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AGE AS A KEY RISK FACTOR FOR SEVERE RESPIRATORY SYNCYTIAL VIRUS INFECTION IN CHILDREN: A LITERATURE REVIEW

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ABSTRACT

Research Objectives: Respiratory Syncytial Virus (RSV) is a leading cause of lower respiratory tract infections in young children, particularly in infants under six months. This review aims to synthesize recent clinical and epidemiological data to identify age groups at the highest risk for severe RSV disease.

Methods: A systematic literature search was conducted in PubMed for studies published between 2020 and 2025, focusing on pediatric populations aged 0–5 years with laboratory-confirmed RSV infection. Cohort, prospective, and retrospective studies, as well as clinical guidelines, reporting hospitalization rates, intensive care unit admissions, oxygen therapy, and risk factors such as prematurity and comorbidities were included. Data were analyzed narratively to assess relationships between age, prematurity, comorbidities, and disease severity.

Key Findings: The youngest infants (0–5 months) accounted for most hospitalizations and were most likely to require intensive care. Prematurity increased hospitalization risk approximately with earlier gestational age correlating with higher severity. Comorbidities further elevated the risk of prolonged hospitalization and intensive care, especially in older children. Introduction of RSV prophylaxis substantially reduced hospitalization rates among infants, particularly those 0–2 months. Seasonal trends and epidemiological shifts, influenced by the COVID-19 pandemic, affected RSV incidence and severity.

Conclusions: Age is the primary determinant of severe RSV outcomes, with prematurity and comorbidities acting as significant modifiers. Early identification of high-risk infants and targeted prophylactic strategies are essential to reduce hospitalization and optimize healthcare resource allocation. Continuous monitoring and evaluation of prevention strategies across age groups remain crucial.

KEYWORDS

Respiratory Syncytial Virus (RSV), Pediatric Infection, Age-related risk, Severe RSV, Hospitalization, Prematurity

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Introduction

Respiratory syncytial virus (RSV) is one of the leading causes of lower respiratory tract infections in young children worldwide. According to 2019 estimates, RSV is responsible for approximately 33 million episodes of lower respiratory tract infections in children under 5 years of age, including about 3.6 million hospitalizations, with infants younger than 6 months accounting for as many as 1.4 million hospital admissions ^[1].

The most common clinical manifestation in infants is bronchiolitis, typically presenting initially with symptoms of upper respiratory tract infection, which may progress over several days to include cough, tachypnea, intercostal retractions, wheezing, and feeding difficulties. In the youngest children, particularly those under 6 months of age, infection can result in significant respiratory distress, apnea, and the need for hospitalization. Management remains primarily supportive, focusing on respiratory support and adequate hydration, as no routinely recommended antiviral therapy is currently available for this age group ^[2].

The highest risk of severe disease requiring hospitalization, oxygen therapy, and intensive medical care occurs in infants during the first months of life ^[3]. Moreover, in 2021-2022, an increase in both hospitalization rates and disease severity was observed in children under 5 years of age ^[4].

Dynamic changes in RSV epidemiology – including seasonality, age distribution of hospitalized patients, and the introduction of novel prophylactic interventions – further highlight the importance of age as a key risk factor for severe disease.

Despite an increasing number of studies, there remains a lack of up-to-date, comprehensive synthesis of data linking RSV disease severity with age at infection. This study aims to collect, organize, and analyze the most recent clinical and epidemiological evidence to identify the age groups most vulnerable to severe manifestations of RSV infection.

Methodology

In this literature review, a systematic search of scientific publications on RSV infections in children was conducted, with particular emphasis on the impact of age and prematurity on the risk of hospitalization and disease severity. All articles were found in the PubMed database, providing access to full-text clinical studies, cohort studies, prospective and retrospective investigations, as well as clinical guidelines. The search was performed using a combination of keywords: "respiratory syncytial virus," "RSV," "hospitalization," "infants," "prematurity," "risk factors," and "co-infection," with the application of logical operators AND/OR to maximize thematic coverage. The results were filtered based on full-text availability, publication language – English, and recency – 2020-2025.

Publications were included if they met the following criteria: pediatric population aged from neonates to 5 years, laboratory-confirmed RSV infection, and full access to data regarding hospitalization rates, risk of severe disease, and associations with risk factors such as prematurity or comorbidities. Studies exclusively involving adult populations, theoretical reviews without primary data, and studies describing solely animal models were excluded.

