The Impact of RSV-Associated Respiratory Disease on Children in Asia

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Abstract

Acute respiratory tract infections (ARTIs) are leading contributors to the global infectious disease burden, which is estimated to be 112,900,000 disability adjusted life years. Viruses contribute to the etiology of ARTIs in a big way compared with other microorganisms. Since the discovery of respiratory syncytial virus (RSV) 61 years ago, the virus has been recognized as a major cause of ARTI and hospitalization in children. The morbidity and mortality attributable to RSV infection appear to be higher in infants $<$ 3 months and in those with known risk factors such as prematurity, chronic lung, and congenital heart diseases. Crowded living conditions, exposure to tobacco smoke, and industrial or other types of air pollution also increase the risk of RSV-associated ARTI. Many epidemiological studies have been conducted in developed countries to understand the seasonal patterns and risk factors associated with RSV infections. Dearth of information on RSV-associated morbidity and mortality in Asian and developing countries indicates the need for regional reviews to evaluate RSV-associated disease burden in these countries. Epidemiological studies including surveillance is the key to track the disease burden including risk factors, seasonality, morbidity, and mortality associated with RSV infection in these countries. These data will contribute to improve the clinical diagnosis and plan preventive strategies in resource-limited developing countries.

Keywords

- acute respiratory tract infections
- respiratory syncytial virus
- epidemiology
- children
- Asia

Introduction

Acute respiratory tract infection (ARTI) is one of the major health issues in infants and children in the world causing morbidity and mortality with an estimated global disease burden of 112,900,000 disability adjusted life years.[1] Respiratory illness is the most common reason for consulting general practitioners and hospitalization in children and adults.[2] For example, in the United States, the incidence of lower respiratory tract infections (LRTIs) among children under 5 years of age is high contributing to 19% of hospitalizations in the general population of children.[3] In developed countries, ARTI rarely causes mortality but contributes to direct and indirect health costs; however, ARTI causes severe morbidity and mortality in developing countries.[4] In the latter, one-third of the deaths in children $<$ 5 years of age are caused by respiratory illness,[5,6] which is 30 to 70 times higher than that reported in developed countries.[7] ARTI-associated morbidity is also high in developing countries due to malnutrition, low birth weight, passive smoking, absence of breastfeeding, low socioeconomic, and overcrowded living conditions.[8]

Viruses contribute to a larger proportion of ARTI-associated morbidity and hospitalizations globally. Around 50 to 90% of the LRTI in young children are caused by respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza viruses, human bocavirus (hBoV), parainfluenza viruses (PIVs), adenoviruses, rhinoviruses, human coronavirus (hCoV), and enteroviruses (►**Table 1**).[8,9] In 1956, RSV was isolated from

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Table 1 Prevalence of respiratory viruses causing LRTI in the world

Country	Age	Sample	Study period	Prevalence %								
				RSV	hMPV	InfV	hBoV	PIV	RhiV	AV	hCoV	EntV
Germany[10]	< 36 mo	1,054	6 y	34	NA	4.7	NA	7.7	NA	NA	NA	NA
Ghana[11]	< 5 y	128	Jan 2008–Dec 2008	18	NA	1	NA	4	NA	13	NA	NA
Spain[12]	< 1 y	99	Jan 2006–Jun 2006	35	25	NA	NA	NA	19	NA	NA	NA
China[13]	Children	34,885	Jan 2001–Dec 2006	23.6	NA	2.0 (InfV A)	NA	4.3 (PIV-3) 0.6 (PIV-1) 0.1 (PIV-2)	NA	1.7	NA	NA
Japan[14]	< 15 y	921	Apr 2000–Mar 2001	20.4	NA	11.9 (InfV A)	NA	3.8	NA	2.9	NA	NA
France[15]	< 36 mo	192	Sep 2001–Jun 2002	30	4	6	NA	NA	21	NA	NA	9
Thaiwan[16]	< 36 mo	48	Apr 2007–Dec 2007	41.7	27.1	NA	6.3	NA	NA	NA	NA	6.3
Mexico[17]	< 15 y	285	NA	85.6	NA	7.2	NA	2.4	NA	NA	NA	NA
Korea[9]	5 y	515	2000–2005	23.7	4.7	4.7 (InfV A) 1.7 (InfV B)	11.3	6.2 (PIV-3) 1.7 (PIV-1)	5.8	6.8	NA	NA
Egypt[18]	< 1 y	450	Nov 2006–Dec 2007	23.8	6.4	NA	NA	6.6 (PIV-1) 3.1 (PIV-2) 8.9 (PIV-3)	NA	18.4	NA	NA
Malaysia[19]	< 24 mo	5,691	1982–1997	84	NA	6	NA	8	NA	2	NA	NA
Turkey[20]	≤2 y	147	NA	55.6	13	9.3	NA	27.8	NA	5.6	NA	NA

Abbreviations: AV, adenoviruses; EntV, enterovirus; hBoV, human bocavirus; hCoV, human coronavirus; hMPV, human metapneumovirus; InfV, influenza virus; LRTI, lower respiratory tract infection; NA, not available; PIV, parainfluenza virus; RhiV, rhinovirus; RSV, respiratory syncytial virus.

chimpanzees with common cold-like illness[21] and this led to the identification of RSV as a causative agent of coryza in chimpanzees.[22] Subsequently, Chanock et al identified the same virus as the cause of LRTI in young infants.[23] The virus was later named as RSV reflecting its ability to form syncytia among infected cells.[24]

RSV is an enveloped virus with a nonsegmented negative sense RNA belonging to the genus *Orthopneumovirus* of the family Pneumoviridae.[25] The virus encodes for 10 genes and 11 proteins.[26] RSV has three surface glycoproteins: the fusion glycoprotein (F), attachment glycoprotein (G), and small hydrophobic (SH) proteins (►**Fig. 1**). G and F proteins are responsible for the initial phases of viral infection through attachment with the infecting cell.[26] The cell fusion is mediated by F, G, and SH proteins and the latter is believed to change membrane permeability.[27] Based on the structural features of the matrix protein (M) and ribonucleoprotein (RNP), there are three morphological forms (a, b, and c) of RSV particles (►**Fig. 2**).[28]

Transmission of RSV occurs mainly via the nose through infected aerosols. RSV remains infectious on many environmental surfaces suggesting that transmission can occur through contact with hands or inanimate surfaces contaminated with infected nasal secretions.[29] Most of the RSV-associated ARTI are community-acquired, but there have also been reports of hospital-acquired RSV infections.[8,30] The likelihood of hospital-acquired RSV infection increases with the duration of hospital stay and gaps in the infections control practices.[31] Based on a previous study, RSV detection in children at the time of admission was 39%, which increased to 62% during the hospital stay.[32]

