



Disease Prevalence Due to Human Respiratory Syncytial Virus (HRSV) and Molecular Nature of G Gene in Different Geographical Region of India: 2005-2022

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 11 Aug 2023	<p>Human respiratory syncytial virus (hRSV) is the leading pediatric respiratory pathogen with high morbidity in the first year of life. The morbidity is particularly high in developing countries. It is the most common cause of infant hospitalization and causes a high burden of disease in the elderly. India is a country with vast geographical differences their unique climatic conditions. So, the prevalence of human RSV in different geographical regions is partially understood for a long time. This review was performed by using a different search engine like Google scholar, PubMed, etc. Significant prevalence and specific RSV virus strain circulation were major keywords used for the search in the Indian pediatric population. Annual incidence rates of RSV-associated hospitalization per 1000 children were highest among infants aged 0–5 months, followed by ages 6–23 months, and lowest among children 24–59 months. hRSV was a substantial cause of hospitalization among children aged < 24 months especially those aged <6 months. Prevalence varies from 2.1% to 44% in different geographical regions. hRSV has a more broadly distributed peak timing. Numerous studies of the correlation between climatic factors and hRSV incidence across latitudes found variable and inconsistent correlations between hRSV incidence & temperature, and relative humidity in different parts of the tropical region. However, genotypes ON1, NA1, GA5, and GA2 in the hRSV-A group and group hRSV-B BA, BA9, and BA12 were predominantly circulated in India.</p> <p>Keywords: Respiratory Syncytial Virus (hRSV), Prevalence, Glycoprotein gene(G)</p>
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1. Introduction

Human Respiratory Syncytial virus (hRSV), subgroups A and B both co-circulate simultaneously in India with either one predominating at a given time. The populations most susceptible to severe hRSV symptoms are a pediatric group (especially infants less than one year of age), immuno-suppressed individuals-those, particularly those with respiratory disorders, and the geriatric age group. Infections of the host cells happen when the two major surface glycoproteins, G and F of the virus come in contact with the cell receptor CX3CR1 and mediate entry by fusion, respectively. This review aims to highlight the current prevalence status, Molecular findings, and circulating RSV strains in the different geographical areas in India. For this study, we have reviewed research publications from India from 2005 to 2022. absence of a systematic surveillance system as well as the emergence and spread of certain genotypes globally within a short period has further strengthened the need for the prevalence and molecular characterization of hRSV. The need for an RSV vaccine for India is obvious and crucial, the persistently high prevalence of hRSV worldwide coupled with the grim

history of the failure of initial FI-RSV vaccine trials in the 1960s pointed to the need for molecular characterization of hRSV, especially at an antigenic level. Genetic variability within each group is also very high, the two major surface proteins namely the G and F glycoproteins contain neutralizing antibody epitopes. The hRSV G gene has the highest variability and hRSV subgrouping is based on G gene diversity. The F gene, although comparatively less variable, is functionally and structurally more complex and contains immunodominant neutralizing epitopes.

2. Methods

The literature search was performed by using google scholar, PubMed, and Indian government-published & unpublished data search with various identical words (Boolean keys). objectives for the search area to find out data about strain prevalence, Molecular study of G/F proteins & Seasonality & risk factor associated with hRSV infection observed in India.

Following are the search keys used for data search.

Respiratory Syncytial Virus + India

Respiratory Syncytial Virus + Molecular Study + India

Respiratory Syncytial Virus + Epidemiology + India

Respiratory Syncytial Virus + Prevalence + India

Respiratory Syncytial Virus + Serotype + India

Manual data were searched by using references cited in original papers. Data were filtered based on the time from April-2005- To March 2022 with the Indian pediatric population (last 15 years) and it is restricted to India only.

Inclusion criteria- A research article on the study of the prevalence or Molecular nature of the RSV virus gene within India has been included in this study.

3. Results and Discussion

Based on our study aim, 12 Indian studies will be selected for this review. (Table 1.) Most of the studies were conducted in south India followed by North India & East India regions. Very few studies were found on a molecular study specifically G-gene sequencing and nucleotide change with the different reference strains. none of the studies was found related to the F-gene molecular study. Gene sequencing was partial which come out with partial phylogeny with partial reference representation.

