

# Risk of Developing Asthma After Lower Respiratory Tract Infections with Respiratory Syncytial Virus During Childhood

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## Abstract:

**Background:** Recent studies indicate causal relationship between infection by respiratory syncytial virus (RSV) and bronchial asthma. We evaluated the incidence of bronchial asthma in children with RSV positive infection early in their childhood in a nation-wide cohort study.

**Methods:** Children (aged between one month and 15 years) were evaluated for the presence of RSV infection when they presented with one or more acute respiratory tract infection symptoms (fever, cough, cold and wheezing) in a major tertiary care hospital in the Kingdom of Bahrain during a period of seven years. RSV detection was done using nasopharyngeal secretion (NPS) samples by direct antigen detection immunofluorescence technique. Number of children who were later diagnosed with asthma was recorded. Serum IgE levels were estimated. Risk of developing bronchial asthma is represented using relative risk (RR) [95% CI]. Children with asthma without prior RSV infection from the same population formed the historical control.

**Results:** A total of 3782 children diagnosed with respiratory tract infection were recruited. We observed that RSV infection at younger age (during infancy) and severe infection were significantly associated with asthmatic episodes RR [95% CI]: 7 [5.5, 8.2]. Additionally, asthmatics with prior RSV infection had significantly higher total IgE levels ( $167 \pm 37$  IU/ml) compared to those without RSV infection ( $92 \pm 17$  IU/ml). Mean (SD) age of children developing asthma with prior RSV infection was 0.7 (0.42) years compared to the historical control [6.8 (3.8) years] and was statistically significant.

**Conclusion:** Infants with RSV infection have an increased risk of developing bronchial asthma later in the childhood. The more severe the RSV infection, the greater is the severity of bronchial asthma as indicted by serum IgE levels. Asthma in children with RSV infection occurs at much younger age compared to those without RSV infection.

**Keywords:** RSV, Respiratory tract infection, Bronchial asthma.

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## Introduction

Bronchial asthma is one of the highly prevalent diseases among children than adults (Dharmage et al, 2019). One in 12 children has been reported to be affected by asthma worldwide (Griffiths et al, 2018). Yearly around 6 million children have been reported to have asthma with 205,000 hospitalizations and 697,000 emergency department visits in United States (Akinbami et al, 2009). Viral respiratory tract infections could have a triggering profound effect on developing asthma or its exacerbations (Krieger, 2010). Early life wheezing episodes secondary to viral upper respiratory tract infection is a major risk factor for the later diagnosis of asthma at age six years (Jackson, 2014). Respiratory syncytial virus (RSV) and rhinovirus are the commonest respiratory agents leading to wheeze in children (Jartti & Gern, 2017). The link between rhinovirus and asthma was studied in different ages and observed to be the most significant predictor of pre-school wheezing at 3 years of age, and later as asthma at 6 years (Jackson et al, 2008; Lemanske et al, 2005). The exact relationship between infection with RSV and the development of childhood asthma remains uncertain. Infections with RSV in early life could play an important role in shaping the secondary immune response to antigens leading to Th2 skewing of the immune response which is an important eliciting factor in asthma pathogenesis (Russell et al, 2017). RSV infection during the first year of life has been reported to increase risk of bronchial asthma in several studies. A study has reported that 15.5% of children with RSV bronchiolitis during their infancy stage developed bronchial asthma compared to only 3.6% without RSV in the same period (Schauer et al, 2002). Henderson et al. in 2005 observed that RSV bronchiolitis during infancy was associated with subsequent wheezing with a cumulative prevalence of asthma at 91 months (Odds ratio of 2.5 [1.4, 4.3]. In a recent study that followed up children for over 16 years revealed an incidence rate of 2.4 [2.3, 2.5]; and adjusted OR of during second year of age: 4.1 [3.9-4.4]; third year of age: 3.2 [3.0-3.3]; and fourth year of age: 2.9 [2.7-3.1]; and fifth year of age: 2.6 [2.5-2.9] of risk of bronchial asthma in RSV positive children compared to those who were negative (Mejias et al, 2020). Although RSV infection has been identified to be the most significant factor influencing wheezing episodes in the later childhood, it is unknown whether RSV is the causative agent for bronchial asthma. One theory put forth recently is the possibility of extrapulmonary persistence of RSV after causing acute respiratory infection playing a vital role in the inception of bronchial asthma (Piedimonte, 2013). Apart from the age of onset and severity of RSV infections, interestingly maternal asthma (exposure to high levels of dog allergen aeroallergen sensitivity at age 3 years and CCL5 expression in nasal epithelia have been identified to increase the risk of bronchial asthma (Bacharier et al, 2012).

