

## Respiratory Viruses Associated with the Genesis and Exacerbation of Asthma

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### Abstract

Asthma is a chronic disorder characterized by inflammation of the airways, with increased mucus secretion and bronchial hyper-reactivity, all of which cause reversible obstruction of air flow. Chronic inflammation, altered epithelium, and airway remodeling increase susceptibility to many environmental factors such as viral infections and allergens.

The epidemiological association between viral bronchiolitis in childhood, especially associated with respiratory syncytial virus (RSV), and the subsequent development of asthma has been described for decades. The different response of children after RSV infection could depend on genetic factors related to the immune balance of the lymphocytes. In recent years, it has been observed that not only RSV bronchiolitis is a risk factor for childhood asthma, but infection by other viruses such as human metapneumovirus and rhinovirus, among others.

Recently, studies based on polymerase chain reaction (PCR) techniques have considerably detected the proportion of asthma exacerbations associated with viruses, identifying RSV and Rhinovirus (RV) as the most frequent.

Both RSV and RV are transmitted primarily through direct contacts and aerosol particles. Both viruses replicate in ciliated epithelial cells of the upper and lower airways, which bind to unique cellular receptors to intercellular adhesion molecule 1 used by RV-B and most RV-As low-density lipoprotein receptors. used by some RV-As, cadherin-related family member 3 (CDHR3) used by RV-C, and CX3CR1 used by RSV. RSV induces apoptosis and necrosis of epithelial cells and generally causes more damage to the airway epithelium compared to RV. Currently in our country, we do not have specific vaccines for RSV and RV.

**Keywords:** Asthma; Respiratory Viruses; Bronchiolitis; Children

### Introduction

Asthma is a chronic disorder characterized by inflammation of the airways, increased mucus secretion, and bronchial hyperresponsiveness, all of which cause reversible obstruction of air flow. Chronic inflammation, altered epithelium, and airway remodeling increase susceptibility to many environmental factors, such as viral infections and allergens [1].

Asthma is the most frequent chronic respiratory disease in the world. It can affect any human being, regardless of all races, ages, or gender. Asthma does not distinguish socioeconomic status or geographic region, since it affects both the population of large cities and marginal and rural areas [2].

Prediction of childhood asthma has been limited for many years to the evaluation of traditional risk factors, such as atopic characteristics (sensitization to aeroallergens, increased blood eosinophil count or atopic eczema), parental asthma, or factors related to atopy parental.

Bronchiolitis is a virus-induced infection with inflammation of the small bronchioles and their surrounding tissue. Clinically, it is characterized as the first expiratory respiratory distress in children younger than 2 years. Other symptoms of the lower respiratory tract include dry cough, tachypnea, hyperinflation, chest retraction, and generalized crepitus or wheezing [1].

Wheezing is defined as a hissing sound during expiration accompanied by dyspnea. Wheezing can be diagnosed if there is a reversible obstruction of the expiratory airway and the disease does not meet the diagnosis of bronchiolitis or asthma. Furthermore, wheezing is divided into different phenotypes based on natural history, such as “early transient”, “persistent” and “late-onset” wheezing. Typically, the last 2 phenotypes are most closely associated with sensitization and asthma [1].

Recurrent wheezing is defined as the parent’s report of at least two episodes of wheezing, with at least one episode in the third year of life. Severe bronchiolitis is defined as hospital admission before the age of 1 year for acute non-bacterial infection of the lower respiratory tract. In the case of allergy there is the term “hyperreactivity” which means an exaggerated response of that structure to a given physical, chemical or biological stimulus, clinically manifesting as a symptom; such is the case of cough, runny nose, itching, or wheezing.

The World Health Organization (WHO) and the International Forum of Respiratory Societies (FIRS) estimate between 300 and 235 million asthma patients worldwide, respectively. In Mexico, according to the WHO, 7% of the population suffers from asthma, which means approximately 8.5 million Mexicans sick with this chronic respiratory disease [2,3]. In 2014, asthma and asthmatic status were reported as the 12<sup>th</sup> cause of morbidity, and the 19<sup>th</sup> place as the cause of general mortality, in the Single Information System for Epidemiological Surveillance (SUIVE) [3]. The prevalence of bronchiolitis is approximately 20% to 30% in the first year and 10% to 20% in the second year of life [1].