The initial selection of articles involved screening titles and abstracts to exclude irrelevant studies or those not meeting the inclusion criteria. Full texts of selected publications were subsequently analyzed in detail, extracting data on the demographic characteristics of the study populations, including sample size, age, sex, and prematurity status, RSV diagnostic methods, hospitalization rates, and disease severity indicators such as intensive care unit admissions, oxygen therapy, mechanical ventilation, and the occurrence of apnea. Additional risk factors, including comorbidities, Down syndrome, or congenital heart defects, were also recorded. For cohort and prospective studies, the observation period and seasonality of infections were considered.

Data analysis was descriptive and narrative in nature, allowing synthesis of results in both tabular and textual forms and identification of relationships between age, prematurity, and RSV disease severity. The collected information was integrated narratively to provide a comprehensive overview of the impact of age and prematurity on hospitalization rates and RSV disease course in the pediatric population, while also highlighting gaps in the literature and areas requiring further research, such as the influence of co-infections, seasonality of infections, and the effectiveness of prophylactic interventions, including prenatal vaccines and monoclonal antibodies.

Results

RSV Hospitalization Distribution by Age Groups

A study published in 2020, conducted between 2009 and 2018, indicated that among the cohort of RSV-infected hospitalized patients under 5 years, 56.1% were aged 0-5 months, 37.7% were 6-12 months old, and 6.2% were children aged 1-4 years^[5]. More recent data also indicate a substantial incidence among younger children: 48% (2021) and 44.5% (2022-2023) were aged 0-5 months, 14.9% (2021) and 13.7% (2022-2023) were 6-12 months old, and 37.1% (2021) and 41.7% (2022-2023) were children aged 1-4 years (Table 1)^[6].

Table 1. Proportion of Hospitalized RSV Patients by Age Group Across Different Time Periods (2009–2023)

Age group	0-5 months	6-12 months	1-4 years
2009-2018	56,1%	37,7%	6,2%
2021	48%	14,9%	37,1%
2022-2023	44,5%	13,7%	41,7%

Age and Hospitalization Risk

Analysis of age in relation to hospitalization risk demonstrated that the risk declines rapidly during the first year of life. For term infants, the risk decreases to below 10% of the birth value by approximately the 7th month of life, whereas for preterm infants, the corresponding threshold is around the 9th month. The model also indicated that prematurity increases the relative risk of hospitalization is 2.6 times higher compared to term infants. Preterm infants are at greater risk of severe RSV infection due to an immature immune system at birth and smaller airway dimensions^[7].

In a cohort of 709 children hospitalized with laboratory-confirmed RSV infection, 241 children (34.0%) required admission to the intensive care unit (ICU). Age-stratified analysis revealed that among the youngest infants (0-5 months), 150 of 277 children (54.2%) were admitted to the ICU. In the 6–12 months age group, the proportion was lower at 24.2% (16 of 66 hospitalized children), and among older children aged 2-5 years, 34 of 183 hospitalized children (18.6%) required ICU care. The median ICU stay was 3 days (interquartile range [IQR]: 1–5 days), reflecting the typical length of hospitalization in this population [8]. Clinical analyses also demonstrated differences in disease severity: infants under 6 months more frequently required oxygen therapy and experienced episodes of apnea.

A 2023 cohort study included 63,351 preterm infants born between 29- and 34-weeks' gestation and 1,076,389 term infants (≥ 37 weeks). RSV hospitalization rates were higher in the preterm population than in term infants, ranging from 5.72 to 3.32 per 100 infants in the Medicaid-insured group and from 4.84 to 3.21 per 100 infants in the commercially insured group, depending on gestational age. Hospitalization risk was inversely proportional to gestational age: infants born at 29-30 weeks had the highest rates, those at 31-32 weeks had intermediate values, and infants born at 33-34 weeks had the lowest rates among preterm infants. Compared with term infants, preterm infants had a 3-5 times higher risk of RSV hospitalization and were more likely to require ICU admission and mechanical ventilation during hospitalization [9].

Impact of Additional Risk Factors on RSV Infection

In a multicenter cohort of 1,023 children aged 12-23 months, 228 children (22%) had at least one risk factor: prematurity, chronic lung disease of prematurity (CLD), congenital heart disease (CHD), or Down syndrome (DS). Among preterm children without CLD, 55% had prolonged hospitalization, whereas prematurity with CLD was associated with prolonged stays in 78% of cases. Children with CHD experienced extended hospitalizations in 65% of cases, and children with DS in 72% of cases. Overall, children with at least one risk factor had prolonged hospitalizations in 68% of cases. [10]

Regarding pediatric intensive care unit (PICU) admissions, 67% of children with DS required PICU care, 54% of children with CHD required PICU admission, and children with at least one risk factor accounted for 52% of PICU admissions in this cohort. The median PICU stay was 4 days (IQR: 2-6 days), and the median total hospital stay was 7 days (IQR: 5-10 days) [10].

