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REVIEW

# Defining the Risk and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Infants with Chronic Lung Disease

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## ABSTRACT

**Introduction**: The REGAL (RSV evidence—a geographical archive of the literature) series provide a comprehensive review of the published evidence in the field of respiratory syncytial virus (RSV) in Western countries over the last 20 years. This third publication covers the risk and burden of RSV infection in infants with chronic lung disease (CLD), formerly called bronchopulmonary dysplasia (BPD).

**Methods**: A systematic review was undertaken of publications between January 1, 1995 and December 31, 2015 across PubMed, Embase, The Cochrane Library, and Clinicaltrials.gov. Studies reporting data for hospital visits/admissions for RSV infection among infants with CLD/BPD who were not prophylaxed, as well as studies reporting RSV-associated morbidity, mortality, and healthcare costs, were included. Burdens of disease data were compared with preterm infants without CLD/

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BPD, other high-risk groups and term infants. Study quality and strength of evidence (SOE) were graded using recognized criteria.

*Results*: A total of 1837 studies were identified and 39 were included. CLD/BPD is a significant independent risk factor for RSV hospitalization [RSVH (odds ratio 2.2–7.2); high SOE]. Infants and young children with CLD/BPD had high RSVH rates which were generally similar in Europe, the United States, and Canada, mostly varying between 12 and 21%. Infants with CLD also had a longer length of hospital stay than other high-risk groups and term infants (high SOE). On average, infants spent 4–11 days in hospital (moderate SOE). Once hospitalized for RSV, affected children were at risk for a more severe course of disease than children with no RSVH (moderate SOE).

*Conclusion*: Severe RSV infection in infants and young children with CLD/BPD poses a significant health burden in Western countries. Further studies focussing on the burden of RSV infection in this well-recognized population at high risk for severe disease are needed to help improve outcomes and plan allocation of healthcare resources.

## INTRODUCTION

Respiratory syncytial virus (RSV) is the most important cause of severe respiratory infection in infants, accounting for over 3 million hospitalizations worldwide each year [1]. Chronic lung disease (CLD) [formerly called bronchopulmonary dysplasia (BPD)] is the most common pulmonary complication of premature birth and increases the risk of RSV infection because it compromises lung function, distorts airway architecture, and promotes a pro-inflammatory milieu [2, 3]. Severe RSV infection is associated with substantial morbidity and constitutes a considerable burden on healthcare systems [4]. During the first 2 years of life, children with CLD/BPD are hospitalized for severe RSV at a higher rate than children born at term or more than 36 weeks gestational age (wGA) [5–7]. High-risk infants, including those with CLD/BPD, also have a significantly higher intensive care unit (ICU) admission rate and length of stay (LOS) in hospital, and require more invasive and longer respiratory support than near-term or full-term infants [8]. There is currently no curative treatment for RSV infection. Treatment focuses primarily on supportive measures, such as providing supplemental oxygen and ensuring adequate hydration. RSV immunoprophylaxis is the mainstay of disease prevention and is indicated for specific children at high risk of developing serious disease. Current published guidelines recommend that RSV immunoprophylaxis is offered to infants with CLD/BPD who require medical therapy, such as supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid treatment, within 6 months before the onset of the RSV season [9–15].

New RSV therapeutics are currently being developed [16]. Therefore, it is important that there is a greater understanding of CLD/BPD as a condition leading to enhanced risk for severe RSV disease in order to improve preventative and management strategies, improve overall patient outcomes, and reduce the burden on healthcare systems. To provide a

comprehensive understanding of severe RSV disease in Western societies, a panel of experts in RSV from the United States, Canada and Europe undertook an evidence-based search of the literature which has accumulated over the past two decades. REGAL (RSV Evidence—a Geographical Archive of the Literature) defines the current state of the art in our understanding of RSV as well as, importantly, identifying gaps in our knowledge and future areas of research. This paper, which represents the third in a series of seven publications covering a range of topics on RSV disease, identifies and describes the risks and associated morbidity and mortality of severe RSV infection requiring hospitalization in infants and young children with CLD/BPD in Western societies.

# METHODS

## Study Objective

REGAL addresses seven specific research questions, covering: overall epidemiology, prematurity, CLD/BPD, congenital heart disease (CHD), long-term respiratory morbidity, other high-risk groups (e.g. Down syndrome), and prevention, management and future perspectives. The systematic reviews undertaken to answer each research question all use the same broad methodology, which has been described elsewhere [17]. The full protocol and generic search terms for the systematic reviews are available as part of the online supplement. In brief, a systematic and comprehensive search of the medical literature electronically indexed in PubMed, EMBASE, the Cochrane Library and clinicaltrials.gov was conducted. The detailed search strategy used free-text search terms combined with Medical Subject Headings (MeSH). As per the ambit of REGAL, only studies conducted in Western

countries were included, which we defined as the United States, Canada, and Europe (including Turkey and the Russian Federation).

