Clinical and Epidemiologic Features of Respiratory Syncytial Virus

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Abstract Since its discovery in 1955, respiratory syncytial virus (RSV) has consistently been noted to be the single most important cause of lower respiratory tract illness in infants <1 year of age. RSV also causes repeat infections and significant disease throughout life. In addition to the young child, persons with compromised immune, pulmonary or cardiac systems, and the elderly have significant risk from infection. Though RSV causes the full spectrum of acute respiratory illnesses, it is most notably associated with signs and symptoms of increased airway resistance manifested as wheezing and, in the young child, diagnosed as bronchiolitis. In temperate climates, RSV occurs as yearly outbreaks usually between late fall and early spring lasting 3–4 months in a community. The timing of outbreaks varies between years and in the same year between regions and even between nearby communities. RSV can be a serious nosocomial pathogen in high risk individuals but nosocomial transmission that can often be prevented with meticulous attention to good infection control practices. High risk groups include the premature infants and persons of any age with compromised cardiac, pulmonary, or immune systems. Risk factors for infection include increased number of children in the household and day care center attendance. There are reasonable

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estimates of the sizable burden of RSV disease in infants and young children and the elderly but less data on disease in older children, the role of RSV in later reactive airway disease (see chapter by M.T. Lotz et al., this volume), and RSV-associated mortality in developing countries. The available data on burden of disease suggests there are at least four potential target populations for a vaccine, the young infant, young children >4–6 months of age, pregnant women, and the elderly. A link between infection in the young infant and later reactive airway disease and mortality in developing countries is needed. Each target population has different vaccine safety and efficacy concerns and may warrant a different type of vaccine.

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1 Introduction

Over a half century ago, Morris et al. (1956) reported an outbreak of colds and coryza among a colony of chimpanzees and the recovery of a new agent, the chimpanzee coryza agent (CCA). Their description of its clinical import and transmission is prescient of the epidemiologic and clinical mein of CCA in humans, now recognized as respiratory syncytial virus (RSV). In chimpanzees, CCA could be transmitted by inoculating respiratory secretions into the nose, it had a high attack rate, and it spread efficiently. The illness, URI symptoms and cough, became evident $\sim$3 days after inoculation and lasted up to 2 weeks. Subsequent studies over the following decades found similar features in human RSV infections globally and have demonstrated the substantial healthcare burden RSV imposes in developed and developing countries. RSV causes repeat infections throughout life but severe disease is most notable in the very young. In this chapter, we summarize our understanding of the clinical and epidemiologic features of RSV disease with a focus on the relevance of these features to developing vaccines.

2 Clinical Features

Primary RSV Infection often occurs during the first encounter with RSV, which is usually in infancy, and essentially all become infected by 2 years of age (Glezen et al. 1986). The singular clinical features of RSV primary infection are that most children are symptomatic, lower respiratory tract involvement is frequent, wheezing is prominent, and the very young, those in the first 3 months of life, are most severely affected (Hall 2012; Kim et al. 1973; Ogra 2004).

Typically, RSV infection starts with several days of mild upper respiratory tract signs, cough, and low grade fever. A worsening cough is usually heralded by lower respiratory tract involvement, and the infant becomes tachypneic and may have progressively more labored breathing, with dyspnea and retractions of the chest wall (Fig. 1). The most common auscultatory signs are crackles and wheezes, but they are often variable over minutes to hours. Radiologic findings most frequently show hyperinflation and peribronchial thickening (Wright and Piedimonte 2011). Scattered interstitial infiltrates may be present, but more characteristic are areas of atelectasis, particularly in the right middle and upper lobes. The physical examination and radiographic findings commonly do not reflect the degree of illness, e.g., severely ill children may have little or no fever and minimal auscultatory findings.

