Review article

Prematurity and the burden of influenza and respiratory syncytial virus disease

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Background: **Respiratory morbidity of former preterm infants and especially those with bronchopulmonary dysplasia (BPD) is high during infancy and early childhood.**

Data sources: **We performed a review based on a literature search including EMBASE, MEDLINE, and CINAHL databases to identify all relevant papers published in the English and German literature on influenza and respiratory syncytial virus infection associated with preterm infant, prematurity, and BPD between 1980 and 2014.**

Results: **Recurrent respiratory symptoms remain common at preschool age, school age and even into young adulthood. Acute viral respiratory tract infections due to different pathogens cause significant morbidity and necessitate rehospitalizations during the first years of life. Influenza virus infection plays a minor role compared to respiratory syncytial virus (RSV) associated respiratory tract infection during infancy and early childhood. Nevertheless, particular morbidity to both viruses is high.**

Conclusions: **The particular burden of both viral diseases in preterm infants is dominated by RSV and its associated rehospitalizations during the first two years of life. Prophylactic measures include vaccination against influenza virus of family members and caregivers and active immunization starting at the age of 6 months, and monthly injections of palivizumab during the cold season to avoid severe RSV disease and its sequelae.**

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Introduction

Respiratory morbidity of former preterm infants and especially those with chronic lung disease (bronchopulmonary dysplasia, BPD) is known to be high during infancy and early childhood. Acute viral respiratory tract infections cause significant morbidity in young children, and this is particularly the fact for the high-risk group of preterm infants. Respiratory syncytial virus (RSV) is the main pathogen involved in lower respiratory tract infections of young infants (bronchiolitis) and although a vaccine is not available, prophylaxis with the monoclonal antibodies palivizumab and motavizumab in high-risk infants has been established world-wide. Influenza virus is a common respiratory pathogen responsible for year by year epidemics including all age groups, and yearly vaccination is an established method for the prevention of the disease. Thus, we chose these two pathogens for a systematic review to define the burden of disease in the population of premature born infants. Main characteristics of the viruses are depictured in Table 1. The review was based on a literature search including EMBASE, MEDLINE, and CINAHL databases to identify all relevant papers published in the English and German language on influenza and respiratory syncytial virus infection associated with preterm infant, prematurity, and BPD between 1980 and 2014. In the following two sections describing respiratory long-term morbidity and respiratory tract infections in general in preterm infants, we present data on influenza virus and RSV and define the burden of diseases. Preventive strategies for both viruses are discussed.

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Table 1. Characteristics of influenza and respiratory syncytial virus (RSV)

Characteristics	Influenza	RSV
Genom	Negative single stranded RNA, segmental	Negative single stranded RNA, not segmental
Family	Orthomyxoviridae	Paramyxoviridae
Types	A, B, C	A, B
Surface antigens	Hemagglutinin, neuraminidase	Glycoprotein-G and -F
Epidemiology	Seasonal Wintertime (northern hemisphere)	Seasonal Wintertime (northern hemisphere)
	Severity of the epidemics varies substantially from year to year	Severity of the epidemics varies substantially from year to year
Incubation time	1-5 d	2-8 d
Transmission	Aerosols, large droplets, direct contact	Large droplets, direct contact
Inoculation	Upper respiratory tract	Upper respiratory tract
Clinical feature	Abrupt onset, fever and rhinitis	Starts as URTI (apneas), signs of respiratory distress
Typical feature	Sepsis-like illness Both in young infants	Bronchiolitis Both in young infants
Sequelae	Acute otitis media, pneumonia	Recurrent wheezing

URTI: upper respiratory tract infection.

Preterm infants with and without BPD and respiratory long-term morbidity

The rates of rehospitalization of extremely low gestational age preterm infants (those born before 28 weeks of gestational age) are several-fold higher than those of term controls, and the rates of hospital re-admission have risen as survival rates have increased over time.[1] Respiratory illnesses are the most common cause of rehospitalization in these early years with more frequent occurrence in those preterm survivors who had BPD. This is also true for preterm infants of 29 to 36 weeks of gestational age, but at lower rates.[2] Over the years, the rates of hospital readmission have declined in childhood, and those who had BPD are no more likely to be readmitted to hospital, for respiratory or other reasons.[1]

Very prematurely born infants who have recurrent wheeze have more severe lung function abnormalities, greater evidence of gas trapping, a higher airways resistance, and lower tidal breathing parameters.[3] Risk factors for increased respiratory morbidity were BPD, male gender, having older siblings aged less than five years and living in rented accommodation; and male gender was a risk factor for every adverse respiratory outcome. Recurrent respiratory symptoms remain common at preschool age, school age and even into young adulthood. Lung function abnormalities are common during the first two years after birth amongst infants born very prematurely, but most tend to resolve with increasing age.[3]

Interestingly, small for gestational age (SGA) infants who were born very prematurely, despite routine use of antenatal corticosteroids and postnatal surfactant, were found to have increased respiratory morbidity at follow-up. SGA was associated with a higher prevalence of respiratory admissions, cough, and use of chest medicines.[4]

Chronic respiratory morbidity is a common adverse outcome of preterm infants who developed BPD, which is still a major cause of long-term lung dysfunction with a heavy burden on health care services and medical resources throughout childhood.[5] BPD makes infants particularly susceptible to lower respiratory tract diseases in childhood, as well as promoting chronic airflow obstruction in adulthood, commonly leading to conditions such as recurrent bronchospasm. The degree of airflow limitation in the first years of life is a good predictor of future lung function.[6] During childhood and adolescence, BPD survivors may have respiratory symptoms and lung function impairments closely resembling those of asthmatic patients, though they usually reveal some different features in terms of airway reversibility that is less noticeable, fewer acute exacerbations and a poorer response to inhaled corticosteroids.[7]

Increased pulmonary arterial pressure is common in infancy in preterm infants who develop chronic lung disease of prematurity. A recent echocardiographic study reported that childhood survivors of BPD had comparable left and right ventricular function at 8-12 years of age to preterm and term-born children, and no evidence of increased pulmonary arterial pressure even after hypoxic exposure.[8]

Longitudinal studies to follow up preterm infants into adolescence found a persistently reduced lung function reflecting airflow limitation.[9] Although an improvement in lung function is usually detectable in children whose clinical condition improves as they grow older, there may still be signs of poor airway growth when they reach school age, especially in children whose respiratory symptoms continue to recur.[5] Gas transfer also remains abnormal in young children who have experienced BPD; it is characterized by a lower than normal gas transfer and alveolar volume at rest, and their failure to increase during exercise, suggesting that the alveolar surface area is reduced.[10] At least half of all children with a history of BPD exhibit laboratory evidence of airway hyperresponsiveness to direct stimuli and to physical exercise, even if they have no clinical history of wheezing or reactive airway disease.[5]

