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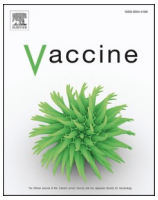

Impact of respiratory syncytial virus on older children: Exploring the potential for preventive strategies beyond the age of 2 years

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ABSTRACT

Objective: Respiratory syncytial virus (RSV) causes significant lower respiratory tract infections (LRTIs) in infants and young children. Current prevention targets those under 2 years. This study aims to evaluate RSV patterns and severity in children older than 2 years and to explore the potential extension of preventive strategies to this demographic group.
Methods: An observational retrospective study at Meyer Children's Hospital (from October 2019 to March 2023) analyzed data from patients between 28 days and 18 years of age with RSV infection. Severity indicators and patient characteristics were compared between two age groups: under 2 years and 2 years and above.
Results: 584 infants and young children were hospitalized due to RSV infection. Epidemic seasons saw a rise in hospitalizations among children older than 2 years. Older children had higher comorbidity (41% versus 9% p=0.000) and prematurity (26% versus 14% $p = 0.001$) rates than those under 2 years.
Conclusion: The study highlights the increased risk of severe RSV LRTIs in children older than 2 years and with prematurity or comorbidities, overlooked by current preventive measures. Prospective studies and cost-effectiveness analyses are needed to determine the necessity of targeted immunization for older children with specific risk factors, aiming to reduce RSV-related morbidity and mortality.

1. Introduction

Human respiratory syncytial virus (RSV) is a single-stranded RNA virus belonging to the recently defined Pneumoviridae family, Orthopneumovirus genus [1]. It is a highly contagious pathogen spread by hand contact, large droplets, and aerosolized particles [2].

RSV causes acute respiratory tract illness at all ages [3]. In infants and young children less than 5 years of age, RSV is the leading cause of severe acute lower respiratory tract infection (LRTI), resulting annually in 33 million infections and >3 million hospitalizations [4]. Further, LRTI is a leading cause of death globally in children under five years, as it is responsible for >100,000 deaths in children between 0 to 60 months of age worldwide [4,5]. Therefore, RSV infection in infants is a global health priority [6]. RSV clinical manifestations vary with the patient's age and health status. In children >2 years of age, RSV usually affects only the upper respiratory tract and is self-limiting. Healthy and premature infants younger than 2 years of age are at higher risk of LRTI manifesting as bronchiolitis or pneumonia [7]. Acute RSV infection may be complicated by respiratory failure, which may require mechanical ventilation and prolonged hospitalization [8].

Children younger than one year old and those who are born just before or during the epidemic season, which is usually from November to March in the Northern Hemisphere, have the highest risk of infection and hospitalization due to RSV [9].

Well-known risk factors for severe RSV disease include premature birth, chronic lung disease (CLD), bronchopulmonary dysplasia (BPD), congenital heart disease (CHD), immunocompromised children, Trisomy 21 and other chromosomal abnormalities, congenital malformations, especially pulmonary and airway anomalies, and cystic fibrosis [10]. Therapy for RSV LRTIs is primarily symptomatic and supportive,

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including frequent monitoring of clinical status and provision of fluid and respiratory support as necessary [11]. Unfortunately, experiencing the illness for the first time does not guarantee immunity against future reinfections [12].

Up to now, though efforts to develop an RSV vaccine or immune prophylaxis remain highly active, with thirty-three RSV prevention candidates in clinical development, no vaccine is available, and the only effective preventive strategy for RSV in childhood is passive immunization through monoclonal antibodies or maternal immunization during pregnancy [13].

Palivizumab is a humanized monoclonal antibody with demonstrated safety and efficacy. Due to its short half-life, it is administered in five monthly doses throughout the epidemic period [14]. The use of Palivizumab is restricted to preterm infants ≤35 weeks gestational age who are less than six months old at the beginning of the seasonal RSV epidemic (November) and to children who are <2 years of age and have significant risk factors, such as BPD, CHD with pulmonary hypertension, or cyanotic heart disease [15].