A previous study in Bahrain observed that 37% of children under the age of two years presenting with bronchiolitis were confirmed with RSV (Salman et al, 2006). We envisaged the present study to evaluate the relationship between early exposure to RSV and developing bronchial asthma in Bahraini children.

## Methods

### Study design, ethics, and study participants

The present study was retrospective in nature, carried out after obtaining approval from the institutional ethics committee (Secondary Healthcare Research Subcommittee: 24-8-20). We carried out the study in compliance to Declaration of Helsinki (World Medical Association). We collected nation-wide data on paediatric patients that had been tested

for the presence of RSV infection during evaluation of respiratory infection in children aged between one month and 15 years when they presented with one or more acute respiratory tract infection symptoms (fever, cough, cold and wheezing) attending a major tertiary care hospital in the Kingdom of Bahrain during a 7 year period (2009 - 2015). RSV detection was made on nasopharyngeal secretion (NPS) samples by direct antigen detection immunofluorescence technique, according to manufacture instructions (Oxoid Company UK).

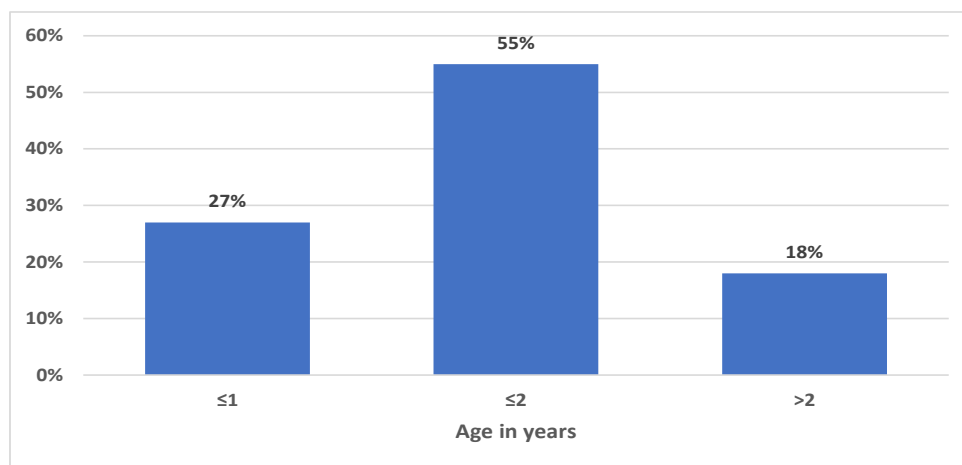
### Study procedure

Following data were obtained for the eligible patients over 7 years: Demographic details (age at time of RSV infections, nationality, and gender). The time interval between RSV infection and asthma diagnosis, and the levels of total IgE were retrieved. Total IgE was measured using Unicap automated machine and ImmunoCAP reagents from Phadia, Pharmacia Diagnostics AB, Uppsala, Sweden. IgE level was considered very high when its serum level exceeded 100 IU/ml; high >25 and less than 100 IU/ml; and low when <25 IU/ml (Unal et al, 2017). We used historical control consisting of asthmatic children without RSV infection reported from the same population (Tabbara et al, 2010). Separate data analysis was carried out for those that