The long-term effects of BPD are still poorly understood. Although respiratory symptoms become milder as they grow up, BPD survivors may reveal persistent pulmonary abnormalities on computed tomography scanning. Thus, the long-term respiratory consequences of a preterm birth may be underestimated or overlooked by providers of adult healthcare.[5]

A systematic review and meta-analysis on the association of preterm birth and childhood wheezing

disorders reported on 30 unique studies involving 1 543 639 children and found an increased risk of wheezing disorders in unadjusted (13.7% *vs*. 8.3%; odds ratio=1.71, 26 studies including 1 500 916 children) and adjusted analyses (odds ratio=1.46, 17 studies including 874 710 children). The risk was particularly high among very preterm children born before 32 weeks of gestation.[11]

Preterm infants and respiratory tract infections

Acute viral respiratory tract infections due to different pathogens including RSV and influenza virus cause significant morbidity in young children.[12-14] Hospitalization rates due to bronchiolitis have been reported to be seven-fold higher in preterm (below 33 weeks of gestational age) than full-term infants.[15] Boyce et al[16] found 159.6 RSV hospitalizations/1000 child-years for preterm infants of 33 to 35 week of gestational age compared to 88.2/1000 for full-term infants at a chronological age below six months. The respiratory vulnerability and substantial respiratory morbidity of moderate and late preterm infants born between 32 to 36 weeks of gestational age were found to be comparable to very preterm infants below 32 weeks of gestational age.[17-19] Hall et al[20] studied RSV-associated hospitalizations in children under 24 months of age. The average rate of RSV admission was 5.2 per 1000 children with 79% of the infants being previously healthy. Only 3% of the RSV cases were related to very preterm infants (below 30 weeks of gestational age), but the RSV-hospitalization rate was 3 times higher compared to full-term infants.

By comparison of outpatient visits due to RSV infection, Paramore et al[21] divided them into several groups of preterm with full-term infants, the highest rates were observed among preterm infants with a gestational age below 32 weeks or those with chronic lung disease. The rates of outpatient RSV infections ranged between 158.7 and 272.6 visits per 1000 children. Interestingly, the authors reported on similar rates between late preterm (33 to 36 weeks) and very preterm infants. A comparison of the rate of hospitalization for RSV bronchiolitis between preterm infants born at 32 weeks' gestational age or less without bronchopulmonary dysplasia and full-term infants cohort study[22] found significantly higher rates of wheezing and recurrent wheezing episodes in preterm infants (below 33 weeks of gestational age) than in full-term infants. Another study[23] reported higher rates of wheezing and similar rates of cough in preterm infants compared to term infants.

An important aggravating factor for respiratory morbidity and respiratory tract infection is the presence of BPD. Approximately 50% of all infants with BPD will be readmitted to hospital during early childhood.[24] Twice as much rehospitalizations due to RSV infection in preterm infants with BPD compared with those without BPD have already been reported.[25,26] Hennessy et al[27] demonstrated that multiple hospital admissions (≥ 3 episodes) were more likely in preterm infants with BPD compared with children without BPD in the first 30 months of age. And again higher rates of multiple rehospitalizations and longer hospital stays have been found in infants with BPD.[28]

BPD and gestational age ≤32 weeks have been mentioned as one of the risk factors in studies focusing on rehospitalizations during early childhood.[29,30] A significantly increased risk for readmission to the intermediate and intensive care unit was seen in infants with gestational age below 32 weeks, moderate to severe BPD and congenital heart failure, respectively.[31] Children with the above mentioned risk conditions also required longer hospital stays and needed more invasive respiratory support.

Regarding lung function and chronic respiratory morbidity, differences have been observed in several studies between preterm infants with and without BPD and term infants. Hennessy et al[27] followed up extremely preterm babies up to 6 years of age and found higher rates of wheezing and associated respiratory symptoms in children with BPD compared with those without BPD and their classmates. In the subgroup with BPD, a previously higher use of inhalative medication (steroids and bronchodilators) was found. Vom Hove et al[32] found the similar results including significantly higher rates of respiratory symptoms and the need for asthma medication at school-age in the BPD children in contrast to those without BPD, and other studies[33-35] revealed a greater respiratory morbidity in children with BPD compared with those without BPD. In moderate preterm infants (32 to 36 weeks of gestational age) compared with term infants, episodes of cough and wheezing, shortness of breath, and medication use were found more frequently at the age of 4 and 5 years.[18] An increased risk for asthma and the need for medical treatment with inhalative corticosteroids were reported in children born between 34 to 36 weeks of gestational age, and recurrent wheezing at the age of 3 years was seen more often in children with a history of late prematurity in contrast to those born between 38 to 40 weeks of gestational age.[36,37]

At the age of 8 to 14 years, evidence of bronchial obstruction was seen in 83% of children with BPD and in 23% of those without BPD,[38] and differences in lung function testing have been reported even at adolescent age in very low birth weight infants with or without BPD.[39,40] A study[41] reported the differences in lung function testing even in preterm infants born at 33 and 34 weeks of gestational age at a mean age of 8 to 9 years compared with term infants, but other studies[33,42-45] reported divergent results in the BPD group.

Preterm infants and influenza

Influenza virus, an RNA virus of the orthomyxoviridae family, is classified into three types A, B, and C. Type A is responsible for most clinical infections in humans and also affects many animal species. Type B resembles about 11% of non-pandemic influenza in humans, whereas type C causes only mild coryza.[46] Influenza A is further subdivided on the basis of the surface glycoproteins hemagglutinin (H) and neuraminidase (N). At least 15 Hs and nine Ns which have been described constitute major virulence factors. While H mediates viral binding to cell receptors, N plays an important part in releasing the virus from the cell following viral replication.[47] Antigenic drift, which resembles minor changes in surface antigens, contributes to seasonal epidemics of influenza A, whereas antigenic shift (major changes in surface antigens) is associated with pandemics.

The 1918 to 1919 pandemic was the first of three pandemics in the 20th century that was associated with an increase in neonatal and infant mortality as well as an increase in preterm delivery.[48] Mortality in those younger than 19 years of age has accounted for up to 12% of deaths due to pneumonia or influenza during some influenza epidemics, and, interestingly, during the 2003-2004 influenza season there were 143 influenza related pediatric deaths documented in the USA, of whom about 40% were younger than 2 years, highlighting the high vulnerability of this age group.[46] In countries with increasing rates of day care, attendance opportunities for exposure and transmission might become even greater than ever before in preschool children. These children are at high risk of respiratory infection and may account for substantial health expenditure.[46]

However, both the burden of morbidity of influenza in childhood and its social impact seem to be substantial. Iskander et al[49] reported in 2009 that in one third (32%) of families of children with influenza at least one of the parents developed influenza like illness during admission or soon after hospital discharge. The parents' disease resulted in an average of 3.2 days of work absenteeism.

