

Disease Burden Due to Respiratory Syncytial Virus in Indian Pediatric Population: A Literature Review

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ABSTRACT: Respiratory syncytial virus (RSV) is one of the leading causes of lower respiratory tract infections in young children. Globally, there is huge disease burden, high treatment cost, and health impact beyond acute episodes due to RSV which necessitate development and implementation of preventive strategies for the control of RSV infection. The disease burden due to RSV in pediatric population across India is still not clearly understood so this literature review was therefore conducted to gather data on disease burden due to RSV in Indian pediatric population. Systematic literature search was performed using PubMed and Google search with different medical subject headings from 2007 to 2020. Studies performed in Indian pediatric population were selected for review. Literature review revealed that in India, epidemiology of RSV infection is well documented in young children (0–5 years) as compared to children from other age groups. The rates of RSV detection in various studies conducted in younger children (0–5 years) vary from 2.1% to 62.4% in India which is higher as compared to children from other age groups. In India, RSV mainly peaks around rainy to early winter season, that is, during months of June through October while smaller peak was noted during December, January, and February. In 2020, higher RSV-associated disease burden was reported among children (<5 years) in low-income and lower-middle-income countries. Considering significant disease burden due to RSV in young Indian children, availability of RSV vaccine would be crucial to prevent RSV infections in children and its spread in the community.

KEYWORDS: Epidemiology, India, respiratory syncytial virus

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Introduction

Respiratory syncytial virus (RSV) is a common respiratory virus that infects the linings of the airways which causes cold-like symptoms (such as sneezing, coughing, and nasal discharge) in patients and is found in both cold and warm climates worldwide. The virus infects both adults and children, but children often have a more severe infection than adults. RSV infection is contagious and spreads easily either by direct contact (kissing, touching, or shaking hands) with infected person or through contact with secretions or droplets as it is carried on secretions or droplets and can live for hours on non-living objects. Upper respiratory infection with rhinorrhea and nasal congestion are major clinical characteristics of RSV infection.^{1,2} In developing countries, RSV reinfection rates vary between 6% and 83% every year.² Reinfections generally are observed to be milder.³ Globally, acute lower respiratory infection (ALRI) is one of the leading causes of morbidity and mortality in children younger than 5 years. Human respiratory syncytial virus (hRSV) is the most common viral pathogen identified in children with ALRI.⁴ In 2005, approximately, 33.8 million new episodes of RSV-associated ALRI occurred worldwide in younger children aged >5 years (22% of ALRI episodes) with at least 3.4 million episodes representing severe RSV-associated ALRI, necessitating hospital admission. Approximately, 66 000 to 199 000 younger children (>5 years) died due to RSV-associated ALRI in 2005, and 99% of these deaths occurred in developing countries.⁵

RSV is a single-stranded, enveloped, ssRNA virus belonging to the Paramyxoviridae family, and genus Pneumovirus. The virus has 10 genes that result in the production of 2 separate proteins. First, RSV attachment (G) protein (envelope protein) which

mediates attachment to the host cell via cell surface glycosaminoglycans and antigenic variability; second, fusion (F) protein which mediates virus entry by directing the fusion of virion envelope and the plasma membrane of the host cell. The F protein has demonstrated activation of Toll-like receptor (TLR)4, and human studies exhibit a correlation between the TLR4 receptor and susceptibility to severe RSV-induced respiratory disease.^{3,6} HRSV (Human Respiratory Syncytial Virus) has been divided into 2 subgroups (HRSV-A and HRSV-B) by reactivity with monoclonal antibody. Currently, HRSV-A has 10 genotypes (GA1–GA7, SAA1, NA1, NA2) whereas HRSV-B has 9 genotypes (SAB1–SAB4, GB1–GB4, BA) with BA having 11 branches (BA1–11).⁷

In high-risk infants such as those with a history of prematurity, incomplete development-damage- hyperactivity of airway, males with cord blood vitamin D deficiency, bronchopulmonary dysplasia (BPD), congenital heart disease (CHD), neuromuscular impairment, immunodeficiency, and Down's syndrome, RSV was considered as a leading cause of lower respiratory tract infection. Risk factors that have been mostly identified to be associated with severe RSV related lower respiratory tract infection include young age (below 6 months at the beginning of RSV season), low socioeconomic status and parental education, crowded living conditions, malnutrition/small for gestational age, family history of atopy or recurrent wheezing, lack of breast feeding, smoking in household, daycare attendance, longer stay in hospital. Other risk factors include viral load and isolates, escape from neutralization, reduction in fracktalkine action, low antibody titer, genetic polymorphism etc.^{8–10} Clinical complications associated with progression of RSV infection include asthma, bronchiolitis, influenza, croup, bronchitis, pneumonia, neurological complications which