The acute illness usually lasts about 5–10 days, but the cough may be prolonged for several weeks. The duration of hospitalization for 918 infants and children under 5 years of age with laboratory-confirmed RSV infection was a median of 2 days and no children died (Hall et al. 2009). The most frequent discharge diagnosis among RSV positive hospitalized infants <1 year of age was

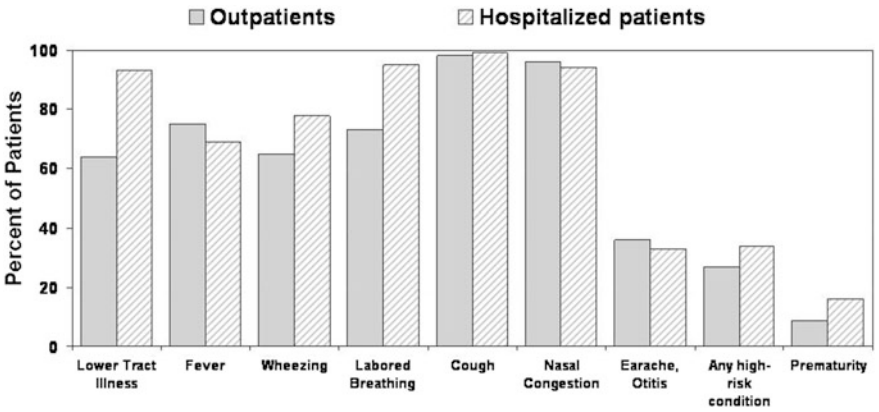

Fig. 1 The clinical characteristics of children less than 5 years of age with respiratory syncytial virus (RSV) infection who were outpatients compared to those who were hospitalized. RSV infection was laboratory confirmed during population-based surveillance of acute respiratory illnesses conducted in counties surrounding Nashville, TN, Rochester, NY, and Cincinnati, OH during 2000–2004. (Data form Hall et al. (2009))

bronchiolitis (85 %) but was asthma (60 %) and pneumonia (51 %) among older children 2–5 years of age. In this same study, RSV positive children seen in a clinician's office or the emergency department were most commonly diagnosed with upper respiratory tract infections (32 %), bronchiolitis (20 %), asthma (13 %), and pneumonia (8 %).

Apnea may develop in 1.2–23.8 % of infants and may be the initial manifestation before other respiratory signs are present (Ralston and Hill 2009). The apnea is generally self-limited, is most common in premature infants, and does not recur with subsequent respiratory infections.

In developed countries, simultaneous or secondary bacterial infection, other than otitis media, is uncommon with RSV infection (McIntosh 1991; Hall et al. 1988; Ralston et al. 2011). Urinary tract infections are the most frequent concurrent infections, identified in about 3 % of infants, and may be coincidental because the age of their initial occurrence is similar to that of RSV (Ralston et al. 2011). In developing countries, secondary bacterial infection or co-infection may be a more substantial contributor to RSV disease (Madhi and Klugman 2004).

Recurrent wheezing and long-term pulmonary sequelae have been reported in up to 30–50 % of infants hospitalized with RSV lower respiratory infection (Sigurs et al. 2010; Sly et al. 2010; Stein and Martinez 2010). However, it is unclear if RSV infection causes the predisposition to recurrent wheezing or a predisposition to recurrent wheezing increases the risk of RSV hospitalization (Stensballe et al. 2009).

RSV Infections among Older Children and Adults are frequent and occur multiple times throughout life independent of antigenic changes in the virus (Hall et al. 1991). Most recurrent infections are symptomatic upper respiratory tract illnesses that tend to be more severe and prolonged than the average cold (Falsey 2007; Hall et al. 1978, 2001). Low grade fever and upper respiratory tract complications, such as sinusitis and otitis media, are common. As many as one-fourth of RSV-infected, healthy adults will have lower respiratory tract signs such as wheezing and cough. Compared to influenza, RSV infection usually has a less acute onset and less fever and systemic symptoms.

The importance of RSV infections among older adults has been increasingly appreciated (Walsh et al. 2007; Walsh 2011; Hall et al. 1976; Falsey et al. 2005) The clinical presentation of RSV in elderly adults is not distinctive and more severe illness is often diagnosed as exacerbation of comorbid conditions, such as chronic obstructive pulmonary disease and congestive heart failure.