Influenza resembles a significant cause of pediatric hospital admission,[50] with a peak in pre-school and school age children.[46,51] The classic clinical features include high fever, headache, myalgia and fatigue, whereas only few have signs of pulmonary involvement.[50,52] Some young infants present with apneic episodes or with a syndrome similar to neonatal sepsis. If pneumonia follows typical influenza, it may be a primary influenza pneumonia or secondary bacterial pneumonia. In comparison, influenza constitutes an uncommon infection within the first 6 months of life, generally presenting with mild symptoms only.[51] This might presumably be related to the reduced contact that neonates generally have with sick adults or children. However, several nosocomial influenza A infection outbreaks within neonatal units have been described.[53-56] These outbreaks usually coincided with epidemics of influenza within the community. Nevertheless, it was difficult to determine the source of infection per each case. Studies[51,54,55] on infants during influenza epidemics reported on high rates of asymptomatic infections. If infants do manifest symptoms, the most common ones are abrupt onset of high fever and symptoms of upper respiratory tract infection,[52-56] and differentiating from bacterial sepsis might be difficult by clinical findings.[50,52,57] The milder form of illness in infants and newborns has been attributed to transplacental acquisition of protective antibodies providing protection for 3 to 6 months after birth.[50,55,58] Another protective factor remains nutritional with breast milk.[50]

However, epidemic and pandemic influenza is associated with a significant mortality in infants.[48] Yen et al[59] concluded that infants who were premature or had chronic underlying disease seemed to be at increased risk for developing severe 2009 H1N1 influenza infection. This might be valid not only for 2009 H1N1 influenza infections. Mechanical ventilation, twin pregnancy, gestational age and birth weight were identified as risk factors for severe infection.[55]

Glezen et al[51] described an 11-day-old term infant who died suddenly from pneumonitis presumably related to influenza A. The infant's mother had developed influenza A (H3N2) 6 days post-partum. The infant, however, had no detectable antibodies against the epidemic virus in his serum. Cunney et al[55] reported a 27-week gestation twin died from influenza A virus-associated hemophagocytic syndrome during an epidemic. van den Dungen et al[60] described a 29-week gestation infant who developed respiratory illness on day 17 of life (viral cultures grew influenza B) with subsequent significant lung injury, neurological complications and finally death.

A recent study[61] reported the burden of influenza hospitalizations in infants in a 10-year period (2003 to 2012) from the United States. The authors of the study found an annual average of hospitalization of 6514 infants with higher rates among infants below three months of age compared with older infants. Three quarters of hospitalizations occurred in otherwise healthy infants, of whom 105 were admitted to the intensive care unit (ICU) and 45 had respiratory failure. Risk factors for admission to the ICU included lung disease (including BPD), cardiovascular disease and neuromuscular impairment. The prevalence of high risk conditions increased from 15% in infants below 3 months of age to 38% in infants of 6 to 12 months of age, and prematurity (14%) was the most commonly described symptom. Of the eight (0.0025%) deaths documented, six were among the very young infants.

Drysdale et al[62] prospectively followed up infants born at <36 weeks of gestational age if they were born between April and September in 2008 or 2009 outside the RSV season. In total, 150 prematurely born infants with a median gestational age of 34 weeks (range: 23-35 weeks) and birth weight of 1880 g (range: 534-3446 g) were recruited, and 16 had a diagnosis of BPD (oxygen dependency beyond 28 days). Multiplex real-time reverse transcription polymerase chain reaction was performed on the nasopharyngeal aspirates in case of hospitalization due to respiratory disease for 9 virus types (influenza A and B, RSV A and B, human metapneumovirus, rhinoviruses, parainfluenza viruses 1-3). Only one (0.7%) male infant of 24 weeks gestational age developed a lower respiratory tract infection (LRTI) needing hospitalization in which pandemic influenza A was detected in nasopharyngeal aspirate. The rate of hospitalization for pandemic influenza A H1N1 virus infection was not significantly different between premature and term-born infants (0.7% *vs*. 0.07%, P=0.12), but a higher rate of hospitalization for other known viral LRTIs (5.3% *vs*. 0.6%, P<0.0001), including RSV LRTIs (3.3% *vs*. 0.5%, P<0.002) was observed.

Kinney et al[63] determined the frequency and severity of acute respiratory infections in infants with BPD following discharge from the neonatal intensive care unit. Of 30 oxygen-dependent children who were younger than 2 years, 10 children were hospitalized on 25 occasions for a mean of 37.6 hospital days per child. Five children were admitted to the pediatric intensive care unit. Respiratory viruses isolated included RSV (n=7), parainfluenza 3 virus (n=3), and adenovirus (n=2). No isolates of influenza A or B were detected.

Influenza virus disease seems to be less severe compared with RSV disease in newborn infants. We recently reported that infants hospitalized because of RSV infection were significantly younger, had longer hospital stays, a more severe course of disease, and required supplemental oxygen more often and with a longer duration of treatment as compared with those infants with influenza virus infection.[64] Seasonal distribution varied, with RSV associated hospitalizations peaking in January and influenza virus associated hospitalizations in February.

There is evidence that influenza strains that infect the brain can lead to altered cognitive and emotional behaviors. Influenza-infected mice exhibited cognitive deficits in a reversal learning version of the Morris water maze.[65] At the same time point in which cognitive impairment was evident, proinflammatory cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor)-α, interferon-α] and microglial reactivity were increased, while neurotrophic (brain-derived neurotrophic factor, nerve growth factor) and immunomodulatory [cluster of differentiation 200, fractalkine-also known as chemokine (C-X3-C motif) ligand 1] factors were decreased in the hippocampus of infected mice. Additionally, influenza induced architectural changes to hippocampal neurons and dentate gyrus gave evidence that neuroinflammation and changes in hippocampal structural plasticity might underlie cognitive dysfunction associated with influenza infection. Comparable central nervous system (CNS) involvement in mice by the inflammatory response in the lung and in different regions of the brain (brainstem, substantia nigra, striatum, and cortex) has been described in case of influenza H5N1 virus infection.[66] CNS involvement during influenza includes a variety of syndromes, more often described in children than in adults, and the major clinical entities are encephalitis or encephalopathy.[67] In etiological studies of encephalitis, influenza A and/or B have been identified in up to 10% of pediatric cases. The onset of neurological symptoms is usually within a few days to a week after the appearance of the first signs of influenza infection. Fever, decreased consciousness, and seizures are common signs and symptoms, and the less commonly seen are focal neurological signs such as paresis, aphasia, cranial nerve palsies and choreoathetosis.[67] During the 1997 to 2001 influenza A epidemics in Japan, 20 children, mainly less than 6 years old but without a history of prematurity, were diagnosed with influenza-associated encephalitis/encephalopathy, of whom 5 patients (25%) died and 8 (40%) exhibited neurologic sequelae.[68]

