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Citation for published version:

Jartti, T, Smits, HH, Bonnelykke, K, Cavkaytar, O, Elenius, V, Konradsen, JR, Maggina, P, Makrinioti, H, Stokholm, J, Hedlin, G, Papadopoulos, N, Rusczyński, M, Ryczaj, K, Schaub, B, Schwarze, J, Skevaki, C, Stenberg-hammar, K & Feleszko, W 2018, 'Bronchiolitis needs a revisit: distinguishing between virus entities and their treatments', *Allergy*. <https://doi.org/10.1111/all.13624>

Digital Object Identifier (DOI):

[10.1111/all.13624](https://doi.org/10.1111/all.13624)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Allergy

Publisher Rights Statement:

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13624

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Bronchiolitis needs a revisit:
distinguishing between virus entities and their treatments

Tuomas Jartti, MD,¹ Hermelijn H. Smits, PhD,² Klaus Bonnelykke, MD,³ Ozlem Cavkaytar, MD,⁴
Varpu Elenius, MD,¹ Jon R. Konradsen, MD,^{5,6,7} Paraskevi Maggina, MD,⁸ Heidi Makrinioti, MD,⁹
Jakob Stokholm, MD,³ Gunilla Hedlin, MD,^{5,6} Nikolaos Papadopoulos, MD, PhD,¹⁰ Marek
Ruszczyński, MD,¹¹ Klaudia Ryczaj, MD,¹² Bianca Schaub, MD,¹³ Jürgen Schwarze, MD,¹⁴
Chrysanthi Skevaki, MD,^{15,16,17} Katarina Stenberg-Hammar, MD,^{5,6,7} Wojciech Feleszko, MD,¹⁰
EAACI Task Force on Clinical Practice Recommendations on Preschool Wheeze.

¹Department of Pediatrics, Turku University Hospital and University of Turku, Turku, Finland;

²Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands;

³COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte

Hospital, University of Copenhagen, Ledreborg Alle 34, 2820, Gentofte, Denmark. ⁴Department of

Pediatric Allergy, Istanbul Medeniyet University Göztepe Training and Research Hospital, Istanbul

Turkey; ⁵Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden;

⁶Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden;

⁷Department of Medicine Solna, Immunology and Allergy Unit, Karolinska Institutet, and

Karolinska University Hospital, Stockholm, Sweden; ⁸Allergy Department, 2nd Pediatric Clinic,

University of Athens, Athens, Greece; ⁹Imperial College Healthcare NHS Trust, London, United

Kingdon; ¹⁰Allergy Dept., 2nd Pediatric Clinic, University of Athens, Greece and Division of Infection, Immunity & Respiratory Medicine, University of Manchester, UK; ¹¹Department of Pediatrics, Medical University of Warsaw, Warsaw, Poland; ¹²Department of Pediatric Pneumonology and Allergy, Medical University of Warsaw, Warsaw, Poland; ¹³Pediatric Allergology, Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, Member of German Center for Lung Research (DZL), LMU Munich, Germany; ¹⁴MRC Centre for Inflammation Research, University of Edinburgh, Queen's Medical Research Institute, Edinburgh, United Kingdom; ¹⁵ Institute of Laboratory Medicine, Philipps Universität Marburg, Marburg, Germany; ¹⁶ Universities of Giessen and Marburg Lung Center (UGMLC), Philipps Universität, Marburg, German Center for Lung Research (DZL), Marburg, Germany.

Short title: Bronchiolitis – distinguishing between viruses matters

Correspondence to: Dr. Tuomas Jartti, the Department of Pediatrics, Turku University Hospital, P.O. Box 52. FIN-20520 Turku, Finland. Phone: +358 40 7270 284. Email: tuomas.jartti@utu.fi. Fax: +358 2 313 1460.

Supported by EAACI grant for the Task Force on Clinical Practice Recommendations on Preschool Wheeze, Zürich, Switzerland, the Universities Giessen and Marburg Lung Center (C. Skevaki), the German Center for Lung Research (82DZL00502/A2; C. Skevaki), and the Deutsche Forschungsgemeinschaft -funded SFB 1021 (C04, C. Skevaki), and the Sigrid Juselius Foundation, Helsinki, Finland (T. Jartti).

The authors have **no conflict of interest** in connection with this manuscript.

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Key words: Bronchiolitis, respiratory syncytial virus, rhinovirus, virus, wheezing

Word count: 4724/4500

Word count of the abstract: 198/200

Figures and tables: 6/10 (6 figures)

References: 100/100

For Peer Review

Abstract

Current data indicate that the 'bronchiolitis' diagnosis comprises more than one condition. Clinically, pathophysiologically and even genetically three main clusters of patients can be identified among children suffering from severe bronchiolitis (or first wheezing episode): 1) Respiratory syncytial virus (RSV) -induced bronchiolitis, characterized by young age of the patient, mechanical obstruction of the airways due to mucus and cell debris and increased risk of recurrent wheezing. For this illness an effective prophylactic RSV-specific monoclonal antibody is available. 2) Rhinovirus -induced wheezing, associated with atopic predisposition of the patient and high risk for subsequent asthma development, which may, however, be reversed with systemic corticosteroids in those with severe illness. 3) Wheeze due to other viruses, characteristically likely to be less frequent and severe. Clinically, it is important to distinguish between these partially overlapping patient groups as they are likely to respond to different treatments. It appears that the first episode of severe bronchiolitis in under 2-year-old children is a critical event and an important opportunity for designing secondary prevention strategies for asthma. As data have shown bronchiolitis cannot simply be diagnosed using a certain cut-off age, but instead, as we suggest, using the viral etiology as the differentiating factor.

Abbreviations

AdV	adenovirus
BoV	bocavirus
CDHR3	cadherin related family member 3
DC	dendritic cell
Eos	eosinophil
Flu	influenza virus
GWAS	genome-wide association studies
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ILC	innate lymphoid cell
MDA	melanoma differentiation-associated protein
MoAb	monoclonal antibody
moDC	monocyte-derived dendritic cells
NK	natural killer cell
n-3 LCPUFA	omega-3 long-chain polyunsaturated fatty acid
OCS	oral corticosteroid
PIV	parainfluenza virus
RIG	retinoic acid inducible gene
RSV	respiratory syncytial virus
RV	rhinovirus
TCE3	third T-cell receptor
Th	T helper
TLR	toll-like receptor
TSLP	thymic stromal lymphopoietin

Introduction

Bronchiolitis is most often described as a virus-induced inflammation of small bronchioles and their surrounding tissue. According to different guidelines, its upper age limit varies from 6 or 12 months, 12 months being preferred by many European countries, to 2 years, used in the U.S.^{1,2,3} Clinically, bronchiolitis is characterized by expiratory breathing difficulty in infants. Other symptoms include cough, tachypnea, hyperinflation, chest retraction, widespread crackles and wheezing. Wheezing is generally not a mandatory criterion. Instead it is a descriptive term, defined as a whistling sound during expiration, often accompanied by dyspnea. It can be caused by obstruction at any level of the lower airways. However, when bilateral/polyphonic, inflammation is probable.

Bronchiolitis presents a huge clinical burden. Depending on the definitions, the prevalence of bronchiolitis has been between 18-32% in the first and 9-17% in the second year of life.^{2,3} At the same time, the overall risk of recurrent wheezing and asthma is 70% before school-age and 50% during schoolyears.^{1,4} However, patient characteristics and the risk of asthma strongly vary inside the bronchiolitis cohort thus revealing different disease entities, some of which have a markedly high risk of subsequent asthma development.

