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Variability of Respiratory Syncytial Virus Seasonality and Mortality

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1. Introduction

The importance of RSV is well recognized, especially in the first few months of life. It is the most prevalent cause of lower respiratory tract infection during infancy causing both bronchiolitis and pneumonia. The spectrum of RSV illness varies from a mild upper respiratory infection that is clinically similar to a cold, all the way to respiratory failure and death from a LRTI. RSV has been demonstrated to cause dual infection both with another virus as well as not uncommonly being associated with a bacterial infection.

Our appreciation of the variety of patterns of seasonality has improved in the last 10 to 15 years because it is more feasible to confirm the presence of RSV than it was 25 years ago. Despite this, there are still many issues because most studies, particularly outside the USA are with small numbers so that assumptions are made when the data is extrapolated to a larger area. As has been demonstrated with the seasonality in Southeast Florida (see below) this may result in misleading conclusions.

Seasonality in the majority of areas in the USA is predictable and follows a similar pattern that is repeated fairly consistently and also is similar in temperate areas around the world. The RSV season in these areas starts in the fall (autumn) and tends to last 4-5 months into the winter. This pattern is evident in both Northern and Southern hemispheres. Various factors impact the seasonality of RSV in other communities and geographic and climactic differences likely are the reason for some of these differences.

Early onset LRTI caused by RSV has also been implicated in the development of disorders of wheezing in children including allergic asthma.

Morbidity and mortality as a result of RSV is a complicated subject because of a multiplicity of issues. This is especially so in the developing countries as well as the impact on the population over 65 years of age.

2. Impact of RSV

At one year of age approximately 69% of infants will demonstrate serologic evidence of RSV infection and by 2 years almost all infants will have been infected [1], of whom 50% will have been infected twice [2]. Repeat infections are common throughout life as there are multiple serologic forms and immunity is short-lived. Subsequent infections tend to be milder [1].

During the first year of life approximately 22% of infants are diagnosed with a lower respiratory tract infection [1]. Bronchiolitis is the most common cause of hospitalization of infants, with more than 120,000 cases annually in the USA [3]. It is impossible to document how many of these are truly a result of RSV infection because the etiology is often not confirmed but more than 50% of the hospitalizations for LRTI are related to RSV [4] and during the RSV season in some communities up to 90-95% of the hospitalizations are caused by RSV.

The World Health Organization and the Bill and Melinda Gates Foundation funded a study to calculate the global incidence of and mortality from episodes of LRTI due to RSV in children younger than 5 years of age in 2005 [5]. This study was published in the Lancet in 2010. The group performed a systematic review of studies published between January 1995 and June 2009.

The major findings state that in 2005, an estimated 33.8 million new episodes of RSV-associated LRTI occurred worldwide in children younger than 5 years with a least 3.4 million severe enough to require hospitalization [5].

The estimations were calculated based on the 36 studies reviewed and the locations are shown in fig. 1. It can be seen from this map that there are many studies in Europe and the USA but there are large gaps worldwide.

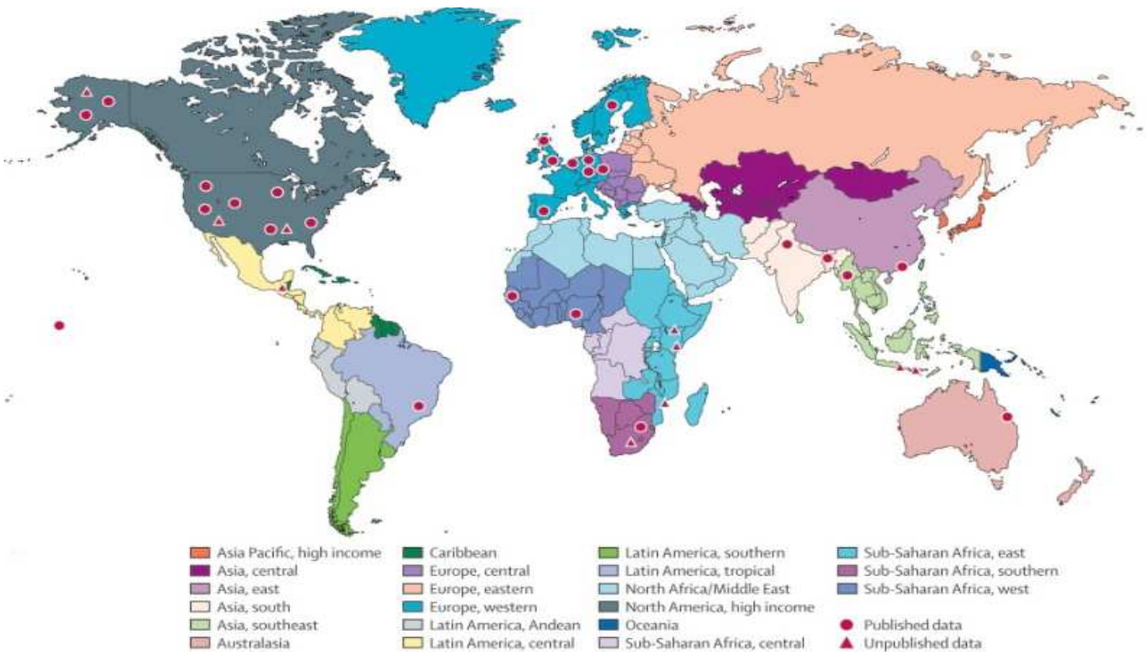


Fig. 1. Global map with circles (published) and triangles (unpublished) indicating the locations of the 36 studies.

2.1 Diagnosis of RSV

Respiratory syncytial virus is an enveloped, negative-sense, ssRNA virus that belongs to the Paramyxoviridae family. The virus has 10 genes that result in the production of 2 separate

proteins. The RSV attachment (G) protein mediates attachment to the host cell via cell surface glycosaminoglycans [6]. The fusion (F) protein mediates virus entry by directing the fusion of the virion envelope with the plasma membrane of the host cell. The F protein has been demonstrated to activate Toll-like receptor (TLR)4 [7], and human studies have shown a correlation between the TLR4 receptor and susceptibility to severe RSV-induced respiratory disease [8].

There are several diagnostic assays that are used to confirm the diagnosis of RSV. The 4 primary methods include virus culture, serology, immunofluorescence antigen detection, and nucleic acid PCR-based tests. Major hospital laboratories use the IFA/DFA which is indirect/direct fluorescent antibody assay. This is a rapid test and so is clinically and practically useful. There are additional tests that can be used in the office or clinic setting using optical immunoassay, for example the BinaxNOW RSV or Clearview RSV. The most accurate test is the PCR or polymerase chain reaction. The PCR is being used more widely because of the accuracy, but it has to be remembered that identification of a particular virus does not necessarily imply that it is causing disease. Samples are usually collected by swab from the nasopharynx or by nasal wash.

