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BIOLOGY OF HUMAN RESPIRATORY SYNCYTIAL VIRUS: A REVIEW

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ABSTRACT
Acute lower respiratory tract infection is one of the major causes of mortality and morbidity in young children worldwide. Respiratory syncytial virus (RSV) is the single most important viral cause of lower respiratory tract infection during infancy and early childhood worldwide. Respiratory syncytial virus belongs to the Pneumovirinae subfamily of the Paramyxoviridae family of enveloped single stranded negative sense RNA viruses. The virus accounts for approximately 50% of all pneumonia and up to 90% of the reported cases of bronchiolitis in infancy. It is a common community–acquired respiratory pathogen without ethnic, socioeconomic, gender, age or geographic boundaries. Moreover, the epidemiological and ecological relationships between Human Respiratory syncytial virus, man and environment have aroused increasing interest in this viral, specie. The present review looks at the nature of this virus with the view to provide more information about its biology which may be useful to the present and future researchers.

Key words: Respiratory virus, Human Respiratory syncytial virus, biology, genome, epidemiology, immunity.

INTRODUCTION

Acute lower respiratory tract infection is one of the major causes of mortality and morbidity in young children world wide (Weber *et al.,* 1999; Openshaw and Tregoning, 2005). Respiratory syncytial virus (RSV) is the single most important viral cause of lower respiratory tract infection during infancy and early childhood world wide (Glezen, 1987; De Graaft *et al.,* 2005). Most children with RSV infection suffer from mild upper respiratory tract infection; however up to 40% of children infected with RSV develop serious lower respiratory tract disease requiring hospitalization (Tripp, 2004). The magnitude and intensity of infection and the host response to RSV infection determine the severity and intensity of the disease (Domachowske and Rosenberg, 1999).

Respiratory syncytial virus belongs to the Pneumovirinae subfamily of the Paramyxoviridae family of enveloped single stranded negative sense RNA viruses (Carpenter *et al.,* 2002). The RSV infection rate in young children approaches 70% in the first year of life, with peak incidence occurring between ages 2 - 4 months (Domachowske and Rosenberg, 1999).

World wide, RSV is the leading cause of infant morbidity from respiratory infections and is so highly contagious that by age two years nearly all children have been infected. Respiratory syncytial virus infection in infancy cause severe bronchiolitis and pneumonia. The virus accounts for approximately 50% of all pneumonia and up to 90% of the reported cases of bronchiolitis in infancy (Glezen, 1987). It may also predispose children to subsequent development of asthma, the most common chronic illness of childhood (Johnston, 1997; Tekkanat *et al.,* 2001). Out breaks of RSV disease are abrupt in onset and can last up to 5 months. These epidemics occur annually at regular, predictable intervals. In temperate climate where there is an annual epidemics during the winter months. In tropical climate, infection is most common during the raining season (Hall *et al.,* 1990). The virus was also reported to be the common cause of admission to the pediatric intensive care unit due to respiratory failure in infancy (Eisenhut, 2006). Nosocomial RSV infections are frequently reported and tend to be more severe, because of co morbidity (Thwaites and Piercy, 2006). The virus is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious materials come into contact with mucous membrane of the eyes, mouth, or nose and possibly through the inhalation of droplets nuclei generated by sneezing or coughing (Hall *et al*., 1980). Symptoms begin most frequently with fever, running nose, cough and sometimes wheezing (Simoes, 1999; Uzel *et al*., 2000). Recovery from RSV infection is mediated largely by the host immune system. Secretory antibodies, serum antibodies, major histocompatibility complex, class 1 restricted cytotoxic T lymphocytes and in the very young maternally derived antibodies serve as specific effectors for protection against RSV infection (Bangham *et al*., 1986; Watt *et al.,* 1986).

Virology of Respiratory Syncytial Virion

The RSV virus is a pleomorphic enveloped virus, has a single, negative-strand genome of 5 X 10^6 kilo Dalton (KD). The genome encodes 10 mRNAs each of which codes for an individual protein (McCarthy and Hall, 2003).