To that end, we propose a differentiation of bronchiolitis subtypes by specific viruses and a broad inclusion of children by extending the upper age limit from 6 or 12 months up to 2 years. Recent data clearly indicate that the two major viral causes of bronchiolitis, respiratory syncytial virus (RSV) and rhinovirus (RV), have distinct genetics, pathogenetic mechanisms, clinical characteristics and responses to treatments both regarding short and long-term outcomes.^{1,5-7} Thus, a general bronchiolitis diagnosis should be revisited, as the identification of different viruses associated with severe bronchiolitis should improve our understanding of the disease and open avenues for precision medicine.

Etiology and risk factors

By definition bronchiolitis is a virus infection, and PCR diagnostics has reached a 100% virus detection rate in severe bronchiolitis.⁸ RSV is the most important causative agent of bronchiolitis during infancy, and it has been detected in 50-80% of the hospitalized bronchiolitis cases (Fig. 1).^{9,10} RV is the second most common viral agent of bronchiolitis during infancy but it starts to dominate virus detection after 12 months (Fig. 1). The next most common viruses in connection to bronchiolitis are human bocavirus and human metapneumovirus followed by parainfluenza virus, adenovirus, coronavirus and influenza virus (Fig. 1). Virus coinfections, mostly with RSV and RV, occur in 10-40% of the severe cases, but reports on their clinical significance are inconclusive.^{9,10}

RSV belonging to the *Pneumovirus* genus in the *Paramyxoviridae* family, is an enveloped single stranded RNA virus with two antigenically different A and B subtypes with 11 and 23 genotypes, respectively.¹¹ Although severe reinfections have been reported in young children, they are generally mild.¹² Main risk factors for RSV-bronchiolitis include prematurity, chronic lung disease (low lung function), congenital heart disease, other underlying medical conditions and young age (1-6 months of age), i.e. conditions in which excessive mucus in the airways is problematic, as well as deficient interferon responses.²

RV belonging to the *Enterovirus* genus in the *Picornaviridae* family is a nonenveloped single-stranded RNA virus and it comprises a genetically diverse group of viruses. It has three distinct subgroups, A-, B- and C, which consist of 83, 32 and 55 genotypes, respectively.^{1,13} This antigenic diversity presents a major challenge when establishing protective immunity and developing vaccines.¹⁴ Risk factors for RV induced bronchiolitis include T helper 2 polarized immune responses, allergen exposure, impaired epithelial barrier, deficient interferon responses and diminished lung function.^{1,15}

Clinical characteristics

Acute bronchiolitis is a clinical diagnosis that requires epidemiological and virological data. In infants, few days of runny nose, fever and cough typically precede the signs of lower respiratory distress (nasal flaring, tachypnoea and subcostal recessions) (Fig. 2).^{1,2} In such a case, respiratory crackles are suggestive of RSV etiology whereas bilateral wheezing is suggestive of RV etiology.¹⁶ A plethora of other respiratory sounds can also be heard.

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4 Most infants with bronchiolitis present a mild clinical form that usually resolves in one to two
5 weeks and can be safely managed at home by well instructed parents. Adequate information
6 concerning the signs of deterioration (including low oxygen saturations) and the need for urgent
7 transfer to hospital is of critical importance.
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12 It is still not clear whether the type of virus detected in the nasopharynx could determine the degree
13 of severity of the infection. Most often RSV infection has been linked to more severe “non-wheezy”
14 bronchiolitis, need for possible intensive care unit admission and prolonged duration of stay.^{17,18}
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16 However, in 2002 a Greek case-control study showed that RV detected in the upper airways could
17 be strongly associated with episodes of increased severity.¹⁹ Other viruses have been less often
18 linked to severe illness.
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24 Since the early 1990’s there have been several efforts towards developing clinical severity scoring
25 tools for bronchiolitis. From the Severity Scoring Tool to Tal and modified-Tal scoring tools, there
26 have been several instruments validated and used both in research and in clinical management
27 settings.^{20,21} However, there is no tool developed to assess both clinical severity and quality of life
28 parameters for these children.
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34 Apart from using merely clinical severity scores, attempts have been made in order to cluster acute
35 bronchiolitis by phenotype. In 2016, four such phenotypes were introduced in two large multicenter
36 studies: Profile A was characterized by RV etiology, history of wheezing, wheezing at presentation,
37 eczema and older age of the patient; profile B by RSV etiology, wheezing at presentation, but no
38 history of wheezing or eczema; profile C was the most severely ill group, with a longer hospital stay
39 and high probability of RSV infections and intensive care unit treatments; and profile D had the
40 least severe illness, including non-wheezing children with a shorter length of hospitalization.¹⁸ The
41 heterogeneity apparent in the clinical profiles of the patients highlight the need for a more
42 personalized approach in the diagnostics and management of this condition.
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49 **Genetics**

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53 While RSV and RV are both common environmental exposures, is severe bronchiolitis relatively
54 rare. It therefore seems likely that other host factors than viruses, such as genetics, are important
55 risk factors as well. Unfortunately, the current understanding of bronchiolitis genetics is rather
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3 limited in this respect. A twin study estimated the heritability of RSV bronchiolitis to be only
4 16%,²² where as the estimated heritability of asthma is more than 50%.²³
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7 At present, genome-wide association studies (GWAS), including replication of identified loci, is the
8 preferred method for gene discovery, but only one, relatively small, GWAS of bronchiolitis has been
9 performed without genome-wide significant findings.²⁴ A number of susceptibility genes have been
10 suggested from candidate gene studies. Most studies focused on RSV-bronchiolitis and the reported
11 associations include genes related to immune regulation and surfactant proteins.²⁵ Several of these
12 genes have also been associated with asthma,²⁵ suggesting that the association between RSV-
13 bronchiolitis and later asthma development might partly be explained by shared genetics.^{1,18}
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20 Nevertheless, bronchiolitis is a poorly defined and highly heterogeneous disease entity with
21 variability in clinical presentation, age at infection, and triggering factors, as well as in the
22 underlying genetic mechanisms. For example, it would be expected that RV-bronchiolitis in older
23 children,¹⁸ a phenotype also characterized by a higher risk of asthma predisposition, would also
24 have a higher degree of shared heritability with asthma.
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30 The strongest asthma locus discovered to date, 17q21, has also been found to be associated with
31 wheezing during the early years of life.²⁶ Furthermore, there is an interaction to be found between
32 this locus and early wheezing in relation to the risk of later asthma. Wheezing episodes during the
33 early years of life are a much stronger risk factor for asthma in children with 17q21 risk variants
34 than in children without it, and this seems more pronounced for episodes triggered by RV than
35 RSV.²⁶
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41 Another asthma gene with a putative role in connection to bronchiolitis is the cadherin-related
42 family member 3 (*CDHR3*). This gene was first discovered as a susceptibility gene for early
43 childhood asthma with recurrent severe exacerbations.²⁷ Only later was it suggested from
44 experimental studies that *CDHR3* also functions as an RV-C receptor.²⁸ This was subsequently
45 confirmed clinically in the COPSAC and COAST birth cohort studies where the *CDHR3* risk
46 variant was specifically associated with early life respiratory episodes triggered by RV-C.²⁹ In line
47 with this, in a meta-analysis of *CDHR3* polymorphism in relation to bronchiolitis found an
48 association was found with non-RSV bronchiolitis, which is likely to be triggered by RV, while
49 there was no association with RSV bronchiolitis.³⁰ Thus, *CDHR3* gene variation could partly
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3 explain bronchiolitis heterogeneity by being associated with a phenotype characterized by recurrent
4 RV infections but not with phenotypes triggered by RSV or other viruses.
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7 Genetic studies might help us in understanding the functional and clinically more relevant subtypes
8 of bronchiolitis and provide basis for the targeted prevention of asthma. For this reason, future
9 studies should be powered toward genome-wide association analyses that are not limited by current
10 knowledge and could therefore allow for the identification of unexpected risk genes and novel
11 disease mechanisms. Optimally, such studies should include various clinical presentations and
12 assessment of viral triggers in order to elucidate subtype-specific mechanisms.
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18 19 **Microbiome**