include seizures, encephalopathy, and abnormal neurological examination.^{11,12}

In 2020, the RSV-associated disease burden among children in 72 Gavi-eligible countries (mostly low-income and lower-middle-income) was estimated at an average of 20.8 million cases, 1.8 million hospital admissions, 40 000 deaths, 1.2 million discounted disability-adjusted life years (DALYs), and US\$611 million discounted direct costs.¹³ Despite huge disease burden due to RSV, high treatment cost and complications so far, the development of a RSV vaccine has lagged behind. Currently, though there are 2 therapies are approved by United States Food and Drug Administration (USFDA) which includes palivizumab for prevention and ribavirin for treatment of RSV infection; ribavirin is practically not used and at the moment there is no treatment other than supportive.¹⁴ There is currently no drug approved for prevention and treatment of RSV infection in children in India. However, American Association of Pediatrics (AAP) and Standard treatment Guidelines by Ministry of Health & Family Welfare for Management of common Respiratory Infections in Children in India¹⁵ recommends the use of inhaled bronchodilators (albuterol, salbutamol, nebulized epinephrine), corticosteroids, antibacterial medications (only in patients who reported comorbid bacterial infections), oral or intravenous fluids (as a supportive care to maintain proper hydration), chest therapy, and oxygen for the treatment of RSV infections.¹⁶ The health impact of RSV infection is significant and goes beyond the acute episode phase so, there is a need for therapy that aimed at reducing the impact of RSV infection by targeting health education, information, and prophylaxis in high-risk populations.¹⁷

However, in recent years, with the advances in understanding of RSV immunopathology and innovation in immunogen design, few RSV vaccines and monoclonal antibodies are still under development and none of the studied preparations have yet been approved.¹⁸ According to review conducted in 2017 by University of Alberta, Canada, RSV will most likely undergo vaccine escape mutation amid any active RSV vaccination program.⁴ Hence, it is important to understand the epidemiology and burden of RSV infection which will help in future for implementation of prevention strategies in India. While the data reported in previous literature review on disease burden due to RSV in Indian pediatric population are unclear. There has been a surge in studies on RSV epidemiology all over the world, including India.² So this narrative review presents the summary of information available on epidemiology and disease burden of RSV infection in Indian pediatric population.

Methodology

Initially the literature search was performed to establish a systematic literature review, but as sufficient data was not available on disease burden or epidemiology of RSV infection in Indian pediatric population to perform meta-analysis, this narrative review was attempted. The systematic literature search was performed using PubMed (Table 1) and Google search (Table 2) with following medical subject headings.

((Respiratory Syncytial Virus) OR (RSV)) AND (etiology)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Risk Factor)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Epidemiology)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Prevalence)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Incidence)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Disease Burden)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Statistics)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Morbidity)) AND (Mortality)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Challenges)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Treatment)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Serotypes)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Genotypes)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Diagnosis)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Treatment)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Management)) AND (India)
 (((Respiratory Syncytial Virus) OR (RSV)) AND (Prevention)) AND (India)

Subject headings mentioned above provided 125 citations, out of which only 15 were qualified for the inclusion, rest of the studies were included based on manual search explained below.

A manual search for additional data was performed using references cited in the original articles as required. Other research/review papers were identified by reviewing the bibliographies of published works and by conducting general web search about the disease. The research conducted to identify the relevant research/review papers are based on the articles/studies published in last 10 to 15 years in Indian pediatric population. The review was limited to data in Indian subcontinent. Only articles published in English language were included in the review.

Search Strategy

PubMed search

Table 1. Search strategy for literature using PubMed.