## Literature Search

In this systematic literature review, we sought to answer the key question: "What is the morbidity, long-term sequelae and mortality of infants and young children with CLD/BPD due to severe RSV lower respiratory tract infection?"

The search for this systematic review included studies conducted in children ≤18 years old and published between January 1, 1995 and December 31, 2015. The target population was infants and young children with CLD/BPD who had 'proven' or 'probable' RSV and had or had not received RSV immunoprophylaxis. We retained only studies that reported RSV hospitalization (RSVH) and outcome data for infants and young children with CLD/BPD. However, studies with mixed pediatric populations hospitalized with RSV were also considered if there were sufficient data on infants and young children with CLD/BPD. We limited publications by excluding meta-analyses and review articles. No language limits were set on the database searches, with the caveat that English translations of at least the abstract had to be available.

The following general terms and limits were used in MEDLINE (PubMed), EMBASE and the Cochrane Library: "RSV" OR "respiratory syncytial virus" AND "lower respiratory tract infection" OR "bronchiolitis" OR "pneumonia" AND "chronic lung disease" OR "CLD" OR "bronchopulmonary dysplasia" OR "BPD" AND "hospitalization" OR "predisposition" OR "risk factor" AND "limits: human, child (birth to 18 years)". The search results were supplemented by a review of the bibliographies of key articles for additional

studies and inclusion of relevant abstracts presented at key meetings. Other significant studies of the target population, published during the drafting of the manuscript, were also included in the review, as identified by the authors. Two reviewers (Smith and Blake) undertook the search, with any disagreements resolved after discussion with a third reviewer (Rodgers-Gray) and Carbonell-Estrany. All authors reviewed the search results, made any additions and amendments, and approved the final list of studies for inclusion.

### Definition of CLD/BPD

It is recognized that the working definitions of CLD and BPD have evolved over recent years, now targeting extremely preterm infants with structurally immature lungs and pulmonary vasculature due to a predominant arrest of lung growth as "new BPD" in contrast to the "original BPD" based on the Northway classification [18–23]. Since studies involving RSV do not uniformly include a definition of CLD/BPD, for completeness all reports describing infants with CLD/BPD were considered for inclusion in this review in order to elucidate the additional risk of RSV infection in infants with respiratory issues at birth. In general terms, we defined BPD in infants born at <32 weeks post-menstrual age as follows, based on established criteria [24]:

– *Mild BPD*: oxygen requirement for the first 28 days but in room air at 36 weeks post-menstrual age
– *Moderate BPD*: oxygen requirement for the first 28 days and oxygen <30% at 36 weeks post-menstrual age
– *Severe BPD*: oxygen requirement for the first 28 days and oxygen >30% or continuous positive airway pressure (CPAP) or

mechanical ventilation at 36 weeks post-menstrual age.

For infants born >32 weeks post-menstrual age, the definition was adjusted for the time endpoint of 56 days of life instead of 36 weeks post-menstrual age [25]. CLD was defined as the continuous need for oxygen or respiratory support beyond 36 weeks post-menstrual age.

### Outcomes of Interest

The outcomes of interest for this review included hospitalization rates due to severe RSV infection, hospital LOS, ICU admission and LOS, oxygen requirement, need for and duration of mechanical ventilation and/or non-invasive ventilation, and case-fatality rates.

### Evaluation of Data

Included publications were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence [26, 27]: level 1 evidence [local and current random sample surveys (or censuses)]; level 2 evidence (systematic review of surveys that allow matching to local circumstances); level 3 evidence (local non-random sample); and level 4 evidence (case-series). For each study, we also conducted a risk of bias assessment using the RTI Item Bank (score of 1 = very high risk of bias; score of 12 = very low risk of bias) for observational studies [28].

### Statement of Ethics Compliance

The analysis in this article is based on previously published studies and does not involve any new studies of human subjects performed by any of the authors.

# RESULTS AND DISCUSSION

## Articles Selected

From the initial literature search, we identified 2422 potentially relevant articles, of which 592 were duplicates (Fig. 1). After phase 1 screening of the titles, 215 articles were considered and reviewed at abstract level, while 183 abstracts were rejected for not meeting the selection criteria, the majority because the studies did not focus on the population of interest (children ≤18 years old in Western countries) or disease of interest (RSV burden or hospitalization). Thirty-nine studies were included of which 32 were identified from the literature search and an additional 7 from reference lists/other sources. Data extraction tables for all 39 studies,

including evidence grades and risk of bias assessments can be found in the online supplement.