RSV alters host cells by initially infecting the epithelial lining of the respiratory airway and nasal passage. The virus influences the expression of genes controlling protein metabolism, inflammation, cell growth, proliferation, nucleic acid regulation, and synthesis.[33] RSV infection causes pneumonia through damaging the respiratory epithelium and bronchociliary apparatus; this results in the collection of fluid in bronchioles and alveoli causing obstruction and collapse of the affected area of the lung. Replication of RSV starts from nasopharynx primarily in the superficial layer of the respiratory epithelium and the virus then descends from the nasopharynx to lower respiratory tract via the respiratory epithelium or inhalation of secretions.[34]

RSV-associated bronchiolitis is the most important cause of admission to the hospital during the first year of infancy.[8] Around 50 and 25% hospitalizations of infants are due to RSV-associated bronchiolitis and pneumonia.[34] RSV is responsible

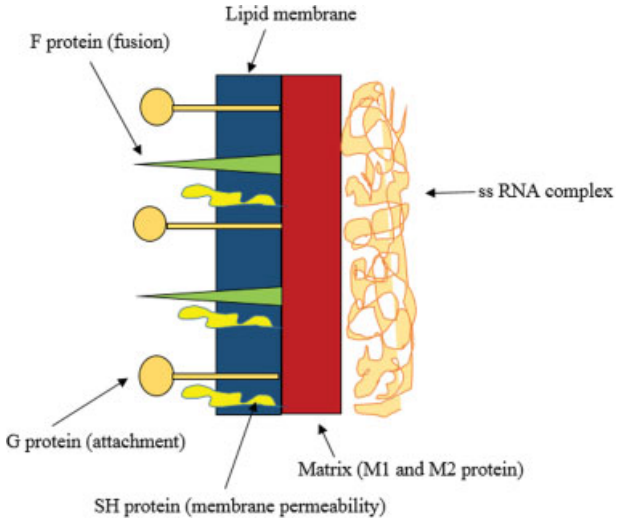

Fig. 1 A schematic diagram showing the cross-sectional layers of RSV. The matrix comprises the M1 and M2 proteins and the viral capsid contains the F and G transmembrane proteins. RSV, respiratory syncytial virus.

for precipitating recurrent wheezes and asthma in susceptible children.[35] Recurrent RSV infections also cause residual parenchymal or airway damage leading to minor abnormalities in lung function in the longer term. The mechanisms involved in RSV-associated recurrent wheeze and asthma are not clear, and whether RSV is directly responsible for asthma or infects children with preexisting broncho-obstructive disease remains unresolved.[36] Recent studies suggest that RSV causes asthma in some infants, but is also capable of attacking infants with a predisposition for wheezing.[36,37] Hospitalized infants aged < 1 year with RSV-associated bronchitis have a tendency to develop asthma and recurrent wheeze for a few years.[38] Here, we review the impact of RSV-associated ARTI on children in Asia including epidemiology, laboratory diagnosis, therapies, and future research priorities.

RSV-Associated Disease Burden

Since the discovery of RSV 61 years ago, the virus has been identified as a major cause of ARTI in infants and the single most common cause of childhood hospitalization.[39] During the past 31 years, RSV has been identified as the cause of severe LRTI in infants and children in developing countries.[39] RSV-associated morbidity and mortality appear to be high in infants < 3 months and children with known risk factors compared with other viral LRTI. Known risk factors for acquiring RSV-associated LRTI include prematurity, chronic lung disease, congenital heart disease, cystic fibrosis, bronchopulmonary dysplasia, down syndrome, compromised immunity, crowded living conditions, and exposure to tobacco or industrial smoke.[9,40] Moreover, RSV-associated ARTI appears to be common in boys than girls;[41] the reason for the male preponderance is believed to be due to immunomodulatory effects of the sex hormones during the early stages of life.[42] Severe RSV-associated respiratory disease has also been recognized as a significant health issue in adult populations, and epidemiological data suggest that the impact of RSV in adults is largely similar to nonpandemic influenza. ARTI due to RSV have been reported in the institutionalized elderly, the immunocompromised, and adults with cardiopulmonary diseases.[43]

The Impact of RSV on Global Child Health

Globally, RSV is commonly associated with childhood ALRI and related hospital admissions, which results with a substantial burden to the health care systems and economy. Approximately 45% of the hospitalizations and deaths are caused by RSV-associated ARTI in infants < 6 months. In 2015, 33.1 million new episodes of RSV-associated ALRI occurred worldwide in children less than 5 years, with at least 3.2 million hospitalizations and 59,600 in-hospital deaths.[44] Moreover, RSV-associated ALRI caused 1.4 million hospitalizations with 27,300 in-hospital deaths in infants < 6 months.[44]

Alaskan native infants have the highest rates of RSV hospitalizations in the world.[42] RSV-associated hospitalization rates for Alaskan native infants, in the rural Yukon–Kuskokwim Delta (YKD) region of Alaska were five times higher than that for the overall United States infant population.[45] From 1993 to 2004 is considered to be the period when the worst RSV outbreaks occurred in the YKD region,

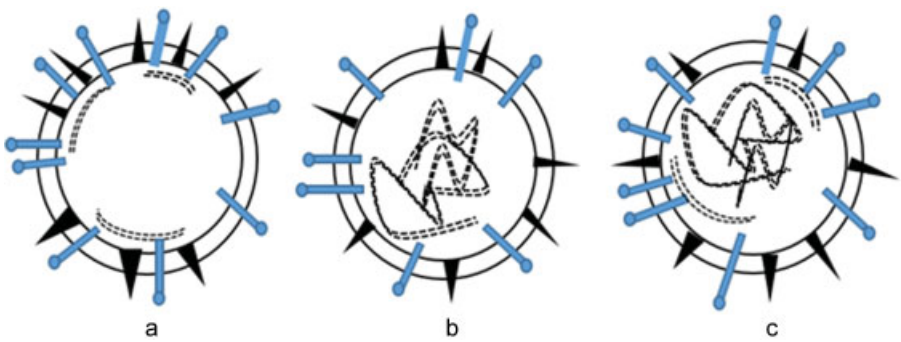

Fig. 2 Three types (**a**–**c**) of spherical RSV particles have been described according to the major structural features of the M protein and RNP: (**a**) Presence of a characteristic layer beneath the membrane with extensive patches of M; (**b**) A large region within the capsid is filled with nucleic material with less contact points and 3 to 4 of RNP are dispersed throughout; (**c**) Nucleic material densely packed within the capsid membrane containing large number of RNP.[28] M, matrix; RNP, ribonucleoprotein; RSV, respiratory syncytial virus.