Nirsevimab is a monoclonal antibody whose extended half-life permits a single intramuscular dose [16]. The European Medicines Agency approved the drug for market use in October 2022 in all healthy and preterm infants during the first RSV season to protect against RSV LRTI; furthermore, Nirsevimab has been tested and demonstrated to be safe in infants with CHD and/or CLD [17].

Abrysvo (Pfizer Inc.) is a single-dose RSV vaccine for pregnant women during 32–36 completed gestational weeks to prevent RSV-associated LRTI in infants younger than 6 months using seasonal administration (i.e., during September through the end of January in most of the continental United States) [18].

Given the significant burden of RSV, protecting infants is crucial to prevent future complications like wheezing and asthma [19].

While current literature focuses on preventing RSV in children under 2 years, those older than 2 years are not offered passive protection and remain at risk of severe infection.

Our aim is to elucidate the epidemiological characteristics and severity of RSV infection in children older than 2 years of age and to explore the possible need to extend preventive strategies to this cohort of patients, currently excluded based on age criteria.

2. Methods

2.1. Study design

An observational retrospective study was undertaken to gather data concerning patients between 28 days and 18 years of age diagnosed with RSV LRTI and admitted to Meyer Children's Hospital in Florence, (Italy) between October 2019 and March 2023. This investigation aimed to assess the severity of RSV infection in older pediatric cohorts, a demographic typically not targeted by preventive strategies against this pathogen.

Inclusion criteria encompassed individuals between 28 days and 18 years of age with confirmed RSV diagnosis, who were admitted to either an inpatient ward or a pediatric intensive care unit (PICU) during the seasonal epidemics from September 1st to March 30th, spanning the years 2019 to 2023. Patients were identified retrospectively by examining electronic medical records, utilizing the 9th edition of the International Classification of Diseases (ICD-9) codes.

Demographic, clinical, and laboratory data were collected in a de-identified manner.

Demographic information included gender and age at admission. Clinical data comprised comorbidities, prematurity (defined as gestational age <37 weeks), presenting symptoms, duration and setting of hospitalization, need for oxygen or ventilatory support, antibiotic administration, and treatment duration. Comorbidities were categorized into specific groups, such as CHD, immunodeficiency, chronic bronchopulmonary disease, airway anatomical anomalies, and neuromuscular disorders, with other conditions classified as "miscellaneous comorbidities" (e.g., chronic kidney failure, intestinal failure, and medium-chain acyl-coenzyme A dehydrogenase deficiency).

Presenting symptoms included both respiratory and gastrointestinal manifestations (i.e., diarrhea, vomiting, and abdominal pain) and fever (defined as body temperature >38.5 °C at least once since symptom onset). Hospitalization settings included pediatric wards and PICU, with analysis conducted on the length of hospital stays (LOS) in both settings.

Laboratory investigations comprised viral detection from nasopharyngeal swabs. Viral analysis of nasopharyngeal swabs was performed targeting various respiratory pathogens including RSV, Influenza (A or B), Parainfluenza (types 1, 2, 3), Adenovirus, Rhinovirus, Bocavirus, Metapneumovirus viruses and SARS-CoV-2, considering the common occurrence of coinfections. Viral detection from nasopharyngeal swabs were performed on hospitalized patients with lower respiratory tract infections of all ages.

Patients were divided into two groups based on age: younger than 2 years old and 2 years and above, to compare severity in these two subsets. Severity criteria included:

- Use and duration of oxygen therapy;
- Need for PICU admission;
- Median length of stay in PICU;
- Median length of total hospitalization.

2.2. Laboratory Methods

Viral analysis of nasopharyngeal swabs was performed using quantitative Real-time Polymerase Chain Reaction (q-RT-PCR). For RNA viruses, reverse transcriptase was conducted before performing Real-time PCR. Viral DNA or RNA was extracted from biological samples, using the MagCore® Viral Nucleic Acid Extraction Kit (RBC Biosciences, Taiwan), and amplified with the TaqPath™ 1-Step qRT-PCR Master Mix (Life Technologies, The Netherland) following the manufacturer's instructions. Each sample was validated by positive and negative controls and each reaction replicated twice. A lack of fluorescent signal increase within 40 cycles indicated a negative result.

