects.

Mechanistically, anti-TSLP therapy attenuates virus-induced hyperinflammatory responses by suppressing downstream type 2 cytokines and eosinophilic inflammation. Clinical trials showed that tezepelumab significantly reduced blood eosinophil counts and fractional exhaled nitric oxide (FeNO) levels, while improving lung function and quality of life^[204]. Importantly, tezepelumab did not increase infection-related adverse events, demonstrating strong safety alongside its robust efficacy in reducing exacerbations. These findings suggest that upstream-targeted biologics may achieve a balance between anti-inflammatory and antiviral needs, offering a novel strategy for the comprehensive management of virus-induced asthma exacerbations.

Improvement of epithelial barrier function

The airway epithelial barrier serves as the first line of defense against pathogens, and its integrity is crucial for preventing virus-induced asthma exacerbations. Studies have shown that bronchial epithelium in asthma patients commonly exhibits barrier dysfunction, characterized by decreased expression of E-cadherin and tight junction proteins, leading to increased permeability and facilitating viral entry and downstream inflammation^[206]. Therefore, enhancing epithelial barrier function is considered a promising strategy to reduce the risk of virus-associated asthma.

Currently, multiple studies are exploring approaches to restore abnormal airway epithelium in asthma. Targeting the WNT/ β -catenin signaling pathway has shown promise: small-molecule inhibitors that block the interaction between β -catenin and the coactivator CBP can suppress EMT and restore E-cadherin-mediated cell-cell adhesion, thereby improving barrier function^[206]. In addition, the TGF- β /SMAD3 pathway also contributes to EMT. Use of the SMAD3-specific inhibitor SIS3 has been shown to upregulate E-cadherin expression and reverse structural abnormalities in allergen-exposed airway epithelial cells^[207].

Epigenetic regulation also plays a key role. In bronchial epithelial cells of asthma patients, elevated expression of histone deacetylases (HDAC1 and HDAC9) increases HDAC activity, which suppresses genes encoding tight junction proteins and compromises barrier stability^[208]. Encouragingly, HDAC inhibitors can upregulate the expression of tight junction proteins such as occludin, enhancing intercellular junctions and potentially restoring epithelial integrity^[209].

Overall, epithelial repair strategies remain in preclinical stages but have demonstrated promising potential in limiting viral invasion and stabilizing airway homeostasis. In the future, combining such approaches with anti-inflammatory and antiviral therapies may offer multi-level protection against virus-induced asthma exacerbations.

Direct antiviral and preventive strategies

Given the role of respiratory viruses in asthma exacerbations, direct interventions targeting the viruses themselves—such as antiviral drugs and vaccines—are indispensable components of asthma management.

RSV and RV are among the most common viral triggers. The long-standing absence of an effective RSV vaccine was broken in 2023 with the approval of GSK's Arexvy and Pfizer's Abrysvo, both authorized for preventing lower respiratory tract infections in older adults^[210-211]. Additionally, the U.S. Food and Drug Administration (FDA) has approved Abrysvo for administration to pregnant women between 32–36 weeks of gestation to protect newborns^[212]. The new long-acting monoclonal antibody nirsevimab was approved in 2022 for passive immunization in infants^[213]. Unlike RSV vaccines, nirsevimab provides passive protection rather than active immune memory, and its use extends RSV prevention to the general infant population entering the first RSV season, including term-born infants without traditional risk factors^[213]. However, current prevention strategies mainly target the first RSV season, whereas second-season protection is generally reserved for selected high-risk children. Therefore, whether reducing RSV-associated lower respiratory tract infection in early infancy can prevent preschool wheeze beyond infancy or school-age asthma remains uncertain. Consistently, previous palivizumab studies suggested reduced early recurrent wheezing in preterm infants^[25], whereas the MAKI trial showed no major effect on physician-diagnosed asthma or lung function at 6 years^[24].

In contrast, RV remains without a broadly protective vaccine or specific antiviral therapy due to

its over 160 strains and marked antigenic diversity. The development of RV-targeted vaccines and neutralizing antibodies is hampered by this extensive variability.

Nonetheless, recent efforts have attempted to overcome this challenge. An adjuvanted rhinovirus vaccine candidate (APL-10 456) has been shown to induce cross-reactive humoral and Th1-polarized cellular immune responses against multiple RV strains in preclinical models, suggesting a potential strategy to address antigenic diversity, although clinical efficacy remains to be established^[214].

Current treatment strategies primarily rely on enhancing host immunity, controlling inflammatory responses, and providing supportive care throughout the course of infection. Nevertheless, direct antiviral approaches are also being actively explored. Vapendavir, an oral capsid-binding inhibitor targeting rhinovirus, has recently been evaluated in a phase 2a placebo-controlled human rhinovirus challenge study in patients with chronic obstructive pulmonary disease (COPD), demonstrating reductions in viral load and respiratory symptom severity. Although not yet studied in asthma, these findings provide proof-of-concept evidence that targeted antiviral therapy may represent a promising future strategy for virus-induced airway exacerbations^[215].