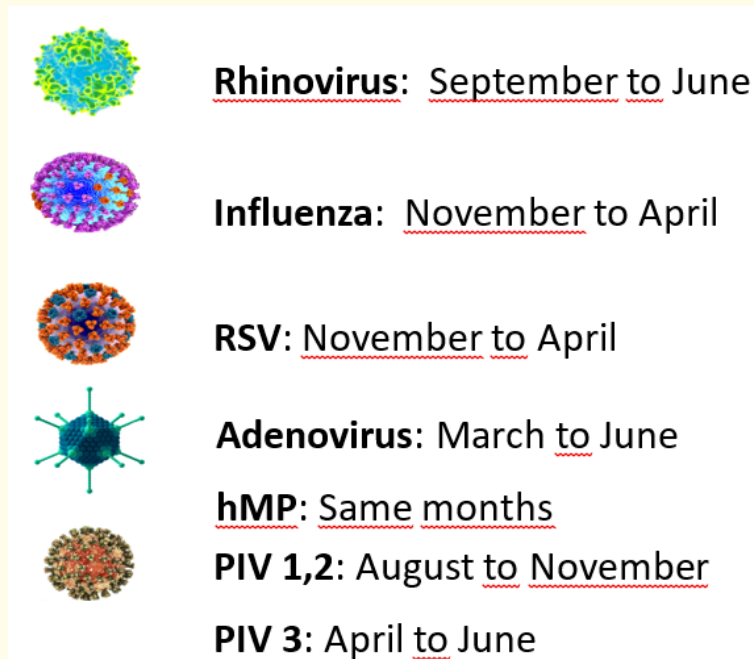
Acute wheezing with rhinovirus (RV) and respiratory syncytial virus (RSV) are early markers of recurrent wheezing. Furthermore, childhood RV-induced wheezing episodes are an important risk factor for subsequent asthma, especially in children with atopic characteristics. Once asthma sets in, exposure to allergens and infections are major triggers for asthma exacerbations in children [1].

After bronchiolitis, the presence of recurrent wheezing in children under 2 years of age has been observed in 75%, 7 - 59% in 2 to 4 years and 25 - 43% in 4 to 6 years. This manifestation has led clinicians who care for these patients to establish erroneous diagnoses and, above all, to implement unnecessary therapies [4].

Seasonal presentation of respiratory syncytial virus (RSV) and influenza activity are reported in the United States only in the winter months; parainfluenza virus (PIV) types 1 and 2 are seen in the fall and PIV-3 in the spring; human metapneumovirus (hMPV) infections are observed year-round, but peak in late winter and spring; and adenovirus is observed throughout the year, but respiratory epidemic adenovirus can occur in late winter and spring. 5 Rhinoviruses circulate throughout the year, with multiple coexisting genotypes and the highest prevalence in temperate climates occurs in early autumn and late spring [1]. Unlike respiratory syncytial virus infection, which peaked in the winter months, rhinovirus was detectable year-round, peaking between July and September, and November [6].

Globally RSV is responsible for approximately 3.4 million hospitalizations annually in children under the age of 57. Each year in the United States, on average, there are approximately 57,000 hospitalizations associated with RSV in children under the age of 5, and the

annual costs are approximately \$ 2.6 billion. Mortality related to RSV pneumonia in the United States is 3.1 per 100,000 people years in children younger than 1 year [5].