2.3. Statistical analysis

SPSS statistical package was used to process data and for statistical analysis.

Pearson's Chi-Squared test was performed to evaluate the association between RSV infection and the categorical variables considered such as gender, age classes, preterm birth, comorbidities, coinfections, oxygen therapy, and ICU admission. The level of statistical significance was set to 5 % (p-value < 0.05). Odds ratio (OR) with 95 % confidence intervals (CI) were used to assess the risk of RSV infection of each categorical variable considered.

3. Results

Five hundred and eighty-four infants and young children, clinically diagnosed with RSV, required hospitalization over the course of the four epidemic seasons spanning from September 2019 to March 2023, as described in Table 1. The analytical focus was specifically directed towards the epidemic seasons of 2019–2020, 2021–2022, and 2022–2023. Notably, the 2020–2021 season exhibited a solitary recorded RSV admission case, a phenomenon likely attributable to its temporal overlap with the onset of the COVID-19 pandemic.

In the 2021–2022 season, hospitalizations due to RSV increased by 154.5 % (252 cases), and in the subsequent 2022–2023 season, there was a rise of 134.3 % (232 cases), in comparison to the pre-pandemic season of 2019–2020 (99 cases). Seasonal analysis (Fig. 1) revealed that the 2019–2020 season exhibited its highest peak in January (38 cases, 38.4 %). Conversely, during the 2021–2022 season, November

Table 1
Characteristics of RSV cases admitted from 2019 to 2023 by epidemic season.

	Total	2019–2020	2021–2022	2022–2023	Var. % 2019–23
Number of cases	**584**	**99**	**252**	**232**	134.3
Female	289	47	120	121	157.4
	49 %	*47 %*	*48 %*	*52 %*	
Median age, days (range)	200	129	256	210	62.8
	(68–699)	(59–437)	(69–715)	(71–751)	
28 days < Age ≤ 6 months	281	60	109	112	86.7
	48 %	*61 %*	*43 %*	*48 %*	
6 months < Age ≤ 12 months	77	11	34	32	190.9
	13 %	*11 %*	*13 %*	*14 %*	
1 year < Age ≤ 2 years	97	15	51	30	100.0
	17 %	*15 %*	*20 %*	*13 %*	
2 years < Age ≤ 4 years	89	9	41	39	333.3
	15 %	*9 %*	*16 %*	*17 %*	
4 years < Age ≤ 6 years	31	3	14	14	366.7
	5 %	*3 %*	*6 %*	*6 %*	
Age > 6 years	9	1	3	5	400.0
	2 %	*1 %*	*1 %*	*2 %*	
Prematurity	99	16	46	37	131.3
	17 %	*16 %*	*18 %*	*16 %*	
Coinfection	131	11	53	66	500.0
	22 %	*11 %*	*21 %*	*28 %*	
Comorbidity	96	11	52	33	200.0
	16 %	*11 %*	*21 %*	*14 %*	
Median LoS, days (range)	7	7	7	7	0.0
	(5–10)	(5–9)	(5–10)	(5–10)	
Oxygen Therapy	542	90	232	219	143.3
	93 %	*91 %*	*92 %*	*94 %*	
Median LoOT (days)	5	4	5	5	25.0
	(3–7)	(2–6)	(3–7)	(3–8)	
PICU admission	138	12	64	62	416.7
	24 %	*12 %*	*25 %*	*27 %*	
Median LoPICU (days)	5	8	5	6	−25.0
	(4–11)	(3–20)	(3–11)	(4–10)	

Column percentages in italics and 1° and 3° quartiles in brackets.
LoS=Length of Stay.
LoOT=Length of Oxygen Therapy.
LoPICU=Length of PICU admission