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22 The complex communities of microbes inhabiting all parts of the human body are collectively
23 termed the microbiome. This immense microbial environment has the potential for stimulating the
24 developing immune system,³¹ as well as act as a disease modifier. The link between microbiome
25 and susceptibility to bronchiolitis and subsequent asthma has been explored both regarding the
26 airway and the gut microbiome, but the mechanisms behind the possible effects remain to be fully
27 understood.
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33 As it comes to the microbiome of the airways, a diverse microbiological continuity exists between
34 upper and lower airways..³² The dramatic development of the microbiome of the airways begins at
35 birth and is influenced by factors such as siblings, day-care attendance, antibiotics and prior
36 infections (Fig. 3).^{33,34} It has been speculated whether this low biomass compartment will obtain a
37 steady colonization pattern over time. Recent studies have suggested that certain microbial
38 colonization patterns prevalent already in early childhood may affect the risk of bronchiolitis and
39 precede the development of persistent wheeze or asthma.³⁵ Furthermore, the severity of the acute
40 respiratory infections may be modulated by the type of microbial community in the airways
41 independent of RSV or RV co-infection, while at the same time, both RSV and RV may increase
42 the severity of the infection independent of the bacteria.³⁴ It has also been shown that antibiotic
43 treatment during acute wheezing episodes in childhood greatly decreases the duration of the
44 symptoms, thus pointing toward microbial effects.³⁶ Likewise, a study of 1005 infants demonstrated
45 that certain airway microbiota profiles seemed to increase the severity of bronchiolitis.³⁷ The rate of
46 intensive care use and the length of hospital stay during the episode of acute bronchiolitis was
47 particularly high in infants with a *Haemophilus*-dominant profile but low in infants with a
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3 *Moraxella*-dominant profile. This, although low in statistical power, was especially apparent in
4 children with RSV bronchiolitis but not found for RV bronchiolitis. In a small randomized trial of
5 40 children hospitalized with RSV bronchiolitis, treatment with azithromycin during the acute
6 episode seemed to alleviate the subsequent risk of long-term respiratory morbidity.³⁸
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10 The microbiome of the human gut is shaped by an extensive ongoing maturation processes over the
11 first years of life. It undergoes rapid development,³⁹ while at the same time providing vast
12 stimulation for the child's developing immune system during a period when these encounters may
13 be critical for the training of the adequate immune responses.³¹ The composition of the microbiome
14 is shaped by the environmental encounters in early life and can be altered or perturbed by factors
15 such as antibiotics, delivery mode and diet.⁴⁰ A recent study demonstrated that children with a
16 delayed microbial maturation of the gut microbiome during the first year of life had a markedly
17 increased risk of recurrent wheezing and later asthma.³⁹ Conversely, an adequate microbial
18 maturation during this period seemed to protect the children, pointing toward possible future
19 preventive measures against childhood respiratory morbidity through manipulation of the
20 microbiome in early life.
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30 **Pathogenesis**

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33 Although RSV and RV viruses, like respiratory viruses in general, are transmitted via direct contact
34 or aerosol particles and replicate in epithelial cells of the airways, show RSV and RV infections
35 various common as well as distinct pathogenic mechanisms. Typically, as a result of innate immune
36 activation, an early burst of type I/III interferons will occur rapidly after respiratory viral infection.
37 This will be followed by an induction of cytokines, including alarmins, chemokines and growth
38 factors that activate and attract innate lymphoid cells, granulocytes, dendritic cells and monocytes
39 to the site of infection.^{1,41,42} The combined effect of the virus and the inflammatory response leads
40 to epithelial cell apoptosis, necrosis and epithelial sloughing, as well as mucus overproduction.
41 However, while RSV infections can lead to severe lower respiratory tract infection primarily in very
42 young children, tend RV infections to result in severe wheezing in slightly older children, those
43 with atopic predisposition in particular.¹ In order to understand these differences, we need a better
44 insight into the immunological events in the lungs in as a response to these early respiratory
45 infections.^{42,43}
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56 *RSV infections*

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4 The initial response of the mucosa to RSV infection is a strong induction of antiviral type I and III
5 interferons and interferon induced genes (Fig. 4A). As RSV has developed potent mechanisms to
6 evade this innate interferon response, is the virus able to infect most infants through RSV-NS1/2
7 proteins inhibiting IRF-3 and STAT-2 reducing both IFN-I and -III responses and RSV-F protein
8 suppressing IRF-1 through EGRF activation.⁴⁴⁻⁴⁷ While severe RSV bronchiolitis is associated with
9 weaker antiviral innate interferon responses, are data on the association between virus genome load
10 and illness severity discrepant.⁴⁷⁻⁴⁸
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17 Furthermore, ineffective inflammatory and adaptive immune responses are important factors that
18 contribute to severe RSV disease. As at birth the immune system is still immature and needs to
19 develop, it depends mostly on the innate immune system in response to toll-like receptor (TLR)
20 ligation and maternal-derived antibodies. At the same time pro-inflammatory innate immune
21 responses are not very prominent as anti-inflammatory cytokines, like interleukin (IL) -10 and
22 transforming growth factor (TGF) -beta, prevail since during pregnancy mother's immune system
23 protects the fetus.⁴⁹ As a consequence, T helper (Th)₁ cell skewing cytokines like IL-12 seem to
24 develop rather slowly in young infants, even in the presence of TLR ligating viruses and increased
25 type I interferon production.^{50,51} Interestingly, the cytokines IL-6 and IL-23, both potent inducers of
26 IL-17 producing T cells, were found to be increased in TLR-stimulated neonatal cells and neonates
27 were shown to have increased numbers of Th₁₇ cells (Fig. 4A).⁵² As enhanced pathology following
28 RSV infections is often associated with increased IL-17 production and this cytokine is more
29 prominent in neonates, the presence of this cytokine may contribute to a more severe disease
30 state.^{53,54} In addition, studies in neonatal mice have shown that there is a spontaneous early wave of
31 innate cytokines like IL-33, a Th₂ skewing cytokine, and a recruitment of innate lymphoid cells
32 (ILC) -2 into the lungs that reaches the maximum at day 14 after birth.^{55,56}
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45 Therefore, age-specific events in neonatal lungs seem to naturally support the initial development of
46 Th₂ immune responses that combined with a yet ineffective activation of innate immunity and IL-17
47 being upregulated in young infants, drive mucus hyperproduction and the promotion of severe
48 pathology during early RSV infections.⁵⁷ In addition, B cell function is not yet developed in very
49 young infants (<6 months of age) and it takes more time to generate a sufficient and sustained
50 antibody production. As at very early phase, babies still rely on maternal antibodies, are babies born
51 from a mother with high circulating neutralizing antibodies better protected from severe diseases.⁵⁸
52 This notion has led to the idea of developing a vaccine for RSV that targets pregnant mothers
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3 instead of young children. Thus through vaccinating the mothers the children would be provided
4 with an increased transfer of protective maternal antibodies against RSV.^{59,60}
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7 *RV infections*

