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Review

Association of respiratory virus types with clinical features in bronchiolitis: Implications for virus testing strategies. A systematic review and meta-analysis

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EDUCATIONAL AIMS

- The reader will come to:
- Understand the importance of differentiating between respiratory syncytial virus (RSV) and rhinovirus (RV)-induced bronchiolitis and the need for more phenotype-specific management for bronchiolitis.
- Review key studies assessing viral-dependent clinical and atopic features in infants with RSV and RV-induced bronchiolitis.
- Understand that despite minor differences in clinical and atopic features between RSV and RV-induced bronchiolitis, microbiological testing remains crucial for distinguishing the viral etiology of bronchiolitis.

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A B S T R A C T

Background: Bronchiolitis is a leading cause of infant hospitalization, linked to respiratory syncytial virus (RSV) and rhinovirus (RV). Guidelines lack specific viral testing for bronchiolitis management. To establish effective management strategies, it is crucial to assess whether specific respiratory virus types are correlated with distinct examination features.

Methods: Through a systematic search of three databases, 21 studies were qualitatively analyzed, with 18 used for meta-analysis. Various outcomes like wheezing on auscultation, fever, atopic traits, and infection severity were evaluated.

Results: RSV-positive bronchiolitis was associated with a higher need for oxygen supplementation (OR 1.78, 95% CI 1.04–3.02) in 5 studies, while RV-positive bronchiolitis was more frequently linked to personal history of eczema (OR 0.60, 95% CI 0.41–0.88) in 6 studies. No significant differences were observed in the other outcomes examined.

Conclusions: Bronchiolitis caused by RSV or RV presents with similar clinical features. Despite the associations between RSV-positive bronchiolitis and need for oxygen supplementation, and RV-positive bronchiolitis and a history of eczema, our study shows that viral etiology of bronchiolitis cannot be determined solely based on clinical presentation.

Tailored management strategies, informed by accurate viral testing, seem crucial in clinical practice for enhancing patient outcomes in severe bronchiolitis.

Introduction

Bronchiolitis, a prevalent lower respiratory infection in children under the age of two, is a heterogeneous disease and a significant cause of infant hospitalization in the United States and Europe [1]. However, emerging evidence is challenging the traditional notion of bronchiolitis as a single disease with a uniform pathobiology [2–8]. Respiratory syncytial virus (RSV) and rhinovirus (RV), the primary viral culprits, have been identified as crucial factors in bronchiolitis severity and long-term complications like asthma [9,10].

Differentiating between RSV and RV-induced bronchiolitis is essential due to their distinct long-term prognosis, implications for management, and potential to guide targeted treatments [3,8,11–13]. Unfortunately, current respiratory viral testing capabilities, particularly in RV detection, are limited, hindering accurate and timely diagnosis. Furthermore, inconsistent bronchiolitis diagnostic criteria across literature and international guidelines further complicate patient management [2,14–16]. Additionally, increased phenotypic heterogeneity is a hurdle in applying effective treatments of bronchiolitis and asthma prevention strategies.

To address these knowledge gaps, a comprehensive systematic review is needed to elucidate the unique clinical profiles of RSV and RV-induced bronchiolitis in children under two years. By characterizing the clinical manifestations and exploring the association between respiratory virus type and clinical features, including atopic traits, this systematic review aims to enhance our clinical understanding of the disease and guide targeted management strategies.

Methods

Search strategy

Three bibliographic databases were searched (MEDLINE through PubMed, Web of Science via webofscience.com, and Cochrane Library) from inception to March 29, 2022. Search terms in each database included all subject headings, abstracts, and/or full texts associated with bronchiolitis, wheezing, and viral respiratory infection. The full PubMed search strategy is available in the Online Supplement. Reference lists were checked for any additional relevant studies. All extracted citations were imported into the EndNote® reference manager (Version X9, Clarivate Analytics, 2018). After removing the duplicates, two reviewers (DA and IO) working independently screened the retrieved titles and abstracts. Subsequently, all potentially relevant publications were assessed in full text. At each stage, uncertainty about the eligibility of studies was resolved through discussion and obtaining consensus by other reviewers (WF, AA, MR, TJ), if necessary. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. It was registered in the National Institute for Health Research's PROSPERO (CRD42020218777).

Eligibility criteria

Main eligibility criteria included publication in the English language, the age group under two years old, the clinical presentation described either as bronchiolitis, acute wheezing episode, or acute lower respiratory tract infection, assessment at the hospital setting (emergency department [ED] and/or ward) or as outpatients assessed by the study investigators, comparison of at least two groups of patients with confirmed viral etiology proof the illness with RSV and RV. Exclusion criteria included duplicate publications and multiple publications regarding the same study group, non-human studies, studies including children presenting with confirmed respiratory infection with only one viral agent (e.g., only RSV-positive cases), studies including children over two years old without a subgroup analysis for patients under the age of two years, or studies with no data on clinical features of interest, study protocols, editorials or review papers, and conference abstracts. Actions were taken to contact corresponding authors when additional clarification and further data were required.

Our primary objective was to investigate whether specific clinical features and patient history could differentiate the viral etiology of bronchiolitis. The analysis focused on several key features:

(a) Presence of wheezing on auscultation.
(b) Occurrence of fever.
(c) Severity of infection, as indicated by admission to the paediatric intensive care unit (PICU).
(d) Personal history of atopy in the child.
(e) Parental history of atopy or asthma.
(f) Additional features identified in the studies that could aid in distinguishing the viral agent during the patient's clinical presentation. These additional features encompassed observations such as crackles on auscultation, weight at enrollment, severity scores, length of hospitalization, hypoxia, need for oxygen supplementation, ventilation support, and mortality rate.

Study extraction and quality assessment

Data were extracted from each included study for the following parameters: (a) study origin, (b) participant details, (c) number of patients with detected RSV or RV, (d) details on wheezing at baseline, patient

and parental history of atopy, the severity of the bronchiolitis episode assessed per viral etiology, (g) mean and the median age at baseline, and (h) potential confounding factor (s) such as prematurity or other co-morbid medical conditions.

Two independent reviewers (DA, IO) assessed the risk of bias in each of the included studies without being blinded to the authors or journal. A modified Newcastle Ottawa Quality assessment scale (NOS) for cross-sectional studies was used to evaluate the quality of included studies [18] (Appendix S2, Online Supplement). Encountered discrepancies were resolved through discussion with all the reviewers. We considered a study awarded nine or more points as a high-quality study in the current review.