It is classified within the Pnuemovirineae subfamily of the paramyxoviridae family order Mononegavirales (Collins and Murphy, 2001). The virus attaches to host cells via the glycoprotein. This is followed by the fusion of the virion envelop with the cell membrane of the host by the action of the fusion glycoprotein F1 cleavage product. If the Fo precursor is not cleaved it has no fusion activity. Virion penetration does not occur and the virus particle is unable to initiate infection. Fusion by F1 occurs at the neutral PH of the extra cellular environment, allowing release of the viral nucleocapsid directly into the cell. This enables the virus to bypass internalization through endosomes (Jawetz *et al.,* 2004). After replication the virus matures by budding from the cell surface. Progeny nucleocapsids form in the cytoplasm and migrate to the cell surface. The M protein is essential for particle formation, probably serving to link the viral envelop to the nucleocapsid. During budding, most host proteins are excluded from the membrane. If appropriate host cell proteases are present, Fo proteins in the plasma membrane will be activated by cleavage. Activated fusion protein will then cause fusion of adjacent cell membranes, resulting in formation of large syncytia (Prescott *et al*., 1996; Jawetz *et al.,* 2004).

Respiratory syncytial virus grows optimally at a PH of 7.5, and inactivated at temperatures between 50-60ºC. Although temperature –sensitive, it is recoverable for hours from countertops and for more than 1 hour from rubber gloves contaminated with RSV-infected nasal secretions (McCarthy and Hall, 2003). It is readily inactivated with soap and water and disinfectants.

The Structure of Respiratory Syncytial Virus

Respiratory syncytial virus is a medium-sized (120-200nm) enveloped virus that contains a lipoprotein coat and a linear minus-sense RNA genome. The genome contains 10 separate genes, each coding for a separate protein, and the gene order has been established unambiguously as 3'-NS1-NS2-N-P-M-SH-G-F-M2-L-5'. The internal helical nucleocapsid contains the linear viral genome to which are complexed many molecules of the nucleocapsid (N) protein, fewer molecules of the phosphoprotein (P) and putative viral polymerase (L). The outer envelop is lined internally with matrix (M) protein and is studded externally with fusion (F) and attachment (G) glycoprotein projections. Another protein (M2) is also present in the viral envelop. Three other proteins, nonstructural proteins 1and 2 (NS1, NS2) and small hydrophobic (SH) are in a position that remains to be determined. The SH protein was shown to be a third integral membrane glycoprotein that is inserted into the outer membrane of infected cells (Mclntosh., 1997). The entire genome of RSV is composed of approximately 15,000 nucleotides long (Dickens *et al.,* 1984).

Structural Proteins

There are three transmembrane glycoproteins, two matrix proteins and three proteins associated with the nucleocapsid. The transmembrane proteins are the attachment glycoprotein (G), the fusion protein (F), and the small hydrophobic protein (SH). The two matrix proteins are M and M2. The three proteins associated with the nucleocapsid are N, P, and L. The fusion protein of RSV is similar to that of the other paramyxoviruses in structure and function. The F protein is a type 1 transmembrane glycoprotein with a Cleaved N-terminal signal sequence and a transmembrane anchor near the C terminus. It is cleaved into two subunits, F1 and F2 that are linked by disulfide bonds, after synthesis and modification by the addition of N-linked sugars (Collins *et al.,* 1996).

The G protein is of particular interest because variability in this protein is greater than that in the other proteins both between and within the major antigenic groups of RSV. The G protein is presumed to be the attachment protein of RSV by analogy to the other Paramyxoviruses and on the basis of experimental data (Levine *et al.,* 1987). However, it is said to lack the hemagglutinin or neuraminidase activity of the other Paramyxovirus attachment proteins. The G protein also differs in size and biochemistry from the other attachment proteins of other Paramyxoviruses (Sullender and Wertz, 1991). Antigenic dimorphism between the subgroups of RSV A and B is mainly linked to the G protein. The A2 strain isolate of RSV, a prototype of the group A viruses, has a G mRNA of 918 nucleotides. The major open reading frame encodes a 298-amino-acid type II membrane protein (Sullender and Wertz, 1991). The G proteins are important antigenically because they stimulate the production of protective immune responses. The G protein is recognized by neutralizing antibodies but does not stimulate significant cytotoxic T-lymphocyte responses (Sullender, 2000).