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10 Rhinoviruses also target directly airway epithelial cells. RV type A frequently causes lower
11 respiratory tract infection, and RV type C in particular is linked to severe wheezing in infected
12 children.^{8,13,61} The increased risk of severe RV infection with wheeze in young children with a
13 strong family history of allergy and asthma may be explained by a partial defect in mucosal anti-
14 viral innate interferon responses, due potentially to early allergic airways inflammation (Fig. 4B).
15 The airway mucosa of asthmatics, who have allergic airway inflammation, has been shown to be
16 associated with reduced type I and III interferon responses.^{62,63} To understand the particularly high
17 pathogenic potential of RV-C it is important to note that *CDHR3* has recently been identified as a
18 unique receptor for RV-C.¹⁸ Interestingly, a polymorphism in the *CDHR3* gene (resulting in a
19 higher expression of *CDHR3* on the epithelial surface) was associated with the increased risk of
20 childhood asthma.²⁷ RV-C has also evolved specific molecular tools to reduce IFN- β expression
21 and downstream signaling in airway epithelial cells,⁶⁴ which may possibly explain the more severe
22 course of respiratory RV-C infections. In addition, RV infections of airway epithelial cells are
23 strong inducers of type 2 innate cytokines, like IL-25 and IL-33, which subsequently initiate or
24 boost type 2 immunity in the lungs via IL-5 and IL-13 producing innate lymphoid cells (ILC) 2 and
25 Th₂ cells (Fig. 4B). Surprisingly, the induction of innate cytokines by RV infections was stronger in
26 airway epithelial cells from asthmatics compared to healthy controls.⁶⁵ Also, the induction of type 2
27 innate cytokines may be more pronounced during early childhood, as compared to adult mice,
28 human rhinovirus infections in neonatal mice showed more pronounced IL-13 and IL-25
29 expression, mucus secretion and airway hyperresponsiveness.⁶⁶ This process may be further boosted
30 or co-occurring by an early spontaneous wave of IL-33-dependent type 2 cytokines and cells in
31 developing lungs of neonatal mice.^{55,56} Overall, although RV infections are linked to the induction
32 of milder epithelial inflammation than RSV infections, they tend to reduce type I IFN expression
33 and cause inflammation with Th2 cell characteristics, disrupted tight junction expression and high
34 cytokine levels that promote bronchospasm, oedema and mucus production and lead to airway
35 obstruction and wheeze.^{1,41}
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54 **Treatment**

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3 Substantial knowledge gaps and controversies exist in the management of acute bronchiolitis. Most
4 guidelines recommend primarily supportive treatment, i.e. oxygen, nasal suctioning, mechanical
5 ventilation and hydration.⁶⁷ High flow oxygen therapy using nasal cannula has shown promising
6 results.⁶⁸ There is conflicting information across clinical guidelines about the role of nebulized
7 hypertonic saline in acute management of bronchiolitis. Only a few current guidelines recommend
8 bronchodilators.² Overall, corticosteroids (see details below), nebulized epinephrine or antibiotics
9 are not recommended.² Because of the current frustration with the existing treatment modalities
10 (high use of bronchodilators, antibiotics and corticosteroids) and as the majority of the previous
11 trials have not been based on virus specific data, is further research required in order to direct focus
12 to more personalized management plans in the treatment of acute bronchiolitis.⁶⁹
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20 *Treatment for RSV*

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24 Palivizumab: Immunoprophylaxis with palivizumab, a humanized monoclonal antibody against the
25 RSV F glycoprotein, decreases the risk of hospitalization due to severe RSV illness among preterm
26 infants (72% reduction), those with chronic lung disease (65% reduction) and hemodynamically
27 significant congenital heart disease (53% reduction).⁶⁰ Interestingly, palivizumab has effectively
28 reduced recurrent wheezing following hospitalization due to RSV, but not asthma.⁷⁰
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34 Ribavirin: Convincing data supporting ribavirin treatment for severe RSV infection are lacking, and
35 its toxicity remains a concern. Therefore, ribavirin is not recommended in the current U.S.
36 guidelines.⁷¹
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41 New treatments: There are currently approximately 28 RSV vaccines and antibodies in preclinical
42 development and another 17 in clinical development.^{59,60} Several new molecules have been
43 identified for the treatment of RSV infection and are currently in (advanced) preclinical or clinical
44 development.^{72,73}
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48 *Treatment for RV*

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51 There are only few agents targeting the inhibition of the attachment of RV to the cell or uncoating
52 viral RNA, and their clinical applicability is continuously questioned due to adverse events
53 (pleconaril, vapendavir) or drug resistance (amantadine, rimantadine).^{72,73}
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3 Prednisolone: In two separate randomized trials oral corticosteroid, prednisolone, has been shown to
4 decrease the time to the physician-confirmed relapse within the following year by 20-30% and to
5 the initiation of asthma controller medication within the following 5 years by 30-40% in first-time
6 wheezing children with RV etiology. These results point out, that early systemic anti-inflammatory
7 control targeting the pre-existing and/or virus-induced airway inflammatory response could
8 significantly affect the natural course of asthma.⁷⁴⁻⁷⁷ Interestingly, all wheezing children with high
9 RV genome load treated with placebo developed a new physician-confirmed wheezing episode
10 within 100 days and initiation of asthma control medication within 14 months.^{76,77}
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17 In conclusion, according to our hypothesis regarding the various entities of bronchiolitis, we
18 emphasize that effective treatment of bronchiolitis should be administered on a more personalized
19 base than currently in practise and include various viral etiological factors. We do believe that
20 existing treatment methods (beta₂-agonists and corticosteroids) can be effective given the
21 assumption that they are intended for a distinct (RV-affected) high-risk group of patients. However,
22 there is an urgent and unmet need for new guidelines which would recognize this discrepancy and
23 for clinicians to understand that there is no more "common bronchiolitis".
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30 **Long-term sequela**