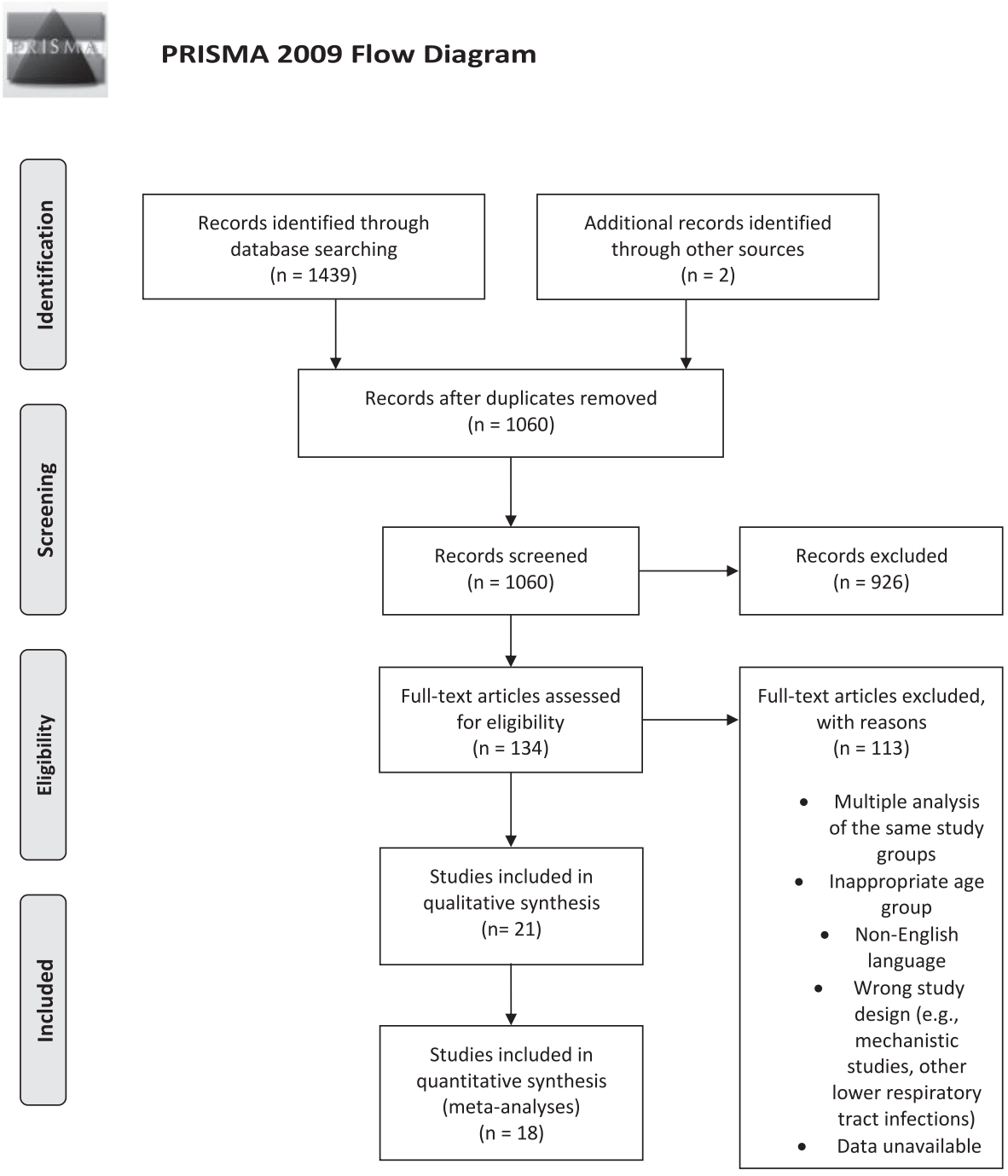

Fig. 1. Flowchart describing the identification, screening, assessment of eligibility, and inclusion criteria.

Data analysis and synthesis

Data collection and curation were performed using a Microsoft Excel program. Review Manager (RevMan) v5.3 software from the Cochrane Collaboration (London, UK) was used to perform meta-analyses, generate forest and funnel plots, and calculate the I^2 statistic. Dichotomous variables were expressed using pooled statistics of odds ratio (OR) and their 95% confidence interval (CI), with a random-effects model using a Mantel-Haenszel method depending on heterogeneity. Heterogeneity was assessed using the I^2 statistic defined by the Cochrane Handbook for Systematic Reviews[19]. I^2 value >50% indicated substantial heterogeneity. Several sensitivity analyses were conducted to test the robustness of the main findings and assess the potential sources of heterogeneity. First, a fixed-effect meta-analysis was conducted to evaluate the consistency of the main results from a random-effect model. Second, to investigate the impact of study quality, we performed sensitivity analyses by prospective and retrospective character of the study. At last, the individual study estimates one at a time were excluded to examine the impact of each study on the overall OR.

Results

Description of the studies and their risk of bias

Following the systematic search, we obtained 1441 publications. The PRISMA flow chart is shown in Fig. 1. We excluded 1307 (91%) studies after screening the titles and abstracts for duplications and for not meeting our inclusion criteria. After we reviewed the full texts of the remaining 134 (9%) studies, 89 (66%) studies were excluded because they had inappropriate study design, including the not eligible age group, lower respiratory tract infection not limited to bronchiolitis, no data on any of our clinical outcome, information only on either RSV or

Table 1
Characteristics of the included studies.