**Figure 1:** Seasonal duration of respiratory virus activity.

*Respiratory syncytial virus (RSV) and influenza activity are seen only in the winter months; parainfluenza virus (PIV) types 1 and 2 are seen in the fall and PIV-3 in the spring; human metapneumovirus (hMPV) infections are observed year-round, but peak in late winter and spring; and adenovirus is observed year-round, but epidemic respiratory adenovirus can occur in late winter and spring. Modified from: Noor A, Fiorito T, Krilov L. Cold weather viruses. Pediatrics in Review. 2019; 40:10. 497-507 DOI:10.1542/pir.2018-0237.*

RSV is the most common cause and is responsible for 80% of hospitalizations associated with bronchiolitis in children. Other cold weather viruses, such as influenza, parainfluenza virus (PIV) type 3, human metapneumovirus (hMPV), adenovirus (Adv), and rhinovirus (RV), also cause bronchiolitis [5,7,8]. In infants younger than 12 months, RV causes approximately 20% to 40% of bronchiolitis or episodes of acute wheezing in the emergency department and hospital and is only overcome by RSV. In children hospitalized for lower respiratory tract disease, RSV is most commonly detected up to 12 months of age, and RV is more common in older children [1,8].

## Etiology

### Respiratory syncytial virus

RSV is a pneumovirus of the Paramyxoviridae family and is a single-stranded enveloped RNA virus with 2 main antigenic groups, A and B; it forms several subgroups with 10 genotypes A and 13 genotypes B [1]. It is transmitted mainly by inoculation of the nasopharyngeal mucosa or the conjunctiva through direct contact with virus-containing secretions, fomites, or droplets. The incubation period is from 2 to 8 days.

It generally manifests for 2 to 4 days with low-grade fevers, runny nose, and nasal congestion followed by cough, tachypnea, and increased respiratory effort manifested by subcostal, intercostal, and supraclavicular retractions; nasal flaring; and grunts. Upon auscultation,

tion, bilateral crackles and scattered wheezing may be present on initial examination and absent afterwards. Chest radiography shows hyperinflation with radiolucency, flattened diaphragm, and peribronchial thickening. Irregular areas of atelectasis may be present, most often in the right upper and middle lobes, which can be misinterpreted as consolidation.

Respiratory disease due to bacterial coinfection with *Streptococcus pneumoniae* or *Staphylococcus aureus* is rare. However, RSV coinfection with respiratory viruses is observed in approximately a third of cases [5].

### Rhinovirus

They are non-enveloped positive chain RNA viruses (1). It is a member of the Enterovirus genus in the Picornaviridae family and is classified into 3 species (RV-A, RV-B and RV-C) divided into more than 100 serotypes.

They represent almost 50% of upper respiratory tract infections in children and adults. RVs have been identified in several studies as the second most common viral infection identified in association with bronchiolitis after RSV [5].

The RV-A and RV-C species cause more serious respiratory diseases than the RV-B species. Symptoms can persist for 10 to 14 days in children. The structural and genetic variability of the rhinovirus has inhibited efforts to develop antivirals [1].

RV-induced severe bronchiolitis/early wheezing is a stronger marker of asthma risk than wheezing episodes caused by RSV or other viruses. The Childhood Origins of Asthma (COAST) study showed that the risk of asthma at 6 years increased if children had RV wheezing (odds ratio [OR], 9.8) versus RSV (OR, 2.6) for the first 3 years, and in addition, 90% of children with RV-induced wheezing in the third year of life had asthma at 6 years (OR, 26) [1]. In a recent meta-analysis that included 15 original articles, it was documented that RV-induced wheezing in the first 3 years of life was associated with an increased risk of wheezing/asthma in later life [7].

In another study in China, children with rhinovirus infection were older and had allergic sensitizations, blood eosinophilia, and leukocytosis more frequently than those with respiratory syncytial virus infection, it was documented that children infected with rhinovirus experienced wheezing earlier than children with respiratory syncytial virus [6]. The combined influence of early viral wheezing and sensitization to aeroallergens has been clearly related to an even higher risk for the development of asthma by our group and others. The history of having a parent with asthma or atopy confers a higher risk of developing early wheezing in patients with respiratory infection by rhinovirus [8].