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33 Severe acute bronchiolitis experienced early in childhood is associated with an increased risk of
34 asthma that may persist into early adulthood.¹ It remains to be elucidated whether bronchiolitis is
35 the cause of lung injury that results in subsequent wheezing episodes and asthma development or if
36 there is an inherent predisposition to both acute bronchiolitis and latter asthma, with bronchiolitis
37 being an early marker of this predisposition. Regardless of possible underlying lung morbidity, the
38 major viral causes of acute bronchiolitis/first wheeze, RSV and RV, seem to have a different course
39 in post-bronchiolitis asthma sequela.
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46 Several observational studies have reported an association between RSV-bronchiolitis and
47 subsequent asthma development. For example, according to a population-based study (n=476) from
48 Tucson, Arizona, and a birth cohort study (n=150) from Australia RSV-induced lower respiratory
49 infection/bronchiolitis during early life is modestly associated with recurrent wheezing/doctor
50 diagnosed asthma at school-age (odds ratio 2.5-4.3) but not with atopy.^{78,79} Similar numbers have
51 also been found in preterm infants.⁸⁰ Only a small cohort study from Sweden has shown an
52 association between RSV-bronchiolitis and later allergic sensitization as well as asthma; by the age
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3 18, 41% of the RSV children were allergic and 39% had asthma compared to the 17% and 9% in the
4 control group, respectively.⁸¹
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8 To address the potential causality between RSV infection and subsequent asthma, prospective
9 studies with RSV-immunoprophylaxis have been performed. Two recent randomized controlled
10 trials showed that in preterm infants palivizumab, an anti-RSV monoclonal antibody, decreased the
11 parent-reported recurrent wheeze, but similar incidence of physician diagnosed asthma at age 6
12 years was found.^{82,83} Long-term effects of RSV prophylaxis appear less likely in infants with atopic
13 family history.⁶⁰ These results clearly indicate that RSV-infection is not causal to the asthma or
14 atopy development. One potential explanation for these results is that children with RSV infection
15 and subsequent asthma development may share common genetic vulnerability and/or environmental
16 exposures that predispose them to both diseases.⁸⁴
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24 In contrast to RSV bronchiolitis, atopy has been clearly associated with childhood asthma
25 development after RV-induced early wheezing. High risk (parental atopy or asthma) birth cohort
26 studies from Wisconsin, US, and Australia have shown that young children suffering from RV-
27 induced wheezing episodes are at high risk of school-age asthma (odds ratio up to, RV vs. RSV, 9.8
28 vs 2.6).⁸⁵⁻⁸⁷ The risk is especially high if children were sensitized at an age younger than 2
29 years.^{85,87} A recent study on hospitalized children show similar results: RV-induced severe first
30 wheezing episode at an age less than 2 years was a risk factor (odds ratio 5.0) for atopic asthma at
31 school-age along with early sensitization and eczema (odds ratio 12 and 4.8, respectively) while
32 RSV was associated with neither atopic nor non-atopic asthma.⁷ Therefore, data from these high-
33 risk birth cohorts suggest that atopic airways have an increased susceptibility for asthma
34 development after RV-induced bronchiolitis.
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43 **Primary and secondary prevention strategies of asthma**

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46 The primary prevention strategies of asthma aim at reducing the incidence of the disease by
47 identifying the individuals at risk and reducing their exposure to the potential risk factors. First, the
48 hygiene hypothesis evolved to cover the environmental microbial burden in general.^{88,89} However,
49 due to recent findings the scope of the hygiene hypothesis has enlarged to to cover the
50 environmental biodiversity in general. Thus, rapid urbanization, pollution and climate change, all
51 leading to the loss of biodiversity, promote chronic noncommunicable illnesses such as asthma,
52 allergies, diabetes, obesity and cancer,⁹⁰⁻⁹² where as frequent contact with animal lipopolysaccharides
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3 present in all we eat, touch and breath prevent atopy, allergic rhinitis and sometimes asthma.^{90,92}

4 Second, conditions during pregnancy are important. Maternal omega-3 long-chain polyunsaturated
5 fatty acid (n-3 LCPUFA) and vitamin D supplementation in the third trimester of pregnancy may
6 reduce the risk of persistent wheeze/asthma and respiratory infections in offspring (Fig 5).^{93,94}
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10 Secondary prevention strategies of asthma aim at avoiding the development of allergic
11 disease/asthma in already sensitized or wheezing subjects.⁹⁵ Thus far, allergen immunotherapy
12 remains as the only treatment available for modifying the course of allergic disease.⁹⁶ However,
13 although in a recent study grass pollen immunotherapy was shown to reduce asthma-like symptoms
14 in children, it did not decrease the development of asthma.⁹⁷ Interestingly though, a systemic anti-
15 inflammatory treatment of the first RV-induced severe wheezing episode markedly decreased the
16 subsequent risk for asthma (Fig. 5).(See treatment chapter).⁷⁴⁻⁷⁷ Also, a year-round and preseasonal
17 treatment with omalizumab has been shown to eliminate the seasonal peaks in asthma exacerbations,
18 most of which are associated with RV infection.⁹⁸ In addition to the reduction of allergic
19 inflammation by preventing IgE binding to its receptor, omalizumab also enhances the IFN- γ
20 response.⁹⁹ Thus, it has been argued that omalizumab may improve the antiviral responses. RSV
21 immunoprophylaxis with palivizumab has also been shown to reduce recurrent wheezing (see
22 treatment and long-term sequela chapters).^{60,70,82,83} In the development of RV vaccine, promising
23 results have been seen with a cross-reactive recombinant capsid protein in a mouse model.¹⁴
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36 Non-specific antiviral approaches to reduce asthma include strategies aiming at enhancing the
37 patient's resistance to multiple respiratory viruses through administration of interferons or other
38 immunostimulatory molecules.^{72,73} Strategies (microbial and others) to promote healthy epithelial
39 barrier and the development of mucosal immune responses that can better resist viral infection
40 might also help in preventing the development of asthma, as well as bacterial lysates, which may
41 reduce the recurrent wheezing by increasing antiviral activity.¹⁰⁰ However, the level of evidence
42 still remains to be low.
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49 Going forward, it will be important to identify the patients at high risk for asthma and to find the
50 specific primary and secondary prevention strategies for each individual patient (Fig. 5), e.g.
51 sensitization, eczema and the first severe wheeze caused by RV appear to predict atopic asthma,
52 while the first severe wheeze before 1-year-age, RV/RSV negative etiology and/or association with
53 parental smoking appear predict nonatopic asthma.⁷ In conclusion, these new insights into viral
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3 virulence, personal risk factors (genetics, allergy, and antiviral immunity) and environmental
4 exposures (farm, urban, microbes and nutrition) provide hope that in future we might be able to
5 reduce the occurrence of childhood asthma (Fig. 5).
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8 9 **Summary**

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11 Clinically and pathophysiologically three main clusters of patients can be identified among children
12 suffering from severe bronchiolitis/first wheezing episode (Fig. 6): 1) RSV-induced bronchiolitis is
13 characterized by young age of the patient and mechanical obstruction of the airways due to mucus
14 and cell debris. For the treatment of RSV-induced bronchiolitis there is a prophylactic RSV-specific
15 monoclonal antibody available that decreases the risk of recurrent wheezing. 2) RV-induced
16 wheezing is associated with atopic predisposition and high risk for asthma, which may be reversed
17 with systemic corticosteroid in patients with severe first episode. RV susceptibility, thus, serves as
18 an important early marker for asthma prone children. 3) Wheeze due to other viruses are likely to be
19 less frequent and severe. Clinically, it is important to distinguish between these three partially
20 overlapping patient groups, as they are likely to respond to different treatments. The first severe
21 episode of bronchiolitis or wheezing in a less than 2-year-old child appears to be a critical event and
22 an important opportunity for designing secondary prevention strategies for asthma. Thus,
23 bronchiolitis cannot simply be diagnosed using a certain cut-off age, but instead, viral etiology
24 should be used as the differentiating factor. For nomenclature, we suggest that there is an RSV-
25 induced bronchiolitis and an RV-induced first wheezing episode to better distinguish these
26 conditions.
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40 **Acknowledgements**