Other viruses that cause respiratory infections in children include rhinovirus, coronavirus, adenovirus and parainfluenza and influenza. The identification of viruses causing lower respiratory infections is further complicated by the presence, uniquely or in combination, of a number of recently recognized viruses. Most important of these is human metapneumovirus (hMPV) that has a similar clinical profile to RSV. The two viruses may be present at the same time but the major differences between RSV and hMPV are that the latter produces milder disease and later in the season. Co-infection with RSV and hMPV has been shown to increase the intensive care unit rate of admission.

hMPV was first discovered in 2001 in the Netherlands [9]. Shortly thereafter it was described in the USA [10]. There is a range of clinical manifestations from mild upper respiratory symptoms similar to the common cold, to severe pneumonia and respiratory failure. Presentation is with cough, and fever may be present and wheeze and myalgia occur.

A more recently identified virus which causes respiratory illness in children is human bocavirus (HBoV). It was shown to have a prevalence of carriage of 3.1% among children with lower respiratory infection [11]. A study in San Diego, California [12], which consisted mainly of hospitalized patients, identified HBoV in 82 children, yielding a prevalence of 5.6% over a continuous 21-month period, with a peak prevalence as high as 14% in the spring and a virtual absence of activity during the summer months. San Diego has a temperate, dry climate. This study demonstrated a significant number of infants with paroxysmal cough which raised the clinical suspicion of pertussis. Additionally they reported a number of infants also had diarrhea.

2.2 Spread of infection

RSV is a virus that is easily spread from an infected individual, especially by touch and transfer from hand to mouth, nose or eyes. People who are infected with RSV may transmit the virus for 3 to 8 days and infants and those with weakened immune systems have the

potential to be contagious for as long as 4 weeks. Schools, daycare centers and hospitals are important reservoirs for spreading the virus. In addition to direct contact with infected secretions the virus can be spread by sneezing or coughing and the virus particles that are inhaled or spread into the mouth, nose or eyes have the potential to infect. RSV may reside on hard surfaces for up to 24 hours or even longer.

RSV infection during the first 4 weeks of life is relatively infrequent in healthy term newborns. Transplacentally derived RSV-specific neutralizing antibody is present in the sera of newborns. The level of passive antibody in the term newborn is similar to the maternal level. Preterm infants have less antibody and the earlier the baby is delivered the lesser antibody is present.

Janssen [13] demonstrated that RSV susceptibility is complex, but that the strongest associations were with polymorphisms in the genes of the innate immune response. This included the transcriptional regulator Jun, alpha interferon (IFN-α), nitric oxide synthase, and the vitamin D receptor. The more recent study of preterm children by the same group [14] also indicated a critical association with innate immune system genes and bronchiolitis susceptibility.

The following table (1), shows some of the risk factors for the acquisition and spread of RSV infection.

Family size
Crowded living conditions
Older siblings in school or day-care
Attendance in day-care
Lack of breast feeding
Exposure to cigarette smoke
Birth in the months prior to the onset of the RSV season
Healthcare workers
Elderly patients in nursing homes
Genetic factors

Table 1. Risk factors for acquiring and spreading RSV.

2.3 Risk of increased severity

There are multiple factors that are associated with more severe disease including the following list shown in Table 2.

Although prematurity is at the top of this list, there are more full-term cases of RSV hospitalized because of the number delivered at each gestational age. Family history of asthma and genetic factors also correlate with more severe RSV disease.

In addition infants in developing countries are at increased risk because of malnutrition and possibly vitamin deficiency, especially vitamins A and D [15]. It also appears that repeated infections requiring hospitalization are more common in developing countries.

RSV, influenza virus, adenovirus, human metapneumovirus, parainfluenza virus and rhinovirus can all cause bronchiolitis, necessitating hospitalization. Second, of these viruses,

RSV has most commonly been reported to be the main cause of hospitalization due to bronchiolitis and increased disease severity, followed by rhinovirus and then by influenza virus. Third, viral coinfection is relatively common, occurring in about 20% of cases. However, there is no consensus on the effect of coinfection on disease severity. The effect may depend upon which viruses coinfect together.

Prematurity
Age less than 3 months
Male gender
Low socioeconomic status
Multiple births
Indoor smoke pollution
Malnutrition
Chronic lung disease of infancy (bronchopulmonary dysplasia)
Hemodynamically significant congenital heart disease
Immune deficiency problems especially severe combined immunodeficiency disorder (SCID) and HIV/AIDS
Severe neuromuscular disorders
Transplant patients
Hematopoietic transplants (bone marrow and stem cell)
Malignancy

Table 2. Factors associated with more severe disease.

3. Influenza

The influenza virus is spread rapidly from person to person. The result may be an influenza pandemic. A pandemic implies a worldwide epidemic that infects a large proportion of the total human population. Epidemic patterns of influenza occur most winters. The pandemic of influenza occurs irregularly. Although the pandemic of 1918 is probably the most well-known there have been about 3 pandemics in each of the last 3 centuries. The 1918 pandemic is also known as the Spanish Flu and resulted in an estimated worldwide mortality of perhaps 30 to 40 million people. Pandemics start when a new strain of the influenza virus is transmitted from an animal species hence the designation of swine flu and bird (avian) flu in recent times.

In February 2010 the CDC updated the recommendation for annual influenza shot to all persons greater than 6 months of age. For persons aged 65 and older the high-dose influenza vaccine (Fluzone), licensed in 2010, is mentioned as an option for this age group. Despite this recommendation the number of people who regularly get a flu shot is dismally low probably around 10%. In undeveloped countries the situation is much worse as there is no public health infrastructure in place to vaccinate large populations.

In 1997 a new subtype of influenza was found in humans, designated H5N1. This virus had only previously been described in birds and its effect on chickens led to the label of "Chicken Ebola". The population of Hong Kong found out in 1997 that it had the potential to be just as deadly in humans. The entire poultry population of ducks, geese and chickens in Hong Kong was destroyed.

The H1N1 strain of swine flu demonstrated the unpredictable nature of potential influenza pandemics in 2009. In the Spanish Flu of 1918 the population that was most threatened by the virus was not the usual population. Typically, the seasonal flu virus results in significant mortality to the very young and the very old. The Spanish Flu was more devastating to the younger adult population. The H1N1 strain also affected a different population with pregnant patients demonstrating the highest rate of mortality.

3.1 Influenza and RSV

Despite the numbers in the young (infants) and old (greater than 65 years) population we do not describe infection with RSV as pandemic. There is however, concern that there is potential for greater numbers of more severe disease with the combination of RSV and influenza virus. When H1N1 was circulating in 2009, it was noted that there was increased RSV transmission.

A comparison was made between the impact of seasonal RSV and influenza for young children locally and nationally [16]. In this study the impact of RSV for children less than 7 years of age was greater than influenza for emergency department visits and hospitalizations. The study evaluated health care resources and impact for 2 winter seasons between 2003 and 2005 in the USA. They estimated that 10.2 emergency department visits per 1000 children were attributable to influenza and 21.5 visits per 1000 to RSV. Children who were aged 0 to 23 months and infected with RSV had the highest rate of emergency department visits with 64.4 visits per 1000 children. Significantly more children required hospitalization as a result of an RSV infection compared with influenza, with calculated national hospitalization rates of 8.5 and 1.4 per 1000 children, respectively. The total number of workdays missed yearly by caregivers of children who required ED care was 246,965 days for influenza infections and 716,404 days for RSV infections.