	Study ID and country	Study Design	Population	Sample size with viral agent detected	Quality assessment scale *
1	Papadopoulos et al. 2002, Greece[20]	Prospective Observational	Inpatients with 1st or 2nd episode of bronchiolitis (<18 mo)	RV = 12 RSV = 50	FAIR
2	Korppi et al. 2004, Finland [21]	Prospective Observational	Inpatients with bronchiolitis (<24 mo)	RV = 26 RSV = 24	GOOD
3	Pitrez et al. 2005, Brazil [22]	Prospective Observational	Inpatients with the 1st episode of bronchiolitis (<6 mo)	RV = 6 RSV = 33	FAIR
4	Jartti et al. 2006, Finland, the Vinku study[23]	Randomized Controlled Trial	Children with the 1st episode of bronchiolitis (data received from author on the exclusively children < 24 mo)	RV = 30 RSV = 31	GOOD
5	Marguet et al. 2009, France [24]	Prospective Observational	Inpatients with the 1st episode of bronchiolitis (<12 mo)	RV = 15 RSV = 96	GOOD
6	Midulla et al. 2010, Italy [25]	Prospective Observational	Inpatients with bronchiolitis (<12 mo)	RV = 16 RSV = 60	FAIR
7	Nascimento et al. 2010, Brazil[26]	Prospective Observational	Patients with the 1st episode of bronchiolitis assessed in ED (<24 mo)	RV = 13 RSV = 36	FAIR
8	Carroll et al. 2012, USA, the TRCI cohort[27]	Prospective Observational	Patients with bronchiolitis (<12 mo)	RV = 41 RSV = 268	FAIR
9	Luchsinger et al. 2014, Chile[28]	Prospective Observational	Children with clinical signs of respiratory distress with crackles or wheezing, or hyperinflation in a chest radiograph assessed in hospital setting and outpatient clinic (<6 mo)	RV = 22 RSV = 74 RSV + RV = 28	GOOD
10	Selvaggi et al. 2014, Italy [29]	Retrospective Observational	Inpatients with bronchiolitis (<12 mo)	RV = 40 RSV = 78	FAIR
11	Turunen et al. 2014, Finland, the Vinku-2 study [30]	Prospective Observational	Children with the 1st wheezing episode assessed in hospital setting (<24 mo)	RV-positive RSV-negative = 71 RSV-positive RV-negative = 18	FAIR
12	Jartti et al. 2014, the MARC-30, Finland[33]	Prospective Observational	Inpatients with bronchiolitis (≤24 mo)	RV = 113 RSV = 172	GOOD
13	Diaz et al. 2015, Chile[31]	Prospective Observational	Children with bronchiolitis assessed in hospital/clinic setting (<24 mo)	RV = 27 RSV = 60 RSV + RV = 28	GOOD
14	Mansbach et al. 2016, the MARC-30, USA[32]	Prospective Observational	Inpatients with bronchiolitis (<24 mo)	RV = 277 RSV = 1302	GOOD
15	García-García et al. 2017, Spain[34]	Prospective Observational	Inpatients with bronchiolitis (<24 mo)	RV = 18 RSV = 116	FAIR
16	Janahi et al. 2017, Qatar [35]	Retrospective Observational	Inpatients with bronchiolitis (≤24 mo)	RV = 58 RSV = 160	FAIR
17	Pierangeli et al. 2018, Italy [36]	Prospective Observational	Inpatients with the 1st episode of bronchiolitis (<6 mo)	RV = 18 RSV = 53	FAIR
18	Hasegawa et al. 2019, the MARC-35, USA[37]	Prospective Observational	Inpatients with bronchiolitis (<12 mo)	Data received from authors: RV-positive RSV-negative = 92 RSV-positive RV-negative = 699	GOOD
19	Arroyo et al. *2020, USA* [38]	Prospective Observational	Inpatients with the 1st episode of bronchiolitis (≤24 mo)	RV = 19 RSV = 11	FAIR
20	Üzüm et al. 2020, Turkey [39]	Retrospective Observational	Inpatients with moderate/severe bronchiolitis (<24 mo)	RV = 59 RSV = 23	FAIR
21	De Paulis et al. 2021, Brazil [40]	Prospective Observational	Children assessed in the hospital setting with 1st episode of bronchiolitis (<6 mo)	RV = 9 RSV = 49	GOOD

RV –Rhinovirus, RSV – Respiratory Syncytial Virus, yo – years old, mo – months old, ED – Emergency Department, RCT – randomized controlled trial.
* Modified Newcastle-Ottawa Quality Assessment Scale. Poor =<6, Fair 7–9, Good =>9.

RV-induced infection, or mechanistic study design, 11 (8%) were excluded because they were reporting the results from the same study group as the included studies, and 13 (10%) were excluded because their full-texts were either not available or in a language other than English. Thus, we included 21 (16% of the assessed full-texts) studies [20–40] in our qualitative evaluation, and 18 (13%) studies in our quantitative evaluation [20–27,29,30,32–35,37–40].

Among the study designs of the eligible studies, 17 (81%) were prospective [20–22,24–28,30–34,36–38,40], 3 (14%) retrospective observational [29,35,39], and one randomized controlled trial (5%) [23]. All the included studies were published between 2002 and 2021 (Table 1). Of these studies, four were done in the USA [27,32,37,38]; five in South America (including Brazil [22,26,40] and Chile [28,31]); 11 in Europe (including Finland [21,23,30,33], France [24], Greece [20], Italy [25,29,36], Spain [34], Turkey [39]); and one in Asia (Qatar [35]).

The risk of bias was generally moderate-to-high after considering the observational designs. However, in light of their case-controlled character, nine studies were assessed to have a low risk of bias against the background of the entire group [21,23,24,28,31–33,37,41].

Sample

The sizes of the studies ranged from 45 to 2207 children (totaling 4396 individuals with either RSV or RV bronchiolitis and 6305 as all study participants). The upper age limit varied among the studies, e.g., with the age of 6 months in four studies [22,28,36,40], 12 months in five studies [24,25,27,29,37], and 24 months in ten studies [21,26,30–35,38,39]. One study recruited exclusively preterm children [22]. Most of the studies recruited patients assessed in the hospital setting (both in ED and in the ward), with only two studies that assessed children in the mixed setting, including the hospital and outpatient clinic [27,28]. Table 1 summarizes the main characteristics of the eligible studies.

Wheezing

We did not identify any difference in the presence of wheezing at enrolment (or check-up) between children with RSV-positive and RV-positive bronchiolitis in six studies [32,33,35,37–39] (n = 2920 children, OR 0.93; 95% CI 0.73–1.18) (Fig. 2). Furthermore, the strength of association did differ between prospective and retrospective studies. However, the retrospective studies show considerably higher levels of heterogeneity (I^2 = 53%) in comparison to the prospective studies (I^2 = 11%). The funnel plot is shown in Appendix S3 (Online Supplement).