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43 The authors thank Mrs Agnieszka Sierakowska for her assistance with preparing the illustrations
44 and Miss Anna Eskola for editing the language for this article.
45

46 **Author contribution statement**

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49 All authors participated in drafting and writing the manuscript. The granting agencies covered costs
50 and played no role in the manuscript preparation.
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Or Peer Review

Legends to the figures

Figure 1. The frequency of viral etiologic agents according to the age of the hospitalized patients with the first episode of bronchiolitis or wheezing. Viral diagnostics were based on PCR (including rhinovirus C species) except for human bocavirus which was based on serology. RSV, respiratory syncytial virus; RV, rhinovirus; BoV, human bocavirus 1; MPV, metapneumovirus; PIV, parainfluenza virus; AdV, adenovirus; CoV, coronavirus; Flu, Influenza.⁸⁻¹⁰

Figure 2. Signs of bronchiolitis. The classic clinical presentation of bronchiolitis starts with symptoms of viral upper respiratory infection. Lower respiratory tract symptoms including persistent cough, tachypnoea and increased work of breathing (as shown by intercostal retractions, use of accessory muscles, grunting or nasal flaring) later follow. The latter symptoms may progress to severe hypoxemia and cyanosis. RSV, respiratory syncytial virus; RV, rhinovirus

Figure 3. Interactions between airway bacteria and virus in disease severity. The environment shapes the bacterial composition from early on and either as a consequence of this or a direct effect whether RSV and RV are prevalent. Interactions between the two in bronchiolitis episodes may determine the severity.

Figure 4. Pathogenesis of respiratory syncytial virus (A) and rhinovirus infection (B) in the airway epithelial cells of healthy children and those at risk. CDHR3, Cadherin related family member 3; DC, dendritic cell; Eos, eosinophil; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; MDA, melanoma differentiation-associated protein; moDC, monocyte-derived dendritic cells; NK, natural killer cell; RIG, Retinoic acid inducible gene; RSV, respiratory syncytial virus; RV, rhinovirus; TCE3, third T-cell receptor; Th, T helper cell; TLR, toll-like receptor; TSLP, Thymic stromal lymphopietin.

Figure 5. Major factors influencing asthma risk in young children suffering from bronchiolitis. RV, rhinovirus; RSV, respiratory syncytial virus; n-3 LCPUFA, n-3 (omega-3) long-chain polyunsaturated fatty acids.

Figure 6. Main entities of bronchiolitis. It is important to distinguish these patient groups since they are likely to respond to different treatments. Also, the first episode of severe bronchiolitis or

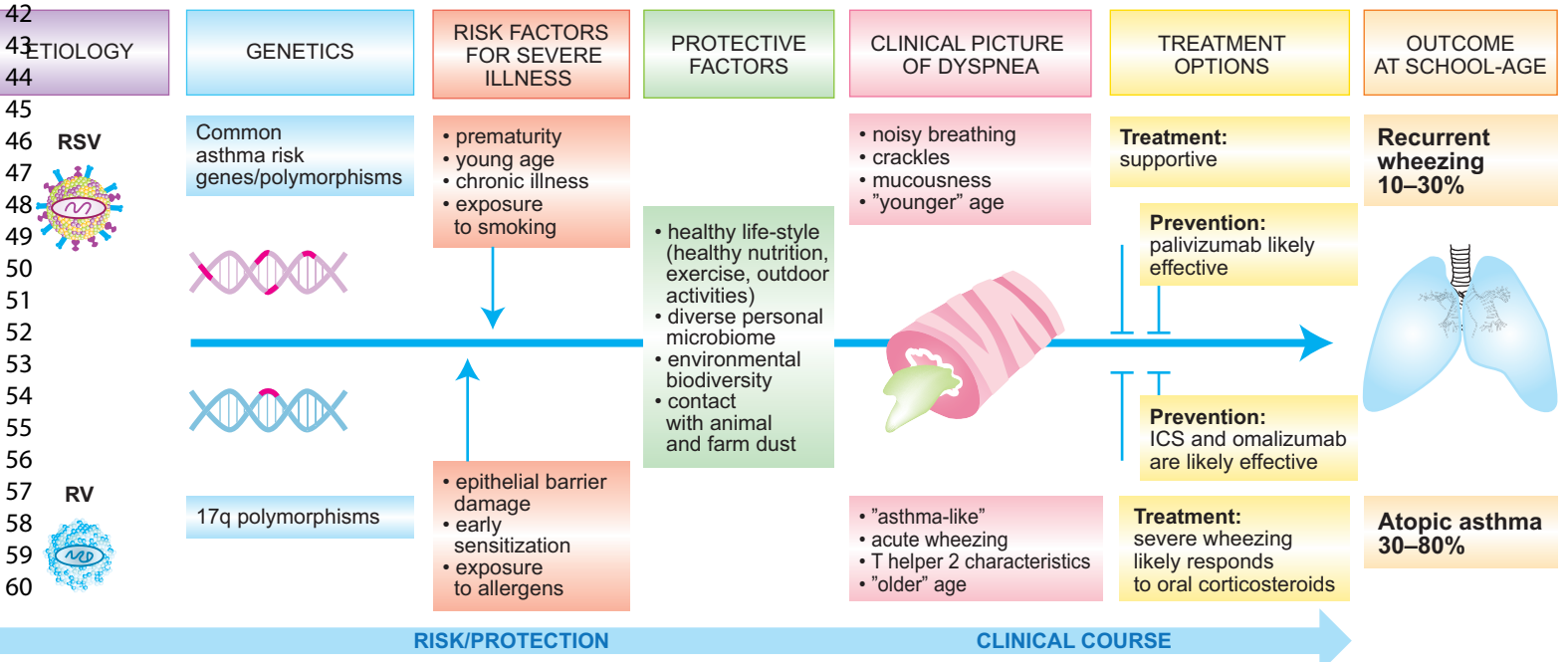
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wheezing in under 2-year-old children appears to be a critical event and an opportunity for designing secondary prevention strategies for asthma. MoAb, monoclonal antibody; OCS, oral corticosteroid; Th, T helper cell.