KEYWORDS	NUMBER OF HITS (PUBMED)	TOTAL NO. OF RELEVANT ARTICLE AFTER ANALYSIS OF INDIVIDUAL ARTICLE INCLUDING DUPLICATES
((Respiratory Syncytial Virus) OR (RSV) AND (etiology)) AND (India)	15	13
((Respiratory Syncytial Virus) OR (RSV) AND (Risk Factor)) AND (India)	4	0
((Respiratory Syncytial Virus) OR (RSV) AND (Epidemiology)) AND (India)	11	0
((Respiratory Syncytial Virus) OR (RSV) AND (Prevalence)) AND (India)	11	0
((Respiratory Syncytial Virus) OR (RSV) AND (Incidence)) AND (India)	11	0
((Respiratory Syncytial Virus) OR (RSV) AND (Disease Burden)) AND (India)	6	0
((Respiratory Syncytial Virus) OR (RSV) AND (Statistics)) AND (India)	5	0
((Respiratory Syncytial Virus) OR (RSV) AND (Morbidity)) AND (Mortality)) AND (India)	7	0
((Respiratory Syncytial Virus) OR (RSV) AND (Challenges)) AND (India)	2	1
((Respiratory Syncytial Virus) OR (RSV) AND (Treatment)) AND (India)	25	0
((Respiratory Syncytial Virus) OR (RSV) AND (Serotypes)) AND (India)	0	0
((Respiratory Syncytial Virus) OR (RSV) AND (Genotypes)) AND (India)	2	0
((Respiratory Syncytial Virus) OR (RSV) AND (Diagnosis)) AND (India)	14	1
((Respiratory Syncytial Virus) OR (RSV) AND (Management)) AND (India)	3	0
((Respiratory Syncytial Virus) OR (RSV) AND (Prevention)) AND (India)	9	0
Total	125	15

Manual search

Table 2. Search strategy for literature using Google (hand search).

S NO.	KEYWORDS SEARCH	TOTAL NUMBER OF RESULTS FOUND VIA HAND SEARCH
1	Pneumococcal infections/diagnostic imaging; pneumococcal infections/diagnosis	00
2	Pneumococcal infections/classification; pneumococcal infections/epidemiology; pneumococcal infections/mortality; pneumococcal infections/etiology; fatality	01
3	Pneumococcal infections/physiopathology; pneumococcal infections/complications	00
4	Pneumococcal infections/prevention and control; pneumococcal infections/economics; pneumococcal infections/therapy; safety; immunogenicity; recommendation; guideline	04
5	Community acquired pneumonia; manifestation	01
6	community acquired pneumonia; challenges	01
Total		07

Included in this review were original prospective, randomized controlled, observational studies involving infants (<6 months), young children (<5 years) and children of less than 18 years of age reporting RSV infection incidence. Studies in adult population (≥ 18 years) were excluded. Studies where investigated RSV infection was hospital acquired pneumonia and case reports, meta-analysis and commentaries were also excluded.

The distribution of studies in Indian population has been described in the Tables 3–5 based on the age wise prevalence, hospital or community, diagnostic procedures, and region (east, west, north, south, and central).

Results

A total of 23 hospital and community-based studies which reported RSV detection rate in India were identified through

Table 3. Age wise distribution of respiratory syncytial virus detection in India (2007-2020).

STUDY	REGION (EAST, WEST, NORTH, AND SOUTH, CENTRAL INDIA)	HOSPITAL/ COMMUNITY BASED	TOTAL SAMPLE TESTED	YEAR	AGE		
					<23 MONTHS OLD (%)	2-5 YEARS OLD (%)	6-18 YEARS OLD (%)
Prevalence							
Panda et al ¹⁹	Eastern India	Hospital	332	2017	7 (2.1)	8 (2.4)	-
Saxena et al ²⁰	North India	Hospital	375	2019	103 (27.46)		-
Yadav et al ²¹	North India	Hospital	130	2016	14 (10.8)		-
Sahu et al ²²	Central India	Hospital	75	2015	33 (44)		-
Kini et al ²³	South India	Hospital	383	2019	94 (24.5)		-
Mishra et al ²⁴	Eastern India	Hospital	300	2016	61 (20.33)		-
Agrawal et al ²⁵	Eastern India	Hospital	1720	2009	177 (10.29)		-
Incidence							
Samad et al ²⁶	India	Hospital	68	2019	2 (2.94)		
Broor et al ²⁷	North India	Community	1279	2007	502/1000 child per year	94/1000 child per year	-
Epidemiology							
Yeolekar ²⁸	Western India	Hospital	385	2008	100 (26)		-
Bharaj et al ²⁹	North India	Hospital	301	2009	61 (20.2)		-
Hemalatha et al ³⁰	South India	Hospital	126	2010	56 (46.66)	-	-
Gupta et al ³¹	South India	Hospital	77	2011	17 (22.1)	-	-
Choudhary et al ³²	Western India	Hospital	843	2013	159 (18.86)		-
Biswas et al ³³	Northeast India	Community	493	2013	39 (7.9)		-
Singh et al ³⁴	North India	Hospital	188	2014	39 (25.16)		1 (3)
Mathew et al ³⁵	North India	Community	428	2015	9 (12.9)		
Saha et al ³⁶	North India	Hospital	505	2015	73 (14.45)	9 (1.78)	-
Saxena et al ³⁷	North India	Hospital	1653	2017	199 (12)		
Swamy et al ³⁸	Northwestern India	Hospital	689	2017	175 (25.40)		-
Broor et al ²⁷	North India	Community	1279	2007	103 (8)		-
Kumar et al ³⁹	North India	Community	85	2018	53 (62.4)	-	-
Disease burden							
Mazumdar et al ⁴⁰	East India	Hospital	880	2013	88 (10)		