Influenza treatment and vaccination

Preliminary data suggest that oseltamivir is safe and well tolerated in the treatment of influenza infection in preterm infants,[69,70] and 1.0 mg/kg per dose twice daily produces oseltamivir carboxylate exposure similar to that in older children receiving 3.0 mg/kg per dose twice daily.[71] Nevertheless, an association with necrotizing enterocolitis has recently been reported.[72]

Receipt of different influenza vaccine during pregnancy was not associated with increased or decreased risk of preterm or SGA birth or congenital malformations.[73-75] These recent findings support the safety of vaccinating pregnant women against influenza during the first, second, and third trimesters.

From a cohort of 683 354 young children (age 6 to 23 months) including 7.7% preterm infants collected over five influenza seasons (2004-2005 to 2008-2009), vaccine effectiveness was estimated using influenza-coded ambulatory visits.[76] Full vaccination was associated with a 19% reduction in influenza-coded ambulatory visits in all children and an 18% reduction in full-term children, but no benefit was found for preterm children and partial vaccination.

Preterm infants and RSV

RSV remains to be the most important cause of acute and lower respiratory tract infection in infants and children. Fifty percent-90% of hospitalizations for bronchiolitis, 5%-40% of those for pneumonia, and 10%-30% of those for tracheobronchitis are caused by RSV.[77] Nearly all children become infected with RSV within two years after birth, and one percent requires hospitalization.[78] RSV is a negative, single strained RNA paramyxovirus of the genus pneumovirus. There are two antigenic subtypes A and B and two main immunodominant surface glycoproteins, the F fusion and the G attachment proteins. Although RSV is considered to be a labile virus, it may remain infectious on nonporous surfaces for hours. The eyes and nose are the major routes of inoculation, and viral replication begins within the respiratory epithelium, with spread occurring mainly through intracytoplasmatic ridges between epithelial cells.

There are well-defined high-risk groups, generally with chronic underlying disorders, in whom infection with RSV is more likely to progress into severe lower respiratory tract infections including healthy infants younger than 3 months of age, premature infants with or without BPD, infants with hemodynamically significant congenital heart disease, immunosuppressed patients, infants with cystic fibrosis, and infants with neuromuscular diseases.[79-81]

The World Health Organization estimates that one third of the 12.2 million annual deaths in children below 5 years are due to acute infections of the respiratory tract, with RSV besides *Streptococcus pneumoniae* and *Haemophilus influenzae* being the predominant pathogens.[82] The severity of RSV outbreaks varying from year to year[83] may be in part due to a variation in circulating strains. RSV has two major antigenic groups, A and B, with additional antigenic variability occurring in each group. The most extensive antigenic and genetic diversity occurs in the attachment glycoprotein G protein on the surface of the virus, the second one is the fusion glycoprotein F that is responsible for cell-to-cell fusion and the formation of syncytia; the latter is up to 95% identical between the two strains.[84]

The year-to-year and seasonal variations in RSV activity are key aspects of RSV epidemiology. RSV peak rates of infection annually occur during the cold season in temperate climates and during the rainy season in tropical climates.[79] In Europe, RSV related rehospitalizations of preterm infants mainly were observed during the winter and spring months ranging from October to May, peaking between December/January and March.[85-90]

Mortality associated with primary RSV infection in otherwise healthy children is estimated to be 0.005% to 0.02%, and is approximately 1% to 3% among hospitalized children.[91,92] The risk for RSV related hospitalization is significantly increased in preterm infants.[93,94] The main factors increasing the risk for a more severe course of RSV disease in preterm infants include small lung volumes, a reduced lung surface area, small airways and an increased air space wall thickness.[95] Additionally, the immune system of preterm infants is immature resulting in low antibody titers and a reduced cellular immunity with reduced virus clearance.[96] Meert et al[97] found that preterm infants in contrast to term infants were more likely to present with apnoea, had a higher incidence of atelectasis/infiltrate and hyperinflation shown by chest roentgenograms, and experienced longer hospital stays as well as higher physiologic stability index and therapeutic intervention scores. Preterm infants were also more likely to require supplemental oxygen, intensive care unit admission, mechanical ventilation, and tube/parenteral feeding. Infants of ≤2 years old and prospectively evaluated for hospitalizations due to viral upper and lower respiratory tract infection over a two-year period[81] were found to have a significantly increased incidence of RSV hospitalization when preterm infants were compared with term infants. RSV related hospitalization was associated with younger age, higher lower respiratory illness scores, more days of hospitalization, oxygen requirement and respiratory support, and prolonged hospitalization in preterm compared with term infants.[88,98]

Several studies reported a decreased risk of hospitalization with increasing gestational age. Observational studies[16,85,90,98-102] revealed that the rates of hospitalization for RSV infection in children born at or before 32 weeks of gestational age varied between 7% and 13% in contrast to 2%-7% in children born after 32 weeks of gestational age. In a study including 59 preterm infants below 33 weeks of gestational age being rehospitalized for RSV infection 25.4% of them required intensive care unit admission for a median of six days and 5.1% required mechanical ventilation for a median of five days.[90] A prospective study[85] on infants younger than 24 months found 58 (21%) of 281 infants hospitalized for respiratory tract infection being RSV positive. RSV positive infants were of younger age (mean 3.5 months), had a higher lower respiratory illness score, and had more days of hospitalization, more days of oxygen requirement, and more days of respiratory support, and those born preterm were hospitalized a longer period.

Groothuis et al[103] first reported the increased risk of preterm infants with BPD for RSV related prolonged hospitalizations, high rates of admission to the ICU, and the need for mechanical ventilation. In their prospective study including 30 infants below 2 years of age with a diagnosis of BPD receiving home oxygen therapy, 11 of 15 hospitalizations were due to an RSV infection. Thirty-

six percent of the infants were admitted to the intensive care unit and 18% required mechanical ventilation.