tested positive for RSV, and for those developing asthma in the follow up period of two years after RSV infection. For those who were RSV positive, we assessed the severity of illness using clinical parameters. Severe RSV infection was defined if there was a diagnosis of bronchopneumonia or severe bronchiolitis with respiratory distress that needing admission in the critical care unit. Patients diagnosed to be positive for RSV infection were further categorized into those who developed asthma and those who did not. Diagnosis of asthma was done clinically as per the documentation by treating physicians from the patients' records. Comparison between the two subgroups was done about their demographic and clinical data. The data were analyzed separately using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.). Mean differences between patients' subgroups were tested by student's t test. Comparison between ratios was done using Z-score test. Chi-square test of association was used for assessing the categorical variables. Relative risk (RR) with 95% confidence intervals [95% CI] was used to represent the risk of association of categorical variables. A p-value of < 0.05 was considered significant.

## Results

### Demographics of the study participants:

During the study period, 3782 children presented with signs and symptoms of acute respiratory tract infections and were checked for RSV. Out of 3782, 948(25.1%) children tested positive for RSV. Three hundred and ninety (41.1%) were females; 531 (57.7%) were Bahraini; and mean  $\pm$  SD age was  $2.4 \pm 1.5$  years. Two hundred and fifty-six (27%) children were below 1 year of age and 521 (55%) were below the age of 2 years, while 171 (18%) were more than 2 years old Fig (1).

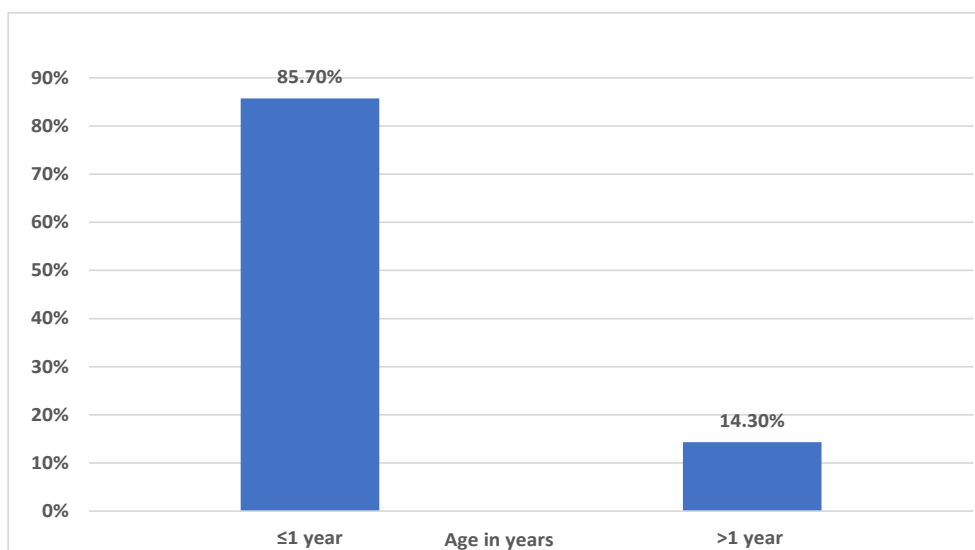


**Figure 1.** Distribution of Age in the RSV positive children during 2009-2015

Total RSV positive N= 948; 256 (27%) children were below 1 year of age and 521 (55%) were below the age of 2 years, while 171 (18%) were more than 2 years old.