3 Transmission

Clinical observations of the spread of RSV within families, daycare, and other groups of children have noted that the transmission of RSV requires close contact with infected individuals or with their secretions (Hall 2007 and Lindsley et al. 2010). These observations and volunteer studies indicate that RSV is primarily

spread by two mechanisms: (1) large particle droplet aerosols (10–100 μm) which are propelled short distances (≤0.9 m) by sneezing, coughing, and even quiet breathing; and (2) by infectious secretions contaminating environmental surfaces followed by self-inoculation (Lindsley et al. 2010; Hall and Douglas 1981; Hall et al. 1981). RSV in the nasal secretions of infants remains infectious on countertops for about 6 h and on cloth and paper tissue for about 30 min (Hall et al. 1980). Survival is also augmented when the humidity is low (≤30 %) as is usual during the winter respiratory season (Miller and Artenstein 1967 and Siegel et al. 2007). The likely portals of inoculation are the nose, eyes, and upper respiratory tract. Although detected in air samples in a fashion suggestive of having spread long distances by small particle aerosols (Lindsley et al. 2010), epidemiologic studies suggest this mode of transmission is uncommon.

Nosocomial spread of RSV is problematic in high risk populations such as pediatric wards and in patients with compromised immune, pulmonary, or cardiac systems (Bont and Nosocomial 2009; Englund et al. 1991; Hall 2000; El Saleeby et al. 2008). Risk of nosocomial RSV primary occurs during community outbreaks but periodic outbreaks can occur outside of the RSV season.

Recommendations for the control of RSV are primarily based on interrupting the assumed major modes of transmission by emphasizing the avoidance of close contact with infected individuals and preventing direct or indirect contact with infectious secretions. However, the ubiquity of infection during the RSV season among all ages and the fact that ill visitors and staff can contribute to nosocomial spread complicates control efforts (see chapter by H.Y. Chu and J.A. Englund, this volume). The U.S. Centers for Disease Control and Prevention (CDC) advises contact precautions in addition to standard precautions (Siegel et al. 2007). Integral to these recommendations is consistent and assiduous hand hygiene, which emphasizes the importance of fomite transmission and the pivotal role that personnel play in nosocomial spread of RSV.

4 Temporal and Geographic Patterns of Community Outbreaks

In temperate climates, RSV regularly causes community outbreaks in fall, winter, and spring months, i.e., November to April in many Northern hemisphere locations and March to October in many Southern hemisphere locations. Within this regularity, however, is substantial variability in the timing and duration of outbreaks. For example, in the USA, the timing of outbreaks for the same region or community between years and between different communities for the same year can vary substantially. Over a 10-year period, U.S. surveillance showed the onset of RSV season occurs between early November and late January in most communities. South census region tends to have earlier onset and the Midwest census region later onset of the RSV seasons (Mullins et al. 2003). Within regions and

between communities there is additional variation. For example, RSV outbreaks in Florida occur as early as July and August in the Miami area and October or November in northern Florida (Light et al. 2008). Even communities within a few miles of each other can have substantially different timing of the onset of RSV outbreaks, e.g., in two communities 25 miles apart the onsets were >4 week different 20 % of the time (Mullins et al. 2003). The duration of RSV outbreaks is usually 12–20 weeks but can be substantially longer, especially in some southern regions. Surveillance studies from other countries have identified other patterns of RSV outbreaks such as alternating years with early and late onset of seasonal outbreaks. Seasonal patterns of community outbreaks in tropical regions are less consistent. In tropical regions, more distant from the equator, RSV outbreaks tend to occur in cool dry or cool wet seasons while in regions closer to the equator RSV tends to be detected throughout the year but with periods of increased activity (Stensballe et al. 2003). In other tropical regions with distinct yearly outbreaks, the timing of these outbreaks can vary more year to year than in temperate climates. Thus, local data is needed to most accurately predict timing of RSV outbreaks in a given community.

Understanding the temporal and geographic patterns of RSV outbreaks has been important for timing of RSV immune prophylaxis, implementing RSV infection control strategies, and estimating the burden of RSV disease. In temperate climates, the regularity of RSV seasonal outbreaks makes it possible to define the months during which RSV transmission is likely to occur and focus RSV immune prophylaxis (From the American Academy of Pediatrics 2009) (see chapter by H.Y. Chu and J.A. Englund, this volume). However, the variability of the time of RSV circulation that occurs between years and between communities makes such predictions imprecise even with local data (Panozzo et al. 2010).