literature search from 2007 to 2020. Out of these, 13 reported epidemiology, 7 reported prevalence, 2 reported incidence rate of RSV while only 1 reported disease burden due to RSV in Indian pediatric population. None of the studies reported mortality due to RSV. Majority of the studies were conducted in north region of India (45.45%), followed by east (18.18%) and south (13.63%) while only 2 studies were from west region and 1 each from central, northwest, and northeast regions. Most studies (more than 90%) reported RSV detection rate in young

Indian children (aged 0 to 5 years). The rates of RSV detection in various hospital and community-based studies vary from 2.1% to 62.4% in children aged 0 to 5 years (based on data from 23 studies) compared to 3% in children aged 6 years and above (based on only 1 study). A study conducted by Broor et al²⁷ reported an incidence rate of 502/1000 child per year for children aged 0 to 23 months and 94/1000 child per year for children aged 24 to 60 months. Table 3 represents age wise distribution of RSV detection in Indian children from 2007 to

Table 4. Prevalence of hRSV-A, hRSV-B, and hRSV-AB among RSV positive cases.

STUDY	HRSV-A (%)	HRSV-B (%)	HRSV-AB (%)
Panda et al ¹⁹	0.93	13	-
Sahu et al ²²	76	24	-
Mishra et al ²⁴	49.18	50.81	-
Samad et al ²⁶	0	100	-
Choudhary et al ³²	3.44	15.42	-
Biswas et al ³³	100	0	-
Singh et al ³⁴	20.1	1.1	-
Swamy et al ³⁸	78.85	11.42	9.71
Parveen et al ⁴¹	77	23	-
Patil et al ⁴²	65.30	34.69	-
Agrawal et al ²⁵	5	95	-
Chadha et al ⁴³	0	98-100	-

2020. Overall, RSV infection is prevalent in young Indian children (≤ 5 years) which indicates positive association between the young age and RSV infection. No significant gender specific differences were observed in RSV positive cases.

A prospective study conducted in children from rural India identified 22 RSV reinfections, accounting for 21% (22/103) of all RSV infections identified. The repeat infections occurred 1 to 27 months after the previous infection which indicates need of RSV vaccination as well as their management.^{27,37} Most of the RSV positive cases were from lower-income groups (suggestive of malnutrition) and from areas with poor sanitation, facilitating the spread of respiratory infections in the community.⁴⁴ Of the 23 studies, 12 studies reported that both hRSV-A and hRSV-B are significantly prevalent in Indian children, while only 1 study detected mixed form of RSV (hRSV-AB). Distribution of hRSV-A, hRSV-B and hRSV-AB among RSV positive cases is presented in Table 4.

The regional distribution of Indian studies reveal that 12 studies are from north region (including 1 from northeast) followed by 4 from east, 3 from south, 2 from west and 1 from central region.

Phylogenetic analysis revealed that all the 3 HRSV A strains were ON1 and all the HRSV B strains were BA9 genotype. In recent years, ON1 and different lineages of BA genotypes have been consistently reported from India and other parts of the world. It was also reported that HRSV A had more number of variable sites than HRSV B suggesting that these amino acids have a high potential for substitution resulting in genetic diversity.⁵

Studies conducted in Indian children reported that Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), real-time Reverse Transcriptase Polymerase Chain Reaction (rt-RT-PCR), Multiplex real-time polymerase chain reaction

(rt-PCR) were most frequently used in clinical setting for the detection of RSV followed by Direct Fluorescent Antibody (DFA), immunofluorescent test (IFT), immune-chromatographic assay, and virus culture. Fever, cough/coryza are the most common symptoms and bronchiolitis, pneumonia are major etiologic factors reported in children who tested positive for RSV infection followed by fast breathing/breathing difficulty, wheezing, chest-in-drawing, nasal discharge/congestion, rhinorrhea, vomiting, diarrhea, and pharyngitis. Diagnostic procedures and methods used in various studies for the detection of RSV in children along with sensitivity and specificity for RSV are presented in Table 5 while symptoms/etiologic factors reported in RSV positive cases in Figure 1.