4. RSV and bacterial infection

Much of the early literature relating RSV and bacterial infection considered the non-respiratory infections. Both otitis media and urinary tract infections were evaluated and the recommendation made that antibiotics were not routinely needed for RSV infections. In 1998 the etiology of childhood pneumonia was evaluated in children less than 5 years of age by Heiskanen-Kosma [17] stressing the relationship of RSV and *Streptococcus pneumoniae* with community acquired pneumonia. The pulmonary aspect of viral LRTI was addressed by Hament [18] who discussed the implication that viral infections facilitate bacterial colonization, adherence and translocation through the epithelial barrier, paving the way for bacterial disease.

The importance of secondary bacterial infection in children with severe RSV bronchiolitis was stressed by Thorburn [19]. The group in Liverpool followed 165 children with median age of 1.6 months admitted to the pediatric intensive care unit. 42.4% of these children, all of whom required mechanical ventilation, had lower airway secretions that were positive for bacteria. Laboratory evaluation, including white cell count, neutrophil count and C-reactive protein, did not distinguish between those who only had RSV and those who had bacterial infection.

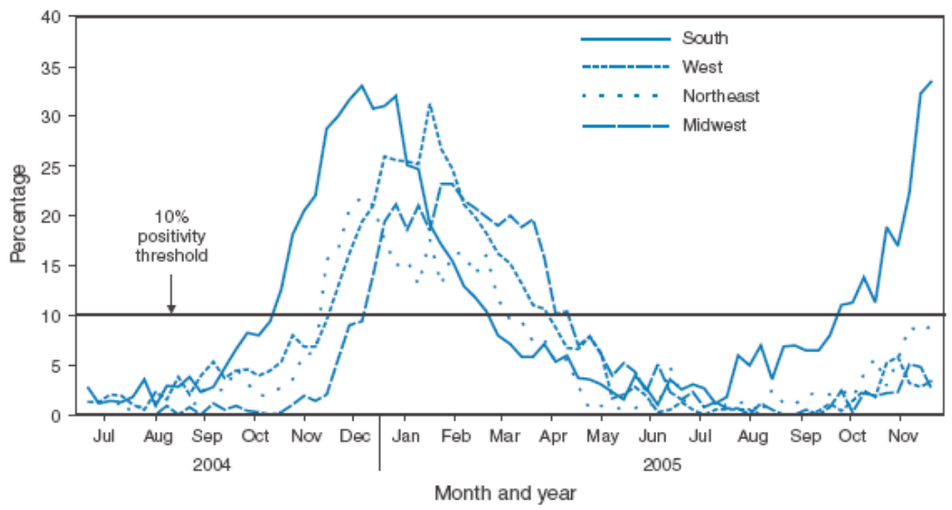
5. Seasonality

The RSV season is defined in various ways. The season is most often described in the USA as the week in which 10% of the laboratory tests are positive for RSV. Tests that are referred for RSV testing from that community will define the season in that community. Some studies have included a positive rate of only 5% to define the season. An alternative approach is to define the season as the period in which there are increased hospitalizations for LRTI especially bronchiolitis. The season usually has a defined onset, from a few or no cases to multiple cases, and an offset which defines the end of the season.

Most communities with temperate climates have a well-defined season of 3 to 5 months usually starting in the Northern hemisphere in October or November and continuing until February or March. It is common for there to be a biennial change from one season to the next whereby the subsequent season is milder or more severe than the preceding. However, this is not predictable and the differences may be more related to climactic changes.

5.1 USA

The Center for Disease Control (CDC) in Atlanta Georgia has reported the seasonality of RSV based on the 10% threshold. The National Respiratory and Enteric Virus Surveillance System (NREVSS) is a voluntary laboratory-based system that tracks trends in RSV and other viruses. They reported 4 regions of the United States from July 2, 2004 to December 3, 2005 as shown in Fig. 2. This demonstrates a clear consistent seasonal pattern with onset between October and December and offset mid-February to April. Of note the South demonstrated at that time an onset of at least a month ahead of the other 3 regions.



* *Northeast:* Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; *Midwest:* Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South:* Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; *West:* Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

Fig. 2. RSV season for 4 areas of USA defined by 10% positive for years 2004-2005. From CDC (NREVSS).

Clinicians in Florida recognized that the season for RSV was not in the same months as the data from CDC suggested. In order to define the seasonality in Florida a retrospective analysis of RSV surveillance data and hospitalizations was conducted for 5 regions of Florida from 2001 to 2004 [20]. The 5 regions within the State of Florida capture data from strategically placed laboratories in the southeast, southwest, central, northwest and north regions. As noted, data from these regions is reported on the Florida Department of Health website (http://www.doh.state.fl.us/disease_ctrl/epi/RSV/rsv.htm). The onset of the RSV season for the purpose of this study was when at least 10% of the RSV specimens submitted were positive during a surveillance week. The majority of the tests were by rapid tests although the specific number identified by rapid test, culture or PCR is not documented.

The evaluation procedures to define RSV season are based on the reporting from regional laboratories. Of necessity the validity of the data is dependent upon the number of samples submitted because if the number is too low then there may be a false positive conclusion. Also the use of hospitalization data is dependent on the accuracy of the patient discharge records which forms the basis of most calculations. In previous studies of hospitalization rates the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes are used. These include 466.11 – RSV bronchiolitis, 480.1 – RSV pneumonia, and 079.6 – other RSV. Review of several studies report admission rates of 13 to 40.8 per 1000 children less than 1 year of age. The majority of studies reporting national data range from 22.8 to 27.4 per 1000 births.

Information pertinent to hospitalization in the State of Florida can be obtained from The Florida Agency for Health Care Administration (AHCA). Regional discharge sets from AHCA for the years 2001 through 2004 were reviewed for the primary and secondary discharge diagnosis of RSV lower respiratory illness for patients less than 12 months of age as well as 12 to less than 24 months of age. The discharge diagnosis of RSV is only documented if there is a positive test for RSV in the chart. The primary objective of the study was to compare the RSV seasonal data from the laboratories with the incidence of ICD-9-CM coded admissions for RSV lower respiratory illness.

The results of this study defined the RSV seasons for the 5 regions in Florida and the percent monthly positive RSV tests and hospitalizations statewide are shown in Fig. 3. There were an additional 27,140 hospitalizations caused by unspecified bronchiolitis (ICD-9-CM code 466.19) and unspecified pneumonia (ICD-9-CM code 486) during this same period. It is likely that a portion of these were also caused by RSV.

The season for RSV varied from year to year and during the period of the study there was circulation of RSV year round in some years and some regions. The longest season was in the southeast and the shortest in the north and northwest. The RSV season, on the basis of positive RSV tests and the hospitalizations for RSV illness are shown for the southeast region in Fig. 4. This shows the prolonged RSV season and the correlation between positive tests and hospitalization.