5 Risk Factors for Infection and Disease

Age and sex are important risk factors for serious RSV disease with the very young and the elderly being the two highest risk groups for serious complications from infection (Sommer et al. 2011 and Langley and Anderson 2011). A review of recent studies of RSV hospitalization rates (Simoes 2003) revealed that approximately 10–28 % of infants hospitalized with RSV are aged below 6 weeks, 49–70 % below 6 months, and 66–100 % below 1 year. Consequently, young age, e.g., <6 months of age, at the onset of RSV season increases the risk of RSV hospitalization (Liese et al. 2003; Carbonell-Estrany et al. 2000; Figueras-Aloy et al. 2008; Law et al. 2004). Male sex has consistently been a risk factor for severe RSV LRTI and analysis of representative studies over the last 30 years found the risk ratio of boys to girls being 1.425:1 (Simoes 2003).

Much of the disease in elderly persons can be attributed to underlying conditions. In a comprehensive 4-year study of RSV in adults (Falsey et al. 2005), 608 healthy adults and 540 high risk adults were followed for one or more RSV

seasons. In addition, 1388 adults 65 years or older or with physician diagnosed congestive heart failure or chronic lung disease hospitalized for an acute respiratory illness were studied. Among those followed prospectively, none of the 46 RSV-infected healthy elderly were hospitalized with their RSV infection while 9 (16 %) RSV-infected high risk adults were hospitalized. Among adults hospitalized with RSV, 80 % had an underlying cardiopulmonary condition. Of note, for many of the adults hospitalized with an RSV infection, the discharge diagnosis was exacerbation of underlying heart or lung disease. In this study, RSV was detected in 11 % of adults hospitalized with the diagnosis of pneumonia, 11 % with the diagnosis of chronic obstructive lung disease, 5 % with the diagnosis of congestive heart failure, and 7 % with the diagnosis of asthma. Over the four study years, 3–10 % of the prospectively followed adults became infected with RSV.

Underlying conditions such as prematurity in the infant and young child has been associated with a risk of hospitalization of 4–14 % depending on the study and gestational age at birth (Sommer et al. 2011 and Langley and Anderson 2011). Otherwise healthy infants <1 year of age have hospitalization rates of 1–3 % (Langley and Anderson 2011). Infants and children with chronic lung disease and prematurity are reported to have a 10–25 % risk of being hospitalized with RSV. Other chronic lung conditions such as cystic fibrosis have been associated with more severe illness with RSV infection (Garcia et al. 2007). Hospitalization rates among infants and children with Down syndrome have been reported as high as 7–11 % depending on presence of associated conditions such as congenital heart disease (Zachariah et al. 2012). The risk of hospitalization among children with congenital heart disease has been reported to be as high as 36 % but more recent estimates suggest lower rates of hospitalization. These lower recent estimates probably reflect better management of the patient's illness. At risk children also have more severe illness when hospitalized as indicated by longer hospital stays, more frequent admissions to the intensive care unit, and more frequent need for mechanical ventilation. Although several risk factors have been associated with a higher frequency of severe RSV-mediated disease, more than 50 % of hospitalizations caused by RSV infections are in infants and children with no known risk factors (Boyce et al. 2000).

RSV infection in immune compromised patients initially can be similar to infection in otherwise healthy persons but they can have a high rate of serious complications and death. Recipients of hematopoetic stem cell transplants (HSCT) have had especially high rates of severe disease and death from RSV infection with those receiving allogenic HSCT's having the greatest risk. The greatest risk is the post HSCT period before engraftment. Delay in engraftment and graft versus host disease also is associated with an increased risk of serious RSV disease. Up to 50 % of RSV infections in HSCT recipients progress to the lower respiratory tract and between 6 and 80 % of lower respiratory tract infections are reported to result in death (Ison 2009 and Shah and Chemaly 2011).

Recipients of other transplanted organs or immune suppressive therapy for cancer or other conditions with moderate levels of immune suppression may also have an increased risk of serious RSV disease, but this risk has not been well

studied (Weigt et al. 2011). Severe immune suppression of any origin, however, likely is associated with a substantially increased risk of complications with RSV infection. Lung transplant recipients have been reported to have a high risk of fatal outcome with RSV infection, up to 10–15 %, as well as risk of new onset and progression of bronchiolitis obliterans syndrome [BOS] and the associated irreversible decline in lung function (Zamora et al. 2011 and Liu et al. 2010). HIV-infection can result in prolonged RSV shedding and may predispose to more severe RSV infection. A large prospective study in South Africa found nearly an eightfold increase in RSV hospitalization in HIV-infected children compared to those without HIV infection (Madhi et al. 2006).