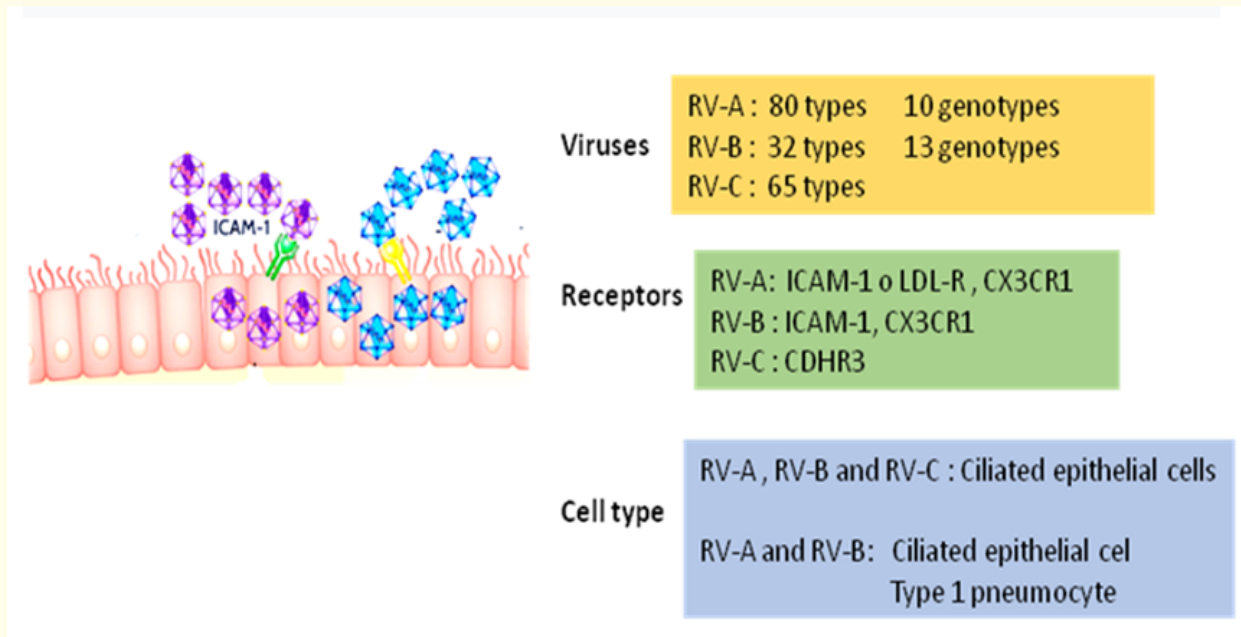
The interaction between allergy and viral infection is complex. This could be explained on the one hand, the allergen can increase the expression level of the intercellular adhesion molecule-1 (ICAM-1) in the epithelial cells of the mucosa, which is the binding molecule for most of the RV serotypes, which facilitates RV infection. On the other hand, respiratory viral infections, including RV, can trigger allergic conditions [9].

### Metapneumovirus

Described in the Netherlands in 2001, human metapneumovirus (hMPV) is an RNA virus belonging to the family Pneumoviridae, genus Metapneumovirus [10]. The incubation period is 5 to 9 days. Upper respiratory tract disease occurs as runny nose, cough, and fever, while lower respiratory tract disease occurs as bronchiolitis, croup, pneumonia, or asthma exacerbation. HMPV affects older children more often compared to younger infants. Therefore, hMPV causes clinically significant influenza-like early childhood disease. In healthy children, viral clearance is usually 7 to 14 days, but in immunocompromised individuals it can be prolonged [4,10-12].

### Influenza

Symptoms of an uncomplicated infection generally include fever, chills, headache, malaise, myalgia, and a non-productive cough. Nasal congestion, sore throat, otitis media, and myositis can also occur. Nausea, vomiting, and diarrhea are more common in children than in adults. In infants, influenza can cause various lower respiratory tract infections, including croup, bronchiolitis, and/or pneumonia.



**Figure 2:** Interactions of the RV and RSV with epithelial cells of the airways. ICAM-1, intercellular adhesion molecule 1; LDL-R, low-density lipoprotein receptor. Modified from: Jartti T, Gern J. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017; 140: 895-906.