Eosinophilia and personal history of atopy

Twelve studies assessed traits of eosinophilic inflammation in the participants [21,23–25,29,30,32,33,36–39], in which a non-significant trend of positive association between RV-induced bronchiolitis and blood eosinophilia was noted[21,23,25,29,30,36] (Table S2, Online Supplement). When considering the six prospective studies [21,23,30,32,33,37,42] (n = 2786 children) investigating the association of RSV-positive bronchiolitis and a personal history of eczema in comparison to RV-positive bronchiolitis, we found a positive association between RV-positive bronchiolitis episode and a history of personal eczema (OR 0.60; 95% CI 0.41–0.88), with moderate heterogeneity (I^2 = 46%) (Fig. 3). The funnel plot is shown in Appendix S4 (Online Supplement).

Parental atopy/asthma

The association of RV-positive bronchiolitis patients with parental atopy or asthma was found to be insignificant in fourteen highly heterogeneous studies (I^2 = 64%) (OR 0.79; 95% CI 0.69–3.64) [20,22–27,30,32,33,35,37–39] (Fig. 4).

Severity of infection and fever

The severity of the viral infection was assessed by a variety of parameters. These parameters included hospital and PICU admission rates, mortality rate, different severity scores (e.g., Respiratory Distress Severity Score), length of hospitalization, hypoxia, need for oxygen supplementation, and ventilation support (Table S4 in the Online Supplement).

When considering the five studies[22,32,37–39] (n = 2486 children) investigating the association of RSV-positive bronchiolitis and a need for oxygen supplementation in comparison to RV-positive bronchiolitis, we found a positive association between RSV-positive bronchiolitis episode and a need for oxygen supplementation (OR 1.78; 95% CI 1.04–3.02) (Fig. 5). Heterogeneity among these studies was high (I^2 = 55%).

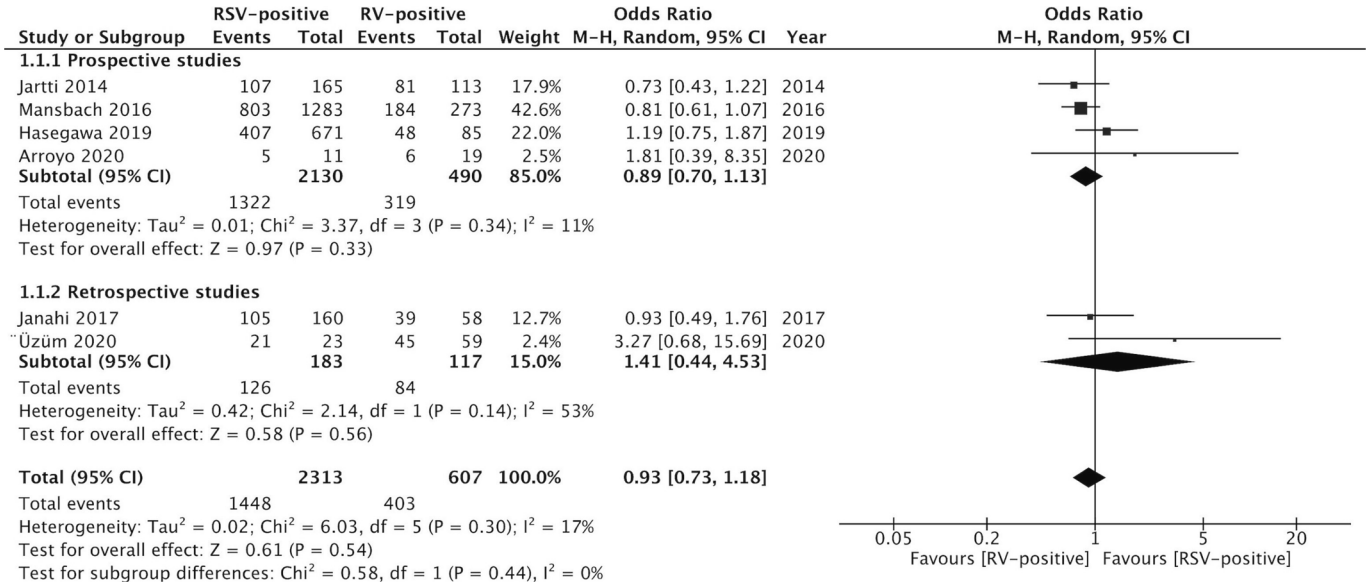

Fig. 2. Forest plot depicting the associations of RSV-positive bronchiolitis and presence of wheezing at enrollment or check-up visit due to acute respiratory infection in comparison with RV-positive bronchiolitis (OR 0.93, 95% CI 0.73–1.18, I^2 = 17%).OR: odds ratio, CI: confidence interval, I^2: heterogeneity statistic.

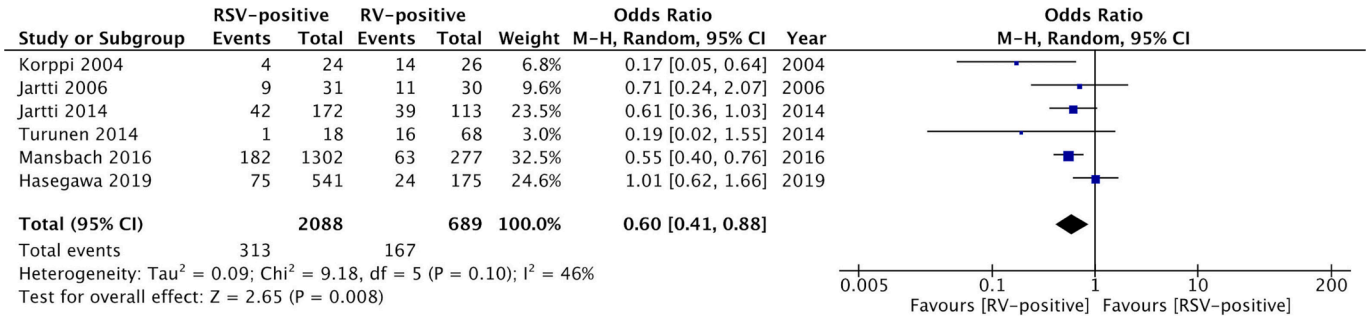

Fig. 3. Forest plot depicting the associations of RSV-positive bronchiolitis and a personal history of eczema in comparison to RV-positive bronchiolitis (OR 0.60, 95% CI 0.41–0.88, I^2 = 46%).OR: odds ratio, CI: confidence interval, I^2: heterogeneity statistic.