During this 4-year period there were more than 23,000 admissions of children less than 24 months of age of which 20,000 (86%) were less than 12 months of age. There were 23 hospitalizations yearly per 1000 live births. More than 90% of the hospital discharges occurred during the defined RSV season.

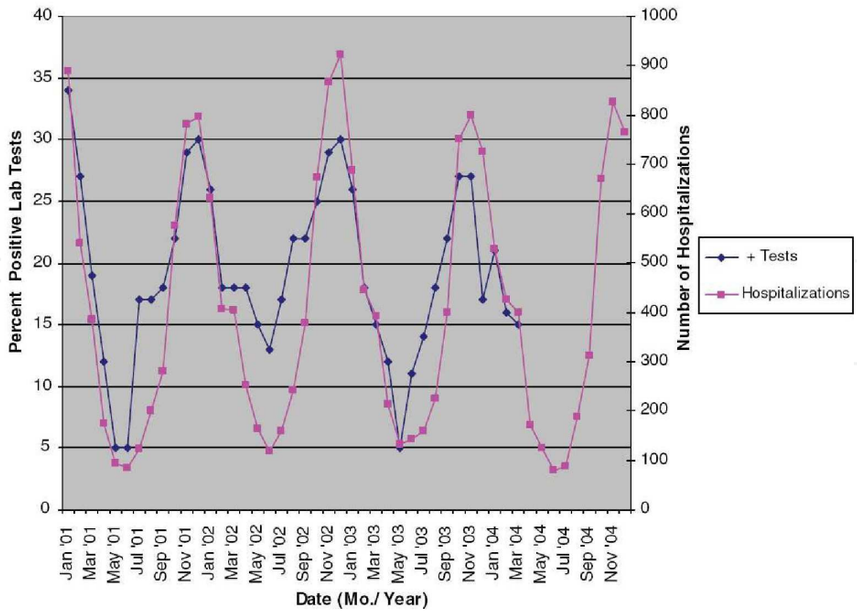


Fig. 3. Total RSV positive tests and hospitalizations for the State of Florida from January 2001 to November 2004.

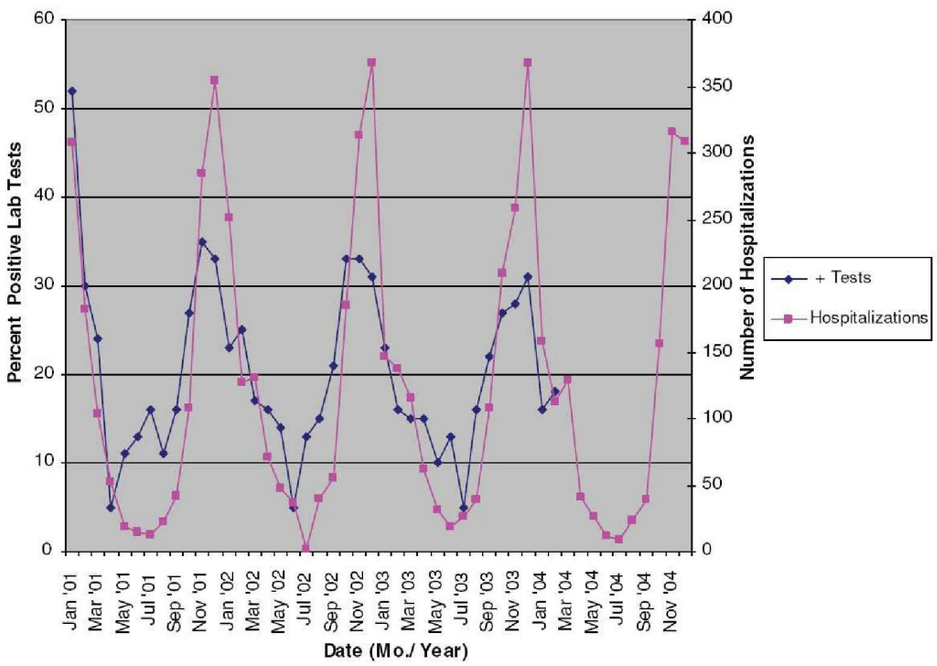
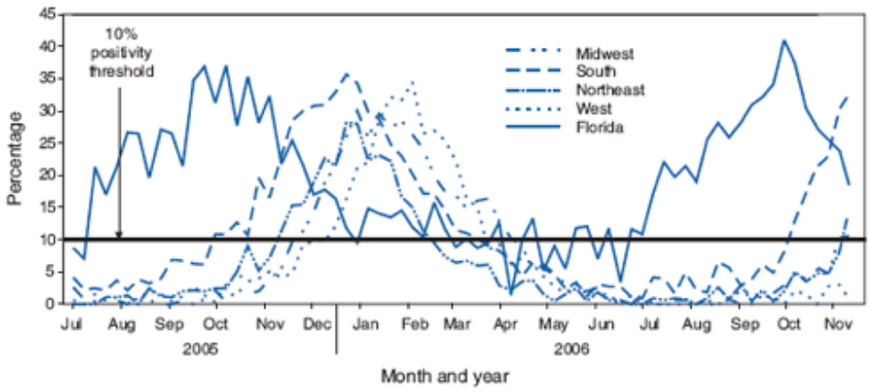


Fig. 4. RSV test data and hospitalization in southeast Florida.

The impact of Florida is demonstrated on the NREVSS of RSV for July 9 2005 to November 18, 2006 in Fig 5. Unlike the majority of the USA, the onset in Florida was in July, peaking in October and offset in April. Further evaluation of the Florida data reveals that the major contributor to the early onset is the tri-county area of Southeast Florida comprising Palm Beach, Broward and Miami-Dade counties [20].



* *Northeast:* Connecticut, Massachusetts, New Hampshire, New Jersey, New York, and Rhode Island; *Midwest:* Illinois, Indiana, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South:* Alabama, Arkansas, Delaware, District of Columbia, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, and Virginia; *West:* Alaska, Arizona, California, Colorado, Hawaii, Montana, Washington, and Wyoming; Florida. Data from Florida were presented separately because they differed substantially from RSV-detection data from the remainder of the South region.

Fig. 5. RSV data for 5 areas of USA with Florida separated, for years 2005-2006. From CDC (NREVSS).

The data for July 2008 to June 2009 with 10 regions and the addition of Florida and the National average are shown in Fig. 6. 238 laboratories from 45 states are included in this summary which included 404,798 tests of which 60,793 were positive. The national data showed onset in the first week of November, continuing for 20 weeks. When the data from Florida is excluded the national RSV season began 2 weeks later. These findings support the position that individual communities need to be aware of their data and how it impacts the onset and duration of the RSV season.