High-risk individuals include children younger than 5 years (and especially < 2 years, who have higher rates of hospitalization for complications), those with chronic illness (including but not limited to asthma, sickle cell disease, diabetes mellitus, cerebral palsy, seizure disorders, and moderate to severe developmental delay), immune compromise, and morbid obesity (BMI  $\geq$  40). Influenza complications may include secondary bacterial infections (most commonly *S. aureus*, group A streptococcus, and *S. pneumoniae*), myocarditis, encephalitis, respiratory failure, shock, and / or a sepsis-like illness [5].

### Parainfluenza

Among PIVs, the most common type is PIV-3, acquired by two-thirds of babies at 12 months of age. Most PIV infections affect the tracheobronchial and lower airways, but similar illnesses have also been reported to influence. PIV-1 is the leading cause of croup (laryngo-tracheobronchitis) and, less frequently, PIV-2 has been isolated. PIV-3 is associated with pneumonia and bronchiolitis [5].

### Adenovirus

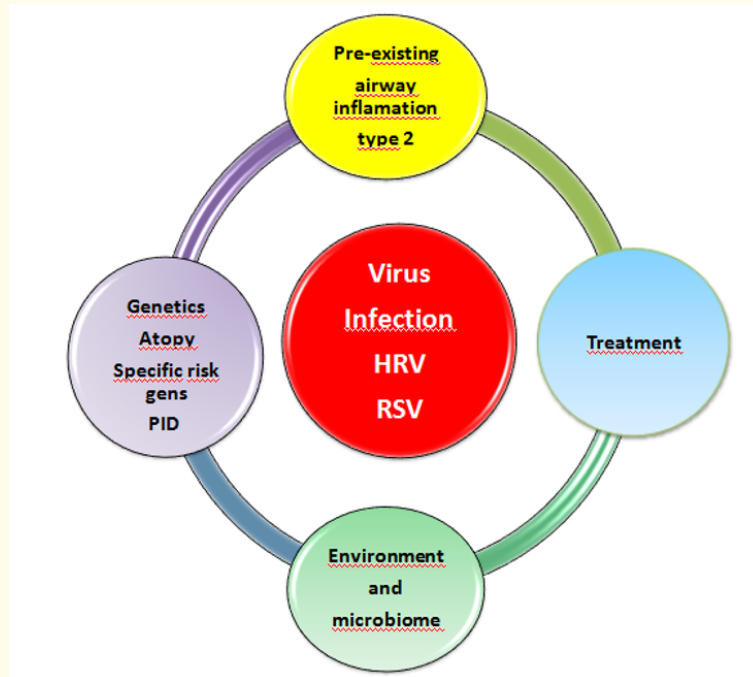
Respiratory infection by Adenovirus (Adv) has a wide spectrum of presentation, from symptoms of “common cold” to pneumonia, although it can also cause pharyngitis/tonsillitis, keratoconjunctivitis, croup, bronchiolitis, otitis media, hepatitis, gastroenteritis, meningitis or encephalitis [5].

### Pathophysiology

Asthma is a heterogeneous disease, where both predisposing factors coexist, which increase the risk of asthma, and triggers, which activate asthma. These interactions explain the heterogeneous clinical expression that can occur in each patient, which is known as phenotype [2].

Among the predisposing factors, associations have been described with alleles of more than 50 genes that participate in the interaction with environmental stimuli, the development of the immune response, the control of inflammation and tissue repair in the airways [3,4].