Table1: Indian Studies

Sr.No	Study/Study Year	Indian Region /City	RSV Positive/Total Sample Tested	Prevalence RSV strain Type	Seasonality	Molecular Study findings/ A. Acid Change
1	Naik et al /2005-2008(1)	Eastern India/Kolkata	RSVA-97/1720 RSVB-80/1720	- BA4	Winter (Nov-Feb)	Two conserved glycolysis sites at 296 & 310 were observed.
2	Babu S et al / 2011-14(2)	South-India/ Chennai	RSVA-84/850 RSVB-40/850	ON1, BA9, BA12	Monsson & Winter	
3	Biswas et al /2009-2012(3)	Eastern India/Assam	RSV -39/497	NA1, GA5	Winter	-
4	Choudhary et al/2009-2012(5)	Western India/Pune	RSVA-29/854 RSVB- 130/854	NA1, ON1 BA9, BA12	Monsoon Winter	-
5	Barde et al/ 2009-14(19)	Central India/Jabalpur	RSVA-31/526 RSVB-31/526	NA1, ON1 BA9	-	-

6	Patil et al 2012-14(16)	South India/ Alappuzha	RSVA-32/130 RSVB-17/130	ON1 BA9,1BA10	Monsoon	ON1-E232G, T253K, P314L BA-S247P, BA9-V271A, I281T BA10-E292G E226D
7	Malhotra et al /2012-14(31)	North west India/Jaipur	RSVA-138 RSVB-20	-	Monsoon	-
8	Sahu M et al /2009-12(18)	Central India/Jabalpur	RSVA-25/75 RSVB- 8/75	-	-	-
9	Anita shet et al /2011-13(33)	South India/Banglore	RSV-94/383	-	Monsoon	-
10	Hindpur et al /2016-17(34)	South India/Chennai	RSVA-27/146 RSVB-5/146	-	Winter	-
11	Singh Ak et al /2011-12(22)	North- India/Lucknow	RSVA-38/188 RSVB-02/188	-	Winter	-
12	Praveen et al /2006(15)	North India/ New Delhi	RSVA-37 RSVB-11	GA5, GA2, BA	-	-

Seasonality of hRSV

The seasonality of hRSV is yet to be determined although overall global hRSV activity has been observed to peak during the winter months [4]. As compared to Influenza, hRSV has a more broadly distributed peak timing. Numerous studies of [23] correlation between climatic factors and hRSV incidence across latitudes found variable and inconsistent correlations between hRSV incidence & temperature, and relative humidity in different parts of the tropical region. In India, hRSV peak activity is mainly reported during the monsoon and winter seasons. [4,5]. However, the overall hRSV incidence is more consistently positively correlated with lower temperatures and higher relative humidity. Certain studies in places from tropical, subtropical as well as temperate regions observed a direct correlation between higher temperature and hRSV incidence. The effect of climatic factors especially temperature may alter humans physiologically and even their social behavior patterns. Survival of lipid-enveloped viruses [29] is enhanced in cooler, drier (less humid) environments. So, RSV may well survive better in air-conditioned environments even in tropical or subtropical countries. Welliver2007 [30] also reported an inverse relation between hRSV activity and UV-B radiation as UV-B may inactivate the virus in the environment or influence susceptibility to RSV by altering host resistance thus stating that temperature, humidity, and ultraviolet B radiation could predict community hRSV activity.

Indian Scenario of hRSV Prevalence & Disease Burden

In India, there are reports of hRSV as an important viral pathogen in pediatric LRTI cases. However, the majority of these reports are based on hospitalized pediatric LRTI cases with a small sample size usually spanning over a very short period.