Detection of RSV infection is one key to preventing and treating disease in high risk patients. In general, antigen detection assays and viral isolation are much less sensitive than molecular techniques but adequate for detecting infection in young children. In adults a sensitive assay, such as real time PCR, is necessary to reliably detect RSV and other viral respiratory infections (Falsey et al. 2002). Attention to good infection control practices inside and outside the health care setting can decrease the risk of infection (Danziger-Isakov et al. 2012) (see section on RSV Transmission).

Living at an altitude higher than 2500 m is associated with an increased risk of RSV hospitalization (relative risk [RR]: 1.30; $P < 0.018$ compared to living at moderate altitudes) and 1–4-year-old children exhibit an 80 % increase in their hospitalization rates (RR: 1.80; $P < 0.001$) (Choudhuri et al. 2006). Altitude could contribute to disease severity by lowering oxygen saturation, impairing respiratory airway ciliary activity, and causing hypoxia-related pulmonary vasoconstriction.

Malnutrition and small for gestational age have most often been studied as RSV risk factors in developing countries. A Kenyan cohort study found children with stunting (height for age z-scores <-2) had a higher rate of RSV ALRI (RR 1.73 [95 %CI 1.08–2.76]) (Okiro et al. 2008). A study from Philippines found that infants who were underweight (weight for age z-scores <-2) at 6 weeks of age had a significantly increased rate of subsequent RSV ALRI hospitalisation (RR 1.60 [95 %CI 1.07–2.41]) and were more likely to be hypoxemic than those who were not (30 % vs. 15 %, $p = 0.03$) (Paynter et al. 2013). Studies focusing on malnutrition in developing countries have concluded that malnutrition is less important to the severity of RSV than to bacterial infections and some studies suggested malnourished children may have less severe disease than well-nourished children (Simoes 2003). Intrauterine growth restriction was found to be an independent risk factor for RSV hospitalization in the Canadian PICNIC- Study (Law et al. 2004).

Day care attendance/older siblings in school or day-care and crowding are significant risk factors for LRTI. Liese et al. (2003) from the Munich RSV Study Group found that the presence of siblings in day-care attendance increased the risk factor for RSV rehospitalisation in preterm infants, while the Canadian PICNIC study (Law et al. 2004) showed that day-care-attendance of children was the single greatest risk factor for RSV hospitalization. Many studies demonstrated a significant effect of increased numbers of persons sharing a bedroom on RSV LRTI

(Simoes 2003). This effect was increased in families with low maternal education and even more in families with low maternal education who had not breast-fed their babies. School- and preschool-aged siblings impart an increased for the young infant to acquire RSV infection. In the Canadian PICNIC study (Law et al. 2004) the presence of preschool-aged siblings was significantly and independently associated with an increased risk for RSV related hospitalization, and a weaker association was found with the presence of school-aged siblings. Crowding, defined as five or more people living in one household, was also demonstrated to be a significant risk factor for RSV related hospitalization. The Spanish FLIP study (Carbonell-Estrany et al. 2000) revealed that only school-aged siblings and the presence of more than four additional residents and visitors at home were risk factors significantly associated with RSV related hospitalization. In the FLIP-2 study (Figueras-Aloy et al. 2008), the effect of school- aged siblings was confirmed but not crowding by use of the same definition. The Munich RSV Study Group (Liese et al. 2003) found that siblings at day care attendance significantly augmented the risk for RSV related hospitalization.

Multiple births carry an increased risk of RSV hospitalization. A study of twins and triplets in Colorado found a significantly higher risk of severe RSV LRTI and hospitalizations compared to matched singletons (Simoes et al. 1993). This finding was confirmed by a study on hospitalization rates in preterm infants aged 29–36 weeks by Resch et al. in (2005) that revealed multiple births being a risk factor for RSV related hospitalization (odds ratio 5.5, CI 95 % 1.439–21.028).