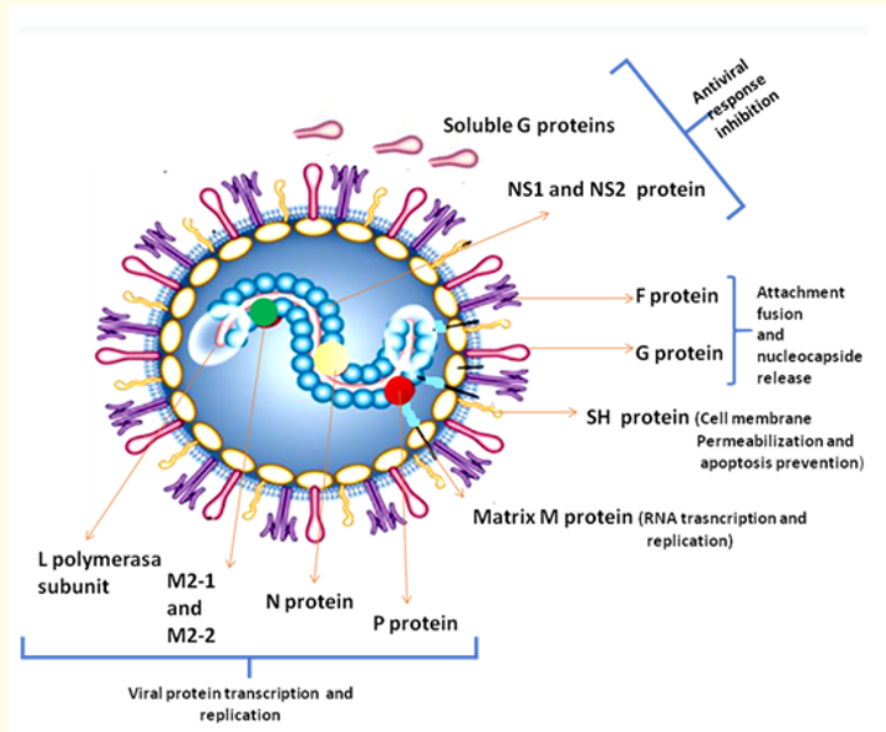
Once this predisposition is established, there are multiple triggers (allergens, infections, environmental pollutants, irritants, temperature changes, exercise, emotions) that can frequently cause exacerbations in patients with asthma [2,3].



**Figure 3:** Factors that contribute to the severity of virus-induced wheezing and subsequent risk of childhood asthma development. Modified from: Jartti T, Gern J. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017; 140: 895-906.

There are several interaction factors that contribute to the strong link between virus-induced wheezing and the risk of childhood asthma. First, some host factors can predispose children to infections and later to asthma. Second, viral wheezing can damage the airways to promote variable airway obstruction. Third, there may be interactions between risk factors and environmental exposures that promote asthma. Finally, the use of antibiotics, urbanization and increased hygiene cause the loss of microbial biodiversity. Low secondary interferon responses at early age, allergic sensitization, or both can increase susceptibility to viral infections and diseases. Many studies have linked RV-induced wheezing in early life with other atopic biomarkers, allergen-specific sensitization, increased eosinophil counts in nasal mucus or blood, or the presence of atopic eczema, which have additive effects. on the risk of asthma [1].

RV and RSV are transmitted primarily through direct contacts and aerosol particles. Both viruses replicate in ciliated epithelial cells of the upper respiratory tract and in medium to large sized lower respiratory tracts. These viruses bind to unique cellular receptors: intercellular adhesion molecule 1 used by RV-B and most of the RV-As low-density lipoprotein receptors used by some RV-As, a member of family 3 related to cadherin (CDHR3) used by RV-C, and CX3CR1 used by RSV. RSV induces apoptosis and necrosis of epithelial cells and generally causes more damage to the airway epithelium compared to RV [8,13,14].



**Figure 4:** Structure of the respiratory syncytial virus. Modified from: Rossi G, et al. Respiratory syncytial virus–Host interaction in the pathogenesis of bronchiolitis and its impact on respiratory morbidity in later life. *Pediatric Allergy and Immunology* 2017; 28(4): 320–331.

After RV binding, infected cells recognize the molecular patterns associated with the RV pathogen through interaction with 2 different families of pattern recognition receptors: the Toll-like receptor (TLR) 2, TLR3, TLR7, and TLR8. and retinoic acid inducible gene I-like receptors. These receptors activate transcription factors (e.g. interferon regulatory transcription factor 7 and nuclear factor  $\kappa$ B) that promote the expression of type 1 and type III interferons and various inflammatory cytokine genes. Both viruses induce cytokines (IL-1, TNF, IL-6, IL-12, IL-18, and IFN- $\gamma$ ), chemokines (CCL3, CCL5, CXCL8, and CXCL10) and growth factors that activate and attract granulocytes, dendritic cells and monocytes at the site of infection. The combined effects of the virus and the inflammatory response lead to epithelial damage and shedding, mucus production, and ultimately airway obstruction causing wheezing [1,13].