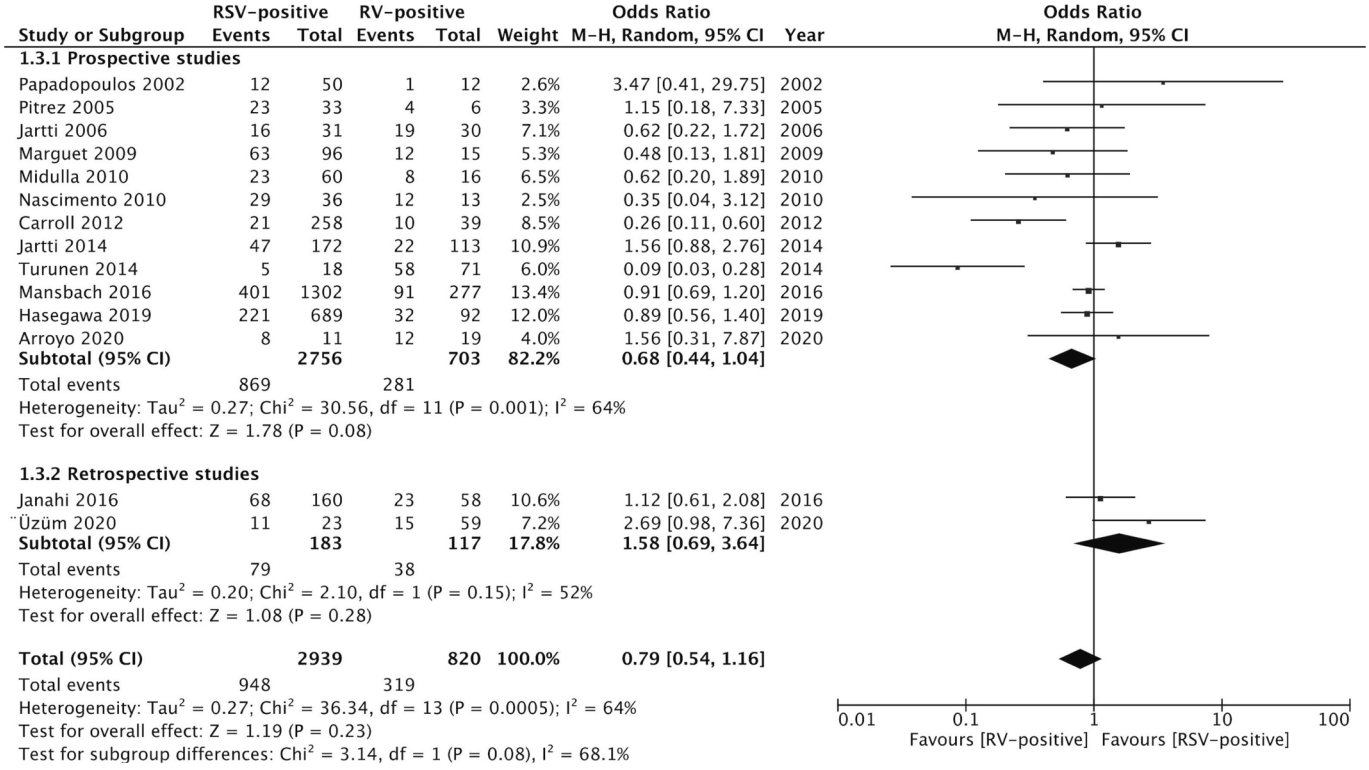

Fig. 4. Forest plot depicting the associations of RSV-positive bronchiolitis and a history of parental atopy (including parental asthma) in comparison to RV-positive bronchiolitis (OR 0.79, 95% CI 0.54–1.16, I^2 = 64%).OR: odds ratio, CI: confidence interval, I^2: heterogeneity statistic.

No significant differences were found between the RSV- and RV-positive bronchiolitis when investigating the other severity parameters, including PICU treatment (OR 0.87; 95% CI 0.36–2.09), a need for ventilation support (OR 1.06; 95% CI 0.70–1.60), or the occurrence of fever (OR 1.19; 95% CI 0.74–1.90). The forest and funnel plots are shown in the Online Supplement (Appendixes S7- S12).

Discussion

Interpretation of findings

Lower respiratory tract infections, such as bronchiolitis, are common among young children, and clinical assessment remains a common approach in outpatient settings. Bronchiolitis is increasingly recognized as a clinical term encompassing a spectrum of varying phenotypes with different underlying immunological and microbiological backgrounds [5,43,44]. Certain phenotypes may carry a higher risk of developing asthma, highlighting the importance of early identification and personalized care. A more personalized approach could be possible by examining specific clinical characteristics of bronchiolitis caused by the most common viral agents, RSV and RV. Our systematic review aimed to assess whether there were associations between RSV or RV etiology and various clinical severity and atopic features. Recently, a simplified approach for distinguishing different bronchiolitis profiles was proposed, with one profile associated with a higher burden for asthma development[45]. This supports our study's dichotomous approach[45].

Our analysis revealed two clinical features that showed some differentiation between the viral etiologies. Firstly, a personal history of eczema was more commonly associated with RV-induced bronchiolitis. Secondly, the need for oxygen supplementation was more commonly associated with RSV-induced bronchiolitis. However, we found no significant association between viral etiology and most of the assessed clinical severity parameters, including mechanical ventilation or PICU admission.

Nevertheless, it is important to note that these factors are not sufficiently different between the groups and lack predictive or discriminatory value at the individual level. Additionally, our findings raise questions regarding the specific risk of RV bronchiolitis in individuals