(Table 1). Estimation of incidence rates of hRSV infection is challenging due to follow-up of patients, diagnosis and laboratory set-up, large population size, and varied demographics of the population. Thus, epidemiological data available is mainly in terms of the total positivity of hRSV cases, clinical manifestations, and outcome of the hRSV positive cases in retrospective cases. Several reports observed hRSV infection in a higher percentage of children with bronchiolitis as compared to those with pneumonia. The highest prevalence was observed in children between the 2 to 6 months age group and the percentage fell as the age increased. In hRSV infected children cough was the leading symptom followed by coryza and fever. Cough and coryza were the main clinical manifestations of hRSV infection. Prevalence peaked during the winter months [11,5]. Saha et al [17] estimated that the annual incidence rates of RSV-associated hospitalization per 1000 children were highest among infants aged 0–5 months, followed by ages 6–23 months, and lowest among children 24–59 months. hRSV was a substantial cause of hospitalization among children aged < 24 months especially those aged <6 months. The presence of cough, fast-breathing, crepitation, and hypoxia served as independent predictors of hRSV infection and although fever was a common symptom among the

hospitalized children, it was not a good predictor of RSV-associated hospitalization. After further evaluation of various case definitions (old ILI, WHO 2011: ARI, SARI, and ILI), the WHO ARI case definition captured the highest incidence cases. Sahu et al 2015 [18] suggested that during pandemic Influenza seasons children of ≤ 2 years of age group with influenza-like illness should be tested simultaneously for hRSV to rationalize antiviral treatment since in a retrospective study they observed that 44% of hospitalized children (<2 years) suspected of influenza-A (H1N1) pandemic09 infection during the 2009 influenza pandemic were positive for hRSV. Studying such aspects is important as due to an emergency during the pandemic, severe ILI pediatric cases which probably had RSV infection may have been treated with Oseltamivir (frontline antiviral used for Influenza A (H1N1) pdm09). This drug is known to have serious side effects in children and has also been shown to prolong RSV shedding [13]. The report of a hospital outbreak of hRSV in immunocompromised hospitalized children during summer [21] may imply that hRSV is an important nosocomial pathogen in immunocompromised patients. There is an unavailability of information on hRSV incidence and disease burden in the elderly population in India.

Molecular Nature of hRSV

The need for molecular characterization of hRSV at the genotypic level was emphasized by Peret et al [16] Numerous findings included co-circulation of both A and B subtypes in the same year with the predominance of either one, distinct hRSV genotypes (GA1 to GA5 for subgroup A and GB1 to GB4 for subgroup B) and further subtypes, pre-dominance of genotypes within a subgroup in a season and that no genotype or subtype predominated for more than one hRSV season. Further, a yearly shift within genotype strains enabled efficient circulation each year. The length of the amino acid residues of the 270-nucleotide fragment (second hypervariable region) also varies among different genotypes. GA1, GA2, GA3, and GA4 possess 86; GA5 and GB1 have 87 while GB2, GB3, and GB4 had 89 amino acid residues. Differences in the length of the deduced amino acid sequences are due to the first nucleotide-position mutations in the first stop codon in the carboxyl terminus of the G protein gene. Stop codon usage also differs. Subgroup A isolates use the UAG stop codon in either nucleotide position 259 or 262. Subgroup B isolates use either the UAA or the UAG stop codons in positions 241, 250, or 262. [25]. Changes in stop codon usage are thought to be associated with antigenic variation in RSV escape mutants that recognize strain-specific epitopes [12]. Patil et al 2017 study observed that the ON1 genotype found in Kerala shows E232G, T253K & P314L were unique amino acid substitutions with an early stop codon at position 298 and 32, and V271A, I281T (BA9) & E226D, E292G (BA10) unique amino acid were observed in strain B. Isolation of similar strains across various geographical regions indicates that outbreak strains may spread rapidly globally. [Shobugawa et al (2009)] reported the emergence of two more new hRSV A genotypes in Niigata, Japan namely NA1 and NA2 which were genetically closer to GA2. The NA1 strains emerged first in Japan, in the 2004–2005 hRSV season, and got subsequently replaced by the NA2 strain that emerged in the 2005–2006 season. They also observed that reinfection caused by NA2 occurred more frequently than reinfections by other genotypes hypothesizing that a weaker neutralizing immune response against NA2 was a cause for a higher rate of reinfection with NA2 strains. NA1 can be further classified into 4 lineages [Hirano 2014]. [Eshaghi et al (2012)] reported the discovery of a novel hRSV A genotype ON1 in Canada with a 72-nucleotide duplication (23 amino acid duplication) in the C-terminal region of the G gene resulting in an increased number of potential glycosylation sites on the G protein which might alter immunogenicity and pathogenicity of the virus. The duplication starts after residue 850 of the G gene (RSV-A2 prototype numbering) and appears to disrupt the codon "GAG" (residue 850–852) coding for E284, switching it to "GGT" and coding for G284, which is followed by a duplication of 23 AAs (QEETLHSTTSEGYLSPSQVYTTS) spanning positions 261–283 and 285–307. Although this in-frame duplication does not cause a frameshift, the predicted polypeptide is lengthened by 24 AAs when compared to the reference NA1 genotype. Ontario's NA1 and ON1 strains displayed an early stop codon as compared to prototype A2. The nucleotide sequence of the G gene from the ON1 genotype is translated to a polypeptide of 322 amino acids, the largest found so far among hRSV-A isolates. Based on virtual viral RNA structure prediction they suggested 'Stem-loop backtracking' as a potential mechanism that could result in such large duplication in this gene.