For influenza viruses, vaccination significantly reduces the risk of asthma exacerbations. In the event of infection with influenza A or B viruses, timely use of neuraminidase inhibitors such as oseltamivir can alleviate disease severity and prevent acute exacerbations^[216]. A retrospective study of the 2009 H1N1 influenza outbreak found that among asthma patients receiving standardized oseltamivir treatment, those infected experienced more wheezing and pneumonia, but their hospitalization and intensive care rates were not significantly different—suggesting that proper antiviral therapy helps mitigate disease progression^[216].

The COVID-19 lockdown period further provided a natural experiment for viral prevention. During lockdown, common respiratory virus detection and pediatric asthma emergency visits declined markedly, and the usual seasonal pattern of childhood asthma exacerbations was suppressed. Conversely, relaxation of restrictions was followed by a rebound in acute respiratory infections and asthma exacerbations^[217-219]. These observations reinforce the contribution of respiratory viruses to seasonal asthma activity and support vaccination, passive immunization, and targeted antiviral strategies as more sustainable forms of primary prevention.

In summary, antiviral and vaccine-based interventions play a critical role in preventing virus-induced asthma exacerbations. RSV vaccines and monoclonal antibodies offer protection to high-risk populations; influenza vaccines and antiviral agents are widely used; and effective strategies against rhinovirus remain under development. Future advancements in broad-spectrum antiviral technologies hold promise for further reducing the burden of virus-associated asthma.

Conclusions

Overall, the relationship between respiratory viruses and asthma is best understood as a dynamic immunopathological network rather than a simple infection-trigger model. The bidirectional interactions among viral pathogens, airway barrier integrity, innate antiviral responses, adaptive immune polarization, and the microbiota collectively determine susceptibility to exacerbations and disease severity. Respiratory viruses exploit pre-existing defects in epithelial and innate antiviral defenses in asthma, while simultaneously amplifying type 2-, Th17-, and

neutrophil-associated inflammation, ultimately driving severe and recurrent exacerbations. This framework not only unifies many previously fragmented observations across virology, immunology, and clinical asthma research, but also highlights a major translational implication: effective treatment of virus-induced asthma will require coordinated control of viral replication, immune dysregulation, and airway structural vulnerability. Future progress in the field will depend on identifying actionable biomarkers, defining exacerbation-prone endotypes, and developing integrated therapies that combine antiviral, immunomodulatory, and barrier-restorative functions. Such advances may shift asthma care from reactive exacerbation control toward mechanism-based prevention.

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Table 1 Age-dependent roles of respiratory viruses in asthma exacerbations

Virus	Preschool children	School-age children/Adolescents	Adults
RV ^[9-21]	Most common cause of viral wheezing and asthma exacerbation; RV-induced wheezing in early life is strongly associated with later asthma development, especially RV-C	Major trigger of asthma exacerbation; association with asthma may persist into adolescence	Most frequently detected virus in adult asthma exacerbations
RSV ^[4, 12, 22-29]	Major cause of bronchiolitis and recurrent wheezing in infancy; severe RSV infection is associated with an increased risk of later asthma development	Increased prevalence of asthma and recurrent wheeze may persist into adolescence	Less common trigger of asthma exacerbation compared with RV
hMPV ^[30-32]	Important cause of bronchiolitis and wheezing in young children; early-life infection may increase the risk of later asthma development	Can trigger asthma exacerbations in children and adolescents	Detected in adult asthma exacerbations, although less frequently than RV and RSV
EV-D68 ^[33, 35-40]	Can induce severe wheezing and respiratory distress in young children; early-life infection may influence later airway inflammation	Strongly associated with acute asthma exacerbations and hospitalization during outbreaks	Less commonly reported in adult asthma
HBoV ^[41-43]	Associated with wheezing and bronchiolitis in young children; may be linked to later asthma development	Limited evidence for an association with recurrent wheezing or asthma	Rarely reported in adult asthma exacerbations
Influenza virus ^[44-51]	Seasonal trigger of wheezing and asthma exacerbation in children	Important cause of acute asthma exacerbations during influenza seasons	Major trigger of severe asthma exacerbations and hospitalization, particularly during influenza A outbreaks
Coronaviruses ^[52-63]	Seasonal coronaviruses may occasionally trigger wheezing or asthma exacerbations	Generally less frequent triggers compared with RV or influenza	SARS-CoV-2 may exacerbate asthma in some patients, although asthma is not consistently associated with worse COVID-19 outcomes

Abbreviations: COVID-19, coronavirus disease 2019; EV-D68, enterovirus D68; HBoV, human bocavirus; hMPV, human metapneumovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RSV, respiratory syncytial virus; RV, rhinovirus.

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