The nucleocapsid-associated proteins include the major nucleocapsid protein (N), the phosphoprotein (P), and the RNA polymerase (L). These proteins together, have been demonstrated to function as the RSV replicase (Grosfeld *et al.,* 1995). The M2 mRNA contains two overlapping translational open reading frames, (ORF) 1 and 2 (Collins *et al.,* 1990). The M2 open reading frame 1 has historically been considered a second matrix protein but has recently been found to colocalise with the nucloecapsid proteins N and P (Fearns *et al*., 1997). The M2 open reading frame 1 protein is a necessary component of the viral replicase, since it ensures efficient production of full-length mRNA. The protein appears to be a negative regulatory factor (Hardy and Wertz 1998).

Non-Structural Proteins

There are 2 nonstructural proteins (NS) 1 and 2. These proteins are found in negligible amounts within the virion and are thought to regulate RNA synthesis or the host's innate immunity (MacLellan *et al*., 2007).

Epidemiology

RSV has a worldwide presence with predictable, yearly epidemics. In temperate climates, RSV usually appears in the community in November or December and persists until April or May. In tropical climates infection is most common during the rainy season (Constantopoulos *et al.,* 2002; McCarthy and Hall, 2003; Jawetz *et al.,* 2004).

Respiratory syncytial virus infects approximately 60 million people and is responsible for an estimated 160,000 deaths annually worldwide (Mohapatra and Boyapelle, 2008). There are two major strains, A and B. Both strains circulate concurrently, with the A strains usually dominating. Several distinct genotypes within these strains predominate within a community. The dominant strains shift yearly, suggesting a mechanism for frequent reinfections by evasion of immunity induced by previous strains (Hall, 2001). Fluctuations in the circulating strains of RSV may contribute to the variation seen in the severity of the annual outbreaks caused by the virus (McConnochie *et al*., 1990, Opavsky *et al.,* 1995). Reinfection occurs frequently, but resulting symptoms are those of a mild upper respiratory infection. In families with an identified case of Respiratory syncytial virus infection, virus spread to siblings and adults is common. The virus causes nosocomial infections in nurseries and on pediatric hospital wards. Transmission occurs primarily via hospital staff members (Jawetz *et al.,* 2004).

Seventy percent (70%) of infants are infected by age 1 and almost all by age 2 years. Serious bronchiolitis or pneumonia is most apt to occur in infants between the ages of 6 weeks and 6 months with peak incidence at 2 months. Respiratory syncytial virus is the most common cause of viral pneumonia in children under age 5 years but may also cause pneumonia in elderly or in immunocompromised persons. RSV infection of older infants and children results in milder respiratory tract infection than in those under age 6 months (Jawetz *et al.,* 2004).

Pathogenesis

Viral transmission occurs by direct inoculation of contagious secretions from the hands or by large-particle aerosols into the eyes, nose, and rarely the mouth (Hall, 2001). High viral titers are present in respiratory tract secretions from infected young children. Inoculum size is an important determinant of successful infection in adults, and possibly in children as well (Jawetz *et al.,* 2004). The prolonged survival of RSV on skin, cloth, and other objects emphasized the importance of fomites in nosocomial spread and of hand washing in controlling infection (Hall *et al.,* 1980).

The incubation period of RSV is two to eight days. Respiratory syncytial virus replicate in the nasopharyngeal epithelium, with spread to the lower respiratory tract one to three days later. The characteristic pathological features of RSV bronchiolitis are inflammation, with edema, and increased secretion of mucus, necrosis and sloughing of the epithelium of the small airways, which obstructs flow in the small airways. The resulting clinical findings of pneumonia with interstitial infiltration, alveolar fillings, and consolidation are the hallmarks of bronchiolitis, especially in adults who die of the disease (Hall, 2001).