Rates of RSV related rehospitalizations in preterm infants with BPD were reported to range from 5.6% to 59% with mortality rates between 0 and 8%.[86,88,90,104-107] Table 2 gives an overview of reported rehospitalization rates in different populations of preterm infants from selected studies. Of 151 children under 1 year of age admitted to the pediatric intensive care unit of the Trousseau Hospital in Paris from 1 January 1996 to 31 December 2003 for the treatment of RSV bronchiolitis with need for mechanical ventilation, 9.1% needed extracorporeal membrane oxygenation support.[108] The frequency of BPD was significantly higher in children who required extracorporeal membrane oxygenation support as compared with those without.

CNS involvement has rarely been described in cases of RSV infection. In a retrospective review including 3856 patients tested positive for RSV for RSV-RNA by reverse transcriptase polymerase chain reaction over a 7-year time period, 8 of 28 patients having undergone magnetic resonance imaging for the evaluation of neurologic symptoms had positive imaging findings.[109] After exclusion of non RSV-related pathologies such as subdural hemorrhage, brain volume loss due to status epilepticus, periventricular leukomalacia, preexisting ventriculomegaly, and hypoxic brain injury, the incidence of RSV-related encephalitis was 0.08% (3 patients). The presence of RSV proteins and RNA in zones of the brain such as the hippocampus, ventromedial hypothalamic nucleus, and brainstem has been demonstrated in RSV infected mice.[110] Interestingly, one month after disease resolution, rodents showed behavioral and cognitive impairment indicating learning impairment caused by RSV as a result of a deficient induction of long-term potentiation in the hippocampus of infected animals.

Table 2. Rates of RSV related rehospitalizations in preterm infants with and without bronchopulmonary dysplasia from selected references

Population	Number of patients	Study years	RSV rehospitalisation rate (%)
BPD[103]	30	1985-1986	59.0
BPD[98]	124	1992-1994	14.5
BPD[104]	149	1994-1995	17.4
BPD[86]	53	1998-1999	7.4
BPD[90]	53	1998-1999	15.0
BPD[100]	108	1999-2000	5.6
PT12[90]	584	1998-1999	13.4
PT12[88]	1029	1992-1996	11.2
PT12[89]	1249	1994-1999	6.6
PT12[86]	717	1998-2000	5.2
PT6[104]	510	1994-1995	8.1
PT6[105]	740	1996-1997	8.1
PT6[87]	801	2001-2003	4.5

RSV: respiratory syncytial virus; BPD: bronchopulmonary dysplasia; PT: preterm (infants); PT12: <12 months of chronological age; PT6: <6 months of chronological age.

Very recently the rate of apnea in case of bronchiolitis has been reported to be 5.16% in infants <12 months of age.[111] Predominant pathogens were RSV (33.3%), rhinovirus (13.7%) and viral coinfections (23.5%), and main risk factors were young age and a history of prematurity. In contrast to findings in animal models, testing of cerebrospinal fluid from infants with RSV infection with neurological manifestations for respiratory RNA viruses (including RSV, influenza A and B, pandemic influenza H1N1, parainfluenza-3, human metapneumovirus, adenovirus, parechovirus, and enterovirus) was negative in all patients, supporting the notion that the mechanism of RSV-induced neurologic manifestations, including apnea, is not direct central nervous system invasion.[112]

RSV treatment and prophylaxis with palivizumab/motavizumab

Therapy of RSV lower respiratory tract infection is mainly symptomatic consisting of nasal suctioning and nebulized 3% hypertonic saline, assisted feeding and hydration, and humidified oxygen delivery in case of hypoxemia. There is still lack of evidence to support the use of bronchodilators, corticosteroids, chest physiotherapy, antibiotics or antivirals in general. Nebulized adrenaline may be sometimes useful in the emergency room and in the hospital setting for treatment as needed.[113] Trials of the antiviral preparation ribavirin for RSV lack sufficient power to provide reliable estimates of the effects, administration is highly difficult, and the substance per se toxic, thus ribavirin might be used in selected cases having severe disease and/or pre-existing diseases.[114] RSV hyperimmunoglobulin was safe and as effective as standard polyclonal immunoglobulin preparations in reducing RSV in the nasopharynx, but no treatment efficacy was observed.[115]

The development of a safe and effective vaccine remains to be an up to date unresolved challenge and treatment of RSV disease is limited to symptomatic therapy. Palivizumab is a humanized monoclonal antibody that provides immunoprophylaxis against RSV by binding to the "A" epitope of the F glycoprotein. Two large double-blind placebo controlled trials including high-risk infants for severe RSV infection showed a significant reduction of RSV related hospitalizations: a 55% reduction in 1502 infants with prematurity and/or BPD[105] and a 45% reduction in 1287 infants with hemodynamically significant congenital heart disease.[116] Palivizumab proved to be safe by intramuscular injection of 15 mg/kg every 30 days for 5 months according to local epidemiology.[117] Recent data suggest further benefits for palivizumab

prophylaxis by reduction of recurrent post-RSV wheezing.[118] Motavizumab, an investigational monoclonal antibody with enhanced anti-RSV activity in preclinical studies, showed a 26% relative reduction in RSV hospitalization in preterm infants with and without BPD,[119] and a 25% relative reduction in RSV hospitalization in infants with hemodynamically significant congenital heart disease compared with palivizumab recipients.[120] Recommendations for the use of palivizumab for prevention of RSV infections in high-risk infants have been published by the American Academy of Pediatrics[121] and been adopted by many national committees. Recently, cost effectiveness of palivizumab prophylaxis was demonstrated in very low birth weight infants[122,123] and those with BPD.[124] At least a Cochrane meta-analysis revealed evidence that palivizumab prophylaxis is effective in reducing the frequency of hospitalisations due to RSV infection, i.e. in reducing the incidence of serious lower respiratory tract RSV disease in children with chronic lung disease, congenital heart disease or those born preterm.[125]

In conclusion, we found the burden of respiratory morbidity being generally high in former preterm infants and aggravated in those with BPD. Influenza virus infection plays a minor role compared with RSV associated respiratory tract infection during infancy and early childhood. Palivizumab and motavizumab are monoclonal antibodies for RSV prophylaxis in preterm infants and palivizumab prophylaxis proved to be effective in the prevention of severe RSV disease requiring hospitalization.