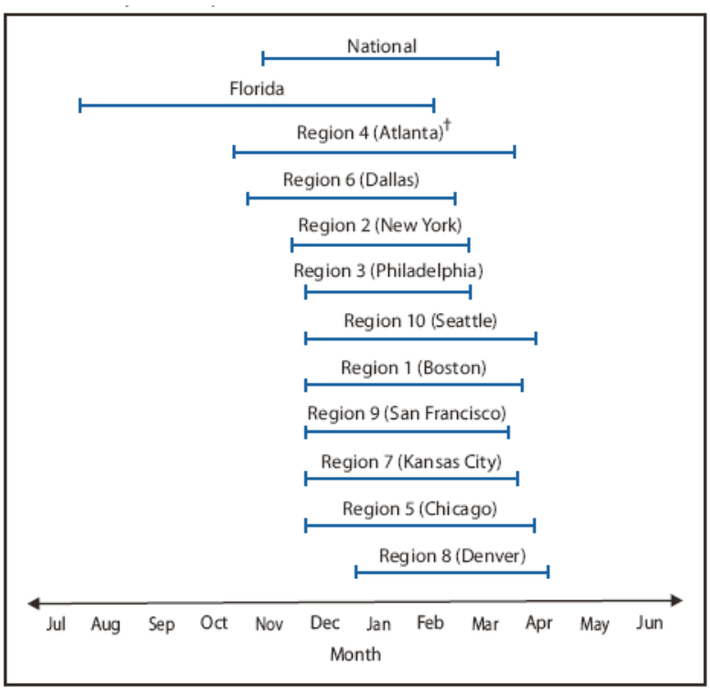


Fig. 6. RSV data for all of USA and 10 regions with Florida separated for the period July 2008 to June 2009. Each line represents the months of RSV season. From CDC (NREVSS).

Weekly updates which show RSV national, regional and state trends are available form the NREVSS website: http://www.cdc.gov/surveillance/NREVSS.

The most recent data from the USA and from Florida are shown in fig. 7a and 7b respectively.

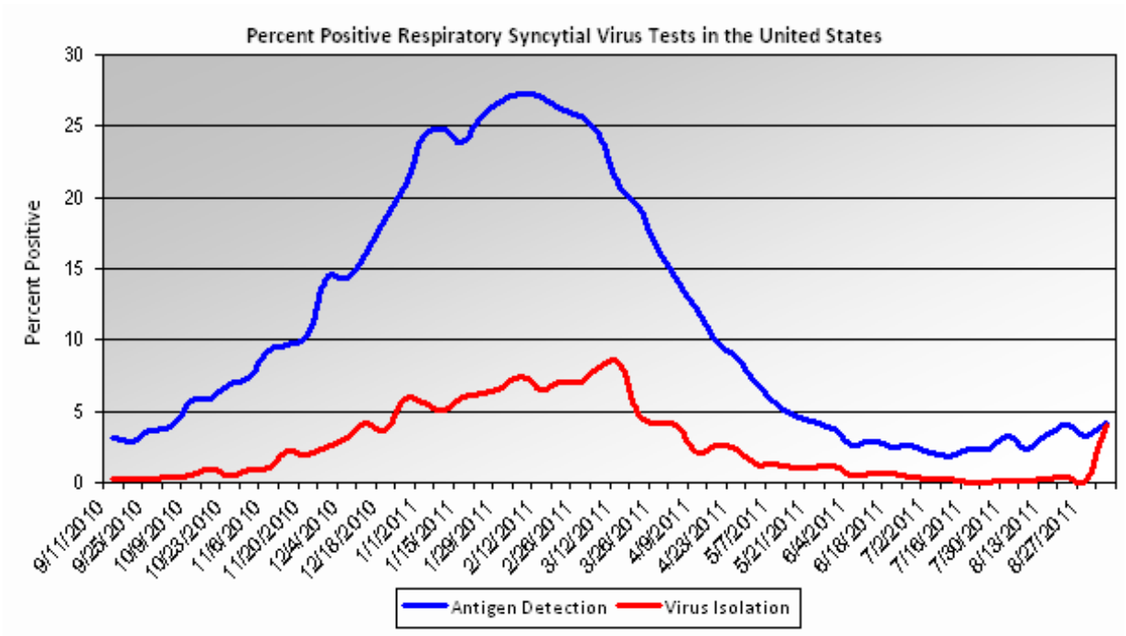


Fig. 7a. Percent positive RSV tests (antigen detection and virus isolation) in the United States. From CDC (NRVESS).

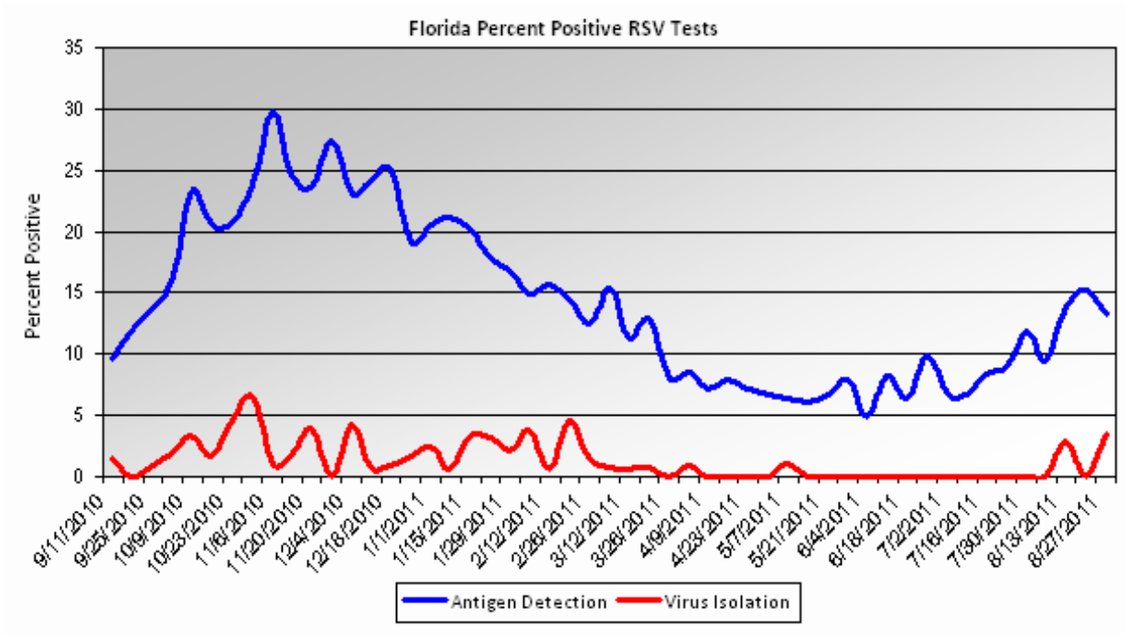


Fig. 7b. Percent positive RSV tests in the State of Florida. From CDC (NRVESS).

6. Developing countries

The impact of seasonality and mortality in tropical and developing countries was reviewed in 1998 [18] . This report was the first of many reviews that have scrutinized the literature to demonstrate the extent of RSV in a global sense. They found that RSV was the predominant viral cause of LRTI in childhood being responsible for 27-96% of hospitalized cases (mean 65%) in which a virus was found. Further that 39% of hospital patients with RSV were under 6 months of age.