Two anti-RSV antibodies reported in studies conducted in Indian children were IgG and IgM. Overall, 72% to 90% of children (aged < 5 years) tested positive for IgG while 36% to 44% for IgM. In a study conducted by Arankalle et al, 96% to 98% of adult population (aged 16-85 years) tested positive for IgG anti-RSV antibody. Anti-RSV antibodies were more in adult population because of prior exposure to RSV.^{45,46} Percentage of population reported positive for anti-RSV antibodies is presented in Table 6.

The RSV strains were classified into genotypes by phylogenetic analysis. Different genotypes of Group A (GA2, GA5, NA1 and ON1) and Group B (GB2, SAB4 and BA) have been reported in studies conducted in Indian pediatric population. BA genotype of Group B has 60 base pair (bp) duplication and ON1 genotype of Group A has 72bp duplication in the G gene. These data may be useful for development of vaccine in India. Different genotype reported in studies conducted in Indian children are presented in Table 7.

Seasonality of RSV in India

In India, RSV activity begins in the rainy season (June–September) and continues to the beginning of winter (October–January) (RSV season duration 2017 = 13 weeks; 2018 = 12 weeks).⁴³ Most Indian studies reported a peak of RSV positive (both hRSV A and hRSVB) cases after the rainy and winter season during the months of July through November in India. A smaller peak was also noted during December, January, and February.^{23,24,27,47,48}

Few Indian studies conducted in North India reported that RSV mainly peaks in winter (November to February) and observed some correlation with low temperature.^{44,49} While few studies reported negative co-relation between RSV cases with temperature and rainfall however a, positive correlation (25%-40%) was observed with cool, dry months (December–February). A mild epidemic of RSV was reported in West Bengal in October–November which did not correlate with a decrease in temperature but correlated with a drop in relative humidity and rainfall.⁴⁴

Study conducted by Hindupur et al⁴⁷ revealed that RSV positive cases correlates with mean monthly maximum temperature, mean monthly minimum temperature and average relative humidity. A study conducted by Mazumdar et al⁴⁰ in

Table 5. Diagnostic procedure and methods used in various studies in India.

STUDY	REGION (EAST, WEST, NORTH, AND SOUTH, CENTRAL INDIA)	TOTAL SAMPLE TESTED	YEAR	DIAGNOSTIC METHOD	SENSITIVITY FOR RSV (%)	SPECIFICITY FOR RSV (%)
Abinaya et al ⁸	South India	33	2020	Multiplex PCR	-	-
Panda et al ¹⁹	Eastern India	332	2017	Multiplex PCR	-	-
Saxena et al ²⁰	North India	375	2019	rt-PCR	90.5 ⁵⁰	99.7 ⁵⁰
Yadav et al ²¹	North India	130	2016	RT-PCR	73% ⁵¹	99% ⁵¹
Sahu et al ²²	Central India	75	2015	qRT-PCR	≥98 ⁴⁴	-
Kini et al ²³	South India	383	2019	DFA	-	-
Mishra et al ²⁴	Eastern India	300	2016	Mono/multiplex rt-PCR	-	-
Agrawal et al ⁴⁴	Eastern India	1720	2009	Conventional RT-PCR	≥95	-
Broor et al ²⁷	North India	1279	2007	DFA	77.8 ⁵²	99.6 ⁵²
Yeolekar ²⁸	Western India	385	2008	IFT	90.1 ⁵³	98.8 ⁵³
Bharaj et al ²⁹	North India	301	2009	Multiplex PCR	100%	88.9%
Gupta et al ³¹	South India	77	2011	DFA	-	-
Choudhary et al ³²	Western India	843	2013	Multiplex RT-PCR	100%	100%
Biswas et al ³³	Northeast India	493	2013	RT-PCR	-	-
Singh et al ³⁴	North India	188	2014	RT-PCR	-	-
Mathew et al ³⁵	North India	428	2015	Multiplex RT-PCR	-	-
Saha et al ³⁶	North India	505	2015	rt-RT-PCR	99.3 ⁵⁴	95.7 ⁵⁴
Saxena et al ³⁷	North India	1653	2017	rt-RT-PCR	-	-
Swamy et al ³⁸	Northwestern India	689	2017	rt-RT-PCR	-	-
Broor et al ²⁷	North India	1279	2007	Virus culture	49.5 ⁴⁴	100 ⁴⁴
Kumar et al ³⁹	North India	85	2018	Immunochromatographic assay	90 ⁵⁵	98.18 ⁵⁵
Mazumdar et al ⁴⁰	East India	880	2013	rt-RT-PCR	-	-