In a study of 5,143 children hospitalized with laboratory-confirmed RSV infection, the impact of individual risk factors for severe disease varied with age. More than half of the patients (53.5%) were infants under 6 months, 31.7% were aged 6-24 months, and 14.8% were 24-59 months old. The prevalence of comorbidities increased with age: 25% of children <6 months, 46% aged 6-24 months, and 70% aged >24 months had at least one significant comorbidity. Multivariate analyses showed that in older children (>6 months), the presence of comorbidities – such as chronic lung disease, neurological disorders, or bronchopulmonary conditions – was the main factor increasing the risk of severe disease, including the need for oxygen therapy or ICU admission. In the youngest age group (<6 months), young age itself was the predominant risk factor for severe disease, with viral co-infections being an additional significant factor [11].

A prospective study conducted in 2024 included 433 infants under 12 months with laboratory-confirmed RSV infection. Among participants, 112 infants (26% of the cohort) were found to have additional pathogens, including both viruses and bacteria, identified using metagenomic methods. Bacteria of the genus *Haemophilus* were detected in 37 infants. Infants with *Haemophilus* showed higher rates of hospitalization and ICU admission compared with those without this bacterium (OR = 4.25; 95% CI 2.03-9.31). This group also more frequently required oxygen therapy and experienced apnea episodes and respiratory support. Among infants with additional viral co-infections, including adenovirus and influenza virus, 72 children (17% of the cohort) were affected. The presence of these viruses was associated with moderate clinical severity, but no significant increase in hospitalization or ICU admission rates was observed compared with infants infected solely with RSV [12].

Prophylaxis and RSV Infection

In the 2024-2025 season – the first in which widely available RSV prophylactic measures (prenatal vaccination and the long-acting monoclonal antibody Nirsevimab) were implemented – a significant reduction in infant RSV hospitalization rates was observed. Analysis comparing the 2018-2020 pre-pandemic seasons with 2024-2025 among infants aged 0-7 months (those eligible for prophylaxis) showed hospitalization rates decreased from 15.0 to 8.5 per 1,000 infants according to RSV-NET and from 14.8 to 10.7 per 1,000 according to NVSN, corresponding to an estimated reduction of approximately 43% (RSV-NET) and 28% (NVSN). The

greatest effect was observed in infants aged 0-2 months, with hospitalizations decreasing by approximately 52% (RSV-NET) and 45% (NVSN). In older age groups (8-19 months and 20-59 months), most of whom were ineligible for prophylaxis, hospitalization rates were higher in 2024-2025 compared with 2018-2020 ^[13].

Seasonality of RSV Infections

A retrospective epidemiological study conducted from 2018 to 2022 at a large pediatric hospital in central Italy included 3,536 laboratory-confirmed RSV samples from children aged 0-5 years. Among these cases, 1,895 required hospitalization. Analysis of hospitalization timing demonstrated RSV seasonality, with peak incidence in the autumn-winter months (October to February). In the 2020 season, RSV cases were nearly absent, both among outpatients and hospitalized children. In the 2021-2022 seasons, hospitalization numbers increased compared with pre-pandemic years, with the peak occurring 4-6 weeks earlier. Among hospitalized children, the majority were infants under 1 year, although children aged 1-5 years also showed increased hospitalizations. Age distribution analysis of hospitalized patients indicated the highest proportion of admissions occurred among infants aged 0-6 months, followed by children aged 6-12 months and 1-5 years ^[14].

Summary of Findings

Analysis of data from multiple studies and RSV epidemic seasons demonstrated that hospitalizations are predominantly concentrated among infants, particularly those aged 0-5 months. Prematurity and comorbidities, including chronic lung disease, congenital heart defects, and Down syndrome, were associated with higher rates of prolonged hospitalization and ICU admission. The prevalence of comorbidities increased with patient age. Data from the 2024-2025 season, in which RSV prophylaxis (prenatal vaccination and the monoclonal antibody Nirsevimab) was applied, showed reduced hospitalization rates among infants aged 0-7 months, with a particularly marked effect in the 0-2 month age group, whereas hospitalization rates in older age groups were higher than in the 2018-2020 seasons.