Clinical recovery from RSV bronchiolitis may occur in the presence of continued virus shedding from upper respiratory tract (Domachowske and Rosenberg, 1999). However, some studies have demonstrated that virus shedding stops coincident with the emergence of specific secretory immunoglobulin A (IgA) at the time of clinical recovery (Meert *et al.,* 1994). An intact immune system seems to be important in resolving an infection, as patients with impaired cell mediated immunity may become persistently, infected with Respiratory syncytial virus and shed virus for months (Jawetz *et al.,* 2004).

Immunity

Protection against and recovery from RSV infection are mediated largely by the host immune system. Secretory antibodies, serum antibodies, major histocompatibility complex, class I-restricted cytotoxic T lymphocytes (CTLs), and in the very young, maternally derived antibodies serve as specific effectors (Bangham *et al.,* 1986; Watt *et al* 1986). The importance of the host immune system in the eradication of RSV is exemplified by the observation that children with primary or acquired immunodeficiency diseases have difficulty in eradicating the virus and shed virus for many months rather than the typical interval of 1 to 3 weeks (Fishaut *et al.,* 1980; Chadwani *et al.,* 1990; Taylor *et al.,* 1990).

The F and G protein are important antigenically because they stimulate the production of protective immune responses. Responses of the F protein include humoral and cytotoxic T-lymphocyte responses (Cherie *et al.,* 1992).

Humoral immunity

Specific RSV-neutralizing antibodies are present in the sera of all full-term newborns by virtue of the transplacental transfer of maternal antibodies. The measurable antibody titres in the newborn are similar to the maternal levels and decline slowly during the first few months of life. After 7 months of age, detectable neutralizing antibody is usually the result of natural infection. Breast-fed infants have the added benefit of maternal antibodies in the form of colostrums (Domachowske and Rosenberg, 1999).

Both serum and secretory antibodies are made in response to RSV infection. Primary infection with one subgroup induces cross reactive antibodies to virus of the other subgroup. Younger infants have lower IgG and IgA secretory antibody responses to RSV than do older infants. An association has been noted between virus-specific IgE antibody and severity of disease. Viral secretory IgE antibodies have been correlated with occurrence of bronchiolitis (Jawetz *et al.,* 2004).

Cellular immunity

Cell- mediated immune response, a probably most important in recovery and viral clearance. The fact that patients with compromised cellular immunity have severe, prolonged disease indicates the importance of CD4 and CD8 T cells in controlling infection.

The exaggerated cellular response engendered by formalin-inactivated vaccine, consisting of eosinophilia and hemorrhagic necrosis that apparently arise from the response of types 1 and 2 helper T cells, has been reproduced in animals (Hall, 2001).

In direct contrast to both parainfluenza and influenza virus infections, RSV infection frequently fails to induce a detectable level of interferon in nasal secretions of infected patients. This observation supports a minor role, if any, for interferon in recovery from RSV infection (Domachowske and Rosenberg, 1999).

It is apparent that immunity is only partially effective and is often overcome under natural conditions; reinfections are common, but the severity of ensuing disease is lessened (Jawetz *et al.,* 2004).

Clinical Manifestations (Pulmonary)

RSV infection is associated with a wide spectrum of symptoms. In young children, illness frequently begins with cough, nasal congestion, and fever. The risk of developing lower respiratory tract disease with a primary infection is at least 50%. After several days of upper respiratory tract symptoms, infants may develop tachypnea, dyspnea, and intercostal retractions. Difficulty in feeding, features of otitis media and hypoxemia are common (McCarthy and Hall, 2003). The primary manifestations of lower respiratory tract disease in infants are bronchiolitis and pneumonia. These two syndromes may be difficult to distinguish and may occur simultaneously. The characteristic clinical features of bronchiolitis are wheezing, rales and rhonchi may be heard in infants. Apnea may be the presenting manifestation of RSV disease, particularly in infant born preterm (McCarthy and Hall, 2003). Symptoms include; difficulty in breathing, which may include breathing more rapidly than normal, wheezing, coughing that, is getting worse. A child may choke or vomit from intense coughing that may be dry or loose (producing mucus). Lethargy, increased tiredness, decreased interest in surrounding or loss of interest in food (Simoes, 1999).