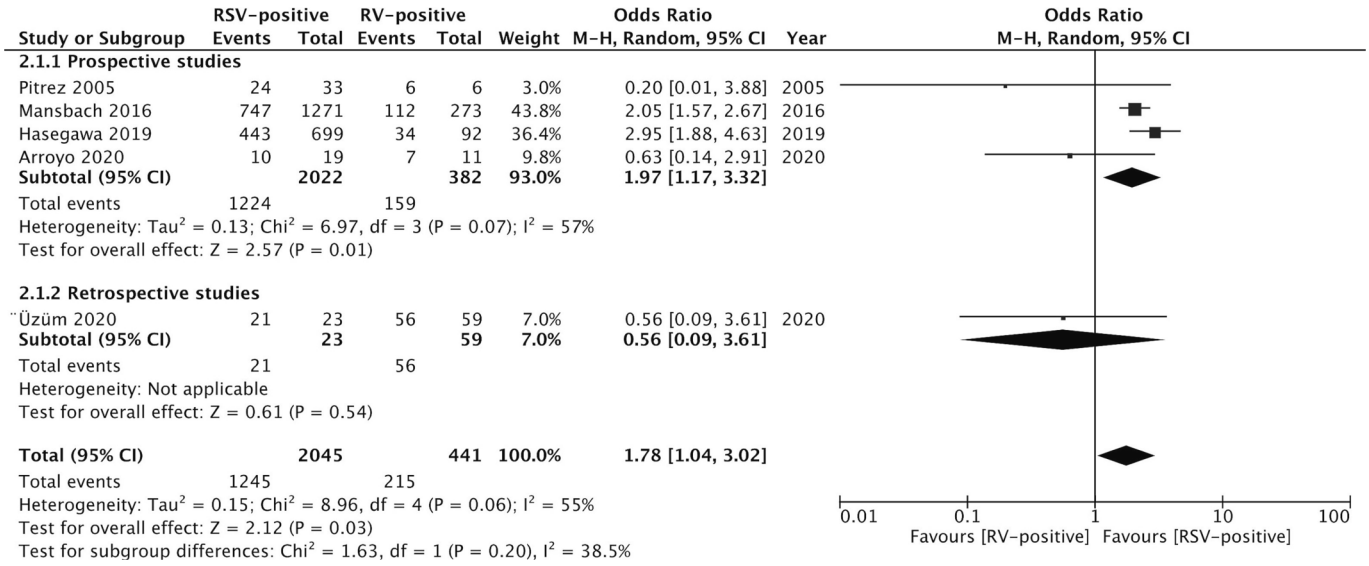

Fig. 5. Forest plot depicting the associations of RSV-positive bronchiolitis and a need for oxygen supplementation during its management in comparison to RV-positive bronchiolitis (OR 1.78, 95% CI 1.04–3.02, $I^2 = 55\%$). OR: odds ratio, CI: confidence interval, I^2: heterogeneity statistic.

with atopic dermatitis (AD), and whether preventing or controlling AD could reduce this risk.

We could not evaluate other clinical features, such as crackles on auscultation or body weight at enrolment, as this information was not available in the included studies.

Strengths of the study

Our study holds notable strengths as the first meta-analysis comparing the viral-dependent clinical and atopic features of the two most common viral agents in bronchiolitis, RSV and RV. We employed raw summary data to recalculate individual study odds ratios (ORs), providing more robust results. Nonetheless, we conducted a comprehensive analysis based on the data from over 20 studies, encompassing various methodologies and exhibiting moderate to high heterogeneity across some clinical outcomes (I^2 from 0% to 64%). The heterogeneity was addressed through sensitivity and subgroup analyses based on the prospective and retrospective nature of the studies.

Limitations and potential confounders

However, there are potential limitations to consider. Several factors contributed to the heterogeneity observed in the included studies. The studies consisted of prospective and retrospective longitudinal cohort studies, randomized controlled trials, and case-control studies. Our review focused on the data collected at a single time-point, i.e., the presentation of acute respiratory tract infection symptoms in a clinic or hospital setting. Furthermore, there were variations in the definitions of our clinical outcomes used in different studies. The inclusion age criteria also differed, including variations in age range and settings (hospital-based or involving outpatients)[27,28].

The use of multiple observational studies with varying inclusion criteria and differences in exposure measurement resulted in expected between-study heterogeneity. To address this, we utilized random-effects meta-analyses and influence analyses ("leave-one-out" method). Moreover, the primary outcomes of the included studies may not have directly aligned with our objectives.

We acknowledge that our study primarily focused on severe episodes of respiratory infections requiring hospitalization (significant selection bias), leading to an imbalance in the number of children included in RSV-positive (n = 3413) versus RV-positive (n = 887) groups. This discrepancy may be due to the increased severity of RSV-induced bronchiolitis, resulting in a larger number of participants recruited in this group.

Additionally, the seasonal bias introduced by studies that only recruited during RSV season and the lack of assessment of RV species or type in most included studies should be acknowledged[46,47]. Co-infections with other viruses and the potential impact of the number of viral triggers on later asthma development were not evaluated[48]. Finally, the admission bias may also have influenced some of the study findings.

Conclusion and further research

In summary, our study identified significant associations between RV-induced bronchiolitis and a personal history of eczema, as well as between RSV infection and the need for oxygen supplementation. However, clinical features alone are unlikely to predict distinctive bronchiolitis phenotypes at the individual level.

Accurate and precise diagnoses of bronchiolitis using quick viral antigen detection tests for respiratory viruses remain crucial. With the recent revolution of viral testing for SARS-CoV-2 infections, it cannot be ruled out that more accessible and rapid testing, such as quick viral antigen detection for RV, including its subtypes, will be available very soon.

Future research should focus on exploring multi-predictor models and individual-patient data analyses to facilitate more personalized management of bronchiolitis. Moreover, prospective studies investigating whether controlling atopic dermatitis could reduce the risk of RV bronchiolitis or childhood asthma following RV infection are highly anticipated.

Directions for future research

- To validate differences in clinical features between RSV and RV-induced bronchiolitis identified in our meta-analysis in a larger cohort of patients, especially by individual-patient data analyses.
- To investigate whether preventing or controlling atopic dermatitis could reduce the risk of RV-induced bronchiolitis.
- To develop a more personalized approach for the management of bronchiolitis and prevention strategies for infants with bronchiolitis at higher risk of childhood asthma.

- To develop quick viral antigen detection tests for rhinovirus, including its three species, to be available in the outpatient care setting.

CRediT authorship contribution statement

Dominika Ambrożej: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Izabela Orzołek:** Conceptualization, Investigation, Writing – original draft. **Heidi Makrinioti:** Conceptualization, Methodology, Supervision. **Jose A. Castro-Rodriguez:** Writing – review & editing, Resources. **Carlos A. Camargo Jr.:** Writing – review & editing, Resources. **Kohei Hasegawa:** Writing – review & editing, Resources. **Nikolaos G. Papadopoulos:** Writing – review & editing, Resources. **James E. Gern:** Writing – review & editing, Resources. **Gustavo Nino:** Writing – review & editing, Resources. **Luiz Vicente Ribeiro Ferreira da Silva Filho:** Writing – review & editing, Resources. **Aya Takeyama:** Writing – review & editing, Resources. **Özlem Üzüm:** Writing – review & editing, Resources. **Aleksander Adamiec:** Writing – review & editing. **Marek Ruszczyński:** Conceptualization, Writing – review & editing. **Tuomas Jartti:** Conceptualization, Writing – review & editing, Resources, Supervision. **Wojciech Feleszko:** Conceptualization, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prrv.2023.09.003.