## Incidence of RSV Hospitalization

Studies from the United States, Canada and Europe have shown that infants with CLD/BPD, particularly those born prematurely, are at high risk for RSV-associated hospitalizations in the first 2 years of life [5, 29–46]. Across a number of studies, CLD/BPD had the highest or, in one case, the second highest, odds ratio (OR) of all independently significant risk factors for RSVH (Table 1). In a retrospective cohort study of 1721 premature infants [23–36 weeks gestational age (wGA)], CLD, defined as ≥28 days of perinatal oxygen, was found to be
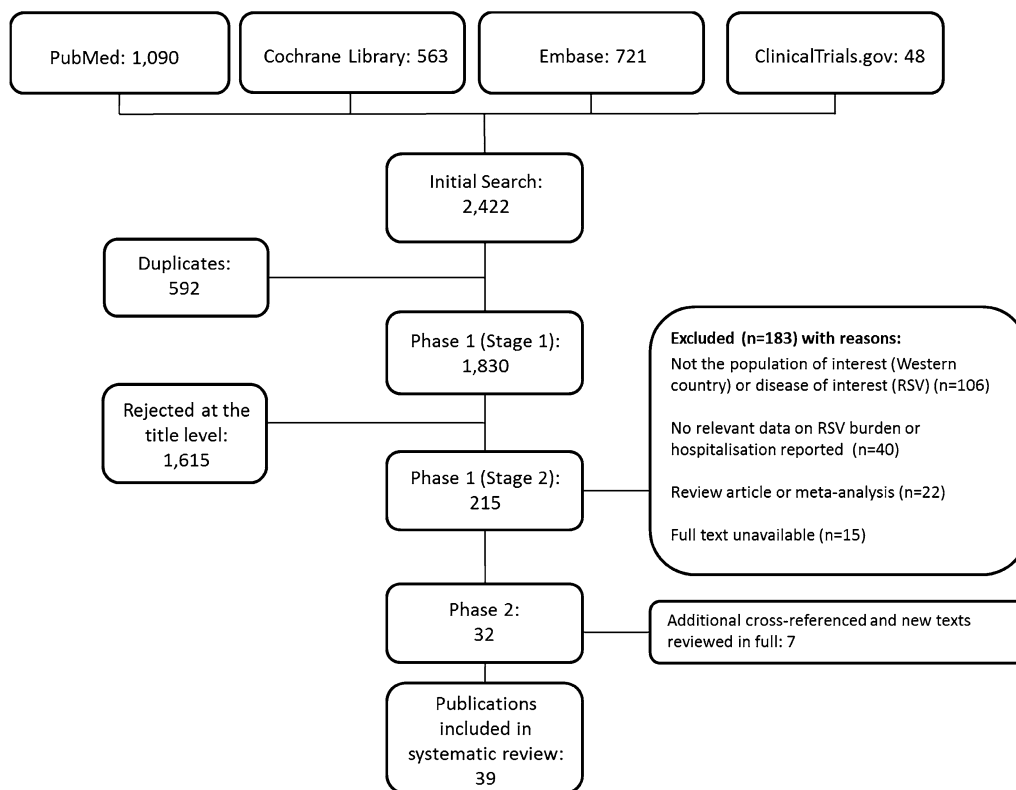


**Fig. 1** PRISMA flow diagram. Epidemiology and burden of RSVH in infants with CLD/BPD. The third reviewer (B.R.G.) and X.C.E. were not required to resolve any disagreements during the review process