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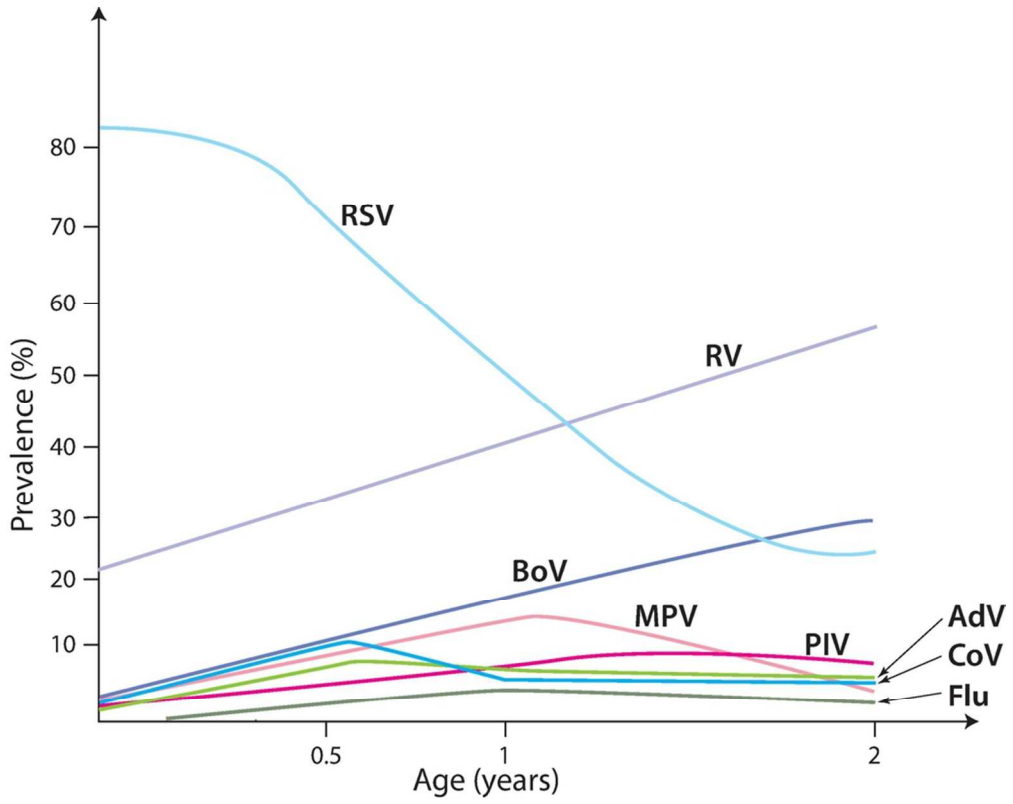


Fig. 1

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Preview

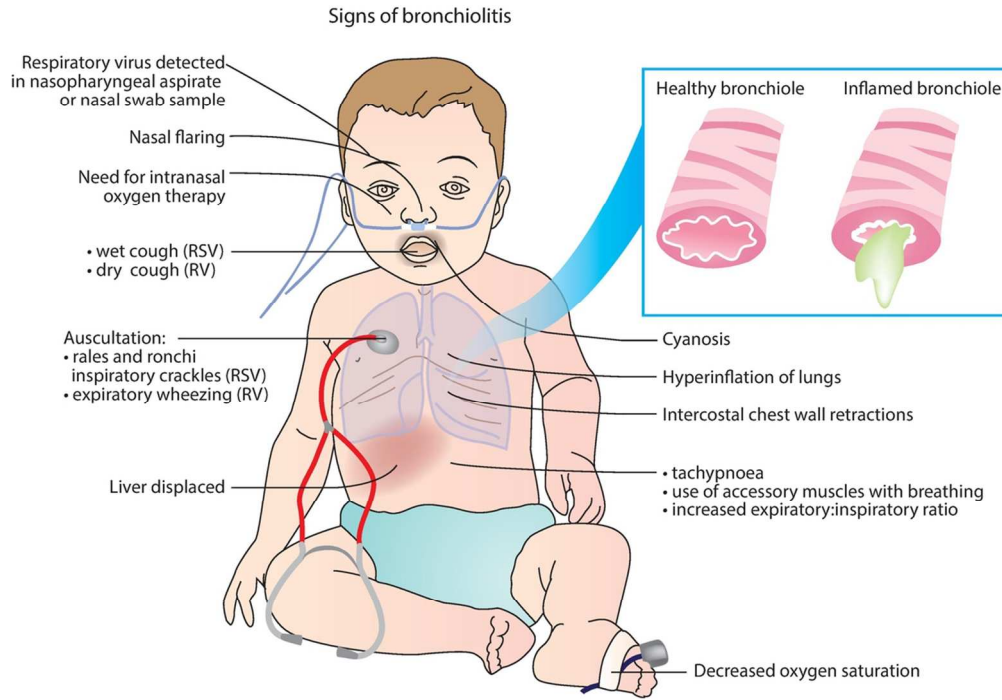


Fig. 2

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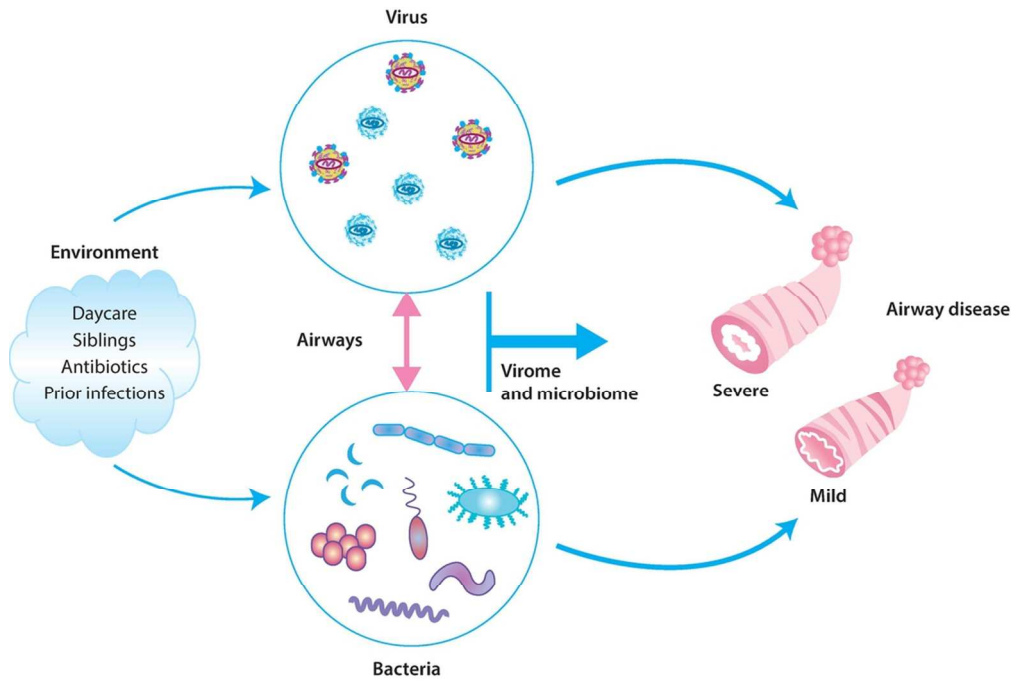