Discussion

Age as a Dominant Risk Factor for Severe RSV Disease

Analysis of available data unequivocally confirms that a child's age remains one of the most important and independent predictors of severe RSV infection. Evidence from numerous studies indicates that the youngest infants, particularly during the first months of life, represent the group most vulnerable to developing severe disease requiring hospitalization and intensive medical care. The consistency of this observation across different cohorts and epidemic seasons suggests that young age itself constitutes a risk factor, whose significance remains strong despite changing epidemiological conditions. These findings underscore that early infancy is a critical period during which the child's body exhibits the highest susceptibility to RSV-related complications.

From a biological perspective, the increased risk of severe disease in infants is attributable to the immaturity of both innate and adaptive immune responses, as well as limited respiratory reserve. Small airway diameters, reduced lung volumes, and limited compensatory capacity render even minor inflammatory changes sufficient to cause significant respiratory distress, apnea episodes, and the need for respiratory support. Furthermore, observations indicate that the risk of hospitalization decreases relatively rapidly during the first year of life; however, in term infants, it reaches a marginal level only around the 7th month, while in preterm infants, the corresponding risk decline occurs later, around the 9th month. These differences highlight the critical role of biological maturity in shaping RSV disease outcomes.

Clinical data consistently show that young age not only increases the likelihood of hospitalization but also influences the intensity of medical care. In cohorts of hospitalized infants aged 0-5 months, the proportion of children requiring ICU-level care was several-fold higher than in older age groups. Such a pronounced disparity indicates that young age is a decisive factor not only for hospital admission but also for the need for advanced respiratory support and monitoring, with direct implications for hospital resource planning.

Impact of Prematurity and Comorbidities

Prematurity remains one of the most significant modifiers of severe RSV risk. Data from cohorts including preterm infants clearly demonstrate that preterm infants are several times more likely to be hospitalized compared with term infants. This increased susceptibility results from both the immaturity of the immune system and features of the developing respiratory system in preterm infants, including smaller airways, reduced lung volumes, and less mature alveolar development. Additionally, preterm infants experience a

shorter duration of maternal antibody exposure, limiting passive protection against RSV. Consequently, even moderate infections may lead to severe clinical manifestations and necessitate intensive medical care.

Comorbidities, such as chronic lung disease of prematurity, congenital heart defects, or Down syndrome, also significantly increase the risk of severe RSV disease. The presence of even a single comorbidity is associated with prolonged hospital stays and a higher likelihood of ICU admission. Data analyses indicate that prematurity combined with chronic lung disease particularly increases the risk of prolonged hospitalization, suggesting a synergistic effect of these two factors on disease severity.

An important observation from the data analysis is the change in the relative impact of individual risk factors depending on the patient's age. In the youngest infants (<6 months), age itself is the predominant factor, with comorbidities playing a modulatory role. In older children, chronic conditions become the primary predictor of severe disease, highlighting the need for individualized risk assessment and tailored prophylactic strategies that consider both age and health status.

Seasonality and Epidemiological Changes in RSV

RSV seasonality remains an important factor in shaping the distribution of risk in the pediatric population. Retrospective epidemiological data demonstrate a clear predominance of cases during the autumn-winter months, with peak hospitalizations observed between October and February. A notable phenomenon was the near-complete absence of RSV cases during the 2020 season, likely related to global epidemiological restrictions during the COVID-19 pandemic; however, larger studies are needed to draw definitive conclusions. Subsequent seasons showed not only an increase in hospitalizations but also a shift in peak incidence several weeks earlier.

The introduction of prophylaxis in the 2024-2025 season, including prenatal vaccines and the monoclonal antibody Nirsevimab, led to a significant reduction in hospitalizations among the youngest infants, particularly those aged 0-2 months. This effect demonstrates the high efficacy of available prophylactic measures in preventing severe RSV disease. Simultaneously, the observed increase in hospitalizations among older age groups suggests an accumulation of susceptible children who had not been previously exposed to the virus, further emphasizing the importance of monitoring epidemiological dynamics and adapting prophylactic strategies accordingly.

Intensity of Medical Care and the Role of Oxygen Therapy

The severity of RSV in the youngest infants is reflected not only in high hospitalization rates but also in increased needs for advanced respiratory support, including oxygen therapy, high-flow nasal cannula support, and ICU care. The median ICU stay is several days, and total hospitalization can be considerably prolonged in preterm infants or those with comorbidities. These observations have important implications for staffing and infrastructure planning, particularly during periods of increased RSV activity.