References

[1] Fujiogi M, Goto T, Yasunaga H, Fujishiro J, Mansbach JM, Camargo CA, et al. Trends in Bronchiolitis Hospitalizations in the United States: 2000–2016. Pediatrics 2019;144(6):e20192614.
[2] Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics 2014;134(5):e1474. e1502.
[3] Rodríguez-Martínez CE, Castro-Rodriguez JA, Nino G, Midulla F. The impact of viral bronchiolitis phenotyping: Is it time to consider phenotype-specific responses to individualize pharmacological management? Paediatric Respiratory Reviews 2020;34:53–8. https://doi.org/10.1016/j.prrv.2019.04.003.
[4] Achten NB, van Rossum AMC, Bacharier LB, Fitzpatrick AM, Hartert TV. Long-Term Respiratory Consequences of Early-Life Respiratory Viral Infections: A Pragmatic Approach to Fundamental Questions. *Journal of Allergy and Clinical Immunology*. In Practice 2022;10(3):664–70. https://doi.org/10.1016/j.jaip.2021.12.005.
[5] Raita Y, Camargo CA, Bochkov YA, Celedón JC, Gern JE, Mansbach JM, et al. Integrated-omics endotyping of infants with rhinovirus bronchiolitis and risk of childhood asthma. The Journal of Allergy and Clinical Immunology 2021;147(6):2108–17.
[6] Dumas O, Hasegawa K, Mansbach JM, Sullivan AF, Piedra PA, Camargo CA. Severe bronchiolitis profiles and risk of recurrent wheeze by age 3 years. The Journal of Allergy and Clinical Immunology 2019;143(4):1371–1379.e7. https://doi.org/10.1016/j.jaci.2018.08.043.
[7] Makrinioti H, Maggina P, Lakoumentas J, Xepapadaki P, Taka S, Megremis S, et al. Recurrent Wheeze Exacerbations Following Acute Bronchiolitis—A Machine Learning Approach. Frontiers in Allergy 2021;2. https://doi.org/10.3389/falgy.2021.728389.
[8] Linssen RSN, Schechter MS, Rubin BK. Bronchiolitis therapies and misadventures. Paediatric Respiratory Reviews 2023;46:49–56. https://doi.org/10.1016/J.PRRV.2022.09.003.
[9] Bacharier LB, Cohen R, Schweiger T, Yin-DeClue H, Christie C, Zheng J, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. The Journal of Allergy and Clinical Immunology 2012;130(1):91–100.e3.
[10] Díez-Domingo J, Pérez-Yarza EG, Melero JA, Sánchez-Luna M, Aguilar MD, Blasco AJ, et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. BMC Infectious Diseases 2014;14(1). https://doi.org/10.1186/s12879-014-0544-x.
[11] Jartti T, Smits HH, Bønnelykke K, Bircan O, Elenius V, Konradsen JR, et al. Bronchiolitis needs a revisit: Distinguishing between virus entities and their treatments. Allergy 2019;74(1):40–52.
[12] Wall MA. Bronchodilators and steroids should not be given in viral bronchiolitis - CON. Paediatric Respiratory Reviews 2019;32:20–2. https://doi.org/10.1016/j.prrv.2019.09.001.
[13] Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. The Journal of Allergy and Clinical Immunology 2017;140(4):895–906. https://doi.org/10.1016/j.jaci.2017.08.003.
[14] National Institute for Health and Care Excellence. *Bronchiolitis : Diagnosis and Management of Bronchiolitis in Children*. NICE; 2015.
[15] O'Brien S, Borland ML, Cotterell E, Armstrong D, Babl F, Bauert P, et al. Australasian bronchiolitis guideline. Journal of Paediatrics and Child Health 2019;55(1):42–53.
[16] Bronchiolitis S. on D and M of. Diagnosis and Management of Bronchiolitis *Pediatrics* 2006;118(4):1774–93. https://doi.org/10.1542/peds.2006-2223.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine 2009;6(7):e1000097.
[18] Wells G, Shea B, O'Connell D, Peterson J, Welch V. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Published online 2000.
[19] Higgins J, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021)*. Cochrane, 2021; 2021.
[20] Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, et al. Association of Rhinovirus Infection with Increased Disease Severity in Acute Bronchiolitis. American Journal of Respiratory and Critical Care Medicine 2002;165(9):1285–9.
[21] Korppi M, Kotaniemi-Syrjänen A, Waris M, Vainionpää R, Reijonen TM. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. The Pediatric Infectious Disease Journal 2004;23(11):995–9. https://doi.org/10.1097/01.inf.0000143642.72480.53.
[22] Pitrez PMC, Stein RT, Stuermer L, Macedo IS, Schmitt VM, Jones MH, et al. Rhinovirus and acute bronchiolitis in young infants. Jornal de Pediatria 2005;81(5):417–20.
[23] Jartti T, Lehtinen P, Vanto T, Hartiala J, Vuorinen T, Mäkelä MJ, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. The Pediatric Infectious Disease Journal 2006;25(6):482–8.
[24] Marguet C, Lubrano M, Gueudin M, et al. In Very Young Infants Severity of Acute Bronchiolitis Depends On Carried Viruses. Morty RE, ed. *PLoS One*. 2009;4(2):e4596. doi:10.1371/journal.pone.0004596.
[25] Midulla F, Scagnolari C, Bonci E, Pierangeli A, Antonelli G, De Angelis D, et al. Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. Archives of Disease in Childhood 2010;95(1):35–41.
[26] Nascimento MS, de Souza AV, de Souza Ferreira AV, Rodrigues JC, Abramovici S, da Silva Filho LVF. Silva Filho LVF da. High rate of viral identification and coinfections in infants with acute bronchiolitis. Clinics 2010;65(11):1133–7.
[27] Carroll KN, Gebretsadik T, Minton P, Woodward K, Liu Z, Miller EK, et al. Influence of maternal asthma on the cause and severity of infant acute respiratory tract infections. The Journal of Allergy and Clinical Immunology 2012;129(5):1236–42.
[28] Luchsinger V, Ampuero S, Palomino MA, Chnaiderman J, Levican J, Gaggero A, et al. Comparison of virological profiles of respiratory syncytial virus and rhinovirus in acute lower tract respiratory infections in very young Chilean infants, according to their clinical outcome. Journal of Clinical Virology 2014;61(1):138–44.
[29] Selvaggi C, Pierangeli A, Fabiani M, Spano L, Nicolai A, Papoff P, et al. Interferon lambda 1–3 expression in infants hospitalized for RSV or HRV associated bronchiolitis. The Journal of Infection 2014;68(5):467–77.
[30] Turunen R, Koistinen A, Vuorinen T, Arku B, Söderlund-Venermo M, Ruuskanen O, et al. The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. Pediatric Allergy and Immunology 2014;25(8):796–803.
[31] Díaz PV, Valdivia G, Gaggero AA, Bono MR, Zepeda G, Rivas M, et al. Pro-Inflammatory Cytokines in Nasopharyngeal Aspirate From Hospitalized Children With Respiratory Syncytial Virus Infection With or Without Rhinovirus Bronchiolitis, and Use of the Cytokines as Predictors of Illness Severity. Medicine 2015;94(39):e1512.
[32] Mansbach JM, Clark S, Teach SJ, Gern JE, Piedra PA, Sullivan AF, et al. Children Hospitalized with Rhinovirus Bronchiolitis Have Asthma-Like Characteristics. The Journal of Pediatrics 2016;172:202–204.e1.
[33] Jartti T, Aakula M, Mansbach JM, Piedra PA, Bergroth E, Koponen P, et al. Hospital Length-of-stay Is Associated With Rhinovirus Etiology of Bronchiolitis. The Pediatric Infectious Disease Journal 2014;33(8):829–34.
[34] García-García ML, Calvo C, Moreira A, Cañas JA, Pozo F, Sastre B, et al. Thymic stromal lymphopoietin, IL-33, and periostin in hospitalized infants with viral bronchiolitis. Medicine 2017;96(18):e6787.
[35] Janahi I, Abdulkayoum A, Almeshwesh F, Alkuwari M, Al hammadi A, Alameri M. Viral aetiology of bronchiolitis in hospitalised children in Qatar. BMC Infectious Diseases 2017;17(1). https://doi.org/10.1186/s12879-017-2225-z.
[36] Pierangeli A, Statzu M, Nenna R, Santinelli L, Petrarca L, Frassanito A, et al. Interferon lambda receptor 1 (IFNL1R) transcript is highly expressed in rhinovirus bronchiolitis and correlates with disease severity. Journal of Clinical Virology 2018;102:101–9.
[37] Hasegawa K, Mansbach JM, Bochkov YA, Gern JE, Piedra PA, Bauer CS, et al. Association of Rhinovirus C Bronchiolitis and Immunoglobulin E Sensitization