**Table 1** Odds ratio for RSV hospitalization of infants with CLD/BPD without RSV immunoprophylaxis

| Study | Country | Design | Definition of BPD/CLD | Odds ratio (95 % CI)[a] BPD/CLD | Other predictors |
|---|---|---|---|---|---|
| Pederson 2003 [49] | Denmark | Retrospective study of 240 infants <28 wGA and/or birthweight <1000 g (12.5% CLD) born 1994–1995, ≤2 years old; 18% rehospitalized for RSV | Continued need for oxygen therapy at 36 weeks post-conceptual age | 2.2 (1.0–5.1) | Discharge between August and October: 2.0 (1.0–3.9) |
| Heikkinen 2005 [6] | Finland | Retrospective cohort study of 35,811 children (0.08 % CLD) born 1991–2000; 2.1% hospitalized for RSV | Continued need for oxygen therapy at 36 weeks post-menstrual age or if children <2 years required medical therapy within 6 months before the start of the RSV season | 6.3[b] (2.2–18.2) | ≤32 wGA without CLD: 3.6[b] (2.7–4.8); 33–35 wGA: 1.9[b] (1.4–2.6) |
| Liese 2003 [31] | Germany | Retrospective cohort study of 1103 infants ≤35 wGA discharged from NICU (1998–1999); 717 included in final analysis (7.4% CLD); 5.2% re-hospitalized for RSV | Continued need for oxygen therapy beyond 36 weeks post-conceptual age | 3.99 (1.4–11.2) | Male gender: 8.7 (2.6–29.1); day care attendance of siblings: 3.9 (1.9–8.3); discharge between October and December: 2.1 (0.99–4.4) |
| Ricart 2012 [29] | Spain | Prospective study of 484 infants <12 months admitted to the pediatric ward or PICU (2007–2008) for acute bronchiolitis; 410 positive for respiratory viruses included in final analysis (29% BPD) | As defined in Jobe and Bancalari [47]: need for oxygen therapy at 36 weeks post-conceptual age | 7.2 (1.2–43.3) | CHD: 4.7 (1.1-19.9); prematurity: 2.6 (1.3–5.1); fever: 1.8 (1.1–3.1) |

**Table 1** continued

| Study | Country | Design | Definition of BPD/CLD | Odds ratio (95 % CI)[a] BPD/CLD | Other predictors |
|---|---|---|---|---|---|
| Carbonell-Estrany 2000 [36] | Spain | Observational, prospective, longitudinal cohort study of 584 infants ≤32 wGA discharged from 15 Spanish neonatal units 1998–1999 (6.5% CLD); 20.2% re-hospitalized for respiratory disease (66.3% documented RSV infections) | Continued need for oxygen therapy at 36 weeks post-conceptual age | 3.1 (1.22–7.91) | Living with school age siblings: 1.86 (1.01–3.4) |
| Erikkson 2002 [38] | Sweden | 12-year retrospective study of 1503 cases of confirmed RSV infection (1987–1998); <24 months old; included infants with CLD (2.2% catchment area; 13% from other areas) | Preterm birth with a need for oxygen at 36 wGA and continuous medication[c] during all or part of the 6 months preceding hospitalization | 2.83 (1.08–7.42) | Previously healthy infants with versus without siblings: 2.42 (2.08–2.81); preterm infants without CLD with versus without siblings: 2.20 (1.37–3.53) |
| Joffe 1999 [32] | US | Retrospective cohort study of 1721 preterm infants (23–36 wGA) admitted post-NICU discharge at the start of the season (124 CLD); 3.2% re-hospitalized for RSV | Oxygen therapy for ≥28 days in the NICU | 3.7 (1.8–7.6) | 23–32 wGA: 2.6 (1.4–5.1); discharge from NICU September–November: 2.7 (1.6–4.7) |

*BPD* bronchopulmonary dysplasia, *CHD* congenital heart disease, *CI* confidence interval, *CLD* chronic lung disease, *NICU* neonatal intensive care unit, *PICU* pediatric intensive care unit, *RSV* respiratory syncytial virus, *wGA* weeks gestational age

[a] Ratio of odds of RSV hospitalization within the study population in the presence or absence of the risk factors/predictors specified in each case

[b] Relative risk

[c] Oxygen and/or inhaled medication and/or corticosteroids

a significant risk factor for RSVH (OR 3.7; $P < 0.001$ vs. those who required <28 days of oxygen) [32]. Similarly, in a population-based cohort study of 1103 infants born <35 wGA, CLD, defined as oxygen requirement beyond 36 weeks post-conceptual age, was found to be independently associated with RSVH [adjusted OR 3.99, 95 % confidence interval (CI) 1.4–11.2] [31]. When restricted to studies using a definition of 'a continued need for oxygen therapy at 36 weeks post-conceptual age', the OR for RSVH was 2.2–3.99. Overall, studies report ORs of between 2.2 and 7.2 for CLD/BPD as a risk factor for RSVH.

The reported incidence of RSVH in infants and young children with CLD/BPD who had not received RSV immunoprophylaxis varies between 12 and 46%, with 8 of 10 studies reporting an incidence of between 12 and 21% (Table 2) [6, 31, 32, 36, 41, 48–52]. In the Munich RSV study, the risk of RSVH was higher in preterm infants (≤35 wGA) with CLD compared with preterm infants (≤35 wGA) without CLD (15.0% vs. 4.4%) [31]. Taken together and discounting any heterogeneity across study populations, the average, weighted incidence of RSVH among 895 children with BPD/CLD in the identified studies (Table 2) was 16.8%. When limited to studies with a definition of BPD/CLD as 'a continued need for oxygen at 36 wGA', the weighted mean was also 16.8%.

