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REVIEW

Defining the Incidence and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Children with Chronic Diseases

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ABSTRACT

Introduction: REGAL (RSV Evidence—a Geographical Archive of the Literature) has provided a comprehensive review of the published evidence in the field of respiratory syncytial virus (RSV) in Western countries over the last 20 years. This review covers the risk and burden of RSV infection in children with underlying medical conditions or chronic diseases (excluding prematurity and congenital heart disease).

Methods: A systematic review of publications between January 1, 1995 and December 31, 2015 across PubMed, Embase, The Cochrane Library, and Clinicaltrials.gov was supplemented by papers identified by the authors through March 2017. Studies reporting data for hospital visits/admissions for RSV infection as well as studies reporting RSV-associated morbidity and mortality were included. Study quality and strength of evidence (SOE) were graded.

Results: A total of 2703 studies were identified and 58 were included. Down syndrome,

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irrespective of prematurity and congenital heart disease (moderate SOE), immunocompromised children (low SOE), cystic fibrosis (low SOE), and neurologic conditions (low SOE) were associated with a significantly increased risk of RSV hospitalization. A number of other congenital malformations and chronic conditions were also associated with severe RSV disease (low SOE). In general, pre-existing disease was also a predisposing factor for RSV-related mortality (low SOE).

Conclusion: Severe RSV infection in infants and young children with underlying medical conditions or chronic diseases poses a significant health burden. Further studies are needed to fully quantify the epidemiology, burden and outcomes in these populations, in particular RSV-attributable mortality.

Keywords: Bronchiolitis; Comorbidity; Congenital malformation; Cystic fibrosis; Down syndrome; Immunocompromised; Neuromuscular impairment; Outcomes; Respiratory syncytial virus lower respiratory tract infection; Transplant

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of childhood lower respiratory tract infection (LRTI) and a major cause of hospitalization in children younger than 5 years of age worldwide [1, 2]. Nearly all children have been infected with this virus at least once by the time they are 2 years of age, and, in most previously healthy children, the infection is self-limited and responds to supportive care [3]. It is well established that certain high-risk groups, including premature infants and those with chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD) and congenital heart disease (CHD), are at risk for severe disease [4–6]. Evidence also suggests that children immunocompromised through the administration of anticancer chemotherapy and especially those being transplanted [hematopoietic stem cell transplant (HSCT) recipients, bone marrow transplant (BMT) recipients, solid organ transplant (SOT) recipients] and those with Down syndrome face an increased risk of severe RSV LRTI [7–11]. Whilst CHD is common in children with Down syndrome (over 30% in those $\leq$1 year of age) [12–14], there is evidence that children with Down syndrome without CHD are also at increased risk of RSV hospitalization (RSVH) [15]. Other infants with chronic conditions, both congenital and acquired, including chromosomal abnormalities other than Down syndrome, congenital malformations, especially pulmonary and airway anomalies, cystic fibrosis, and human immunodeficiency virus (HIV) may also be associated with an increased vulnerability to severe RSV LRTI [10, 16, 17].

The clinical and economic burden of RSV LRTI in pediatric populations at high risk of severe disease is considerable [18–22]. Studies indicate that children with underlying medical conditions and RSV LRTI are admitted to hospital for longer periods of time, have a higher requirement for oxygen therapy, and more often require hospitalization in pediatric intensive care units (PICUs) than previously healthy children with RSV LRTI [21, 22]. A greater understanding of the epidemiology and burden of RSV LRTI in these children is required in order to develop strategies to reduce the morbidity and mortality associated with the disease. This paper, which represents the sixth in a series of seven publications covering a range of topics on RSV disease—The REGAL (RSV Evidence—a Geographical Archive of the Literature) series—identifies and describes the incidence and associated morbidity and mortality of RSV infection among children with underlying medical conditions or chronic diseases that place them at high risk for severe disease.