and RSV-associated hospitalization rates rose to 38 to 248 per 1,000 during that period. Infants from indigenous Canadian populations, Germany, the United States, New Zealand, and Europe also have high hospitalization rates with RSV-associated ARTI.[46]

The Impact of RSV on Child Health in Asia

Based on studies conducted in Asia, the most common cause of LRTI in children is RSV (►**Table 2**). In Hong Kong, RSV-associated hospitalization has been described in children < 5 years.[64] In Japan, RSV-associated LRTI occurred in 31.4% of a sample of 535 children aged < 3 years.[47] In Lanzhou, China, RSV was detected in 40.71% of the children with ARTI.[50] In another study, RSV accounted for 25.0% of the LRTI cases in Harbin, China.[51] In Hong Kong, RSV has been detected in young infants with chronic lung disease, neurodevelopmental conditions, and congenital heart disease; these risk factors significantly increased the risk of RSV infection.[65]

Information on the impact of RSV in childhood ARTI in South East Asian countries is scanty. In Malaysia, RSV is the most common respiratory virus identified in children ≤ 6 months, accounting for 81.3% of the LRTI cases.[53] Data from Lombok, Indonesia, suggest that 16% of LRTI deaths are caused by RSV.[66] In Vietnam, RSV, influenza A, and rhinoviruses contribute to pneumonia along with multiple viral and coinfections with bacteria.[67] In Bhaktapur, Nepal, RSV infections were detected in 15.1% of the study sample,[58] and in India RSV accounted for 57% of ARTI cases.[64] In Bangladesh, RSV has been identified as the predominant (81%) viral pathogen causing pneumonia in children in rural areas.[60] In urban areas of Bangladesh, the overall incidence of RSV-associated pneumonia is 40/100 child years.[61]

In temperate regions of Asia RSV causes outbreaks mostly during the fall or winter; in tropical regions of Asia RSV outbreaks usually peak in hot or rainy seasons, but can occur at any time of the year with genotype shifting.[68] Based on the severe acute respiratory infection (SARI) surveillance in

Table 2 Incidence and seasonality of RSV infection in Asian countries

Country	Duration of the study	Age	Incidence %	Seasonality
Japan	Jul 1997–Jun 2000[54]	< 3 y[47]	31.4[47]	Common in winter and a peak in Dec[47]
	Nov 2001–Jul 2004[55]	Pediatric patients[48]	37.1[48]	Winter–spring with a peak in Dec (2001–2003) and a peak in Nov (2003–2004)[48]
China	2010[49]	< 5 y[49]	33.1[49]	Throughout the year, with a peak from Sep to Jan[49]
	2006–2009[50]	≤ 14 y[50]	40.71[50]	Fixed seasonal rhythm, with a peak from Nov to Apr[50]
	Jan 2008–Dec 2008[51]	16 y[51]	25.0[51]	Early spring to winter, with a peak from Jan to Apr[51]
Hong Kong	Jan 2004–Dec 2004[52]	≤3 y[52]	11.6[52]	No winter seasonality[3] and peak in Mar and Sep[52]
Malaysia	1982–2008[53]	≤ 5 y[53]	81.3[53]	Throughout the year with a seasonal peak from Sep to Dec[53]
Indonesia	Jan 1995–Jun 2009[43]	< 5 y[43]	16[43]	Throughout the year[43]
Vietnam	2009–2010[54]	< 2 y[54]	48[54]	Peak during rainy season from May to Oct[54]
Philippines	2012–2013[55]	Children[55]	28.1[55]	Peak activity occurs in Jan[55]
Taiwan	Jan 2001–Dec 2005[56]	2 y[56]	60.7[56]	Showed a biennial pattern, with peaks in spring and fall[56]
Thailand	Sep 2003–Dec 2007[57]	All ages[57]	8.9[57]	Detected most month of the year with a peak from Jun to Oct[57]
Nepal	Jul 2004–Jun 2007[58]	< 5 y[58]	15.1[58]	Rainy season and winter season with a peak from Jul to Apr[58]
South India	NA	< 5 y[59]	57[59]	Rainy season (Aug–Nov)[59]
Bangladesh	1993–1996[60]	< 24 mo[60]	81[60]	NA
	2009–2011[61]	Children[61]	40/100 child y[61]	Throughout the year with a peak from Dec to Feb[61]
Pakistan	2011–2012[62]	Children[62]	71.4[62]	Winter season with a peak from Dec to Jan[62]
	Aug 2009–Jun 2012[63]	< 5 y[63]	19[63]	Peak in Sep coinciding with the rainy season[63]

Abbreviations: NA, not available; RSV, respiratory syncytial virus.

China, RSV has been mostly detected in infants year around with peaks from autumn to winter.[49] In contrast to these findings reported from the mainland China,[58] RSV seasonality has not been noted in winter in Hong Kong.[65] In Japan, cocirculation of different RSV genotypes has been observed every year with shifts in genotypes within a season.[48] In Nepal, the largest peaks of pneumonia occur during RSV peak seasons in rainy and winter periods from July to April.[58,69] In India, RSV outbreaks occur in the rainy season from August to November.[59]

The Impact of RSV on Childhood ARTI in Sri Lanka

Childhood hospitalization due to RSV-associated ARTI is common in Sri Lanka.[70] RSV is recognized as the most common cause of viral ARTI among children in Sri Lanka, as in many other countries. RSV contributes to 90.6% of virus-associated ARTI based on the findings of a small-scale study of children admitted to Kegalle General Hospital with ARTI.[70] This study also described that RSV infections occurred predominantly from July to September.[70] A study based on Gampola and Anuradhapura Teaching Hospitals reported incidences of 31.3 and 28/100,000 person years, respectively, for RSV among infants with ARTI. In Anuradapura (which is located in the dry zone), RSV was detected throughout the year with a peak from May to July in both 2013 and 2014. In Gampola (located in the wet zone), RSV was again detected throughout the year, but peaked during December to January in 2013.[64] Larger studies are needed to fill the gap in understanding the local seasonality, disease burden, and severity of RSV-associated ARTI in Sri Lanka.[64]

Epidemiology of RSV Infections

Data on the incidence and mortality of RSV-associated ARTI in Asian developing countries have not been published and thus the extent of this infection's contribution to mortality remains uncertain. According to the World Health Organization (WHO), almost three-fourths deaths in infants occur due to RSV-associated pneumonia in Southeast Asia and sub-Saharan Africa.[71] The Pneumonia Etiology Research for Child Health (PERCH) project evaluated the etiological agents causing severe pneumonia in children from seven developing counties including two in Asia, Bangladesh and Thailand. This study showed a significant association between hospitalization of children and RSV-associated pneumonia in Bangladesh.[72] Therefore, regional estimates of RSV-associated ARTI burden in Asian developing countries with local seasonal patterns, risk factors, and virus evolution would improve our understanding of RSV epidemiology in these countries.