There are several mechanisms underlying the association between RV wheezing in early life and the subsequent development of wheezing/asthma. First, RV infections can increase sensitization of the airways by altering the epithelial barrier. Second, RV can induce epithelial release of ‘new innate cytokines’ (TSLP, interleukin (IL) -25 and IL-33), creating a permissive environment for type 2 differentiation of dendritic cells, T cells, and innate lymphoid cells, leading to the production of proasthmatic cytokines IL-4, IL-5, and IL-13. Finally, RV infection can regulate the expression of genes that can increase susceptibility to asthma. These findings demonstrate that RV infection can activate a number of pathways that can have deleterious effects on the rapidly growing airways of young children [7,14].

#### Associated factors

Other factors associated with the development of asthma are preterm labor and low birth weight are associated with infant wheezing disorders in developed western settings, but the observed associations could be confounded by socioeconomic status. Children born late preterm (34 to < 37 weeks) had a higher risk of hospitalization for asthma and other wheezing disorders [15,16].

The risk of wheezing associated with exposure to tobacco smoke was higher in children with an allergic versus non-allergic family history. In a meta-analysis, it is reported that the incidence of wheezing and asthma in children and young people increases by at least 20%, so preventing parents’ smoking is of vital importance for the prevention of asthma [17,18].

Cumulative exposure to allergens during the first three years was associated with allergic sensitization, and sensitization at three years was associated with recurrent wheezing. In contrast, first-year exposure to cockroach, mouse, and cat allergens was negatively associated with recurrent wheezing [19,20].

**Virus identification**

Clinical practice guidelines do not recommend routine tests for viral bronchiolitis because it does not change the treatment for the individual patient. However, viral tests such as multiplex polymerase chain reaction (PCR) assays are useful for epidemiological monitoring, hospital cohort of patients, definitive diagnosis and limitation of unnecessary antibiotic use [4,5]. Several new respiratory viruses and their subgroups and especially rhinovirus (RV) diagnoses, have improved markedly, for example RV-C does not grow in conventional cell cultures, delaying its discovery until 2006, approximately 50 years after the first discovery. Because RVs have many nucleotide sequences in common between the RNA genomes of the various serotypes, especially in the non-coding region at end 5', PCR assays have been designed and widely used for the detection of RV. Over the past 5 to 10 years, the availability of multiplex PCR has proven to be the most sensitive viral detection method for RSV, with a sensitivity and specificity of 100% and 89%, respectively. Other methods for detection of RSV include viral culture which was previously the standard, but they need 3 to 5 days to observe a syncytial cytopathic effect, in addition to the required experience; and RSV antigen detection assays are less sensitive than PCR but have good specificity and are less expensive [5].

For detection of the influenza virus, samples should ideally be collected within the first 72 hours of illness because the amount of viral particles released is decreased as the disease progresses. PCR is highly accurate and is considered the gold standard for influenza testing. These assays can detect nucleic acids in respiratory samples for prolonged periods and have improved sensitivity compared to rapid antigen detection assays.