During the first 2 years of life, children with CLD/BPD are hospitalized for severe RSV at a higher rate than children born at term (≥36 wGA) [5–7]. There is also some evidence that children with CLD/BPD have higher RSVH rates than those with CHD [7] or preterm infants without comorbidities [5, 7]. In a retrospective cohort study of all children <3 years old

enrolled in the Tennessee Medicaid program from July 1989 through June 1993 (248,652 child-years), the estimated RSVH rate per 1000 children in the first and second year of life was higher for those with BPD compared with other high-risk populations (Table 3) [7]. A population-based cohort study performed in the UK also reported higher RSVH rates during the first year of life among infants with CLD [56.2 per 1000 infants (95% CI 49.9–63.2)] compared with those born prematurely [47.3 per 1000 infants (95% CI 44.4–50.2)] and those born at term [22.4 per 1000 infants (95% CI 21.8–22.9)] [5]. In contrast, a Finnish study [6] showed that whilst significantly higher RSVH rates were reported for children with CLD than for children born at >36 wGA without CLD (12.0% vs. 1.9%; $P = 0.003$), differences in the admission rates between children with CLD and those born at ≤35 wGA were not significant. Comparing rates observed in various studies, particularly in children with CLD/BPD, is extremely difficult because of differences in methodology and the demographics of the study populations.

Data suggest that RSVH rates for infants with CLD/BPD have steadily decreased over the past 15 years [42, 53]. Findings from an 11-year cohort study (1998–2008) conducted in the US suggest that RSVH in children aged <2 years with CLD have steadily decreased even while all-cause hospitalizations in this high-risk population remained unchanged [53]. On average, about 966 hospitalizations for RSV (range 98–1373) per year were reported for children aged <2 years with CLD. Over the study period, the predicted rate of RSVH decreased significantly, by 48% (from 93.78 to 49.06 per 1 million children; $P = 0.013$). The authors suggest reasons for this decrease may

**Table 2** Hospitalization for RSV infection in the first 2 years of life in children with CLD/BPD who had not received RSV immunoprophylaxis

| Study | Country | Study participants | Definition of BPD/CLD | Number of children with CLD/ BPD | RSV hospitalization rate (%) |
|---|---|---|---|---|---|
| IMpact-RSV study 1998 [48] | US, UK and Canada | ≤24 months old[a] | Clinical diagnosis of BPD requiring ongoing medical treatment (i.e. supplemental oxygen, steroids, bronchodilators, or diuretics within the previous 6 months) | 266[c] | 12.8 |
| Pedersen 2003 [49] | Denmark | Preterm infants <28 wGA and/or birthweight <1000 g | Continued need for oxygen therapy at 36 weeks post-conceptual age | 30 | 30.0 |
| Heikkinen 2005 [6] | Finland | Preterm infants ≤35 wGA[b] | Continued need for oxygen therapy at 36 weeks post-menstrual age or if children <2 years required medical therapy within 6 months before the start of the RSV season | 25 | 12.0 |
| Grimaldi 2004 [52] | France | Preterm infants ≤32 wGA | Oxygen dependency at 28 days after birth | 26 | 46.2 |
| Liese 2003 [31] | Germany | Preterm infants <35 wGA | Continued need for oxygen therapy at 36 weeks post-conceptual age | 53 | 15.1 |
| Carbonell-Estrany 2000 [36] | Spain | Preterm infants ≤32 wGA | Continued need for oxygen therapy at 36 weeks post-conceptual age | 38 | 21.1 |
| Deshpande 2003 [41] | UK | Preterm infants <37 wGA | Continued need for oxygen therapy at 36 weeks post-menstrual age | 64 | 15.6 |
| Greenough 2001 [50] | UK | Preterm infants <32 wGA | Oxygen dependency beyond 28 days after birth | 235 | 19.1 |
| Thomas 2000 [51] | UK | Preterm infants <32 wGA | Continued need for oxygen therapy at 36 weeks post-conceptual age | 34 | 8.8 |
| Joffe 1999 [32] | US | Preterm infants ≤36 wGA | Oxygen therapy for ≥28 days in the NICU | 124 | 14.5 |

*BPD* bronchopulmonary dysplasia, *CLD* chronic lung disease, *NICU* neonatal intensive care unit, *RSV* respiratory syncytial virus, *wGA* weeks gestational age

[a] Study also included infants born ≤35 wGA and ≤6 months old

[b] Study included infants born ≥36 wGA, but all infants with CLD born ≤35 wGA

[c] Placebo group with BPD

**Table 3** RSV hospitalization rates for high-risk populations [7]

| Group | RSV hospitalization rate per 1000 children | |
|---|---|---|
| | First year of life | Second year of life |
| BPD | 388 | 73 |
| CHD | 92 | 18 |
| ≤28 wGA | 70 | 30 |
| 29 to <33 wGA | 66 | 8 |
| 33 to <36 wGA | 57 | 11 |
| Term (with no underlying medical condition) | 30 | 4 |