Seasonality of RSV Infections

A few projects have been conducted in developed and developing countries to understand the seasonal patterns of RSV infection compared with other respiratory pathogens and to identify the risk factors for severe respiratory disease.[66] These projects have shown that RSV seasonality depends on the geographic location and altitude of a given country or a region. RSV-associated respiratory disease epidemics tend to occur in clusters during a particular season. Although the occurrence of RSV outbreaks varies among continents, the general pattern is that they start in coastal areas and spread to inland areas.[39] In countries experiencing tropical and semitropical climates and located far from the equator, RSV outbreaks occur in cool dry and cool wet seasons. In regions closer to the equator, RSV outbreaks occur throughout the year with periods of peak activity.[39] RSV outbreaks have been reported year around with a slight increase in the rainy seasons in equatorial islands like Singapore, Fiji, Taiwan, and Hawaii.[40] In countries north of the equator like India, outbreaks have been reported predominantly during the rainy season.[40] RSV peaks have been reported in the winter months in most of the European countries although the infections remain relatively consistent throughout the year.[40] Although there are predictions made on RSV seasonality patterns, the predictions are not reviewed systematically at a global level, in parallel with surveillance data for many other respiratory viruses like influenza in the last decade.

RSV diversity is influenced by the physiology of the host, host–virus interactions, social behavior of people, and transmissibility of the virus. The absence of a global picture of RSV seasonal patterns is a hindrance to planning public health strategies to combat RSV outbreaks. An extensive review of the literature, together with proper laboratory surveillance in different geographical areas, remains to be conducted on a global scale.

RSV outbreaks have periodic emergence patterns and the reason for that is not clear. Even though geographic and climatic factors have a clear association with epidemics, the RSV epidemic pattern is also related to human behavior.[39] Due to similarities in risk factors, influenza and RSV epidemics often overlap.[73] In temperate areas, RSV and influenza activities both peak during the winter. However, there is greater diversity in the behavior of the two viruses in tropical countries, where RSV has been reported in 80% of areas, and influenza in 50% of areas, during the same outbreak.[74]

Risk Factors

Repeated RSV infections are associated with increased prevalence of atopy in children and their families.[34] Some investigations were performed to explore whether there is a connection between RSV-associated bronchiolitis in infancy and subsequent development of allergic sensitization or clinical allergy.[75] These studies confirm the association between recurrent RSV infections and atopy in children. Conversely, children with atopy and recurrent RSV infections also had more siblings and smoking parents.[36] Children with recurrent RSV infections had cardiopulmonary conditions than those with influenza or bacterial infections. Thus, RSV infection in children is associated with asthma, atopy, and other forms of bronchial obstructive diseases.[76]

Trials performed in the United States, the United Kingdom, Japan, Canada, and Denmark revealed the significance of crowded living conditions and exposure to tobacco smoke as risk factors for severe RSV disease.[40] Likewise, a study in Sri Lanka found that 31.3% of children with RSV-associated ARTI were from a household with at least one smoker.[64] Also, according to research conducted in Sri Lanka and Kenya, there is a close association between rural inhabitance and hospitalization due to RSV infection suggesting that rural inhabitance may also be a predisposing factor for RSV infection.[64,71] The time of birth has a significant association with RSV-induced bronchitis,[77] and moreover, birth during the winter virus peak season confers risk for childhood asthma.[78] Immunosuppression is another independent risk factor for RSV infection and the risk of mortality increases with the progression of infection from upper to lower respiratory tract.[77] Among adults, presence of a chronic pulmonary disease, physician-diagnosed congestive heart failure, and functional disability increase the risk of RSV-associated serious ARTI.[79,80] Moreover, hospitalization is a risk factor for severe RSV infection and mortality attributed to RSV-associated ARTI.[40]

Virus Evolution

Virus evolution contributes to the emergence of new strains of RSV, while old RSV stains disappear under the selective pressures created by the new ones.[81] Pathogenicity and the fitness are strong in emerging RSV stains, which are widespread and cause recurrent infections and outbreaks.[82] The G and F proteins are considered as important antibody targets as changes occur in these areas to avoid the host immune responses.[83] RSV evolution is associated with accumulation of amino acid changes and antigenic variations in the G protein.[84] Even though the sequence variability of RSV is concentrated on the G gene, the rapid pace of infection underlines the contribution of the full genome to virus evolution.[83] According to the sequence variability in the F gene, mutations in the F protein are mostly deleterious, therefore, only a few sites in the F gene are under positive selection pressures.[85] RSV appears to undergo sequential evolution like influenza B, which has evolved through interactions between influenza A and C. It has been shown that multiple lineages of RSV originate from cocirculation of RSV subtypes.[81] RSV subtype B shows significantly faster rate of evolution than the subtype A, with a higher variation in the protein length, stop codon usage, and mechanisms for variation in the G gene.[46]

The other explanation for the change of genotypes over time is the rapid distribution of new genotypes as they emerge around the world at the same time.[81] A study conducted in New Zealand on the evolution of the G gene sequence noted the circulation of RSV stains that were related to those circulating in nearby countries during the same period. This finding supports the emergence and spread of RSV stains between closer neighboring regions.[46] A combination of factors including virus persistence in defined areas and continuous reintroductions from different areas are believed to be responsible for RSV epidemics resulting from new subtypes.[86]

Laboratory Diagnosis of RSV Infection

Respiratory viruses tend to circulate at the same time making it difficult to identify their individual contributions on the disease burden.[87] Moreover, the chances of detecting viruses in clinical specimens may be constrained by inadequate sample volume or quality, or by the laboratory techniques used. Isolation attempts often fail due to the lability of the virus.[88] However, the laboratory diagnosis should be sensitive and specific to identify viruses causing ARTI.[87] Thus, timely detection of RSV resulting from a rapid and an efficient assay is important.[89] Many laboratory tests are often limited to a single virus, rather than allowing detection of multiple respiratory viruses. Although widely used techniques like viral culture and antigen detection have greater sensitivity over direct antigen testing (►**Fig. 3**) from respiratory samples, their ability to detect only a single pathogen is a limitation.[90] Molecular techniques (►**Fig. 3**) are highly effective and have facilitated the identification of previously known and new viruses.[91] Moreover, molecular characterization of different respiratory viruses for epidemiological purposes has been performed using different types of conventional and advanced DNA sequencing methods (►**Fig. 3**).