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References

1 Doyle LW, Anderson PJ. Pulmonary and neurological follow-up of extremely preterm infants. Neonatology 2010;97:388-394.
2 Resch B, Pasnocht A, Gusenleitner W, Müller W. Rehospitalisations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29-36 weeks gestational age. J Infect 2005;50:397-403.
3 Greenough A. Long-term respiratory consequences of premature birth at less than 32 weeks of gestation. Early Hum Dev 2013;89 Suppl 2:S25-S27.
4 Peacock JL, Lo JW, D'Costa W, Calvert S, Marlow N, Greenough A. Respiratory morbidity at follow-up of small-for-gestational-age infants born very prematurely. Pediatr Res 2013;73:457-463.
5 El Mazloum D, Moschino L, Bozzetto S, Baraldi E. Chronic lung disease of prematurity: long-term respiratory outcome. Neonatology 2014;105:352-356.
6 Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946-1955.
7 Bhandari A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary dysplasia. Pediatrics 2009;123:1562-1573.
8 Joshi S, Wilson DG, Kotecha S, Pickerd N, Fraser AG, Kotecha S. Cardiovascular function in children who had chronic lung disease of prematurity. Arch Dis Child Fetal Neonatal Ed 2014;99:F373-F379.
9 Filippone M, Bonetto G, Cherubin E, Carraro S, Baraldi E. Childhood course of lung function in survivors of bronchopulmonary dysplasia. JAMA 2009;302:1418-1420.
10 Mitchell SH, Teague WG, Reduced gas transfer at rest and during exercise in school-age survivors of bronchopulmonary dysplasia. Am J Respir Crit Care Med 1998;157:1406-1412.
11 Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med 2014;11:e1001596.
12 Iwane MK, Edwards KM, Szilagyi PG, Walker FJ, Griffin MR, Weinberg GA, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004;113:1758-1764.
13 Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225-231.
14 Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999;282:1440-1446.
15 Gouyon JB, Rozé JC, Guillermet-Fromentin C, Glorieux I, Adamon L, DI Maio M, et al. Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study. Epidemiol Infect 2013;141:816-826.
16 Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000;137:865-870.
17 Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks' gestational age. Pediatrics 2010;126:115-128.
18 Vrijlandt EJ, Kerstjens JM, Duiverman EJ, Bos AF, Reijneveld SA. Moderately preterm children have more respiratory problems during their first 5 years of life than children born full term. Am J Respir Crit Care Med 2013;187:1234-1240.
19 Resch B, Paes B. Are late preterm infants as susceptible to RSV infection as full term infants? Early Hum Dev 2011;87 Suppl 1:S47-S49.
20 Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics 2013;132:e341-e348.
21 Paramore LC, Mahadevia PJ, Piedra PA. Outpatient RSV lower respiratory infections among high-risk infants and other pediatric populations. Pediatr Pulmonol 2010;45:578-584.
22 Fauroux B, Gouyon JB, Roze JC, Guillermet-Fromentin C, Glorieux I, Adamon L, et al. Respiratory morbidity of preterm infants of less than 33 weeks gestation without bronchopulmonary dysplasia: a 12-month follow-up of the CASTOR study cohort. Epidemiol Infect 2014;142:1362-1374.
23 Pramana IA, Latzin P, Schlapbach LJ, Hafen G, Kuehni CE, Nelle

M, et al. Respiratory symptoms in preterm infants: burden of disease in the first year of life. Eur J Med Res 2011;16:223-230.
24 Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol 2014;100:145-157.
25 Resch B, Kurath S, Manzoni P. Epidemiology of respiratory syncytial virus infection in preterm infants. Open Microbiol J 2011;5:135-143.
26 Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. J Pediatr 1998;133:188-192.
27 Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, et al. Respiratory health in pre-school and school age children following extremely preterm birth. Arch Dis Child 2008;93:1037-1043.
28 Cunningham CK, McMillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. Pediatrics 1991;88:527-532.
29 Pezzotti P, Mantovani J, Benincori N, Mucchino E, Di Lallo D. Incidence and risk factors of hospitalization for bronchiolitis in preterm children: a retrospective longitudinal study in Italy. BMC Pediatr 2009;9:56.
30 Ralser E, Mueller W, Haberland C, Fink FM, Gutenberger KH, Strobl R, et al. Rehospitalization in the first 2 years of life in children born preterm. Acta Paediatr 2012;101:e1-e5.
31 Berger TM1, Aebi C, Duppenthaler A, Stocker M, Swiss Pediatric Surveillance Unit. Prospective population-based study of RSV-related intermediate care and intensive care unit admissions in Switzerland over a 4-year period (2001-2005). Infection 2009;37:109-116.
32 Vom Hove M, Prenzel F, Uhlig HH, Robel-Tillig E. Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. J Pediatr 2014;164:40-45.
33 Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. Am J Respir Crit Care Med 2010;182:237-245.
34 Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. J Pediatr 1998;133:188-192.
35 Broström EB, Thunqvist P, Adenfelt G, Borling E, Katz-Salamon M. Obstructive lung disease in children with mild to severe BPD. Respir Med 2010;104:362-370.
36 Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young children: practice-based study. Pediatrics 2011;128:e830-e838.
37 Escobar GJ, Ragins A, Li SX, Prager L, Masaquel AS, Kipnis P. Recurrent wheezing in the third year of life among children born at 32 weeks' gestation or later: relationship to laboratory-confirmed, medically attended infection with respiratory syncytial virus during the first year of life. Arch Pediatr Adolesc Med 2010;164:915-922.
38 Pelkonen AS, Hakulinen AL, Turpeinen M. Bronchial lability and responsiveness in school children born very preterm. Am J Respir Crit Care Med 1997;156:1178-1184.
39 Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 2006;118:108-113.
40 Halvorsen T, Skadberg BT, Eide GE, Røksund OD, Carlsen KH, Bakke P. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. Acta Paediatr 2004;93:1294-1300.
41 Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. Thorax 2012;67:54-61.
42 Kaplan E, Bar-Yishay E, Prais D, Klinger G, Mei-Zahav M, Mussaffi H, et al. Encouraging pulmonary outcome for surviving, neurologically intact, extremely premature infants in the postsurfactant era. Chest 2012;142:725-733.
43 Guimarães H, Rocha G, Pissarra S, Guedes MB, Nunes T, Vitor B. Respiratory outcomes and atopy in school-age children who were preterm at birth, with and without bronchopulmonary dysplasia. Clinics (Sao Paulo) 2011;66:425-430.
44 Konefał H, Czeszyńska MB, Merritt TA. School-age spirometry in survivors of chronic lung disease of prematurity in the surfactant era. Ginekol Pol 2013;84:286-292.
45 Welsh L, Kirkby J, Lum S, Odendaal D, Marlow N, Derrick G, et al. The EPICure study: maximal exercise and physical activity in school children born extremely preterm. Thorax 2010;65:165-172.
46 Teo SS, Nguyen-Van-Tam JS, Booy R. Influenza burden of illness, diagnosis, treatment, and prevention: what is the evidence in children and where are the gaps? Arch Dis Child 2005;90:532-536.
47 Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. Lancet 2000;355:827-835.
48 Reid A. The effects of the 1918-1919 influenza pandemic on infant and child health in Derbyshire. Med Hist 2005;49:29-54.
49 Iskander M, Kesson A, Dwyer D, Rost L, Pym M, Wang H, et al. The burden of influenza in children under 5 years admitted to the Children's Hospital at Westmead in the winter of 2006. J Paediatr Child Health 2009;45:698-703.
50 Munoz FM. Influenza virus infection in infancy and early childhood. Paediatr Respir Rev 2003;4:99-104.
51 Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. Influenza virus infections in infants. Pediatr Infect Dis J 1997;16:1065-1068.
52 Kao HT, Huang YC, Lin TY. Influenza A virus infection in infants. J Microbiol Immunol Infect 2000;33:105-108.
53 Bauer CR, Elie K, Spence L, Stern L. Hong Kong influenza in a neonatal unit. JAMA 1973;223:1233-1235.
54 Sagrera X, Ginovart G, Raspall F, Rabella N, Sala P, Sierra M, et al. Outbreaks of influenza A virus infection in neonatal intensive care units. Pediatr Infect Dis J 2002;21:196-200.
55 Cunney RJ, Bialachowski A, Thornley D, Smaill FM, Pennie RA. An outbreak of influenza A in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2000;21:449-454.
56 Munoz FM, Campbell JR, Atmar RL, Garcia-Prats J, Baxter BD, Johnson LE, et al. Influenza A virus outbreak in a neonatal intensive care unit. Pediatr Infect Dis J 1999;18:811-815.
57 Dagan R, Hall CB. Influenza A virus infection imitating bacterial sepsis in early infancy. Pediatr Infect Dis 1984;3:218-221.
58 Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis 1980;142:844-849.
59 Yen CJ, Louie JK, Schechter R. Infants hospitalized in intensive care units with 2009 H1N1 influenza infection, California, 2009-2010. Pediatr Infect Dis J 2012;31:e52-e55.
60 van den Dungen FA, van Furth AM, Fetter WP, Zaaijer HL, van Elburg RM. Fatal case of influenza B virus pneumonia in a preterm neonate. Pediatr Infect Dis J 2001;20:82-84.
61 Chaves SS, Perez A, Farley MM, Miller L, Schaffner W, Lindegren ML, et al. The burden of influenza hospitalizations in infants from 2003 to 2012, United States. Pediatr Infect Dis J 2014;33:912-919.
62 Drysdale SB, Alcazar M, Wilson T, Smith M, Zuckerman M, Wedderburn CJ, et al. Pandemic influenza A (H1N1) virus 2009