Data are from a retrospective cohort study of all children <3 years old enrolled in the Tennessee Medicaid program from July 1989 through June 1993 (248,652 child-years)

*BPD* bronchopulmonary dysplasia, *CHD* congenital heart disease, *RSV* respiratory syncytial virus, *wGA* weeks gestational age

include improved neonatal intensive care unit (NICU) and outpatient management of CLD, and possibly increased use of RSV immunoprophylaxis in this high-risk population [53].

## Morbidity and Healthcare Resource Utilization

Studies have demonstrated that hospitalization due to RSV infection among infants with CLD/BPD not only leads to an increased risk of morbidity but also increased healthcare resource utilization, including admission to NICU, oxygen supplementation, and mechanical ventilation [8, 30, 38, 41, 51, 54–59]. The typical length of stay in hospital for RSV infection for infants with CLD/BPD is 4–11 days compared to 2–5 days in premature or term infants without CLD/BPD (Table 4) [38, 41, 51, 57, 58]. Multivariate analyses have shown CLD/BPD to be significantly and independently associated with a complicated course of disease and use and duration of mechanical ventilation [54, 55]. BPD (oxygen dependency beyond 28 days) has

been associated with a requirement for extracorporeal membrane oxygenation (ECMO) support (OR 11.8, 95% CI 2.2–63.1; $P = 0.004$) [54].

Data from the Canadian PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) study [60] showed that there were no significant differences among infants with BPD and those with other pulmonary disorders (cystic fibrosis, recurrent aspiration pneumonitis, pulmonary malformation, neurogenic disorders interfering with pulmonary toilet, and tracheoesophageal fistula) for the morbidity measures: duration of hospitalization, ICU admission, duration of ICU stay, mechanical ventilation and duration of mechanical ventilation (overall hospitalization rate: 91 for infants with BPD vs. 68 for infants with other pulmonary disorders). However, the relatively small sample sizes of the respective sub-populations may have influenced the findings [60].

Greenough et al. [50] reported that preterm infants with CLD who require hospitalization for RSV infection have significantly greater morbidity in the first 2 years after birth than

**Table 4** Length of hospital stay, requirement for oxygen, intubation and/or mechanical ventilation, and mortality for infants with CLD/BPD without RSV immunoprophylaxis

| Study | Country (timeframe) | Study participants | Definition of BPD/CLD | Length of hospital stay, median days (IQR) | ICU admission (%) | Oxygen therapy (%) | Mechanical ventilation (%) | Case-fatality rate (%) |
|---|---|---|---|---|---|---|---|---|
| Eriksson 2002 [38] | Sweden (1987–1998) | 49 children with CLD hospitalized with RSV (median age: 9.1 months) vs. 108 children without CLD hospitalized with RSV (median age: 2.9 months) vs. 1212 children without risk factors[a] hospitalized with RSV (median age: 2.3 months) | Preterm infant requiring oxygen at 36 wGA and continuous medication[b] during all/part of the 6 months preceding hospitalization | 8 (4–30) vs. 5 (2–9) vs. 3 (2–4) | 29 vs. 34 vs. 13 | NR | 24 vs. 10 vs. 2 | 2.0 vs. 0.9 vs. 0.2 |
| Duppenthaler 2001 [58] | Switzerland (1998–2000) | 9 children with CLD hospitalized with RSV (median age: 9.3 months) vs. 216 children born >35 wGA without CLD hospitalized with RSV (median age: 3.7 months) | NR | 8 (2–17)[c] vs. 6.4 (1–30)[c] | 0 vs. 11.6 | NR | NR | 0 vs. 0.5 |
| Thomas 2000 [51] | UK (1995–1997) | 3 children with CLD hospitalized with RSV (median age: NR) | Continued need for oxygen therapy at 36 weeks post-conceptual age | 18[d]; 16[e] | NR | NR | NR | 0 |

**Table 4** continued

| Study | Country (timeframe) | Study participants | Definition of BPD/CLD | Length of hospital stay, median days (IQR) | ICU admission (%) | Oxygen therapy (%) | Mechanical ventilation (%) | Case-fatality rate (%) |
|---|---|---|---|---|---|---|---|---|
| Deshpande 2003 [41] | UK (1996–1999) | 10 children with CLD hospitalized with RSV (median age: 53 weeks) vs. 53 children born ≤36 wGA hospitalized with RSV (median age: 23.7 weeks) | Continued need for oxygen therapy at 36 weeks post-menstrual age | 3.5 (2–9) vs. 2 (1–4) | NR | NR | NR | NR |
| Zaw 2003 [57] | UK (1995–1999) | 4 children with RSV infection who developed BPD in SCBU (median age: NR) vs. children without BPD (median age: NR) | Oxygen dependency beyond 28 days after birth | 10.5 vs. 2.5 ($P = 0.04$) | NR | 100 vs. 28.6 ($P = 0.02$) | NR | NR |