They identified community studies and hospital-based studies. The community based studies, ranging from 1963 to 1989 reported RSV positivity by culture and immunofluorescence. The greatest number of patients studied was from India with less than 10% of the samples positive for RSV. The highest rates of positive RSV culture were from South America and the Phillipines.

The hospital-based studies that they reviewed also demonstrated RSV by culture and immunofluorescence. The studies were from South America, Asia and Africa from 1972 to 1990 with very variable rates of positivity to RSV. Of the samples tested that demonstrated a virus, RSV contributed an average of 65% of the positive results (range 27-96%).

Trying to demonstrate rates of LRTI was difficult with the paucity of data available at that time. The reported incidence varied from 10/1,000 children under one year hospitalized in Israel to 198/1000 child years from birth to 18 months in a study from Colombia.

In tropical and subtropical climates with seasonal rainfall, the outbreaks of RSV were more associated with the rainy season rather than the cold season. They found that the peak of the RSV season occurred one to two months after the onset of the rains [21].

In temperate climates, as well as Mediterranean and desert climates, the RSV season corresponds to the cold season.

In Singapore, the seasonal trends of viral respiratory infections were reviewed by Chew [22]. They reviewed the viral isolates from 1990 to 1994 and 3904 positive viral reports. RSV was the most dominant with 72% of the total. The RSV trends were associated with higher environmental temperature, lower relative humidity and higher maximal day-to-day temperature variation. There was a definite season noted related to these climate features. Although the influenza A outbreaks were not associated with meteorological factors, influenza B isolates were positively associated with rainfall.

A larger study from Malaysia [23] included 5691 children less than 24 months hospitalized with LRTI between 1982 and 1997. The RSV season showed a seasonal pattern with peaks in the months of November, December and January. The rate of RSV infection appeared to correlate with the number of rain days and inversely with the monthly mean temperature.

7. Variability of seasons

The differences in reported incidence of RSV infection are of necessity difficult to elucidate because of the multiplicity of factors that impact the incidence.

Various studies provide information that help to evaluate the overall picture. Brazil is a tropical and subtropical country and the RSV season peaks in the fall (autumn) and extends

into the winter with a corresponding increase in hospital admissions for lower respiratory illnesses. This study [24] showed that in 1995-1996 RSV was the most prominent virus causing severe lower respiratory disease including bronchiolitis and pneumonia. It was found in 41.8% of the cohort. A further study in the same area [25] performed indirect immuofluorescent assay and demonstrated that RSV contributed 73% of the viruses that were identified in the population less than 5 years of age admitted for severe respiratory illness. Although the studies were different in terms of enrollment the point is made that there is variability in diagnosis of viral infection in the same location at differing time periods.

8. Climate

Year round prevalence of RSV in the USA has been reported in Florida, Hawaii, Texas and Alaska. Certainly warm equatorial areas demonstrate a long season of RSV especially if rainfall persists throughout the year.

To try and explain the climactic differences, this study [26] compared the data at several large cities which are geographically and climactically diverse. The cities were 1. near Bethel, Alaska, USA, 2. Mexico City, Mexico, 3. Delhi, India, 4. Miami, Florida, USA, 5. Houston, Texax, USA, 6. Tucson Arizona, USA, 7. Buffalo, New York, USA 8. Winnipeg, Canada and 9. Santiago, Chile. The sites were chosen because of their interest in defining seasonality and climate differences between the communities.

Data concerning mean temperatures, dew point, relative humidity and precipitation was obtained for the nine cities and is shown in Table 3.

City	Lat[1]	Temp[2]	Dew[3]	Hum[4]	Prec[5]
Mexico City	19.2 N	22.5	6.3	52.4	16.3
Miami Florida	25.8 N	24.2	19.1	56.7	18.0
Delhi India	28.4 N	23.9	13.9	52	13.5
Houston Texas	29.6 N	20.4	15	49.5	13.0
Tucson Arizona	32.1 N	20.2	1.9	19.3	2.5
Santiago Chile	33.2 S	14.4	7.8	66	0.3
Buffalo New York	42.6 N	8.9	3.2	54	9.7
Winnipeg Canada	49.5 N	14	-3.8	71.5	0.5
Bethel Alaska	60.5 N	-1.6	-3.8	n.a	0.4

[1]Latitude, [2]Mean temperature, centigrade, [3]Dew point [4]Humidity [5]Precipitation, mm per week

Table 3. Data concerning climate and humidity for the 9 cities.

The cities were warm and wet (Miami, Mexico City, Delhi and Houston), warm and dry (Tucson), cold and wet (Buffalo) and cold and dry (Winnipeg and Bethel). Santiago, Chile is in the Southern hemisphere with intermediate weather conditions. The relationship of mean temperature to RSV activity showed that the number of RSV cases increased when the mean temperature was 24-30^{0}C and again when the temperature was in the range 2-6^{0}C. In relation to humidity, RSV activity increased when the mean relative humidity was between 45 and 65% and ultraviolet B radiance was inversely related to the number of RSV cases. The dewpoint, which indicates relative humidity, correlated significantly with RSV activity.

Published reports from prior studies were discussed in this article [26] by Yusuf and tended to confirm their findings. In Singapore and Malaysia where temperatures are constant and rainfall is generally heavy, there is RSV activity throughout the year. In Gambia (West Africa) and Vellore, (India) it is hot and the rainfall is directly associated with RSV activity. In Riyadh, which is hot and dry, RSV activity occurs in the winter when there is some rainfall and lower temperature. In colder climates they further speculate that cold temperatures are more important than humidity.

Interesting speculation from this article [26] propose that high humidity and stable high temperatures enable RSV to be sustained well enough in large-particle aerosols to permit year round transmission of the virus. Onset of drier weather appears to reduce aerosol transmission of the virus.

9. Management of RSV bronchiolitis

The American Academy of Pediatrics convened a committee and partners to develop an evidence-based clinical practice guideline with recommendations for diagnosis and management of first onset RSV bronchiolitis [27].

It can be seen from Table 4 that the management is essentially supportive.