in a prospectively followed cohort of prematurely born infants. Pediatr Infect Dis J 2012;31:91-92.
63 Kinney JS, Robertsen CM, Johnson KM, Gaddis M, Wheeler R, Jackson MA, et al. Seasonal respiratory viral infections. Impact on infants with chronic lung disease following discharge from the neonatal intensive care unit. Arch Pediatr Adolesc Med 1995;149:81-85.
64 Resch B, Eibisberger M, Morris N, Müller W. Respiratory syncytial virus- and influenza virus-associated hospitalizations in infants less than 12 months of age. Pediatr Infect Dis J 2011;30:797-799.
65 Jurgens HA, Amancherla K, Johnson RW. Influenza infection induces neuroinflammation, alters hippocampal neuron morphology, and impairs cognition in adult mice. J Neurosci 2012;32:3958-3968.
66 Jang H, Boltz D, McClaren J, Pani AK, Smeyne M, Korff A, et al. Inflammatory effects of highly pathogenic H5N1 influenza virus infection in the CNS of mice. J Neurosci 2012;32:1545-1559.
67 Studahl M. Influenza virus and CNS manifestations. J Clin Virol 2003;28:225-232.
68 Yoshikawa H, Yamazaki S, Watanabe T, Abe T. Study of influenza-associated encephalitis/encephalopathy in children during the 1997 to 2001influenza seasons. J Child Neurol 2001;16:885-890.
69 Pannaraj PS, Tam B, Akan D. Oseltamivir treatment and prophylaxis in a neonatal intensive care unit during a 2009 H1N1 influenza outbreak. J Perinatol 2011;31:487-493.
70 Tsagris V, Nika A, Kyriakou D, Kapetanakis I, Harahousou E, Stripeli F, et al M. Influenza A/H1N1/2009 outbreak in a neonatal intensive care unit. J Hosp Infect 2012;81:36-40.
71 Acosta EP, Jester P, Gal P, Wimmer J, Wade J, Whitley RJ, et al. Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis 2010;202:563-566.
72 Holgate SL, Bekker A, Rabie H, Cotton MF. Oseltamivir use in low-birth weight infants during the 2009 nH1N1 influenza a outbreak in the Western Cape, South Africa. J Trop Pediatr 2012;58:102-106.
73 Nordin JD, Kharbanda EO, Vazquez Benitez G, Lipkind H, Vellozzi C, Destefano F, et al. Maternal influenza vaccine and risks for preterm or small for gestational age birth. J Pediatr 2014;164:1051-1057.
74 Chavant F, Ingrand I, Jonville-Bera AP, Plazanet C, Gras-Champel V, Lagarce L, et al. The PREGVAXGRIP study: a cohort study to assess foetal and neonatal consequences of in utero exposure to vaccination against A(H1N1)v2009 influenza. Drug Saf 2013;36:455-465.
75 Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA 2012;308:165-174.
76 Shen S, Campitelli MA, Calzavara A, Guttmann A, Kwong JC. Seasonal influenza vaccine effectiveness in pre- and full-term children aged 6-23 months over multiple seasons. Vaccine 2013;31:2974-2978.
77 Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001;344:1917-1928.
78 Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543-546.
79 Simoes EA. Respiratory syncytial virus infection. Lancet 1999;354:847-852.
80 Arnold SR, Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, et al. Variable morbidity of respiratory syncytial virus infection in patients with underlying lung disease: a review of the PICNIC RSV database. Pediatric Investigators Collaborative Network on Infections in Canada. Pediatr Infect Dis J 1999;18:866-869.
81 Wilkesmann A, Ammann RA, Schildgen O, Eis-Hübinger AM, Müller A, Seidenberg J, et al. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. Pediatr Infect Dis J 2007;26:485-491.
82 Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q 1992;45:180-191.
83 Hall CB, Walsh EE, Schnabel KC, Long CE, McConnochie KM, Hildreth SW, et al. Occurrence of groups A and B of respiratory syncytial virus over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 1990;162:1283-1290.
84 Sullender WM. Respiratory syncytial virus genetic and antigenic diversity. Clin Microbiol Rev 2000;13:1-15.
85 Resch B, Gusenleitner W, Müller W. The impact of respiratory syncytial virus infection: a prospective study in hospitalized infants younger than 2 years. Infection 2002;30:193-197.
86 Liese JG, Grill E, Fischer B, Roeckl-Wiedmann I, Carr D, Belohradsky BH, et al. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003;162:230-236.
87 Resch B, Gusenleitner W, Müller WD, Haas J. Observational study of respiratory syncytial virus-associated hospitalizations and use of palivizumab in premature infants aged 29-32 weeks. Eur J Clin Microbiol Infect Dis 2006;25:120-122.
88 Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 2000;154:55-61.
89 McCormick J, Tubman R. Readmission with respiratory syncytial virus (RSV) infection among graduates from a neonatal intensive care unit. Pediatr Pulmonol 2002;34:262-266.
90 Carbonell-Estrany X, Quero J, Bustos G, Cotero A, Doménech E, Figueras-Aloy J, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group. Pediatr Infect Dis J 2000;19:592-597.
91 McIntosh K. Respiratory syncytial virus infections in infants and children: diagnosis and treatment. Pediatr Rev 1987;9:191-196.
92 Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases. Philadelphia: Saunders, 1998: 2084-2111.
93 Kristensen K, Dahm T, Frederiksen PS, Ibsen J, Iyore E, Jensen AM. Epidemiology of respiratory syncytial virus infection requiring hospitalization in East Denmark. Pediatr Infect Dis J 1998;17:996-1000.
94 Resch B, Gusenleitner W, Mandl C, Müller W. Epidemiology of respiratory syncytial virus infection in Southern Austria. Pediatr Infect Dis J 2000;19:587-588.
95 Wert SE. Normal and abnormal structural development of the lung. In: Polin RA, Fox WW, Abmann SH, eds. Fetal and neonatal physiology. Philadelphia: Saunders, 2004: 784-794.
96 Ballow M, Cates KL, Rowe JC, Goetz C, Desbonnet C. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. Pediatr Res 1986;20:899-904.