Recurrent infections with RSV continue throughout life, although disease typically is milder and generally localized to the upper respiratory tract. Cough may be more severe and persistent, than that observed with other common cold agents, such as rhinovirus. Significant lower respiratory tract disease is uncommon, but can occur in healthy older children and adults, and infection may be followed by a prolonged period of airway hyperactivity. In the elderly, particularly those who have chronic illness, RSV may cause significant lower respiratory tract illness (McCarthy and Hall, 2003).

Extrapulmonary Manifestations of Severe RSV Infection

Extrapulmonary manifestations suggest that RSV may infect organs other than the lung. It is unlikely that systemic co-infection with bacterial pathogens is responsible for most extrapulmonary manifestations. Previous studies have shown that serious bacterial infection is present in 0.6 to 1.2% of children admitted with RSV infection (Randolph *et al*., 2004). Extrapulmonary presentations of severe RSV infection were first highlighted in a report on an epidemic affecting infants admitted to a children's hospital in Cleveland, USA (Njoku and Kliegman., 1993). The most commonly reported cases of cardiovascular manifestation of RSV were interstitial myocarditis (Eisenhut, 2006) and multifocal arterial tachycardia (Armstrong and Menahem, 1993; Donnerstein *et al.,* 1994; Playfor and Khader., 2005).

Acute neurological signs and symptoms such as central apneas, seizures, feeding/ swallowing difficulties, muscle tone abnormalities, as well as abnormalities of the cerebrospinal fluid (CSF), and electroencephalogram (EEG) abnormalities were found in some patients with RSV infection (Kho *et al.,* 2004).

Central apnea

Respiratory arrest for more then 20 seconds and/or bradycardia with accompanying cyanosis or oxygen desaturation below 90% have been found in 16 to 21% of children admitted to hospital with RSV infection. The most important risk factor associated with apnea in RSV infected patients was age below two months. Apnea on admission is associated with increased risk for recurrent apneas, and these children did have a significantly increased probability of requiring mechanical ventilation (Kneyber *et al.,* 1998).

Seizures

Seizure types found to be associated with RSV infection include both generalized tonic-clonic and partial seizures with altered consciousness and focal motor features or eye deviation (Sweetman *et al.,* 2005).

Other manifestations includes raised antidiuretic hormones; ADH (Hanna *et al*., 2003), prolactin and leptin inbalance (Tasker *et al*., 2004), association with hepatitis (Griffin *et al*., 1979), hypothermia (Njoku and Kliegman, 1993), exenthems, thrombocytopenia and conjunctivitis (Fujishima *et al*., 1995).

Diagnosis

Respiratory syncytial virus often is diagnosed accurately in young children based on the season plus a typical history and finding on physical examination. In older children and adults, however, the signs and symptoms of RSV are less characteristic and may easily be attributed to other pathogens.

A definitive diagnosis of RSV may not be necessary for children who have mild disease, laboratory confirmation however is important for hospitalized patient and those at increased risk for severe disease (McCarthy and Hall, 2003). The diagnosis can be by antigen detection by viral isolation, and other serological techniques.

Antigen detection: Direct identification of viral antigen in clinical samples is rapid and sensitive. Immunoflurescence on exfoliated cells or ELISA on nasopharyngeal secretions is commonly used. A nasal wash or nasal aspirate is a good source of virus. Large amounts of virus are present in nasal washes from young children (10^3-10^8 plaque forming units (PFU) per millitre), but much less is present in specimens from adults (<100 PFU/ml). ELISA kits are useful for rapid diagnosis (Jawetz *et al.,* 2004).

Isolation and identification of virus: Respiratory syncytial virus can be isolated from nasal secretions. It is extremely labile. Samples should be inoculated into cell cultures immediately; freezing of clinical specimens may result in complete loss of infectivity. Human heteroploid cell lines Hela and HEP-2 are the most sensitive for viral isolation. The presence of RSV can usually be recognized by development of giant cells and syncytia in inoculated cultures. It may take as long as 10 days for cytopathic effects to appear (Mclntosh, 1997).