Treatment Options for RSV

Ribavirin is the only licensed antiviral treatment for RSV infections and has shown promising results in placebo-controlled studies with administration at the beginning of the illness to children who are more prone to get life-threatening complications.[76] However, the drug is less used clinically, at least in part because of a lack of confidence in its efficacy.[92] Factors such as the inconvenience of administration and toxicity also compromise its therapeutic potential in severe RSV infections.[93]

Palivizumab (Synagis) is a drug approved for use in selected risk groups, such as infants with chronic lung disease, congenital heart disease, and history of prematurity.[94] It is a monoclonal antibody (mAb) that targets one of the proteins in RSV subtypes A and B.[95] However, palivizumab is only around 40% effective in reducing RSV-associated hospitalization rates in premature infants and high risk children.[96] While this prophylactic treatment may be effective in reducing RSV-associated morbidity in infants, high cost and inconvenience of administration have limited it use.[97]

An effective vaccine against RSV has not been available yet, and clinical experience of both inactivated and attenuated test vaccines have not shown great promise. In one trial, RSV-infected children were administrated an inactivated vaccine named “lot 100” and following the vaccination, vaccinees developed severe respiratory disease. Infants aged under 23 months showed a higher incidence of pneumonia (60%) in the vaccinated group compared with the placebo group that had only an 8% incidence of pneumonia.

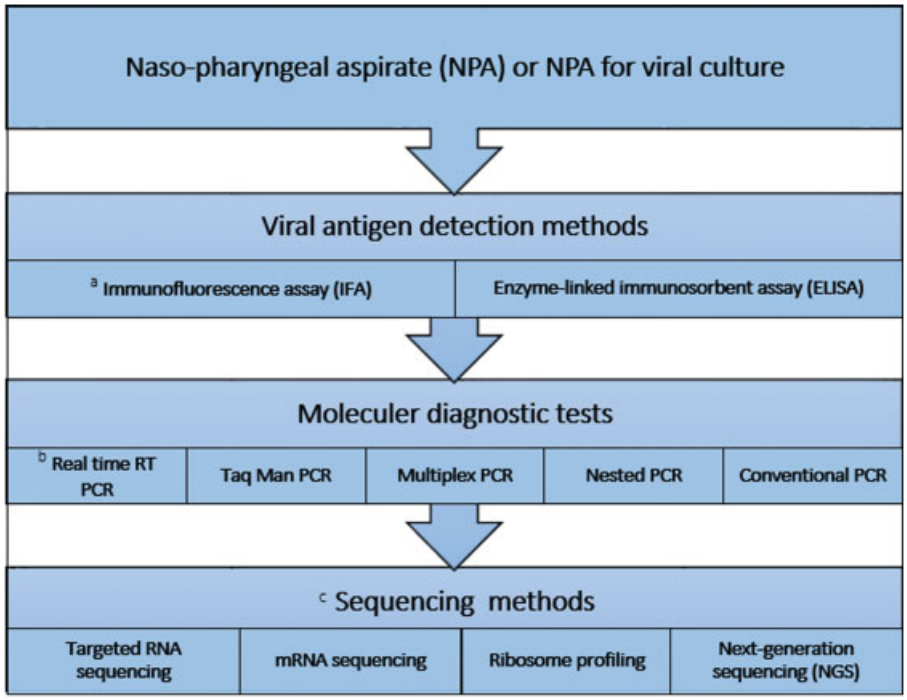

Fig. 3 Laboratory diagnosis of RSV infection using NPA. When NPA is not available nasal swabs can be used but the chances of viral antigen or nucleic acid detection in the nasal swab is low when compared with that in the NPA. (**a**) Immunofluorescence assay has been used in many diagnostic laboratories to detect RSV antigen. (**b**) Real-time PCR has been used in well-equipped laboratories to detect RSV nucleic acid and is the gold standard test. However, other types of PCRs have also been used to detect RSV nucleic acid depending on the availability. (**c**) Sequencing is done to understand the local, regional, and global epidemiology of different RSV types. PCR, polymerase chain reaction; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus.

The vaccine was reported to induce the production of a neutralizing antibody against F and G proteins but the reason for the increased respiratory disease in the vaccinated children was not clear.[34]

An RSV live-attenuated vaccine (LAV) with enhanced immunogenicity was tested in cotton rats and this vaccine exhibited thermal stability, efficacy, and immunogenicity. This genetically modified vaccine candidate merits consideration as the next-generation RSV vaccine design for humans.[98] Many other experimental vaccines are being tested on animal models and inactivated vaccines have shown superiority over attenuated vaccines in eliciting humoral and cell-mediated immunity. Recombinant vaccines with the expression of F, G, and N genes are currently under investigation. The common obstacles in the progress of developing a RSV vaccine are the young age group that needs to be protected and the fact that individuals experience continued reinfections with RSV even in the presence of humoral immunity.[34]

Future RSV Research Priorities

Poor growth of RSV in vitro, lack of suitable animal models, and instability of RSV in test environments have limited RSV research. More research is needed to address different aspects of RSV structure, function, and infection. The genome structure of the negative strand RNA, three-dimensional structure of the virus, and virion structure should also be evaluated to identify immunogenic proteins as vaccine candidates.

Due to limited therapeutic options to treat RSV-associated respiratory disease, the development of effective novel therapies must be high priority too. Currently, the effect of administering RSV neutralizing antibodies is being studied. These studies have also progressed to evaluating the effectiveness of combination therapy with these antibodies and antivirals like ribavirin.[99] Combinations of intravenous palivizumab and ribavirin have also been studied in high-risk RSV disease in children; such combination therapy has been reported to be effective, and associated with reduced mortality rates.[100] The combination of two mAbs (130–6D and 131–2G), which are reactive to the central conserved region (CCR) of RSV G protein, has also shown promising results in reducing the pulmonary inflammation caused by RSV compared with the effect of these antibodies alone in reducing the inflammation.[99] Finally, mucolytic agents such as recombinant human deoxyribonuclease (rhDNase) have shown promising results based on the improvements shown on chest X-rays,[78] but more work is needed to evaluate the effectiveness of these drugs.