Other factors of uncertain association with disease have sometimes been linked to RSV disease. Lower socioeconomic status and parental education have been reported to be risk factors for RSV infection in some studies (Glezen et al. 1981 and Jansson et al. 2002) but not in other studies (Figueras-Aloy et al. 2008; Anderson et al. 1988; McConnochie and Roghmann 1960). In combination with other risk factors, maternal education was positively correlated with RSV related hospitalization in the Tucson study (Holberg et al. 1991). Lack of breast feeding was not found to be an independent risk factor for RSV disease or hospitalization, in epidemiologic studies of normal infants after accounting for other risk factors (Law et al. 2004 and Resch et al. 2005). In Denmark, the largest case control study of RSV hospitalization, that included all known risk factors in the model, did not include breastfeeding in any of the models of protection against RSV hospitalization (Stensballe et al. 2006). However, some studies, in more restricted populations (Carbonell-Estrany et al. 2000 and Bulkow et al. 2002) or older studies (Holberg et al. 1991) did find that the absence of breast-feeding in combination with other risk factors like crowding, passive smoke exposure or low socioeconomic status significantly increased the risk for development of RSV LRTI.

Maternal smoking and indoor smoke exposure contribute to lower respiratory tract infection (LRTI) in infants and young children (Simoes 2007), but it is not clear that it specifically contributes to risk of RSV LRTI (Carroll et al. 2007). An early case control study from the US showed an increased risk of bronchiolitis in families with $\geq$1 smoker (McConnochie and Roghmann 1960) but several other prospective case–control studies showed a significant effect in univariate analysis

($P = 0.018$ and 0.0004, respectively) but not in multivariate analysis (Bulkow et al. 2002; Sigurs et al. 1995; Juntti et al. 2003). A large cohort study in Arizona showed no significant effect of environmental tobacco smoke exposure in a multivariate analysis (Holberg et al. 1991) while a more recent large nested case–control study from the Danish birth cohort (2564 infants and children hospitalized with RSV and 12816 age-matched controls) (Stensballe et al. 2006), found an association between tobacco smoke exposure and an increased risk of hospitalization with RSV (odds ratio: 1.35; 95 % confidence interval: 1.20–1.52). A recent study implicated maternal smoking during pregnancy in ICU admission in infants and children with bronchiolitis (Mansbach et al. 2012). Among premature infants, several studies have found an association between maternal smoke exposure and RSV disease (Liese et al. 2003; Carbonell-Estrany et al. 2000; Figueras-Aloy et al. 2008; Law et al. 2004; Carbonell-Estrany and Quero 2001) but in only two was smoke exposure found to be an independent risk for RSV hospitalizations (Carbonell-Estrany et al. 2000 and Law et al. 2004).

A family history of atopy or asthma In the Canadian PICNIC—study (Law et al. 2004) a history of eczema in a first degree family member was found to be an independent protective factor for RSV hospitalization. However, no association was found for family history wheezing or any other allergic disorder. Data from the Spanish FLIP-2- study (Figueras-Aloy et al. 2008) confirmed these findings showing that a family history of wheezing did not reach statistical significance. In the previous FLIP—study, (Carbonell-Estrany et al. 2000) however, a history of wheezing in the family was found to be of statistical significance, whereas the interaction between a history of asthma or eczema in the family did not reach statistical significance in the multivariate logistic regression analysis. Finally the large Danish study established the role of an atopic disposition for hospitalization of infants with RSV bronchiolitis: the adjusted relative risk of RSV hospitalization in the offspring was 1.11 for maternal atopic dermatitis, 1.72 for maternal asthma, and 1.23 for paternal asthma (Stensballe et al. 2006).

6 Burden of RSV Disease: Industrialized Countries

Young Infants and Children are at higher risk for severe complications and hospitalization with RSV infection. RSV also accounts for significant outpatient disease and disease in older children and adults. Estimates from the U.S. National Hospital Discharge Survey (NHDS) from 1980 to 1996 indicated bronchiolitis was the leading cause of all hospitalizations for infants, and that RSV was the most frequent cause of bronchiolitis and all lower respiratory tract disease among young children (Shay et al. 1999). An estimated 74,000–1,26,000 hospitalizations for infants in the USA resulted from RSV each year between 1994 and 1996, and the number of RSV hospitalizations appeared to be increasing in both the USA and Canada, especially among those less than 6 months of age (Shay et al. 1999 and Langley et al. 2003). The annual RSV hospitalization rates estimated from national

discharge and insurance databases generally have been 25–40 per 1,000 for infants and 6–10 times lower in the second year of life (Boyce et al. 2000; Zhou et al. 2012; Holman et al. 2004; Leader and Kohlhase 2003). More recent estimates for 1997–2006 showed the RSV-coded hospitalization rates were 26 per 1,000 infants and 1.8 per 1,000 children 1–5 years old and caused an estimated 24 % of all hospitalizations among children under 5 years of age (Stockman et al. 2012).