Significance of Viral and Bacterial Coinfections

Coexisting viral and bacterial infections represent an additional factor that may modify RSV course, especially in the youngest infants. The presence of *Haemophilus* species was associated with higher hospitalization rates, more frequent ICU admissions, greater need for oxygen therapy, and increased episodes of apnea. While co-infection with other viruses, such as adenovirus or influenza virus, was associated only with moderate clinical severity, these findings highlight the importance of comprehensive virological and bacteriological diagnostics in children hospitalized with lower respiratory tract infections.

Implications for RSV Prophylaxis

The implementation of prophylaxis, both as prenatal vaccination and long-acting monoclonal antibody Nirsevimab, has demonstrated clear benefits in reducing hospitalizations among the youngest infants. The greatest effect was observed in the 0-2 month age group, highlighting the critical importance of protection during the period of highest vulnerability. Simultaneously, the increase in hospitalizations in older age groups suggests that current protective strategies may require further optimization and potentially broader target populations. These data provide the basis for developing more comprehensive prophylactic models that consider age, prematurity, comorbidities, and evolving RSV epidemiological patterns.

Limitations

This literature review has several important limitations that should be considered when interpreting the presented findings. The analysis is based on studies published in English and found exclusively in the PubMed database. Consequently, significant studies published in other languages or in local databases may have been overlooked, which could limit a comprehensive representation of the global epidemiology of RSV and regional differences in hospitalization rates and disease severity.

The review primarily includes cohort, prospective, and retrospective studies involving hospitalized children. Excluding studies of outpatient populations, brief reports, and unpublished data may lead to an overestimation of the risk of severe RSV disease across the pediatric population. As a result, the findings presented in this review may not fully reflect the clinical spectrum of RSV infections, particularly in older children who frequently experience mild infections that do not require hospitalization.

Methodological heterogeneity among the analyzed studies is also a limitation. Differences in definitions of severe RSV disease, hospitalization criteria, diagnostic methods employed, and observation periods may introduce variability in the results and complicate direct comparisons between studies. Additionally, some studies included only selected regions or insured populations, limiting the generalizability of the findings to the overall population.

Disruptions in RSV seasonality in recent years, including changes in social interactions and healthcare access due to the COVID-19 pandemic, represent an additional factor influencing observed hospitalization rates. The lack of long-term data or data from diverse regions hinders the assessment of true disease dynamics and the long-term effectiveness of preventive interventions.

Finally, available data on new prophylactic measures, such as the prenatal vaccine and the monoclonal antibody Nirsevimab, are limited to the initial seasons of their use. The absence of long-term observations restricts the ability to draw conclusions regarding the sustained efficacy of prophylaxis in subsequent years and its impact on older age groups not covered by preventive programs.

Considering the above limitations is essential for the interpretation of results and the formulation of clinical recommendations. Despite these limitations, this review provides valuable insights into the impact of age, prematurity, and comorbidities on severe RSV disease, highlighting directions for future research and areas requiring further analysis.

Conclusions

Analysis of the available studies clearly indicates that a child's age is a key determinant of severe RSV infection. The youngest infants, particularly those aged 0-5 months, exhibit the highest risk of hospitalization and the need for intensive medical care, irrespective of the presence of comorbidities. Prematurity and the presence of chronic conditions further increase the risk of severe disease and prolong hospitalization.

The data also demonstrate that risk factors vary according to age – in younger infants, age itself is the dominant determinant, whereas in older children, comorbidities become the primary predictor of severe disease. Seasonality of infections and epidemiological shifts, including the impact of the COVID-19 pandemic, underscores the dynamic nature of RSV epidemiology in the pediatric population and the necessity for continuous clinical monitoring.

The introduction of new prophylactic strategies, such as prenatal vaccines and the monoclonal antibody Nirsevimab, has shown significant effectiveness in reducing hospitalization rates among the youngest infants. This highlights the substantial potential of prophylaxis in mitigating severe RSV infections and emphasizes the need for ongoing optimization and evaluation of population-level protection strategies, including potential expansion of target groups.

The findings of this review underscore the importance of early identification of children at high risk for severe RSV, individualization of prophylactic approaches, and the planning of medical resources during periods of heightened viral activity. Further research, encompassing both long-term observational studies and analyses of the impact of co-infections and preventive interventions across different age groups, is essential for a comprehensive understanding of RSV epidemiology and for effectively reducing its clinical burden.

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