During Infancy With Development of Recurrent Wheeze. JAMA Pediatrics 2019; 173(6):544.

[38] Arroyo M, Salka K, Perez GF, Rodríguez-Martínez CE, Castro-Rodriguez JA, Gutierrez MJ, et al. Phenotypical Sub-setting of the First Episode of Severe Viral Respiratory Infection Based on Clinical Assessment and Underlying Airway Disease: A Pilot Study. Frontiers in Pediatrics 2020;8. https://doi.org/10.3389/fped.2020.00121.

[39] Üzüm Ö, Kanık A, Eliaçık K, et al. Comparison of clinically related factors and treatment approaches in patients with acute bronchiolitis. Turk Pediatri Ars 2020; 55(4):376–85. https://doi.org/10.14744/TurkPediatriArs.2020.46144.

[40] De Paulis M, Oliveira DBL, Thomazelli LM, Ferraro AA, Durigon EL, Vieira SE. The importance of viral load in the severity of acute bronchiolitis in hospitalized infants. Clinics (São Paulo, Brazil) 2021;76:e3192.

[41] Calvo C, García-García ML, Blanco C, Pozo F, Flecha IC, Pérez-Breña P. Role of Rhinovirus in Hospitalized Infants With Respiratory Tract Infections in Spain. The Pediatric Infectious Disease Journal 2007;26(10):904–8. https://doi.org/10.1097/INF.0b013e31812e52e6.

[42] Takeyama A, Hashimoto K, Sato M, Sato T, Tomita Y, Maeda R, et al. Clinical and epidemiologic factors related to subsequent wheezing after virus-induced lower respiratory tract infections in hospitalized pediatric patients younger than 3 years. European Journal of Pediatrics 2014;173(7):959–66.

[43] Zhu Z, Camargo CA, Raita Y, Freishtat RJ, Fujiogi M, Hahn A, et al. Nasopharyngeal airway dual-transcriptome of infants with severe bronchiolitis and risk of childhood asthma: A multicenter prospective study. The Journal of Allergy and Clinical Immunology 2022;150(4):806–16.

[44] Hurme P, Komulainen M, Tulkki M, Leino A, Rückert B, Turunen R, et al. Cytokine expression in rhinovirus- vs. respiratory syncytial virus-induced first wheezing episode and its relation to clinical course. Frontiers in Immunology 2022;13. https://doi.org/10.3389/fimmu.2022.1044621.

[45] Fujiogi M, Dumas O, Hasegawa K, Jartti T, Camargo CA. Identifying and predicting severe bronchiolitis profiles at high risk for developing asthma: Analysis of three prospective cohorts. EClinicalMedicine 2022;43:101257. https://doi.org/10.1016/j.eclinm.2021.101257.

[46] Jackson DJ, Gern JE. Rhinovirus Infections and Their Roles in Asthma: Etiology and Exacerbations. *Journal of Allergy and Clinical Immunology*. In Practice 2022;10 (3):673–81. https://doi.org/10.1016/j.jaip.2022.01.006.

[47] Bergroth E, Aakula M, Elenius V, Remes S, Piippo-Savolainen E, Korppi M, et al. Rhinovirus Type in Severe Bronchiolitis and the Development of Asthma. The Journal of Allergy and Clinical Immunology. In Practice 2020;8(2):588–595.e4.

[48] Garcia-Garcia ML, Calvo C, Ruiz S, et al. Role of viral coinfections in asthma development. Schildgen O, ed. *PLoS One*. 2017. 12(12):e0189083. doi:10.1371/journal.pone.0189083.