Circulation of hRSV genotypes in India

hRSV subgroups A and B both co-circulate simultaneously in India with either one predominating at a given time. The earliest available partial G gene sequences date back to the 1990s. hRSV strains isolated during 1995 clustered in genotypes GA2, GA3, and GA5. In 2002, only GA5 was predominant. Currently, too, limited reports exist on hRSV circulation at the genotype level. However, genotypes ON1, NA1, GA5, and GA2 in the hRSV-A group and group hRSV-B BA, BA9, and BA12 were predominantly circulated in India. The reports represent the north, south, east, west, central, and northeast zones of India. (Table-1) From 2002 to 2003, circulation of GA2 and GA5 of subgroup A and BA of subgroup B with hRSV A as the predominant subgroup was reported in a rural community in Delhi [15,16]. Parveen et al. also reported re-infections with different genotypes and even different subgroups. BA genotype of hRSV B was prevalent from 2005 to 2006 in Kolkata [1] Between 2009 to 2012, Western India observed circulation of NA1 and ON1 genotypes of subgroup A, GB2, BA9, and BA12 of subgroup B [5]. BA genotype of hRSV B was the predominant group in circulation [9]. During the same period, hRSV A genotype NA1 was predominant with GA5 co-circulating in Dibrugarh (Assam-North East India). This was the first report of NA1 circulation in India. The Northeast states are closer to Japan where the emergence of the NA1 genotype was first reported [3]. [Babu S. et al 2016] reported predominant circulation of the ON1 genotype of hRSV A and co-circulation of BA9 and BA12 of subgroup B in Tamil Nadu (South India) between 2011 to 2014. In central India, circulation of NA1, ON1 of hRSV A, and BA9 of hRSV B were reported [19].

Annual incidence rates of RSV-associated hospitalization per 1000 children were highest among infants aged 0–5 months, followed by ages 6–23 months, and lowest among children 24–59 months. hRSV was a substantial cause of hospitalization among children aged < 24 months especially those aged <6 months. The prevalence varies from 2.1% to 44% in different geographical regions. The median age for a subject is 5-15 months whereas 89% of cases were found less than 2 years of age.

4. Conclusion

Data from reference studies conducted in India reveals that there is a high prevalence of RSV infection in an early stage of a child. As compared to Influenza, hRSV has a more broadly distributed peak timing. Numerous studies of the correlation between climatic factors and hRSV incidence across latitudes found variable and inconsistent correlations between hRSV incidence & temperature, and relative humidity in different parts of the tropical region. According to them a high proportion of RSV virus associated with ALRI was seen among hospitalized children in India. However, genotypes ON1, NA1, GA5, and GA2 in the hRSV-A group and group hRSV-B BA, BA9, and BA12 were predominantly circulated in India.

Limitation of Study:

Study review data applies to the Indian region only.

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