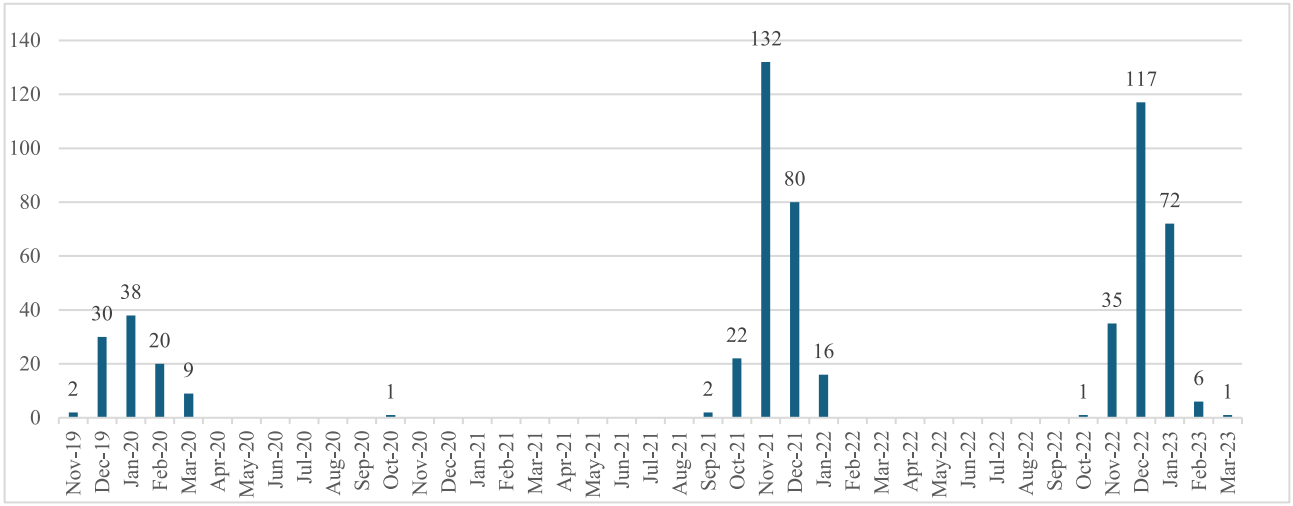

Fig. 1. Seasonality of RSV cases admitted (2019–2023).

witnessed the highest peak (132 cases, 52.4 %), while in the subsequent 2022–2023 season, December recorded the peak of hospitalizations with 117 cases (50.4 %).

Over time, the sample of hospitalized children showed the following main characteristics:

– *Age distribution*: Of the 584 hospitalization cases considered over four epidemic seasons, 78 % involved children under 2 years of age (61 % under one year, 17 % between 1 and 2 years). Hospitalizations for children over 2 years of age were less frequent, accounting for 15 % in the 2 to 4-year age group, 5 % in the 4 to 6-year age group, and 2 % in those over 6 years. Older age groups showed the highest growth rates, with increases of 333 %, 367 %, and 400 %, respectively. In

2019, children older than 2 years represented 13 % of total admissions, rising to 25 % by 2023.

- *Prematurity*: ninety-nine children (17 %) had a history of prematurity. The incidence of pre-term children has stabilized at around 16 %, despite the increase of 131 % from 2019 to 2023.
- *Comorbidities*: ninety-six children (16.4 %) presented comorbidities, with prevalence rates fluctuating from 11 % in 2019–2020 to 21 % in 2021–2022 and 14 % in the latest epidemic season. Comprehensive frequencies of all identified comorbidities are documented in Table 2, with CHD (31.3 %) and neurological/neuromuscular diseases (27.1 %) emerging as the most common.
- *Coinfections*: an overall number of 131 cases (22 %) involving coinfections were identified, with an incidence rising from 11 % in 2019–2020 to 28 % in 2022–2023. Coinfections detected in the analyzed RSV cases are outlined in Table 3. The most prevalent coinfections observed were RSV with Bocavirus (61 cases) and RSV with Adenovirus (24 cases).