As the immune responses elicited by viruses are specific despite their structural and pathogenic similarities, work is needed to identify the fundamental aspects of the immune response in RSV infections. For instance, very little information is available on the mechanisms of mucin (MUC) expression in human epithelial cells during an RSV infection and its

contribution to immune response. As MUC is recognized as an important component of the immune response, further research on this would bring a better understanding on the role of MUC in rendering protection in RSV infections. Moreover, research on the immune response in primary, secondary, homotypic, and heterotypic RSV infections would help to design immunoprophylactic strategies. Conversely, identifying the role of the respiratory microbiome in severe RSV infections will help to understand the impact of microbiome in disease severity as well as in protection.

The evolution of RSV around the globe is not fully understood, and thus sequence analysis of the stains will provide knowledge about the ancestry of the RSV and its evolution. Studies should also be performed to gather information on seasonality patterns and transmission dynamics according to regional differences in RSV seasonality data with climatic and population data.[82] Better understanding of the epidemiology of ARTI in developing countries would provide options for preventive measures in a timely manner as use of respiratory precautions and health education can be undertaken in different target populations.

Conclusion

Respiratory syncytial virus has a worldwide distribution and it contributes to significant morbidity and mortality in infants compared with other respiratory pathogens. Regional seasonality of RSV infections is pronounced. In equatorial countries, RSV is seen year-round, but there is an association with the rainy season in tropical and semitropical countries north of the equator, and with the dry season south of the equator. Changes in temperature and humidity correspond with the spread of the disease. Many host and environmental risk factors contribute to RSV-associated ARTI and hospitalizations including prematurity, overcrowded living conditions, passive exposure to tobacco smoke, and bronchopulmonary dysplasia/chronic lung disease. Detecting RSV-associated ARTI in resource-limited countries will contribute to minimizing irrational antibiotic use. Research is needed to develop effective vaccines and antiviral agents to tackle the increasing RSV-associated ARTI burden.

Conflict of Interest
None declared.

References

1 Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349(9063):1436–1442
2 Creer DD, Dilworth JP, Gillespie SH, et al. Aetiological role of viral and bacterial infections in acute adult lower respiratory tract infection (LRTI) in primary care. Thorax 2006;61(01):75–79
3 Peck AJ, Holman RC, Curns AT, et al. Lower respiratory tract infections among American Indian and Alaska Native children and the general population of U.S. Children. Pediatr Infect Dis J 2005;24(04):342–351
4 Gröndahl B, Puppe W, Hoppe A, Kühne I, Weigl JA, Schmitt HJ. Rapid identification of nine microorganisms causing acute respiratory tract infections by single-tube multiplex reverse transcription-PCR: feasibility study. J Clin Microbiol 1999;37 (01):1–7
5 Forgie IM, Campbell H, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in children in a rural community in The Gambia. Pediatr Infect Dis J 1992;11(06):466–473
6 Technical Advisory Group on ARI. A program for controlling ARI in children: memorandum from a WHO meeting. Bull World Health Organ 1984;64:47–58
7 Roca A, Loscertales MP, Quintó L, et al. Genetic variability among group A and B respiratory syncytial viruses in Mozambique: identification of a new cluster of group B isolates. J Gen Virol 2001;82(Pt 1):103–111
8 Bezerra PG, Britto MCO, Correia JB, et al. Viral and atypical bacterial detection in acute respiratory infection in children under five years. PLoS One 2011;6(04):e18928
9 Choi EH, Lee HJ, Kim SJ, et al. The association of newly identified respiratory viruses with lower respiratory tract infections in Korean children, 2000-2005. Clin Infect Dis 2006;43(05): 585–592
10 Wasem S, Weichert S, Walther S, et al. Lower respiratory tract disease in children: constant pathogens - constant management?! Klin Padiatr 2008;220(05):291–295
11 Kwofie TB, Anane YA, Nkrumah B, Annan A, Nguah SB, Owusu M. Respiratory viruses in children hospitalized for acute lower respiratory tract infection in Ghana. Virol J 2012;9:78
12 Camps M, Ricart S, Dimova V, et al. Prevalence of human metapneumovirus among hospitalized children younger than 1 year in Catalonia, Spain. J Med Virol 2008;80(08):1452–1460
13 Tang LF, Wang TL, Tang HF, Chen ZM. Viral pathogens of acute lower respiratory tract infection in China. Indian Pediatr 2008; 45(12):971–975
14 Numazaki K, Chiba S, Umetsu M, et al. Etiological agents of lower respiratory tract infections in Japanese children. In Vivo 2004;18 (01):67–71
15 Jacques J, Bouscambert-Duchamp M, Moret H, et al. Association of respiratory picornaviruses with acute bronchiolitis in French infants. J Clin Virol 2006;35(04):463–466
16 Sung CC, Chi H, Chiu NC, et al. Viral etiology of acute lower respiratory tract infections in hospitalized young children in Northern Taiwan. J Microbiol Immunol Infect 2011;44(03): 184–190
17 Noyola DE, Rodríguez-Moreno G, Sánchez-Alvarado J, Martínez-Wagner R, Ochoa-Zavala JR. Viral etiology of lower respiratory tract infections in hospitalized children in Mexico. Pediatr Infect Dis J 2004;23(02):118–123
18 Shafik CF, Mohareb EW, Yassin AS, et al. Viral etiologies of lower respiratory tract infections among Egyptian children under five years of age. BMC Infect Dis 2012;12:350
19 Chan PW, Goh AY, Chua KB, Kharullah NS, Hooi PS. Viral aetiology of lower respiratory tract infection in young Malaysian children. J Paediatr Child Health 1999;35(03):287–290
20 Hatipoğlu N, Somer A, Badur S, et al. Viral etiology in hospitalized children with acute lower respiratory tract infection. Turk J Pediatr 2011;53(05):508–516
21 Wright PF, Wright MD. Progress in the prevention and treatment of RSV infection. N Engl J Med 2014;371(08):776–777
22 Blount RE Jr, Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med 1956;92(03):544–549
23 Schickli JH, Dubovsky F, Tang RS. Challenges in developing a pediatric RSV vaccine. Hum Vaccin 2009;5(09):582–591
24 Chanock RM, Kim HW, Vargosko AJ, et al. Respiratory syncytial virus. I. Virus recovery and other observations during 1960 outbreak of bronchiolitis, pneumonia, and minor respiratory diseases in children. JAMA 1961;176:647–653
25 Vandini S, Biagi C, Lanari M. Respiratory syncytial virus: the influence of serotype and genotype variability on clinical course of infection. Int J Mol Sci 2017;18(08):1717