Abbreviations: DFA, direct fluorescent antibody; rt-RT-PCR, real time reverse transcriptase polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; rt-PCR, real time polymerase chain reaction; IFT, immunofluorescence test.

eastern region of India reported peak of RSV infection in the month of June and second peak in the month of September from 2010 to 2011. In light of these findings, a study conducted by Swamy et al³⁸ therefore suggested that palivizumab prophylaxis can be planned to be given to infants from post-monsoon to end of winter.³⁸ Data on month wise distribution of RSV infection cases in India reported in published studies is presented in Table 8.

RSV as a Co-Infection

Six (6) studies reported RSV as co-infection along with other respiratory infections which was highly reported in children aged 0 to 5 years. Studies conducted in Indian children from various regions indicated strongest association between RSV and acute lower respiratory infections (ALRI), acute

respiratory infection (ARI), upper respiratory infection (URI), lower respiratory tract infection (LRTI) and influenza.^{8,19,23,24,39,40,45,48,49} A study from north India reported 90% and 86% of the RSV-associated hospitalization rates in children with ARI aged <2 years and <5 years, respectively.³⁶ Outcome of the study conducted by Saxena et al³⁷ reported simultaneous diagnosis of RSV with influenza in pediatric population which shows that patients with influenza can be considered as high-risk group for RSV infection.

A prospective study conducted in children from rural India reported RSV in 8% of URIs, 7% of ALRIs, and 21% of severe ALRIs. The RSV associated ARI incident rate was highest in the first year of life while RSV associated ALRI incident rate was actually higher in the 12 to 23 months group as compared to other ages, whereas for RSV associated severe ALRI, the