Prospective studies with population-based surveillance have provided more defined rates of RSV hospitalizations among young children (Hall et al. 2009 and Iwane et al. 2004). A 4-year study conducted by the CDC prospectively examined laboratory-confirmed RSV infections among children <5 years of age in counties in three states (Hall et al. 2009). Among over 5,000 enrolled children, 18 % had RSV infections. RSV was associated with 20 % of hospitalizations for acute respiratory illnesses during November–April, 18 % of emergency department visits, and 15 % of office practice visits. The annual rates of hospitalization were 3 per 1,000 for children under 5 years of age and 17 per 1,000 infants, among those under 6 months of age. In comparison to the hospitalization rates for influenza or parainfluenza viruses in this same population, rates for RSV were 3 times higher among children under 5 years of age and 6–8 times greater among infants. Similar rates of RSV-associated hospitalizations have been reported from other industrialized countries with rates reported of 9–28/1,000 children for the first year of life and 3–6/1,000 for children <5 years of age (Fjaerli et al. 2004; Forster et al. 2004; Nicholson et al. 2006; van Gageldonk-Lafeber et al. 2005; Eriksson et al. 2002).

Outpatient Disease with RSV infection confers appreciable clinical and economic burden, but it is less well estimated or appreciated. Information on the RSV burden from outpatients is limited and underappreciated. Few studies have defined and characterized the national healthcare impact from confirmed RSV illnesses among ambulatory patients, especially among those cared for in pediatric offices. In emergency departments in the USA, the average yearly rate of bronchiolitis has been estimated during 1992–2000 as 26 per 1,000 children under 2 years of age, and 64 % of ED visits for bronchiolitis were RSV positive (Mansbach et al. 2008) Among children under 8 years of age, the rate of emergency department visits for RSV during the winter has been estimated as 21.5 per 1,000 children (Bourgeois et al. 2009). The prospective, population-based CDC studies showed annual rates, 28 per 1,000 children under 5 years of age, and 55 per 1,000 under 6 months (Hall et al. 2009).

Visits for RSV illness among pediatric practices are notably greater. In the population-based study of German outpatients, the annual rate of RSV infection was 77 per 1,000 children under 3 years of age (Forster et al. 2004). In the USA, population-based surveillance showed rates of RSV visits to pediatric offices were 80 per 1,000 children less than 5 years old and 132 per 1,000 children under 6 months of age.(Hall et al. 2009) Extrapolating these results to the entire U.S. population suggests that among children <5 years of age, RSV results in 1 of 334 hospitalizations, 1 of 38 emergency department visits, and 1 of 13 pediatric office visits each year.

Older Children and Adults also suffer significant RSV associated disease but the impact on healthcare resources is least well recognized among older children and

healthy adults. RSV infection is frequent in adults in families with young children, as high as 40 %, but usually undiagnosed (Hall et al. 1976). In a prospective virus surveillance study of healthy adults, the 211 RSV infected adults had substantial disease with infection. 40 % of infected adults missed work and the average duration of the RSV illness, 10 days, was twice that of acute respiratory infections from other viruses. Among military recruits, RSV is also a major cause of acute respiratory illness and causes ward confinement at rates similar to that of influenza (O'Shea et al. 2005). The morbidity and mortality associated with RSV in adults is greatest in those with comorbidities. In a 4-year study of 608 health community dwelling adults ≥65 years of age, 540 adults with cardiopulmonary disease, and 1,388 adults hospitalized with an acute respiratory illness, 3–13 % of the various cohorts were infected each year (Falsey et al. 2005). Among the prospective healthy cohort, 17 % saw their clinician during an RSV infection and none was hospitalized. In contrast, among the high-risk group, 29 % had office visits, 9 % visited the emergency department, and 16 % required hospitalization. In a recent study, it was estimated that yearly rates of RSV hospitalization among persons 50–64 years old was 0.82/1,000 and 2.5/1,000 persons ≥65 years of age or about 40,000 and 1,25,000 hospitalizations/year respectively in the USA (Widmer et al. 2012).