1a. Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Clinicians should not routinely order laboratory and radiologic studies for diagnosis (recommendation).
1b. Clinicians should assess risk factors for severe disease such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency when making decisions about evaluation and management of children with bronchiolitis (recommendation).
2a. Bronchodilators should not be used routinely in the management of bronchiolitis (recommendation).
2b.A carefully monitored trial of α-adrenergic or ß-adrenergic medication is an option. Inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial using an objective means of evaluation (option).
3. Corticosteroid medications should not be used routinely in the management of bronchiolitis (recommendation).
4. Ribavirin should not be used routinely in children with bronchiolitis (recommendation).
5. Antibacterial medications should only be used in children with bronchiolitis who have specific indications of the coexistence of a bacterial infection. When present, bacterial

infection should be treated in the same manner as in the absence of bronchiolitis (recommendation). 6a. Clinicians should assess hydration and ability to take fluids orally (strong recommendation). 6b. Chest physiotherapy should not be used routinely in the management of bronchiolitis (recommendation). 7a. Supplemental oxygen is indicated if SpO_2 falls persistently below 90% in previously healthy infants. If the SpO_2 does persistently fall below 90%, adequate supplemental oxygen should be used to maintain an SpO_2 at or above 90%. Oxygen may be discontinued if SpO_2 is at or above 90% and the infant is feeding well and has minimal respiratory distress (option). 7b. As the child's clinical course improves, continuous measurement of SpO_2 is not routinely needed (option). 7c. Infants with a known history of hemodynamically significant heart or lung disease and premature infants require close monitoring as oxygen is being weaned (strong recommendation). 8a. Clinicians may administer palivizumab prophylaxis for selected infants and children with CLD or a history of prematurity (less than 35 weeks' gestation) or with congenital heart disease (recommendation). 8b. When given, prophylaxis with palivizumab should be given in 5 monthly doses, usually beginning in November or December, at a dose of 15 mg/kg per dose administered intramuscularly (recommendation). 9a. Hand decontamination is the most important step in preventing nosocomial spread of RSV. Hands should be decontaminated before and after direct contact with patients, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves (strong recommendation). 9b. Alcohol-based rubs are preferred for hand decontamination. An alternative is hand-washing with antimicrobial soap (recommendation). 9c. Clinicians should educate personnel and family members on hand sanitation (recommendation). 10a. Infants should not be exposed to passive smoking (strong recommendation). 10b.Breastfeeding is recommended to decrease a child's risk of having LRTD (recommendation). 11. Clinicians should inquire about use of CAM (option).

Table 4. Recommendations for diagnosis and management of bronchiolitis

Following the AAP Guideline there has been additional information. A promising new development is the use of hypertonic saline inhalation. A recent trial of this treatment, which has been successfully used for patients with cystic fibrosis, reported a reduction of 26% in the length of hospitalization for infants with acute viral bronchiolitis [28].

10. RSV Prevention

The history of development of a vaccine against RSV is complicated. Infants may respond inadequately because of immunologic immaturity or suppression because of maternal antibodies. In the 1960's a formalin inactivated RSV vaccine was studied in infants.

Unfortunately, not only did it not provide protection, but it also resulted in worse disease in vaccinated infants. 80% of the study infants were subsequently hospitalized and 2 died despite the fact that the RSV vaccine was an inactivated virus [29].

Palivizumab is the only FDA approved monoclonal antibody for RSV. It targets the F (fusion) glycoprotein, inhibiting viral entry into host cells. It was approved following a randomized, double-blind placebo-controlled trial that was conducted at 139 centers in the USA, the United Kingdom and Canada during the 1996-1997 RSV season. The patient population included prematurity (less than 35 weeks gestation) or bronchopulmonary dysplasia (BPD). They were randomized to receive 5 injections of either palivizumab, 15 mg/kg or a placebo. Children were followed for 150 days and the primary endpoint was hospitalization with confirmed RSV infection. Palivizumab prophylaxis resulted in a 55% reduction in hospitalization for RSV (10.6% of the placebo group and 4.8% of the treated group). Premature infants who did not have BPD had a reduction in hospitalization for RSV (8.1% placebo, 1.8% palivizumab).

As noted above, the majority of infants admitted with LRTI caused by RSV are full-term. More severe disease is associated with prematurity, chronic lung disease and congenital heart disease as major co-morbidities. There continues to be controversy concerning the optimal recommendations for the prescription of palivizumab. Several studies have been performed to evaluate the cost effectiveness of prophylaxis with palivizumab. The selection of infants who qualify for prophylaxis is defined in the Red Book from the Section of Infectious Diseases of the American Academy of Pediatrics [30]. The most recent iteration of the Red Book has this update which indicates which infants are eligible for 3 doses of palivizumab rather than the previously recommended 5 doses (Table 5). The other issue relates to the onset of the season that indicated the north central and southwest regions of Florida, onset of RSV occurs in late September to early October. Regions of southeast Florida have an onset of RSV in July. Children in these communities should receive palivizumab during the 3-5 months when they will be most likely to need coverage against peak RSV activity. Children with co-morbidities may require more than 3 or 5 doses because they are at higher risk for mortality.

Infants Eligible for a Maximum of 5 Doses
Infants younger than 24 months of age with chronic lung disease and requiring medical therapy
Infants younger than 24 months of age and requiring medical therapy for congenital heart disease
Preterm infants born at 31 weeks, 6 days of gestation or less
Certain infants with neuromuscular disease or congenital abnormalities of the airways
Infants Eligible for a Maximum of 3 Doses
Preterm infants with gestational age of 32 weeks, 0 days to 34 weeks, 6 days with at least 1 risk factor and born 3 months before or during RSV season.

*Data taken from Table 3.60. *Red Book 2009: p.560 [31]*

Table 5. Criteria for eligibility for 5 or 3 palivizumab doses.

The difficulty of only permitting 5 doses relates to those infants with chronic lung and cardiac disease that may be at risk for the first 2 years of life and perhaps even longer. In southeast Florida the season is longer than 5 months.

Also infants who are at risk for severe RSV who undergo cardiopulmonary bypass and are receiving palivizumab should receive palivizumab after surgery because the antibody will be "washed out" during bypass.

Prophylaxis in immunocompromised children has not been studied in randomized trials. The AAP policy states that these patients may also benefit from prophylaxis, however, more specific recommendations are not made at this time. Although the Cystic Fibrosis Foundation has recommended: "for infants with cystic fibrosis (CF) under 2 years of age that the use of palivizumab be considered for prophylaxis of respiratory syncytial virus", the Red Book suggests that "there is insufficient data to determine the effectiveness of palivizumab use in this patient population. Therefore, a recommendation for routine prophylaxis in patients with CF cannot be made."

11. Morbidity and mortality

The relationship between RSV infection in infancy and subsequent development of wheezing disorders has also been difficult to define. Again, there are probably a multiplicity of reasons that wheezing is impacted by RSV lower respiratory infection. Stein [32] reported in the Tucson respiratory study that RSV LRTI was an independent risk factor for wheezing up to 11 years of age, but not at 13 years. On the other hand Sigurs [33] showed that RSV infection requiring hospitalization in infancy was a risk factor for allergic asthma in early adolescence.

11.1 Mortality

Developed countries

In the developed countries the mortality from RSV induced respiratory infection in children is less than 1%. There are specific conditions that are associated with increased mortality and these are shown in Table 6 which is similar to Table 2 which showed the population at risk for severe disease. The first three are most important during infancy, the next group is important in childhood, and the population over 65 years of age is at risk for morbidity and mortality. Older children, and adults less than 65 years of age, who have no co-morbid conditions should not be at risk for severe RSV-associated illness.

Prematurity
Chronic lung disease (bronchopulmonary dysplasia)
Hemodynamically significant congenital cardiac disease
Immune deficiency
Complication of hematopoietic transplantation
Malignancy
Age over 65 years

Table 6. Factors associated with increased mortality.