Table 1 also contains indicators of the severity of bronchiolitis cases by RSV, such as the use of oxygen therapy and intensive care.

- *Oxygen therapy*: oxygen therapy was administered to 93 % of hospitalized children, with a median duration of 5 days, constituting 71 % of the overall median LOS. As depicted in Fig. S1, the utilization of high-flow oxygen therapy escalated from 43.3 % in the 2019–2020 season to 49.3 % in the 2022–2023 season; meanwhile, the utilization of non-invasive ventilation (NIV) and mechanical ventilation rose from 11.1 % of cases in the initial epidemic season to 26.9 % in the final one.
- *PICU admission*: 12 % of children needed transfer to the PICU, with seasonal distributions ranging from 12 % in 2019–2020 to 27 % in 2022–2023. The median LOS in the PICU was 5 days (range).

When comparing patients under 2 years of age with those older than 2 years, significant differences emerge concerning disease severity at admission and patient characteristics (Table 4). From a severity standpoint, the proportion of admissions to PICU is twice as high in the younger group compared to the older group (27 % vs. 13 %; p = 0.002; OR = 2.39; CI 1.38–4.14). Conversely, the rate of patients who did not require oxygen therapy is more than double in the older group compared to the younger group (13 % vs. 5.5 %; p = 0.005; OR = 2.61; CI 1.36–5.00).

From a patient characteristic perspective, a notable discrepancy arises between children older than 2 years and those under 2 years old regarding comorbidity rates, with 41 % of cases in the older group, contrasting with the 9 % observed in the younger age group (p = 0.000; OR = 0.15; CI 0.09–0.24). Among children older than 2 years, the most prevalent conditions are neurological/neuromuscular diseases (30.2 %), followed by CHD (24.5 %), and other miscellaneous conditions (24.5 %) (Table 2).

Moreover, the prevalence of prematurity was higher among RSV cases older than 2 years compared to those under 2 years (26 % versus 14 %; p = 0.001; OR = 0.47; CI 0.29–0.75). Furthermore, within the older age group, more than half of the cases were born prematurely, with 23 % classified as high and 29 % as extreme prematurity (Table 5).

Table 2
Comorbidities in RSV cases (under and over 2 years of age) admitted from 2019 to 2023.

	<2 years		≥2 years		Total	
	N	Rate	N	Rate	N	Rate
Comorbidities	**43**	**9.5 %**	**53**	**41.1 %**	**96**	**16.4 %**
- Anatomical defects of the airways	7	16.3 %	5	9.4 %	12	12.5 %
- Chronic lung disease/ bronchodysplasia	2	4.7 %	4	7.5 %	6	6.3 %
- Immunodeficiency	2	4.7 %	2	3.8 %	4	4.2 %
- Neurological/neuromuscular diseases	10	23.3 %	16	30.2 %	26	27.1 %
- Congenital Heart Disease	17	39.5 %	13	24.5 %	30	31.3 %
- Malformations Gastrointestinal tract	3	7.0 %	0	0.0 %	3	3.1 %
- Other	3	7.0 %	13	24.5 %	16	16.7 %

4. Discussion

Our study found a significant and increasing hospitalization of children between 2 and 6 years of age for RSV-related LRTI, sometimes requiring PICU admission. Due to the limited number of patients older than 6 years and the exceedingly mild nature of their clinical presentation, this age group was not covered in the description of the study results and discussion.

One possible reason for the increase in RSV disease in children older than 2 years is the 'immune debt' hypothesis. This theory suggests that the low RSV transmission during the COVID-19 pandemic led to more children being RSV-naive. Consequently, with fewer exposures to the virus, children did not develop necessary immunity, resulting in higher susceptibility and a rise in severe RSV cases once transmission resumed [20]. Another factor to consider is potential changes in RSV testing practices across different seasons. Variations in testing protocols, increased awareness, and improved diagnostic capabilities could have contributed to the increased detection and reporting of RSV cases in older children.