Mortality associated with RSV infection is relatively rare among young children in developed countries. Less than 500 fatal cases are estimated to occur in the USA per year (Leader and Kohlhase 2003; Shay et al. 2001; Thompson et al. 2003). Among older children and adults under 50 years of age mortality is generally the lowest. In the Netherlands, excess mortality during the winter related to RSV was not observed among those 1–18 years of age, was slight (0.3 per 1,00,000) among 18–49 year olds, and markedly increased among those 50–64 years (5.4) and those ≥65 years of age (98.7) (Jansen et al. 2007).

Economic burden of RSV disease in the USA and in other developed countries is appreciable. The greatest proportions of these costs are engendered by RSV illness among infants and the elderly. In the USA, the total annual RSV costs for infants have been estimated during 1997–2000 as $202 million for emergency department visits and $2.6 billion for hospitalizations (Leader and Kohlhase 2003). In comparison, estimates of the cost of RSV-associated disease in Australia were substantially lower, i.e., annual direct healthcare cost in 2005 of $24–$50 million for children <5 years of age and $20–$40 million for infants (Ranmuthugala et al. 2011). Among the elderly in the USA, the annual direct costs of RSV hospitalizations was estimated in 1995 as $150–$680 million, and more recently as exceeding $1 billion (Falsey et al. 2005 and Han et al. 1999).

7 Burden of RSV Disease: Developing Countries

Two recent estimates of the burden of RSV disease have been made, one estimating the global incidence of and mortality from episodes of acute lower respiratory infection due to RSV in children younger than 5 years in 2005 (Nair

et al. 2010) and a more recent estimate of the Global Burden of Diseases (GBD) 2010, that included estimates of RSV specific mortality for all age groups (Lozano et al. 1990). The first estimate by Nair et al. utilized a systematic review of data published between January, 1995, and June, 2009, and ten unpublished population-based studies, utilizing the CHERG methodology, estimated that in 2005, 33·8 (95 % CI 19·3–46·2) million new episodes of RSV-associated ALRI occurred worldwide in children younger than 5 years. Of these about 10 % or 3·4 (2·8–4·3) million episodes required hospital admission. It was estimated that 66,000–1,99,000 children younger than 5 years died from RSV-associated ALRI in 2005, with 99 % of these deaths occurring in developing countries. The second estimate, by Lozano et al. (1990), is part of a GBD study of 291 causes of death. This cause of death analysis has been performed at the country level for 187 countries with models available from 1980 to 2010. The estimates for RSV used systematic reviews of published data and metanalysis using GBD Bayesian meta-regression methods. These generated region-age-sex specific estimates that were then applied to estimates of lower respiratory tract infections (the so called Aetiology Modeling). Using these methods, it has been estimated that RSV causes 234,000 deaths in children <5 years of age. Since the majority of acute respiratory deaths globally occur in the community without etiologic studies, it is difficult to validate these estimates. Better data on RSV mortality in the community in developing countries is needed.

8 Comment

The clinical and epidemiologic features of RSV disease foretell both difficulties and promise for developing an RSV vaccine. For example, repeat infections and serious disease throughout life suggest that inducing a protective immune response will be difficult. On the other hand, high titers of neutralizing antibodies correlate with protection and anti-F protein neutralizing antibody (palivizumab) prophylaxis protects the high risk infant and young child from serious disease. The substantial burden of disease throughout life suggests that there are at least four target populations that should be considered for vaccine development, the young infant to prevent the maximum amount of disease in children; the child over 4–6 months of age who is better able to respond to a vaccine but still suffers sufficient disease to warrant vaccination (especially in developing countries); pregnant women to offer protection to her infant during the period of highest risk—the first few months of life; and the elderly to protect them from serious complications of infection. Since each population has different safety and efficacy challenges, each may require a different approach to vaccination. Matching a candidate vaccine to the most appropriate target population is important to improve its chance of success. Understanding the epidemiology of RSV is also important to choosing a study population that is suited to efficient evaluation of candidate vaccines.

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