**Comparison between children with prior RSV infection developing asthma and those who did not:**

Sixty-seven children (7%) out of the total 948 who were RSV positive, were diagnosed with bronchial asthma clinically by the physicians. IgE was positive in 42 children (4.4% from total RSV positive children and 62.7% of asthmatic RSV positive children). Distribution of IgE in RSV positive cases according to age is shown in Fig (2); 85.7% were equal or less than 1 year old while 14.3% were more than 1 year old. Table 1 shows the comparison of characteristics between children that developed asthma and those who did not following RSV infection. Children with RSV infection early in life were at significantly higher risk of developing bronchial asthma later in life. Mean (SD) latent time observed between the documentation of RSV infection and first asthma episode was  $3.4 \pm 3$  months. We observed that significantly higher proportions of patients with bronchial asthma had severe RSV infection compared to those who did not. The estimated RR [95% CI] was 7 [5.5, 8.2]. Significantly higher levels of total IgE were observed in children developing asthma following RSV infection than those who did not (Table 1).



**Figure 2.** Distribution of IgE in RSV Positive Cases According to Age (N= 42)

**Table 1.** Comparison of characteristics of children with RSV infection who developed asthma later and who did not

Variables		RSV with asthma (n=67)	RSV without asthma (n=881)	P values
Mean (SD) age at the time of admission for RSV infection (in months)		8 ± 5	18.0 ± 7	< 0.0001
Nationality	Bahraini: Non-Bahraini	39 (58%): 28 (42)	492 (55.8%): 389 (44.2%)	0.7 <sup>a</sup> ; 0.5 <sup>b</sup>
Gender	Male: Female	37 (55.2%): 30 (44.8%)	432 (49%): 360 (51%)	0.3 <sup>a</sup> ; 0.5 <sup>b</sup>
Time interval (in months) bet. RSV infection & asthma diagnosis		3.4 ± 3	NA	NA
Number (%) of children with severe RSV infection		58 (86%)	113 (12.8%)	<0.0001
IgE level (IU/ml)		167 ± 37	92 ± 17	< 0.0001

a – between group; and b – within group.

### Comparison between asthmatic children with RSV compared to historical controls (asthmatic children without RSV infection):

Ninety-five children were diagnosed with asthma, and they were RSV negative as observed as historical control. The characteristics of these groups are mentioned in Table 2. It can be observed that those with RSV developed asthma at significantly younger age compared to those without RSV infection.

No significant difference was found in the mean IgE level between the two groups.

**Table 2.** Comparison of characteristics of asthmatic children with RSV with those without RSV infection (historical controls)

Variables	Asthmatic with RSV infection (n=67)	Asthmatic without RSV infection (Historical control) (n=95)	p-values
Mean (SD) age in years	0.7 (0.42)	6.8 (3.8)	0.0001
Boys [n (%)]	37 (55.2)	61 (64.2)	0.2
Ig E level (IU/ml)	167 (37)	113 (171)	0.4
Bahraini: Non-Bahraini (n)	58: 42	78: 17	0.0002

## Discussion

We evaluated the risk of bronchial asthma in a nationwide cohort of 3782 children presenting with respiratory tract infection. We observed that RSV infection at younger age (during infancy) and severe infection were significantly associated with asthmatic episodes. Additionally, asthmatics with prior RSV infection had significantly higher total IgE levels compared to those without RSV infection.

Severity of RSV infection has also been attributed as one of the risk factors for bronchial asthma later in the childhood. Escobar et al. In 2010 observed that children diagnosed with RSV infection with outpatient clinic visits or hospitalization had significantly higher risk of bronchial asthma than those who did not. We defined severe RSV infection as admission to critical care unit in the present study and observed that such children had seven times greater risk of bronchial asthma in later childhood. This is similar to what was reported by Carroll et al in 2009, on a population-based study, where the authors

observed that the risks of bronchial asthma to be 1.86 [95% CI, 1.74-1.99], 2.41 [95% CI, 2.21-2.62], and 2.82 [95% CI, 2.61-3.03] when children with RSV infection had visits in the outpatient, emergency department, and hospitalization groups respectively. A recent study observed that children with severe RSV infection during infancy that subsequently develop wheezing episodes had relatively higher quantities of *Hemophilus*, *Moraxella*, and *Klebsiella* with significantly elevated airway levels of lipopolysaccharides and cytokines that those who did not develop wheezing, thus addressing the role of airway microbiome together with the host immune response in the immune pathogenesis (Zhang et al, 2020).