Among these older children, two well-established risk factors linked to severe RSV infection were primarily noted: prematurity and comorbidity. Nevertheless, despite recognizing these risk factors, proactive RSV immunization before the onset of the epidemic season was not pursued for these children. This hesitance mainly stemmed from the limited age indications outlined for monoclonal antibodies, currently in use, such as Palivizumab or Nirsevimab.

As a result, children over the age of 2, especially those with prematurity or comorbidities, were not eligible for prophylactic RSV passive immunization. This gap in preventive measures emphasizes the need to evaluate over time whether the eligibility criteria should be extended or whether alternative strategies should be considered to protect this vulnerable population from RSV-related morbidity and mortality. Van Hasselt et al. undertook a systematic review of studies including children 0–18 years of age, describing the proportion of RSV-related admissions to a PICU and relative risks of invasive mechanical ventilation for children who were born preterm. They found that premature children had a greater risk compared to children born at term. Though the majority of severely affected children were younger than 2 years, they included children 0–18 years of age [21]. This data suggests that RSV immunization for premature children might also be extended to older children.

Wilkesmann et al. conducted a prospective multicenter study to assess the severity of RSV LRTI in children with clinically relevant neuromuscular impairment (NMI). They confirmed the hypothesis that children with NMI have an increased risk for severe RSV disease as they have a higher mortality and a higher risk of mechanical ventilation than children without NMI. Furthermore, they found that the median age at diagnosis was higher in NMI patients. They concluded that it might be reasonable to include NMI as a cofactor in the decision algorithm of passive immunization against RSV [22].

A recent systematic review and meta-analysis demonstrated more severe RSV-LRTI among children <5 years with underlying CHD, as compared to those without CHD, supporting a need for improved RSV preventive strategies in children older than one year [23].

Furthermore, a recent systematic review of the literature and a meta-analysis examined the risk factors associated with poor outcomes of RSV-LRTI in children <5 years old. They defined poor outcomes as the need for supplemental oxygen, mechanical ventilation, PICU admission, prolonged hospital stays, and mortality. Significant risk factors were

Table 3
Coinfections in RSV cases admitted from 2019 to 2023.

	Adenovirus	Bocavirus	Rhinovirus	Parainfluenza	Influenza	Covid	Total
Adenovirus	**16**	6	2				**24**
Bocavirus	6	**51**	1	2		1	**61**
Rhinovirus	2	1	**16**	1		1	**21**
Parainfluenza		2	1	**8**			**11**
Influenza					**12**		**12**
SARS-CoV-2		1	1			**14**	**16**

Table 4
Group "under 2" and Group "2 and above" years of age of all RSV cases admitted from 2019 to 2023. Differences and significance.

	<2 years	≥2 years	<2 years	≥2 years	Chi- square	p value	OR	CI (95 %)	
								Inf	Sup
	455	**129**	**%**	**%**					
Gender					0.001	0.974	1.01	0.68	1.49
Male	230	65	50.55	50.39					
Female	225	64	49.45	49.61					
PICU Admission					10,023	0.002	2.39	1.38	4.14
Yes	121	17	26.59	13.18					
No	334	112	73.41	86.82					
Oxygen therapy					7,776	0.005	2.61	1.36	5.00
Yes	430	112	94.51	86.82					
No	25	17	5.49	13.18					
Prematurity					10,402	0.001	0.47	0.29	0.75
Yes	65	34	14.29	26.36					
No	390	95	85.71	73.64					
Coinfection					2,102	0.147	0.72	0.46	1.13
Yes	96	35	21.10	27.13					
No	359	94	78.90	72.87					
Comorbidity					73,224	0.000	0.15	0.09	0.24
Yes	43	53	9.45	41.09					
No	412	76	90.55	58.91					

PICU: Pediatric Intensive Care Unit.

Table 5
Degree of prematurity in RSV cases (Group "under 2" and Group "2 and above" years of age) admitted from 2019 to 2023.