97 Meert K, Heidemann S, Abella B, Sarnaik A. Does prematurity alter the course of respiratory syncytial virus infection? Crit Care Med 1990;18:1357-1359.
98 Joffe S, Escobar GJ, Black SB, Armstrong MA, Lieu TA. Rehospitalization for respiratory syncytial virus among premature infants. Pediatrics 1999;104:894-899.
99 Heikkinen T, Valkonen H, Lehtonen L, Vainionpää R, Ruuskanen O. Hospital admission of high risk infants for respiratory syncytial virus infection: implications for palivizumab prophylaxis. Arch Dis Child Fetal Neonatal Ed 2005;90:F64-F68.
100 Carbonell-Estrany X, Quero J, IRIS Study Group. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. Pediatr Infect Dis J 2001;20:874-879.
101 Law BJ, Langley JM, Allen U, Paes B, Lee DS, Mitchell I, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatr Infect Dis J 2004;23:806-814.
102 Figueras-Aloy J, Carbonell-Estrany X, Quero-Jiménez J, Fernández-Colomer B, Guzmán-Cabañas J, Echaniz-Urcelay I, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. Pediatr Infect Dis J 2008;27:788-793.
103 Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82:199-203.
104 Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. Pediatrics 1997;99:93-99.
105 Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102:531-537.
106 Thomas M, Bedford-Russell A, Sharland M. Hospitalisation for RSV infection in ex-preterm infants-implications for use of RSV immune globulin. Arch Dis Child 2000;83:122-127.
107 Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child 2001;85:463-468.
108 Flamant C, Hallalel F, Nolent P, Chevalier JY, Renolleau S. Severe respiratory syncytial virus bronchiolitis in children: from short mechanical ventilation to extracorporeal membrane oxygenation. Eur J Pediatr 2005;164:93-98.
109 Park A, Suh SI, Son GR, Lee YH, Seo HS, Eun BL, et al. Respiratory syncytial virus-related encephalitis: magnetic resonance imaging findings with diffusion-weighted study. Neuroradiology 2014;56:163-168.
110 Espinoza JA, Bohmwald K, Céspedes PF, Gómez RS, Riquelme SA, Cortés CM, et al. Impaired learning resulting from respiratory syncytial virus infection. Proc Natl Acad Sci U S A 2013;110:9112-9117.
111 Ricart S, Rovira N, Garcia-Garcia JJ, Pumarola T, Pons M, Muñoz-Almagro C, et al. Frequency of apnea and respiratory viruses in infants with bronchiolitis. Pediatr Infect Dis J 2014;33:988-990.
112 Erez DL, Yarden-Bilavsky H, Mendelson E, Yuhas Y, Ashkenazi S, Nahum E, et al. Apnea induced by respiratory syncytial virus infection is not associated with viral invasion of the central nervous system. Pediatr Infect Dis J 2014;33:880-881.
113 Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newbornsand infants. Ital J Pediatr 2014;40:65.
114 Ventre K, Randolph A. Withdrawn: ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2010;(5):CD000181.
115 Rodriguez WJ. Therapy of RSV. In: Weisman LE, Groothuis JR, eds. Contemporary diagnosis and management of respiratory syncytial virus. Pennsylvania: Handbooks in Health Care, 2000: 136-152.
116 Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532-540.
117 Subramanian KN, Weisman LE, Rhodes T, Ariagno R, Sánchez PJ, Steichen J, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. Pediatr Infect Dis J 1998;17:110-115.
118 Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013;368:1791-1799.
119 Carbonell-Estrany X, Simões EA, Dagan R, Hall CB, Harris B, Hultquist M, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. Pediatrics 2010;125:e35-e51.
120 Feltes TF, Sondheimer HM, Tulloh RM, Harris BS, Jensen KM, Losonsky GA, et al. A randomized controlled trial of motavizumab versus palivizumab for the prophylaxis of serious respiratory syncytial virus disease in children with hemodynamically significant congenital heart disease. Pediatr Res 2011;70:186-191.
121 Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements-Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics 2009;124:1694-1701.
122 Weiner LB, Masaquel AS, Polak MJ, Mahadevia PJ. Cost-effectiveness analysis of palivizumab among pre-term infant populations covered by Medicaid in the United States. J Med Econ 2012;15:997-1018.
123 Mahadevia PJ, Masaquel AS, Polak MJ, Weiner LB. Cost utility of palivizumab prophylaxis among pre-term infants in the United States: a national policy perspective. J Med Econ 2012;15:987-996.
124 Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling ofsubgroup analyses. Health Technol Assess 2011;15:iii-iv, 1-124.
125 Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev 2013;(4):CD006602.

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