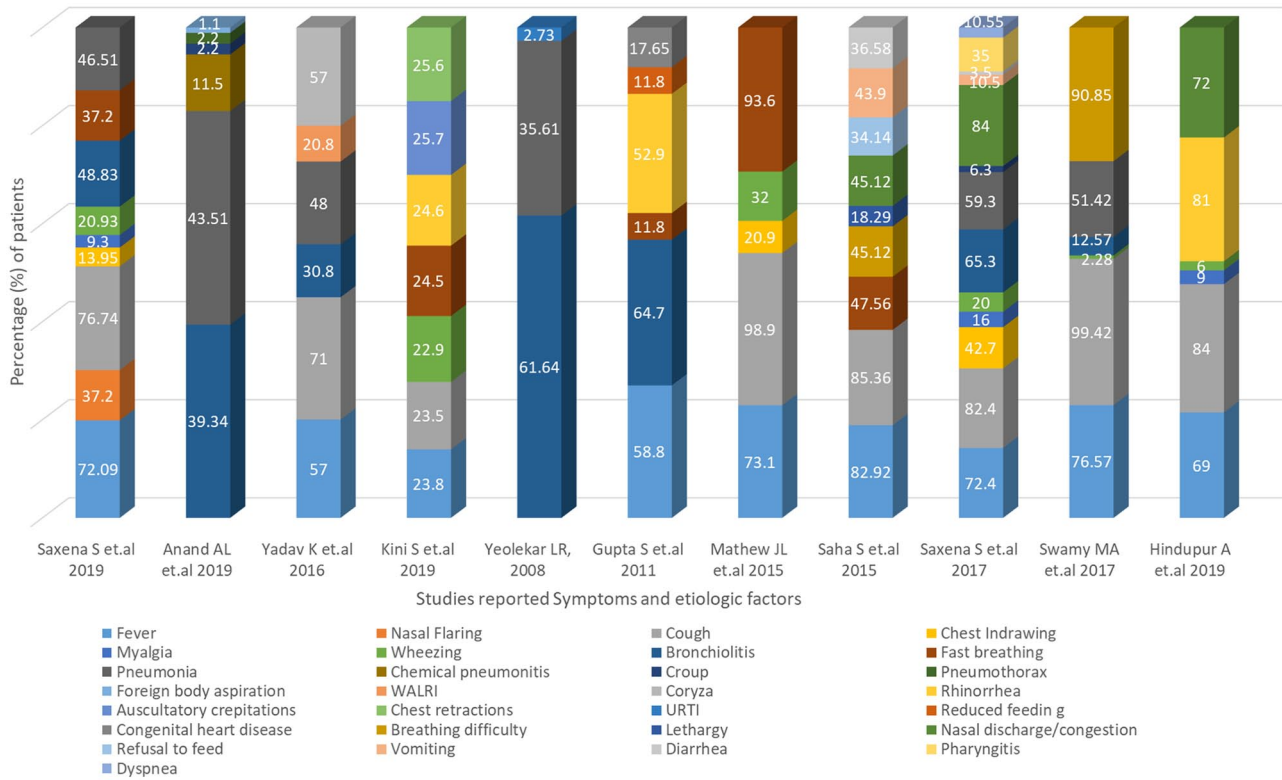


Figure 1. Symptoms and etiologic factors reported in RSV positive cases. WALRI, wheezing associated lower respiratory tract infection; URTI, upper respiratory tract infection; sore throat.

Table 6. Percentage of patients (aged <5years) with positive anti-RSV antibodies (serotype).

STUDY	IGG (%)	IGM
Anand et al ⁴⁵	72	44
Arankalle et al ⁴⁶	90.21	35.95

incident rate was slightly higher in the 0 to 11 month as compared to the 12 to 23 month group.²⁷ Overall, above data indicates that RSV is an important cause of ALRI, ARI, URI, LRTI, and influenza in Indian children. Studies that reported RSV as a co-infection are provided in Table 9.

Discussion

This article provides a review of current knowledge on disease burden due to RSV in Indian pediatric population based on published data since 2007 to 2020. We identified and included relevant studies published since 2007, from all regions of India and including different high-risk groups to provide a comprehensive picture of the RSV burden.

RSV is the most common pathogen identified in young children with acute lower respiratory infections (ALRI), primarily pneumonia and bronchiolitis.⁴ In our review, the RSV (both hRSV-A and hRSV-B) detection rate was found to be significantly higher in young Indian children (aged 0-5 years old) as compared to older children (aged 6-18years), which indicates that younger age population are more likely to have

Table 7. Molecular epidemiological studies of respiratory syncytial virus from India.

STUDY	GENOTYPE
Parveen et al ⁴¹	RSV-A: GA2, GA5
	RSV-B: BA
Patil et al ⁴²	RSV-B: BA
Agrawal et al ²⁵	BA (BA 7, BA 9, BA 10, BA 12)
Raghuram et al ⁵⁶	RSV-A: NA1, ON1
	RSV-B: BA (BA9, BA10)
Haider et al ⁵⁷	RSV-A: NA1, ON1
	RSV-B: GB2, BA (BA9, BA12)
Haider et al ⁵⁸	RSV-A: NA1, ON1
Choudhary et al ⁵⁹	RSV-B: SAB4, BA (BA9)
Biswas et al ³³	RSV-A: GA5, NA1
Hindupur et al ⁴⁷	RSV-A: ON1
	RSV-B: BA9

RSV infection while no significant gender specific differences were reported in RSV positive cases. RSV infection may decrease with increase in age however older age population can also be susceptible for RSV infection so they should not be neglected as a target population for the prevention of RSV

Table 8. Month wise distribution of RSV infection cases in India.

STUDY	JANUARY-MARCH (%)	OCTOBER-DECEMBER (%)	APRIL-JUNE (%)	JULY-SEPTEMBER (%)
Abinaya et al ⁸	36.4	39.1	-	92.3
Panda et al ¹⁹	8	10	12	18
Anand et al ⁴⁵	30.60	-	-	-
Yadav et al ²¹	92.85	-	-	7.14
Biswas et al ³³	72	-	-	-
Singh et al ³⁴	61-5	22-70	-	-
Mazumdar et al ⁴⁰	0.68	4.77	24.65	15.68

Table 9. Studies reporting RSV as a co-infection.