*BPD* bronchopulmonary dysplasia, *CLD* chronic lung disease, *IQR* interquartile range, *NR* not recorded, *RSV* respiratory syncytial virus, *SCBU* special care baby unit, *wGA* weeks gestational age

[a] No CLD, cardiac lesions, respiratory tract malformation, other chronic disease, or preterm

[b] Oxygen and/or inhaled medication and/or corticosteroids

[c] Median (range)

[d] Total ward days for premature infants (<32 wGA) with CLD on home oxygen (in first RSV season encountered)

[e] Total ward days for premature infants (<32 wGA) with CLD who had stopped home oxygen in prior 6 months (in first RSV season encountered)

those without RSV infection. In this retrospective study, 235 preterm infants (<32 wGA) who were admitted to NICU during the first week after their birth and subsequently developed CLD (defined as an oxygen dependency beyond 28 days after birth) were followed until they were 2 years of age. Forty-five infants (19 %) had at least one hospital admission for a proven RSV infection. Compared with preterm infants (<32 wGA) with CLD/BPD with probable bronchiolitis and those with other respiratory problems, preterm infants with CLD/BPD and proven RSV infection had a longer length of stay in hospital (median: 21 vs. 6.5 and 8 days, respectively; $P < 0.001$) and longer duration of stay in pediatric wards (median 16 vs. 4.5 and 6 days, respectively). Outpatient attendances per infant during the first 2 years of life were also significantly higher in the RSV proven group ($P < 0.01$), as were primary care consultations for respiratory illnesses ($P < 0.05$) compared with the other groups [50]. Findings from a subsequent retrospective study of 190 of the original cohort of 235 children with CLD, published in 2004, showed that children who had been hospitalized with a proven RSV infection in the first 2 years required more health care for respiratory problems in years 2–4 inclusive [61].

These retrospective studies demonstrate that severe RSV infection in preterm children with CLD/BPD causes considerable morbidity, as indicated by their significantly higher use of health care resources compared to full-term children hospitalized for RSV infection [38, 41, 50, 51, 57, 58, 61]. However, too few data are available on infants with CLD/BPD admitted to NICU to allow more detailed conclusions to be drawn. This highlights the need for more studies specifically considering severe RSV infection in infants with CLD/BPD, as the majority of data in this high-risk group come from mixed populations of previously healthy children and preterm infants with and without CLD/BPD.

## Healthcare Costs

Data from the published literature show that RSVH in preterm infants with CLD is associated with substantial healthcare costs [4, 50, 61, 62]. In the 2001 retrospective study by Greenough et al. [50], preterm infants with CLD who had a proven RSV infection generated significantly higher costs of care, approximately three times those who were RSV-negative. In the subsequent study, published in 2004, costs were assessed over a 3-year period when the children were aged 2–4 years [61]. Compared with the non-RSVH group, these infants continued to incur significantly greater costs of care for respiratory problems in later childhood [median £2630 (€4000, US $4800), range £124–18,091 vs. £1360 (€2500, US $3000), range £5–18,929] [61]. In a population-based cohort study of 3458 infants and children hospitalized for severe RSV infection during the RSV seasons 1996–1997 to 1999–2000 in the Netherlands, RSVH costs were higher for infants with BPD (€5785) than for other high-risk groups, including those with lower gestational age (€5555), and lower birth weight (€3895). The authors observed that the differences in RSVH costs were mainly due to a longer duration of hospitalization [4]. Similarly, an observational, retrospective survey in Spain that analysed all RSVHs for children up to 5 years of age reported during the 1997–2011 period found that the average LOS and hospital costs

were significantly higher in high-risk children, including those with BPD [62].

Estimates of RSVH costs have been reported in other studies, but these were not differentiated by patient characteristics such as CLD/BPD, making comparisons difficult.

### Case-Fatality Rates

Few studies in the published literature on RSVH report case-fatality rates in infants with CLD/BPD, and therefore it is difficult to ascertain from the available data the precise number of true RSV deaths in this high-risk population. There are currently no data to suggest that case-fatality rates are higher in those children with CLD/BPD than in healthy term children or premature children without CLD/BPD [38, 51, 58, 63, 64].