	<2 years		≥2 years		Total	
	N	Rate	N	Rate	N	Rate
Preterms	**65**	**14.3 %**	**34**	**26.4 %**	**99**	**17.0 %**
Mild: 36 + 6–34 weeks	40	61.5 %	9	26.5 %	49	49.5 %
Moderate: 33 + 6–32 weeks	11	16.9 %	7	20.6 %	18	18.2 %
High: 31 + 6–28 weeks	7	10.8 %	8	23.5 %	15	15.2 %
Extreme: <28 weeks	7	10.8 %	10	29.4 %	17	17.2 %

neurological disease, Trisomy 21, CLD, immunocompromised status, prematurity, CHD, underlying disease, viral coinfection, low birth weight, actual underweight, any comorbid condition, and age <6 months [24,25]. Children carrying many of these recognized risk factors are not targeted for RSV prevention yet.

Another systematic review revealed that children with Down Syndrome have a higher risk of severe RSV infections (higher hospital admission, mortality, length of stay, oxygen supplementation, PICU admission, and respiratory support) than children without such a syndrome. Currently, Palivizumab is not recommended routinely to prevent RSV infection in patients with Down Syndrome who do not qualify for other reasons (e.g., CHD, CLD, or prematurity) [26].

A nationwide survey on RSV infections in Japan conducted by Mori et al. showed that children affected by immunodeficiencies are also at significant risk of severe RSV disease. This survey led to the approbation of a new indication for Palivizumab use in children with immunocompromised conditions in Japan [27,28].

Currently, both healthy children and those with comorbidities older than 2 years are not offered active nor passive protection from RSV but are exposed to potentially severe infection [29].

Palivizumab reduces RSV-related hospitalizations and may reduce RSV infections. Further research is needed to establish the effect of this immunization on children with comorbidities at increased risk for severe RSV disease [30].

Additional efforts should be made to potentiate the prevention of RSV infection in children. The future availability of monoclonal antibodies, as well as other preventive measures, may help reduce the burden and severity of RSV infection among pediatric patients [31]. In fact, the discovery and imminent availability of monoclonal antibodies initially prioritize achieving maximal coverage within high-risk populations, specifically healthy, preterm infants under 2 years of age.

Nevertheless, upon achieving this primary objective and contingent upon the optimal efficacy and safety data, the use of these antibodies could be considered for extension to children older than 2 years with specific underlying risk factors. However, the need to extend these strategies to age groups beyond 2 years will require longitudinal evaluation, especially as we move past the COVID-19 pandemic and new data from prospective studies become available.

It's noteworthy that the risk of severe RSV infection doesn't seem to diminish at age 2 for these vulnerable patients. This is due to the persistent nature of prematurity and comorbidities, which are non-modifiable factors likely to heighten susceptibility to severe infections throughout childhood in these individuals.

5. Conclusion

In conclusion, our research underscores the significant risk of severe RSV infection in children older than 2 years with prematurity and/or comorbidities. Currently, active, or passive protection from RSV is not provided to these vulnerable groups. Prospective studies and cost-effectiveness analyses are necessary before establishing the need for RSV prevention in these patients. These studies will help optimize immunization efficacy and timing in younger children and assess the benefits of extending these measures to vulnerable children over 2 years of age. Adapting prevention strategies, based on robust evidence, is crucial to reduce RSV-related morbidity and mortality in children. This approach could also decrease RSV circulation within families and lower overall healthcare costs.

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CRediT authorship contribution statement

Valentina Guarnieri: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Chiara Macucci:** Writing – review & editing, Writing – original draft, Data curation. **Antonella Mollo:** Validation, Data curation. **Sandra Trapani:** Writing – review & editing, Visualization, Validation, Supervision. **Maria Moriondo:** Supervision, Methodology. **Marina Vignoli:** Validation, Methodology. **Silvia Ricci:** Writing – review & editing, Visualization, Validation, Supervision. **Giuseppe Indolfi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

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.

Data availability

Data will be made available on request.

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All authors have participated in the conceptualization, design, data curation and analysis of this study, as well as in the drafting and review of the manuscript. No potential competing interests of the authors have been disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126170.

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