STUDY	REGION (EAST, WEST, NORTH AND SOUTH INDIA)	TOTAL SAMPLE TESTED	YEAR	AGE		
				<23MONTHS OLD (%)	2-5YEARS OLD (%)	6-18YEARS OLD (%)
Abinaya et al ⁸	South India	33	2020	30	37.50	22.22
Panda et al ¹⁹	Eastern India	332	2017	28.57		
Anand et al ⁴⁵	South India	72	2019	77.78		
Kini et al ²³	South India	383	2019	5.5		
Mishra et al ²⁴	Eastern India	300	2016	31.14		
Mazumdar et al ⁴⁰	East India	880	2013	5.90		

infection which will help in reducing transmission in communities. The calculated incidence of RSV infection in hospitalized Indian adult patients after hematopoietic stem cell transplantation is 4% per year.²⁶ Similar data was reported in literature review conducted by Broor et al⁴⁹ in Indian population. Majority of RSV positive cases were reported after the rainy and winter season during the months of July through November in India while smaller peak was reported in December, January and February which was slightly similar to the data from countries in the Northern Hemisphere.⁶⁰ While minor changes were reported between different seasons from year to year globally and this variability can affect vaccination campaigns or development of vaccines. Availability of local seasonality data will help in optimization of the prevention, diagnosis, and treatment of RSV infections.

Data from this literature review reported strongest association between RSV and ALRI, ARI, URI, LRTI, and influenza which may help in identifying high risk patients who can have active immunization with a vaccine at an early stage of infection. Morbidity and mortality are greatly increased in children with bacterial co-infections or superinfections. Therefore, early detection of the virus is a critical step in the initiation of proper care, and the prevention of further spread of the virus in community.⁵² It is also essential to fasten community surveillance for the identification of high-risk patient and initiate effective

infection control measures, which help to reduce the length of hospital stay. RSV has emerged as a major cause of a variety of respiratory infections; there is therefore a need to have rapid, more sensitive, and highly specific diagnostic tests/methods for the detection of RSV. This literature review identified Multiplex PCR (100% sensitivity and specificity³² and real time RT-PCR (99.3% sensitivity and 95.7% specificity⁵⁴ as the most commonly used diagnostic tests with high sensitivity and specificity for the detection of RSV infection.

Globally, higher disease burden due to RSV has kept vaccine development on high priority but development of safe and effective vaccines is still facing scientific challenges.⁴⁹ Considering significant prevalence of RSV in Indian children there is a need to provide effective interventions for the prevention of RSV which require understanding of current dynamics of maternal anti-RSV antibodies, so that necessary preventive measures can be planned and executed. Serological data in the study conducted by Arankalle et al⁴⁶ revealed that, approximately 30% of infants by the age of 3 months and almost the entire infant population by the age of 6 months is devoid of anti-RSV antibodies which indicates that children (0-6 months) need early protection with the vaccine-induced immune response. Furthermore, it is suggested that below mentioned 3 target populations would be the appropriate age groups for vaccination.

The epidemiology and burden of RSV infection suggest that there are at least 3 distinct target populations for RSV vaccines⁴⁹:

- Pregnant women to protect newborns both by transplacental transfer of antibodies and by blocking transmission
- Infants (<6 months of age) who have the highest risk of severe disease
- Children >6 months of age to prevent disease in them and reduce potential transmission to younger children

Neutralizing antibody titers of greater than or equal to 1:64 and greater than or equal to 1:256 for hRSV-A and hRSV-B respectively, were shown to be protective in relation to RSV-associated hospitalizations.⁴⁶ Currently, monoclonal antibodies and antiviral medications are available for the prevention and treatment of RSV infections which were reported to be expensive and thus, reserved for high risk infants, mainly in high income countries.

It has been estimated that the cost of prophylaxis with monoclonal antibodies and treatment with antivirals would be more than 10 times the actual cost of longer hospitalization in untreated patients and this magnitude is likely to be much more in India. In addition, the high-risk infants would still be at risk of succumbing to other more common viral and bacterial infections. Due to high cost of monoclonal antibodies and their transient effect, active vaccination would be most cost-effective approach for the prevention of RSV infections and their transmission to high-risk individuals which can cover a large population.^{61,62}

RSV infections impose a significant burden among children under the age of 5 years and are among major causes of pneumonia mortality in India.⁴ This necessitates the need of a RSV vaccine in India to prevent RSV infections in children and its spread in the community.

Conclusion

Data reported in various studies conducted in different regions of India revealed higher incidence rate (62.5%) and disease burden of RSV infection in younger children (aged 0-5 years) as compared to children of other age groups (6 years and older). RSV mainly peaks around rainy season to early winter season, that is, during the months of June through October. Considering a significant burden of RSV infections in young Indian children (aged 0-5 years), availability of a RSV vaccine would be crucial to prevent RSV infections in children and its spread in the community.

Author Contributions

Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Writing— Original Draft Preparation, Writing—Review and Editing: Canna Ghia and Gautam Rambhad.

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