Fig. 3

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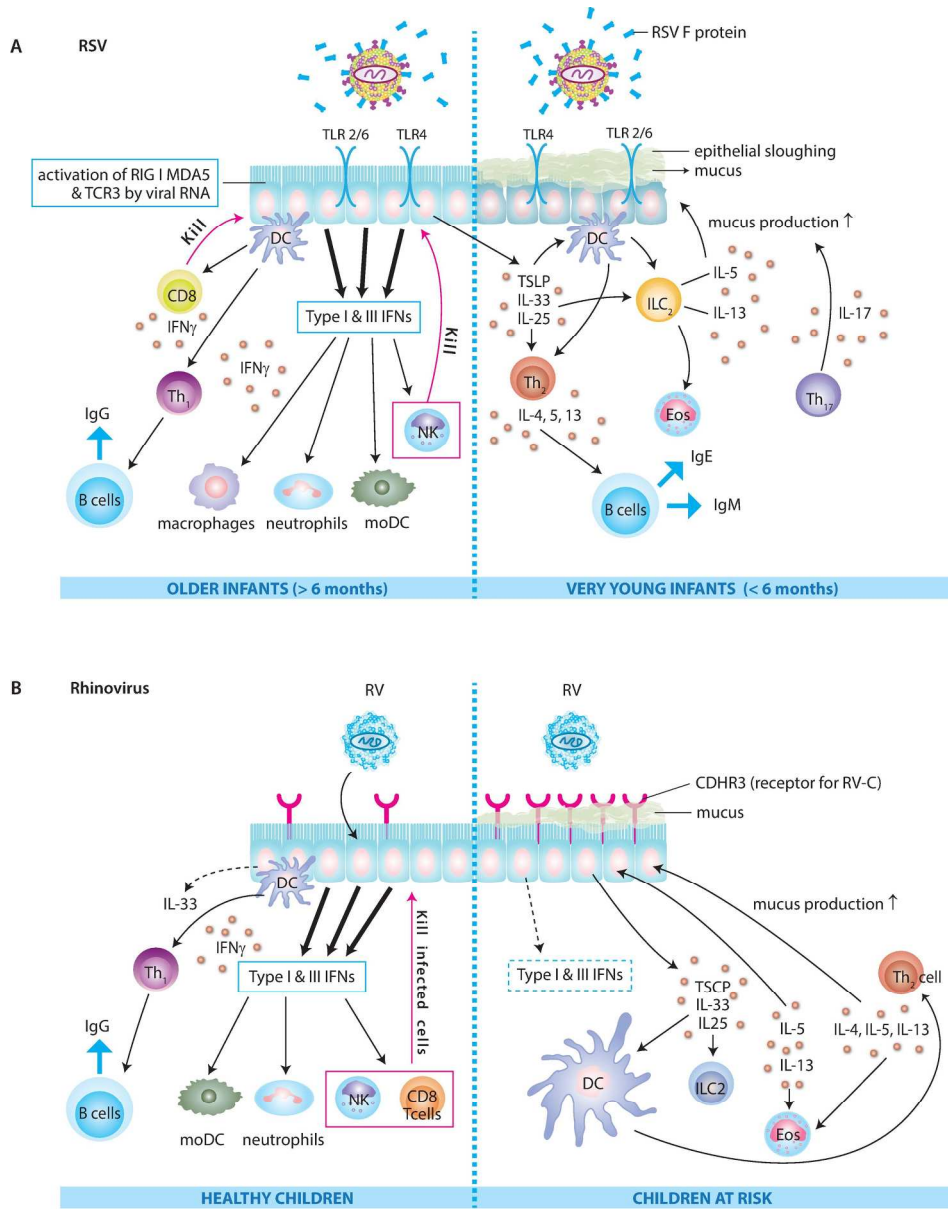


Fig. 4

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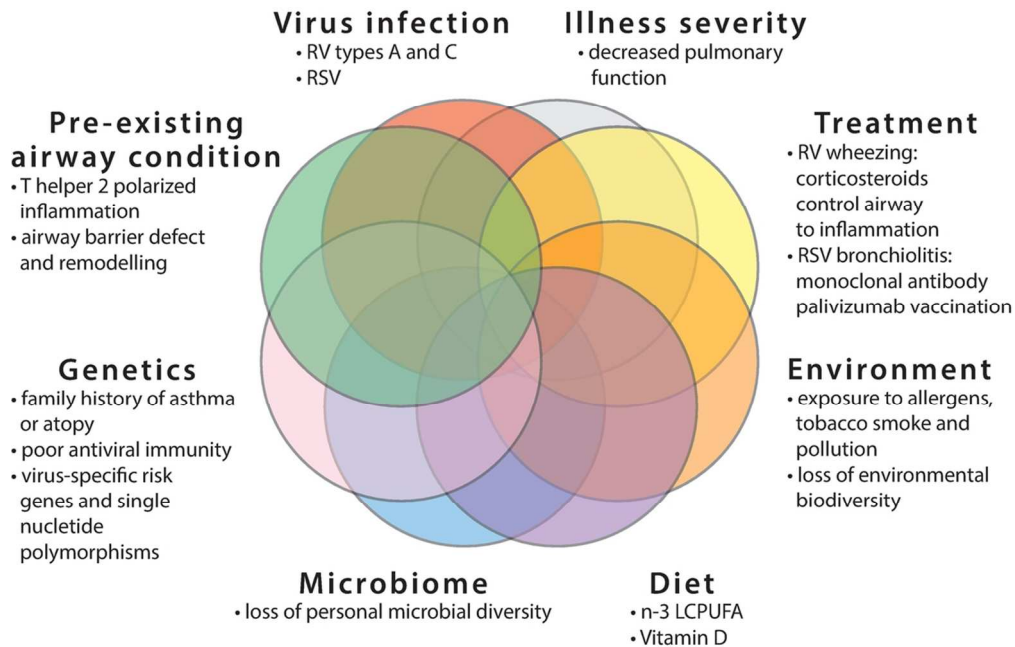


Fig. 5

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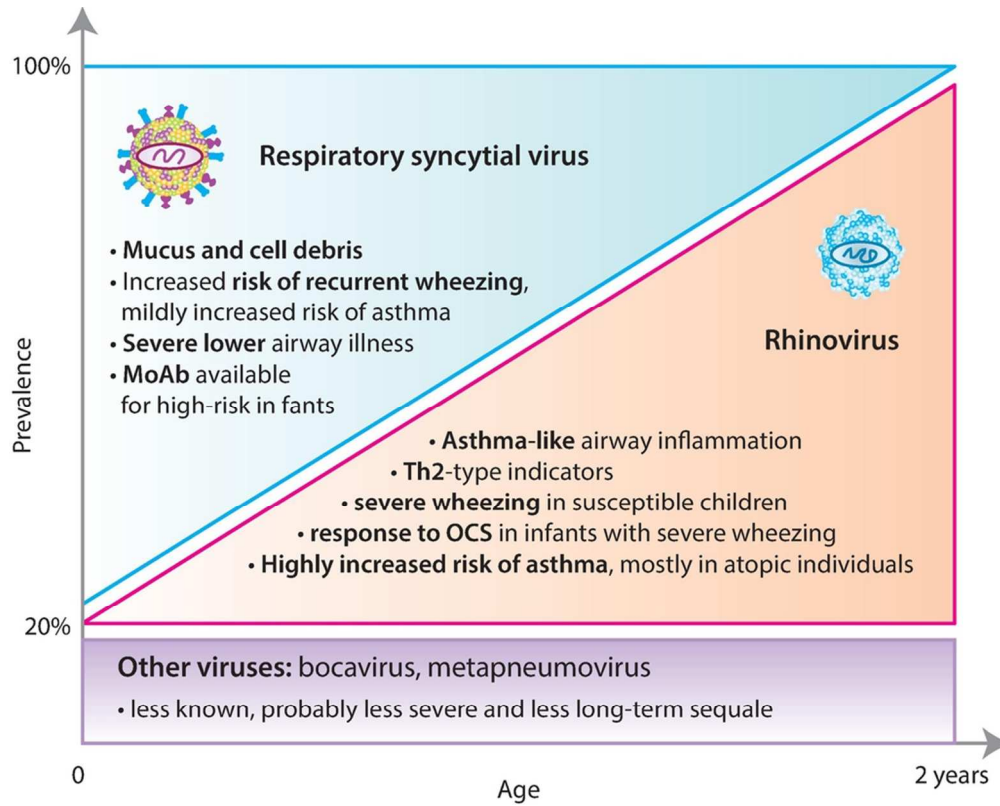


Fig. 6

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