## LIMITATIONS

There are two main limitations that merit consideration. First, the changing definitions of CLD/BPD over time may have affected the cross-comparisons that were generated between studies. Second, there was a lack of studies specifically investigating CLD/BPD. The majority of the studies identified comprised mixed populations, a proportion of which had CLD/BPD. In addition, other factors, such as improvements in medical practice over time and the type of RSV testing and surveillance systems employed will have influenced interpretation of the results. New studies should recognize that the established criteria for the definition of BPD [24, 65] may be used as a framework but are in a state of evolution [18, 22, 66] and, ideally, should include control for prematurity (stratified by gestational age) as

another well-recognized risk factor for RSVH. This will enable more meaningful comparisons between studies and thereby a more reliable assessment of the true burden of RSV infection in this at-risk population.

## CONCLUSIONS

This review has assessed, quantified and summarized all the key evidence for the burden of RSV infection in infants and young children with CLD/BPD in Western countries over the last 20 years. Data show that this specific population are particularly susceptible to developing severe RSV disease necessitating re-hospitalization and medical therapy, including supplemental oxygen and mechanical ventilation, following discharge from NICUs. Data suggest that the course of illness is more severe in children with CLD/BPD compared with otherwise healthy preterm infants and is associated with longer duration of hospital stay. Rates of RSVH among this high-risk group in European countries appear to be generally similar to those in the United States and Canada.

This systematic review provides further evidence that severe RSV infections in infants and young children with CLD/BPD still pose a significant health burden in Western countries. Most of our knowledge, however, has come from studies conducted more than a decade ago. These findings highlight the need for more up-to-date studies of the relative importance of CLD/BPD as a risk factor for severe RSV disease. Improved surveillance of this population will provide a more informative insight into the burden of disease to help improve outcomes and plan allocation of health care resources.

## SUMMARY BOX

| Key statements/findings | Level of evidence[a] |
|---|---|
| CLD/BPD is a highly significant independent risk factor for RSVH (OR 2.2–7.2) | Level 1 (level 1 studies: $n = 2$; risk of bias[b]: 11.0) |
| CLD/BPD has been associated with a higher rate of RSVH than other high-risk groups (e.g. CHD, preterm without comorbidities) and term infants | Level 1 (level 1 studies: $n = 3$; risk of bias[b]: 10.7) |
| The reported incidence of RSVH in infants and young children with CLD/BPD who have not received RSV immunoprophylaxis mostly varies between 12 and 21% | Level 1 (level 1 studies: $n = 3$; risk of bias[b]: 10.7) |
| Median stay in hospital for RSV infection in children with CLD/BPD is 4–11 days | Level 1–2 (level 1 studies: $n = 1$; level 2 studies: $n = 2$; risk of bias[b]: 10.7) |
| CLD/BPD is significantly and independently associated with a complicated course of disease, involving use and duration of mechanical ventilation and requirement for ECMO support | Level 1–3 (level 1 studies: $n = 1$; level 3 studies: $n = 1$; risk of bias[b]: 10.0) |

Key areas for research

More up-to-date research and specific studies are needed on the burden of severe RSV infection in infants and young children with CLD/BPD

Comparison of the morbidity and mortality incurred by infants with 'OLD' versus 'NEW' CLD/BPD

*BPD* bronchopulmonary dysplasia, *CHD* congenital heart disease, *CLD* chronic lung disease, *ECMO* extracorporeal membrane oxygenation, *LOS* length of stay, *OR* odds ratio, *RSVH* respiratory syncytial virus hospitalization
[a] Level 1: Local and current random sample surveys (or censuses); level 2: Systematic review of surveys that allow matching to local circumstances; level 3: Local non-random sample; level 4: case-series [26, 27]
[b] Average RTI Item Bank Score [28], where 1 = very high risk of bias and 12 = very low risk of bias

MedImmune, Janssen, Gilead and Novavax. Paul Checchia has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. He has also received research grant funding from AstraZeneca. Brigitte Fauroux has received compensation as a neonatology board member from AbbVie. Josep Figueras-Aloy has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. Paolo Manzoni has acted as a speaker for AbbVie, and as an expert advisor for AbbVie, TEVA, Medimmune, AstraZeneca, Janssen, and has received honoraria in this regard. Bosco Paes has received research funding from AbbVie Corporation and compensation as an advisor or lecturer from AbbVie and MedImmune. Eric Simões has received grant funding to his institution from Medimmune Inc, Glaxo Smith Kline Inc, and received consultancy fees to the institution, from AbbVie. Xavier Carbonell-Estrany has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard.

*Compliance with Ethics Guidelines.* The analysis in this article is based on previously published studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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