26 Eshaghi A, Duvvuri VR, Lai R, et al. Genetic variability of human respiratory syncytial virus A strains circulating in Ontario: a novel genotype with a 72 nucleotide G gene duplication. PLoS One 2012;7(03):e32807

27 Fuentes S, Tran KC, Luthra P, Teng MN, He B. Function of the respiratory syncytial virus small hydrophobic protein. J Virol 2007;81(15):8361–8366

28 Kiss G, Holl JM, Williams GM, et al. Structural analysis of respiratory syncytial virus reveals the position of M2-1 between the matrix protein and the ribonucleoprotein complex. J Virol 2014;88(13):7602–7617

29 Hall CB. Respiratory syncytial virus: its transmission in the hospital environment. Yale J Biol Med 1982;55(3–4):219–223

30 French CE, McKenzie BC, Coope C, et al; Noso-RSV Study Group. Risk of nosocomial respiratory syncytial virus infection and effectiveness of control measures to prevent transmission events: a systematic review. Influenza Other Respir Viruses 2016;10(04):268–290

31 Hall CB, Hall CB. Nosocomial respiratory syncytial virus infections: the "Cold War" has not ended. Clin Infect Dis 2000;31(02): 590–596

32 Avendaño LF, Larrañaga C, Palomino MA, et al. Community- and hospital-acquired respiratory syncytial virus infections in Chile. Pediatr Infect Dis J 1991;10(08):564–568

33 Zhao D, Peng D, Li L, Zhang Q, Zhang C. Inhibition of G1P3 expression found in the differential display study on respiratory syncytial virus infection. Virol J 2008;5:114

34 Heilman CA. Respiratory syncytial and parainfluenza viruses. J Infect Dis 1990;161(03):402–406

35 Erdman DD, Weinberg GA, Edwards KM, et al. GeneScan reverse transcription-PCR assay for detection of six common respiratory viruses in young children hospitalized with acute respiratory illness. J Clin Microbiol 2003;41(09):4298–4303

36 Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. Br Med J (Clin Res Ed) 1982;284(6330):1665–1669

37 Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. Expert Rev Anti Infect Ther 2011;9(09):731–745

38 Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol 2005; 16(05):386–392

39 Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003;22(2, Suppl):S21–S32

40 Simoes EA, Carbonell-Estrany X. Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. Pediatr Infect Dis J 2003;22(2, Suppl)S13–S18, discussion S18–S20

41 Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. Trop Med Int Health 1998;3(04):268–280

42 Nagayama Y, Tsubaki T, Nakayama S, et al. Gender analysis in acute bronchiolitis due to respiratory syncytial virus. Pediatr Allergy Immunol 2006;17(01):29–36

43 Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Microbiol Rev 2000;13(03):371–384

44 Shi T, McAllister DAL, O'Brien KL, et al; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390(10098):946–958

45 Borse RH, Singleton RJ, Bruden DT, Fry AM, Hennessy TW, Meltzer MI. The economics of strategies to reduce respiratory syncytial virus hospitalizations in Alaska. J Pediatric Infect Dis Soc 2014;3(03):201–212

46 Matheson JW, Rich FJ, Cohet C, et al. Distinct patterns of evolution between respiratory syncytial virus subgroups A and B from New Zealand isolates collected over thirty-seven years. J Med Virol 2006;78(10):1354–1364

47 Law BJ, Carbonell-Estrany X, Simoes EAF. An update on RSV epidemiology: a developed country perspective. J Res Med 2002; 96:2–7

48 Sato M, Saito R, Sakai T, et al. Molecular epidemiology of respiratory syncytial virus infections among children with acute respiratory symptoms in a community over three seasons. J Clin Microbiol 2005;43(01):36–40

49 Huo X, Fang B, Liu L, et al. Clinical and epidemiologic characteristics of respiratory syncytial virus infection among children aged <5 years, Jingzhou City, China, 2011. J Infect Dis 2013;208 (03, Suppl 3):S184–S188

50 Jin Y, Zhang RF, Xie ZP, et al. Newly identified respiratory viruses associated with acute lower respiratory tract infections in children in Lanzou, China, from 2006 to 2009. Clin Microbiol Infect 2012;18(01):74–80

51 Zhang HY, Li ZM, Zhang GL, Diao TT, Cao CX, Sun HQ. Respiratory viruses in hospitalized children with acute lower respiratory tract infections in Harbin, China. Jpn J Infect Dis 2009;62(06):458–460

52 Chan DCW, Chiu WK, Ip PLS. Respiratory syncytial virus and influenza infections among children ≤3 years of age with acute respiratory infections in a regional hospital in Hong Kong. HK J Paediatr 2007;12:15–21

53 Khor CS, Sam IC, Hooi PS, Quek KF, Chan YF. Epidemiology and seasonality of respiratory viral infections in hospitalized children in Kuala Lumpur, Malaysia: a retrospective study of 27 years. BMC Pediatr 2012;12(32):32

54 Do LAH, Bryant JE, Tran AT, et al. Respiratory syncytial virus and other viral infections among children under two years old in southern Vietnam 2009–2010: clinical characteristics and disease severity. PLoS One 2016;11(08):e0160606

55 Malasao R, Okamoto M, Chaimongkol N, et al. Molecular characterization of human respiratory syncytial virus in the Philippines, 2012–2013. PLoS One 2015;10(11):e0142192

56 Lee JT, Chang LY, Wang LC, et al. Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001-2005 – seasonality, clinical characteristics, and disease burden. J Microbiol Immunol Infect 2007;40(04):293–301

57 Fry AM, Chittaganpitch M, Baggett HC, et al. The burden of hospitalized lower respiratory tract infection due to respiratory syncytial virus in rural Thailand. PLoS One 2010;5(11):e15098

58 Mathisen M, Strand TA, Sharma BN, et al. RNA viruses in community-acquired childhood pneumonia in semi-urban Nepal; a cross-sectional study. BMC Med 2009;7:35

59 Cherian T, Simoes EA, Steinhoff MC, et al. Bronchiolitis in tropical south India. Am J Dis Child 1990;144(09):1026–1030

60 Hasan K, Jolly P, Marquis G, et al. Viral etiology of pneumonia in a cohort of newborns till 24 months of age in rural Mirzapur, Bangladesh. Scand J Infect Dis 2006;38(08):690–695