There is significant mortality from RSV infection in both solid and hematologic transplants. Bone marrow and stem cell transplant patients are at especially significant risk for the development of difficult to treat RSV infection.

Intensive care units for newborns and children have lowered the mortality from RSV associated illness in developed countries to less than 1% of severe RSV LRTI. Children with significant lung and cardiac disease have reported mortality due to RSV LRTI of approximately 3% of intensive care admissions and this number continues to improve. Reported mortality rates of complications of hematopoietic transplant illness secondary to RSV have approximated 50%.

The paediatric intensive care unit at the Royal Liverpool Children's Hospital, U.K. admitted 406 RSV positive patients from 1999 to 2007 [34]. Of the deaths that were attributed to RSV, all of them had pre-existing medical conditions: chromosomal abnormalities 29%, cardiac lesions 27%, neuromuscular 15%, chronic lung disease 12%, large airway abnormality 9% and immunodeficiency 9%. Nosocomial and hospital-acquired disease comprised a significant proportion of morbidity and mortality related to RSV.

11.2 Globally

In 1992 the World Health Organization estimated that one third of the 12.2 million annual deaths in children under 5 years of age are the result of acute respiratory infections dominated by RSV, *Streptococcus pneumoniae* and *hemophilus influenzae* [35]. In developing countries calculations of mortality rates from lower respiratory tract infection are based on extrapolations of regional studies. It is difficult to calculate the impact of RSV because there are additional factors that are involved. Before the introduction of measles vaccination the measles virus was responsible for considerable morbidity and mortality related to pulmonary disease. The countries that have strong programs to provide protection against measles have demonstrated a shift in the etiologies and outcomes of lower respiratory infections.

Bacterial infection overshadows RSV in developing countries with *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Hemophilus influenzae* playing major roles in morbidity and mortality of lower respiratory infections.

The Lancet study, discussed earlier [5], estimated that 66,000 to 199,000 children younger than 5 years of age died from RSV associated acute lower respiratory infection in 2005 with 99% of these occurring in developing countries.

11.3 Adults

RSV is definitely one of the most important respiratory viruses in children, especially during the first year of life. Children older than 2 years of age without confounding medical conditions continue to be reinfected with RSV. The infection usually results in an upper respiratory infection that is very similar to the common cold. Children who have hyperactive airways may have wheezing associated with this upper respiratory illness. This also applies to the healthy adult who may have cold symptoms and some may wheeze.

The importance of influenza virus in the elderly population is well known. Although RSV may coexist with influenza, the data supports the notion that RSV is a major contributor to mortality in the population greater than 65 years of age. The impact of RSV is difficult to evaluate because the rapid antigen detection tests are relatively insensitive in adults and few

tests are ordered by medical practitioners in this age group. It has been suggested that deaths attributed to influenza in the past may more correctly be a result of RSV infection.

Falsey [36] reported that according to the National Center for Health Statistics of the CDC, in 1999 the numbers of discharges from USA hospitals for pneumonia was 1.3 million, chronic obstructive pulmonary disease, 0.76 million and asthma 0.35 million. It was then calculated that 177,525 admissions per year were accounted for by RSV and that the death rate from RSV would be 8% which comes to 14,000 annual deaths. An earlier study by Thompson [37] reported a similar finding of 11,321 deaths.

RSV pneumonia is a major complication of adults who are immunocompromised. Ebber [38] reported the results of bronchoalveolar lavage in 11 patients aged 21 to 77 years of age who were undergoing treatment for leukemia or lymphoma, or who were post-bone marrow transplant. The 11 patients had proven RSV and the mortality was 55% (6 patients). Of interest, 8 of the 11 had also bacterial or fungal infection.

It is important to be aware that although RSV infection in the immunocompromised patient is more likely during the RSV season of the community, it is well known that this population, as well as the solid organ transplant population may be infected with RSV outside the defined season.

IgA is considered to play an important role in the protection of initial infection with RSV. It is possible that reduced levels of IgA may impair the protective effect of subsequent RSV infections. Older individuals have reduced virus-specific antibodies and decreased T-cell numbers compared to younger individuals after inactivated influenza immunization. Elderly individuals do have similar neutralizing antibody titers which suggests that the reduction in neutralizing antibodies is not the cause of the more severe disease in the population over 65 years of age.

Increased susceptibility of the elderly to RSV infection may lie within the CD8 T-cell arm of the adaptive immune system. The numbers of RSV-specific CD8 T cells is decreased in old age which limits the ability to produce cytokines.

12. RSV vaccine

It has been challenging to find an appropriate vaccine against RSV. The extremes of age, the very young and the very old are the populations that stand to benefit most from a vaccine. The young infant has an immature immune system that is dominated by Th2-type response and in the presence of maternal antibody response to the vaccine is unpredictable. Older people have decreased numbers of T cells which would reduce the response to the vaccine.

13. Conclusion

Frequent handwashing is probably the greatest public health intervention that is available at the present time. Awareness of the season of RSV both in the hospital or clinic and in the community allows for interventions including cohorting and avoidance measures to reduce the spread of the virus.

Awareness of the seasonality of RSV permits appropriate timing of preventive programs that have the potential to reduce the impact of RSV. The RSV season that is repeated each

year in temperate climates during the winter, may vary significantly in terms of onset, duration and severity from year to year. In tropical and sub-tropical climates it appears that the humidity is more of a dominant factor in terms of timing of the season, usually peaking 2-3 months after onset of the season, and varying with the temperature.

The number of health care dollars (and other currencies) that are spent as a result of the impact of RSV, is in the billions. It is clear that the development of a vaccine that reduces the morbidity and mortality of RSV-associated disease has the potential to save money and save lives.

14. Abbreviations

CDC: Centers for Disease Control and Prevention

RSV: respiratory syncytial virus

LRTI: lower respiratory tract infection

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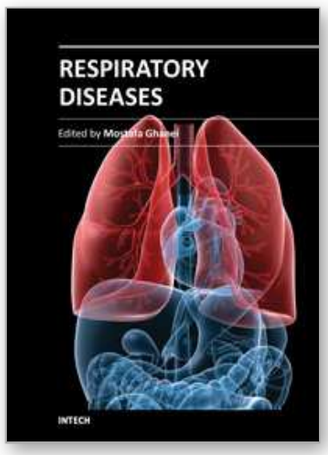

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Medicine is an ever-changing science. In this regard, Respiratory medicine is not an exception and has been evolving during recent years. As new research broadens our knowledge, advanced methods for diagnoses are better understood, providing genetic and underlying pathophysiology of diseases and new clinical experiences. Consequently, publications of new resources along with revisions of previous ones are required. The book Respiratory Diseases brings practical aspects of pulmonary diseases. It contains the result of years of experience through expert clinicians in this field from different scientific centers. The respiratory diseases are discussed according to epidemiology, pathology, diagnosis, treatment, and prognosis. It includes updated resources of the pathogenesis and some molecular aspects of the aforementioned diseases and is recommended reading for all clinicians and medical students, especially pulmonologists, to access highlighted respiratory diseases in this book.

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