Elevated IgE is an important laboratory test that helps in diagnosing asthma. In our study there was a significant rise in IgE in RSV asthmatic compared to those with RSV without asthma. Tabbara et al found a mean IgE concentration of 113 IU/ml with above 200 IU/ml in 21% and above 400% in 9.5% children. Comparison with the historical group from the same population revealed that those with RSV infection developed asthma at younger age. RSV infection was observed to result in airway hyper-activity. Sigurs et al. in a prospective age-matched study observed that 50% of RSV infected children with bronchiolitis tested positive for skin-prick tests as against 22% of the controls; and 45% had elevated serum IgE levels compared to 26% of the controls (Sigurs et al, 2005).

Since years back the association of RSV and asthma was a topic of interest for different scientists. Welliver et al in 1981 published an article addressing this issue. They recognized that RSV viral specific IgE cell bound develops and can be detected in serum only if free in severe cases and asthmatic children with RSV infection; they postulated that IgE response in respiratory mucosa is an important feature in the immunopathology of RSV infection (Welliver et al, 1981). Moreover, a key factor for sensitization could be failure to switch off expected Th2 phenotype. Indeed, environmental factors in addition to genetic factors have a great role. The balance between Th1 and Th2 immune response following RSV infection may lead to the different immunopathology observed (Ogra, 2004).

## Conclusion

We observed in a nation-wide study that RSV infection at younger age (during infancy) and severe infection were significantly associated with asthmatic episodes. Also, asthmatics with prior RSV infections had significantly higher total serum IgE levels compared to those without RSV infection. Asthma in children with RSV infection occurs much at much younger age compared to those without RSV infection. It is imperative to vaccinate against RSV during infancy and treat RSV infection with anti-viral drugs like ribavirin to ameliorate the risk of bronchial asthma in the later childhood.

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# مخاطرة الإصابة بالربو عند الأطفال بعد الإصابة بالتهاب الجهاز التنفسي السفلي بالفيروس المخلوي التنفسي

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## المُستخلص

الهدف: لقد اشارت الدراسات الحديثة العلاقة السببية بين الإصابة بالفيروس المخلوي التنفسي والإصابة بمرض الربو. الطريقة: في هذه الدراسة التي تمت في مجمع السلمانية الطبي، قمنا بتقييم 3782 من الاطفال تتراوح اعمارهم بين شهر واحد و15 سنة، الذين اصابوا بالتهاب التنفسي، في الفترة 2015-2019، وتابعنا الحالات التي اصبحت بالربو لاحقاً، كما قمنا بقياس معدل الاجسام المضادة من النوع (E) في الدم.

النتائج: ولقد بينت الدراسة ان الإصابة بالفيروس المخلوي التنفسي في سن مبكرة قد تؤدي الى الإصابة بنوبات ربو في سن مبكرة والخطر النسبي 7 [5.5 – 8.2]، كما اوضحت الدراسة ان معدل الاجسام المضادة من النوع (E) في الدم عند الاطفال المصابون بالربو مع وجود اصابة سابقة بالفيروس المخلوي التنفسي هي اعلى [167 IU/ml] من الذين لم يصابوا سابقاً بالفيروس [92 IU/ml]، كما ان متوسط عمر الاطفال الذين اصابوا بالربو مع وجود اصابة سابقة بالفيروس هي 7 اشهر مقارنة بسن اكبر 6 سنوات و8 اشهر عند الاطفال المصابون بالربو مع عدم وجود اصابة سابقة بالفيروس.

الاستنتاج: خلصت الدراسة ان الاطفال المصابون بالفيروس المخلوي هم أكثر عرضة للإصابة بالربو في سن مبكرة.

الكلمات المفتاحية: RSV، عدوى الجهاز التنفسي، الربو القصبي.

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