Definitive diagnosis can be established by detecting viral antigen in infected cells using a defined antiserum and the immunofluorescence test. More rapid isolation of RSV can be achieved by spin-amplified inoculation of vials containing tissue cultures growing on cover slips. Cells can be tested 24-48 hours later by immunoflourescence. Detection of RSV is strong evidence that the virus is involved in a current illness because it is almost never found in healthy people (McCarthy and Hall, 2003; Jawetz *et al.,* 2004).

Serology: serum antibodies can be assayed in a variety of ways- Immunofluoresence, ELISA, and NT tests are all used. Measurements of serum antibody are important for epidemiologic studies but play only a small role in clinical decision making (Jawetz *et al.,* 2004).

Nucleic acid detection: polymerase chain reaction assays are useful for subtyping RSV isolates and for the analysis of genetic variation in outbreaks (Jawetz *et al.,* 2004).

Treatment

Therapy for RSV remains largely supportive. These supportive measures mainly involved the use of supplemental oxygen and mainly fluid and electrolytes balance as well as close monitoring of the patients for disease progression. In those with severe disease, drug treatment can be considered (McCarthy and Hall, 2003).

Ribavirin, a synthetic nucleoside delivered as a small particle aerosol, was approved for the treatment of RSV lower respiratory tract infection and licensed in 1985 for use in hospitalized children in the United States (Domachowske and Rosenberg, 1999). Ribavirin which is a broad spectrum antiviral agent interferes with expression of mRNA and inhibits protein synthesis (McCarthy and Hall, 2003). It is administered as aerosols via oxygen hood, tent, or mask until improvement is seen (Usually 3 to 7 days). Longer courses may be helpful in immunocompromised patients who have more severe disease and prolonged shedding of the virus. Ribavirin may be administered to a patient on a ventilator, but special care must be taken because deposition of drug in the system may cause clogging of small airways (McCarthy and Hall, 2003). Toxicity has not been observed with therapy in infants, although further studies of the use of ribavirin for treatment of RSV infections are needed. The American Academy of Pediatrics (AAP) has recommended that decision about ribavirin therapy be based on the individual clinical situation and the physician's experience.

A variety of different structural formats have been explored in the past few years. Interesting leads for future discovery and lead development include a group of biphenyl relatives (represented by CL-387626) that bind to RSV fusion (F) protein; 2-5A-antisense oligonucleotides that target the RSV genomic RNA. Rho A-derived peptides that block Rho A GTPase interaction with RSV fusion (F) protein; and several compounds of presently unknown mechanism of action, such as benzodithiins (Torrence, 2000).

Complications

Children at increased risk for severe RSV disease include infants born preterm and infants who have chronic lung disease or functionally important congenital heart disease. Children with certain neurological disorder, who are immunocompromised, or have multiple congenital anomalies (Jawetz *et at.,* 2004). Respiratory Syncytial Virus infection is associated with most frequent complications, which include:

Apnea: This is where breathing stops for about 15 to 20 seconds. This usually occurs only in babies who were born prematurely (McCarthy and Hall, 2003).

Severe bronchiolitis: This is as a result of inflammation of the small air passages (bronchioles) that usually affects children younger than 2 years.

Pneumonia: This is inflammation of the lungs; it causes difficulty in breathing and

reduces oxygen supply to the bloodstream (Selwyn, 1990; Jawetz *et al.,* 2004).

Otitis media: this could be due to RSV or a superimposed bacterial pathogen (McCarthy and Hall, 2003; Radolph *et al*., 2004).

Asthma: RSV bronchiolitis has been associated with the development of recurrent episodes of bronchiolar obstruction, specific IgE production, and establishment of asthma (Welliver *et al.,* 1981; Sigurs *et al.,* 1995; Richardson *et al.,* 2005; Hegele *et al.,* 2008; Mohapatra and Boyapalle, 2008).