61 Homaira N, Luby SP, Petri WA, et al. Incidence of respiratory virus-associated pneumonia in urban poor young children of Dhaka, Bangladesh, 2009-2011. PLoS One 2012;7(02):e32056

62 Bashir U, Alam MM, Sadia H, Zaidi SSZ, Kazi BM. Molecular characterization of circulating respiratory syncytial virus (RSV) genotypes in Gilgit Baltistan Province of Pakistan during 2011-2012 winter season. PLoS One 2013;8(09):e74018

63 Ali A, Yousafzai MT, Waris R, et al. RSV associated hospitalizations in children in Karachi, Pakistan: implications for vaccine prevention strategies. J Med Virol 2017;89(07):1151–1157

64 Muthulingam A, Noordeen F, Morel A. Viral etiology in hospitalized children with acute respiratory tract infection in the Kegalle area of Sri Lanka. J Pediatr Infect Dis 2014;9(04):167–170

65 Hon KL, Leung TF, Cheng WY, et al. Respiratory syncytial virus morbidity, premorbid factors, seasonality, and implications for prophylaxis. J Crit Care 2012;27(05):464–468

66 Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010; 375(9725):1545–1555
67 Yoshida LM, Suzuki M, Thiem VD, et al. Population based cohort study for pediatric infectious diseases research in Vietnam. Trop Med Health 2014;42(2, Suppl):47–58
68 Al-Toum R, Bdour S, Ayyash H. Epidemiology and clinical characteristics of respiratory syncytial virus infections in Jordan. J Trop Pediatr 2006;52(04):282–287
69 Mathisen M, Strand TA, Sharma BN, et al. Clinical presentation and severity of viral community-acquired pneumonia in young Nepalese children. Pediatr Infect Dis J 2010;29(01):e1–e6
70 Jayaweera JAAS, Noordeen F, Morel AJ, et al. Viral burden in acute respiratory tract infections in hospitalized children in the wet and dry zones of Sri Lanka. Int J Infect Dis 2016;45(01):463
71 Hammitt LL, Kazungu S, Morpeth SC, et al. A preliminary study of pneumonia etiology among hospitalized children in Kenya. Clin Infect Dis 2012;54(02, Suppl 2):S190–S199
72 Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008;86(05):408–416
73 Thompson WWT, Shay DK, Weintraub E, et al. Mortality associated with Influenza and RSV in the United States. JAMA 2003; 289(02):179–186
74 Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS One 2013;8(02): e54445
75 Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000; 161(05):1501–1507
76 Dowell SF, Anderson LJ, Gary HE Jr, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. J Infect Dis 1996;174(03):456–462
77 Stewart KD, Nguyen V, Nguyen S. RSV infection in the immunocompromised host. US Pharm 2013;38:8–10
78 Wu P, Dupont WD, Griffin MR, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med 2008;178(11):1123–1129
79 Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. J Infect Dis 2004; 189(02):233–238
80 Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352(17):1749–1759
81 Cane PA, Pringle CR. Evolution of subgroup A respiratory syncytial virus: evidence for progressive accumulation of amino acid changes in the attachment protein. J Virol 1995;69(05): 2918–2925
82 Heminway BR, Yu Y, Tanaka Y, et al. Analysis of respiratory syncytial virus F, G, and SH proteins in cell fusion. Virology 1994; 200(02):801–805
83 Agoti CN, Otieno JR, Munywoki PK, et al. Local evolutionary patterns of human respiratory syncytial virus derived from whole-genome sequencing. J Virol 2015;89(07):3444–3454
84 Venter M, Madhi SA, Tiemessen CT, Schoub BD. Genetic diversity and molecular epidemiology of respiratory syncytial virus over four consecutive seasons in South Africa: identification of new subgroup A and B genotypes. J Gen Virol 2001;82(Pt 9):2117–2124
85 Gaunt ER, Jansen RR, Poovorawan Y, Templeton KE, Toms GL, Simmonds P. Molecular epidemiology and evolution of human respiratory syncytial virus and human metapneumovirus. PLoS One 2011;6(03):e17427
86 Zou L, Yi L, Wu J, et al. Evolution and transmission of respiratory syncytial group a (RSV-A) viruses in Guangdong, China 2008–2015. Front Microbiol 2016;7:1263
87 Coiras MT, Aguilar JC, García ML, Casas I, Pérez-Breña P. Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. J Med Virol 2004;72(03):484–495
88 Vilcek S, Elvander M, Ballagi-Pordány A, Belák S. Development of nested PCR assays for detection of bovine respiratory syncytial virus in clinical samples. J Clin Microbiol 1994;32(09): 2225–2231
89 Hu A, Colella M, Tam JS, Rappaport R, Cheng SM. Simultaneous detection, subgrouping, and quantitation of respiratory syncytial virus A and B by real-time PCR. J Clin Microbiol 2003;41(01): 149–154
90 Osiowy C. Direct detection of respiratory syncytial virus, parainfluenza virus, and adenovirus in clinical respiratory specimens by a multiplex reverse transcription-PCR assay. J Clin Microbiol 1998;36(11):3149–3154
91 Ali SA, Gern JE, Hartert TV, et al. Real-world comparison of two molecular methods for detection of respiratory viruses. Virol J 2011;8:332
92 Rodriguez WJ, Hall CB, Welliver R, et al. Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. J Pediatr 1994;125(01):129–135
93 American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. J Pediatr 2006;118(04):1774–1793
94 Turner TL, Kopp BT, Paul G, Landgrave LC, Hayes D Jr, Thompson R. Respiratory syncytial virus: current and emerging treatment options. Clinicoecon Outcomes Res 2014;6:217–225
95 Hu J, Robinson JL. Treatment of respiratory syncytial virus with palivizumab: a systematic review. World J Pediatr 2010;6(04): 296–300
96 Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in preventing RSV hospitalization in high risk children: a real-world perspective. Int J Pediatr 2014; 2014:571609
97 American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. J Pediatr 2014;134:415–420
98 Stobart CC, Rostad CA, Ke Z, et al. A live RSV vaccine with engineered thermostability is immunogenic in cotton rats despite high attenuation. Nat Commun 2016;7(13916):13916
99 Caidi H, Harcourt JL, Tripp RA, Anderson LJ, Haynes LM. Combination therapy using monoclonal antibodies against respiratory syncytial virus (RSV) G glycoprotein protects from RSV disease in BALB/c mice. PLoS One 2012;7(12):e51485
100 Chávez-Bueno S, Mejías A, Merryman RA, Ahmad N, Jafri HS, Ramilo O. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. Pediatr Infect Dis J 2007;26(12):1089–1093