**Diagnosis of asthma and differential diagnoses**

Signs and Symptoms	Alternative Diagnoses
Persistent runny nose	Infectious/allergic rhinosinusitis
Stridor; noisy breathing worsens when crying, eating, supine, or with respiratory infection	Narrowing of the upper airway, croup, intrinsic tracheitis, laryngomalacia, extrinsic tracheal stenosis, vascular ring, tumor.
Acute onset of coughing, wheezing, or stridor during food or play; history of suffocation, recurrent pneumonia at the same site	Foreign body inhalation Food aspiration/gastric content.
First episode wheezing in children <1 year	Bronchiolitis
Sick contacts, focal signs on chest x-ray	Pneumonia, atelectasis, tuberculosis, whooping cough.
Serious paroxysms of cough, possibly initially associated with a 'scream'	Pertussis
Premature birth, prolonged supplemental oxygen needed ± mechanical ventilation.	Bronchopulmonary dysplasia
Symptoms since childhood, recurrent pneumonia, focal signs on chest radiography	Congenital pulmonary malformation of the airways.
Chronic wet cough, palpitations, growth retardation, recurrent pneumonia, childhood onset, ± steatorrhea.	Bronchiectasis, cystic fibrosis
Neonatal respiratory failure, early onset throughout the year, daily cough, and nasal congestion ± situs inversus.	Primary ciliary dyskinesia

**Table 1:** Signs/symptoms that suggest an alternative diagnosis for asthma.

**Source:** FM Ducharme, SD Dell, D Radhakrishnan, et al. *Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. Can Respir J* 2015; 22: 135-143.



### Treatment

The basis of treatment in infants and young children with RSV infection is supportive, primarily attention to hydration and respiratory support. The use of bronchodilators, corticosteroids or inhaled hypertonic saline is not recommended, the use of ribavirin is not recommended due to its unproven efficacy.

Immunoprophylaxis against RSV approved by the FDA in 1998 is performed with palivizumab, a humanized monoclonal antibody that targets a highly conserved epitope on RSV glycoprotein F. Two randomized, multicenter, double-blind, placebo-controlled trials have shown a reduction in hospitalization related to RSV by 50% to 55%. The current guidelines of the American Pediatric Association recommend prophylaxis with palivizumab in the following cases [5,8]:

1. Infants born less than 29 weeks 0 days of gestation plus 12 months or less at the beginning of the season for RSV.
2. Infants in their first year after birth who have chronic lung disease using the definition of supplemental oxygen requirement for the first 28 days of life and again in their second year of life if they continue to require medical therapy (primarily oxygen) for lung disease chronic within 6 months of the start of the RSV season.
3. Infants younger than 12 months with cyanogenic or cyanogenic heart disease who receive medications to control heart failure and will require heart surgery. Palivizumab is administered intramuscularly at a dose of 15 mg/kg once every 30 days during the RSV season up to 5 doses.

In influenza infection, rapid treatment (ideally, < 48 hours from the onset of symptoms) with oseltamivir, a neuraminidase inhibitor that acts as a competitive inhibitor by binding to the active site of the enzyme, is recommended. The early blocking of this activity prevents the formation of virions and leads to the aggregation of viruses on the cell surface, preventing the subsequent infection of new cells. There are currently 3 antiviral medications available to treat influenza in children: oral oseltamivir, inhaled zanamivir, and intravenous peramivir. A new antiviral agent, baloxavir, was approved in October 2018 for use in patients older than 12 years with uncomplicated influenza [22,23].

### Prophylaxis

Vaccines: For RVs the development of a vaccine is hampered by the large number of serotypes and the immunity specificity of the serotype. The large number of antigenically distinct types of RV has been a barrier to vaccine development. Approximately 60 vaccine candidates are at different stages of development for RSV. There is no available vaccine for hMPV or prophylactic antibody for prevention, but there are several candidates in development. There is a live oral vaccine for targeting adenovirus serotypes 4 and 7, approved by the FDA in 2011 for use exclusively by military personnel 17 to 50 years of age with increased risk of lower respiratory tract infection by these serotypes.

The best preventative measure against influenza is annual seasonal vaccination for children 6 months and older, the AAP recommends preferential use of the inactivated vaccine over the live attenuated vaccine. The effectiveness of the influenza vaccine is moderate, and a seasonal influenza vaccination history does not exclude a diagnosis of influenza.

### Conclusion

Most asthmatic exacerbations in children are associated with viral infections, especially with RSV and RV, knowing the pathophysiology of asthma is essential to determine and direct a specific treatment, always keeping in mind the alterations in the immune response, compared to viral infections in genetically predisposed subjects, who are the main implicated in the virus-asthma association, and make awareness measures for the parents to vaccinate their children.

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