RSV in Immunocompromised Patients

Immunocompromised adults and children, especially those undergoing bone marrow transplantation are at high risk of severe and often fatal RSV disease (McCarthy and Hall 2003). In severely immunocompromised children and adults, mortality rates from RSV can nearly reach 90%. Respiratory syncytial virus infections account for about one-third of respiratory infections in bone marrow transplant. Pneumonia develops in about one-half of infected immunocompromised children and adults, especially if infection occurs in the early post-transplant period. Infections in the elderly may cause symptoms similar to Influenza virus disease. Pneumonia may develop in 10-20% of those infected and mortality rates of 2-5 % (Jawetz *et al.,* 2004).

Prevention

Various strategies can be used to prevent RSV transmission in the community and the hospital. Close contact with individuals who have respiratory symptoms or fever should be avoided when possible and frequent hand washing is advised.

Patients who have suspected RSV infection should be identified on admission and placed in contact isolation. Good hand washing is critical and the most important single method of infection control. Staff should be educated about the modes of spread of RSV and that shedding of RSV typically lasts about 3 to 8 days, but may persist for weeks, particularly in immunosuppressed patients (McCarthy and Hall, 2003).

Prophylactic administration of antibody to RSV has been shown to decrease severe disease. Currently two products have been approved for use in selected children at high risk for RSV disease. The first licensed product was Respiratory syncytial virus intravenous immune globulin (RSV-IGIV) (RespiGam). Approval of this agent in 1996 followed completion of the multicenter prevent trial. The other approved agent for prophylaxis is palivizumab (Synagis), a humanized IgG-1 monoclonal antibody that binds to the F protein of RSV. It is estimated to have 50 to 100 times more activity than RSV-IGIV and is administered intramuscularly. The Unites States food and drug administration approved its use in 1998 following a placebo controlled, multicenter trial (the IMpact study) involving high–risk children similar to those studied in the prevent trial (Atkins *et al.,* 2000; Sharland and Bedford-Russell, 2001; McCarthy and Hall, 2003).

The American Academy of Pediatrics recommends that palivizumab and RSV-IGIV be considered for prophylaxis against RSV in children who are younger than 2 years of age, have chronic lung disease, and have received medical therapy for it, in the prior 6 months, as well as infants born at 32 or fewer weeks gestation. None of the two products are currently licensed for use in infants who have congenital heart disease (McCarthy and Hall, 2003).

Vaccine Development

The reasons why an RSV vaccine is not yet available arise from multiple problems with its development. The first, and most important, is the possibility that vaccination will potentiate naturally occurring RSV disease, as observed with the formalin-inactivated vaccine (Domachowske and Rosenberg, 1999). Newborns and very young infants may not mount a protective immune response because of relative immunologic immaturity or because of suppression of their immune response due to circulating maternally derived anti-RSV antibodies (Collins *et al.,* 1996; Falsey and Walsh, 1996). Another important consideration in the development of an effective RSV vaccine is the need to provide protection against multiple antigenic strains of RSV in the two major groups, A and B. A number of strategies have been implemented recently to generate safe and effective sub unit, inactivated, and live attenuated virus vaccines (Falsey and Walsh*,* 1997). Currently, the two most promising candidate vaccines to be studied in clinical trials are an RSV F subunit vaccine (for immunization of patients who have already had their primary RSV infection, such as the elderly and older RSV seropositive children with conditions predisposing them to severe RSV disease (Hildreth and Paradiso, 1993; Paradiso *et al.,* 1994; Piedra *et al.,* 1996, Falsey and Walsh, 1997, Groothius *et al.,* 1998). Cold passaged, temperature-sensitive (cpts) attenuated RSV strains (Karron *et al.,* 1997). While this cold passaged, temperature-sensitive mutant appears immunogenic, retained virulence has been observed in older children, precluding the study of this variant in infants (Domachowske and Rosenberg, 1999). Another possibility is to immunize infants with an attenuated RSV vaccine to optimize the Th1-type response and then to immunize them with a subunit vaccine to boost both anti-F and anti-G neutralizing antibody production (Domachowske and Rosenberg, 1999).

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