METHODS

The primary objective of REGAL was to provide a comprehensive understanding of severe RSV disease in Western societies, defined as the United States, Canada, and Europe (including Turkey and the Russian Federation), over the last 20 years. Seven specific research questions were addressed by a panel of experts in RSV

from the United States, Canada, and Europe. Previous publications have addressed: the overall burden and epidemiology of RSV disease [2]; the disease in premature children [4]; those with CLD [5]; CHD [6]; and long-term respiratory morbidity following RSV infection [23]. In this review, we sought to answer the following question: What is the predisposition of children with underlying medical conditions or chronic diseases (other than CLD and CHD) to severe RSV infection and related hospitalization?.

The systematic reviews undertaken to answer each research question all use the same broad methodology, which was described in detail in the first publication [2]. For the current review, due to the number of chronic conditions of interest, two separate comprehensive literature searches were undertaken in PubMed, EMBASE, and the Cochrane Library and the results combined. Both searches included studies published between January 1, 1995 and December 31, 2015. For the first literature search, we used the following general terms and limits combined with Medical Subject Headings (MeSH): "RSV" OR "respiratory syncytial virus" AND "Down syndrome" OR "trisomy 21″ AND "hospitalization" OR "predisposition" OR "risk factor" AND "limits: human." The corresponding terms and limits for the second search were: "RSV" OR "respiratory syncytial virus" AND "bone marrow" OR "stem cell" OR "hematopoietic cell" OR "solid organ" OR "liver" OR "renal" AND "transplant" OR "immunodeficiency" OR "immunocompromised" OR "cancer" OR "leukemia" OR "malignancy" OR "cerebral palsy" OR "cystic fibrosis" OR "neuromuscular impairment" OR "neurological disorder" OR "special populations" AND "limits: human". For both searches, age restrictions were not employed to enable capture of studies with mixed populations of children and adults.

The inclusion criteria were studies reporting 'proven' or 'probable' RSV infection in specific populations of children (aged ≤18 years): Down syndrome with or without CHD, immunodeficiency, neuromuscular impairment, cystic fibrosis, congenital airway anomalies (CAA), and other rare congenital and metabolic disorders. For completeness, studies reporting on mixed populations of healthy children and children with underlying chronic conditions/comorbidities and those including RSV immunoprophylaxis were included and the relevant data extracted where possible. Studies with the specific purpose of assessing RSV immunoprophylaxis were excluded from this systematic review. Also excluded were studies reporting solely on infants and children with CHD or CLD/BPD, since these high-risk groups were covered in separate publications in the REGAL series [5, 6]. 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 relevant studies published in 2016 and during the drafting of the manuscript were also included in the review, as identified by the authors.

Outcomes of Interest

In the absence of a standardized definition of severe RSV disease, we have taken this to be 'RSV infection requiring hospitalization' (RSVH) [2]. The following were outcomes of interest for this review: incidence of RSV, RSVH rates, hospital length of stay (LOS), PICU admission and LOS, oxygen requirement, need for and duration of mechanical ventilation and/or non-invasive ventilation, case fatality rates, and risk factors for severe RSV infection requiring hospital admission.

Evaluation of Data

Included publications were assessed against the Oxford Centre for Evidence-Based Medicine Levels of Evidence [24, 25] (Supplementary Material 1—REGAL Protocol). Each study was also subject to a risk of bias assessment using the RTI Item Bank for observational studies (score of 1 = very high risk of bias; score of 12 = very low risk of bias) [26]. No quantitative data synthesis was undertaken due to salient differences between studies in terms of design, patient populations, RSV testing, recording and availability of outcomes, and differences in clinical practice between countries and over time.

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.

RESULTS

Articles Selected

From the two literature searches, 2692 potentially relevant articles were identified, of which 607 were reviewed at abstract level following initial screening of titles (Fig. 1). Screening of abstracts resulted in a further 560 articles being rejected for not meeting the inclusion criteria, predominantly for not being focused on Western countries and/or RSV. The 47 relevant studies from the literature searches were supplemented by 11 studies identified from reference lists and other sources, resulting in a grand total of 58 studies included in the review. The online supplement includes data extraction tables for all 58 studies, including evidence grades and risk of bias assessments.

Incidence of RSV Infection and Outcomes

Down Syndrome

Clinical studies performed in the United States [15, 22, 27], Canada [28], and Europe [7, 10, 29–32] have demonstrated that children with Down syndrome are at increased risk of severe RSV disease and resulting morbidity, independent of concomitant CHD. Incidence

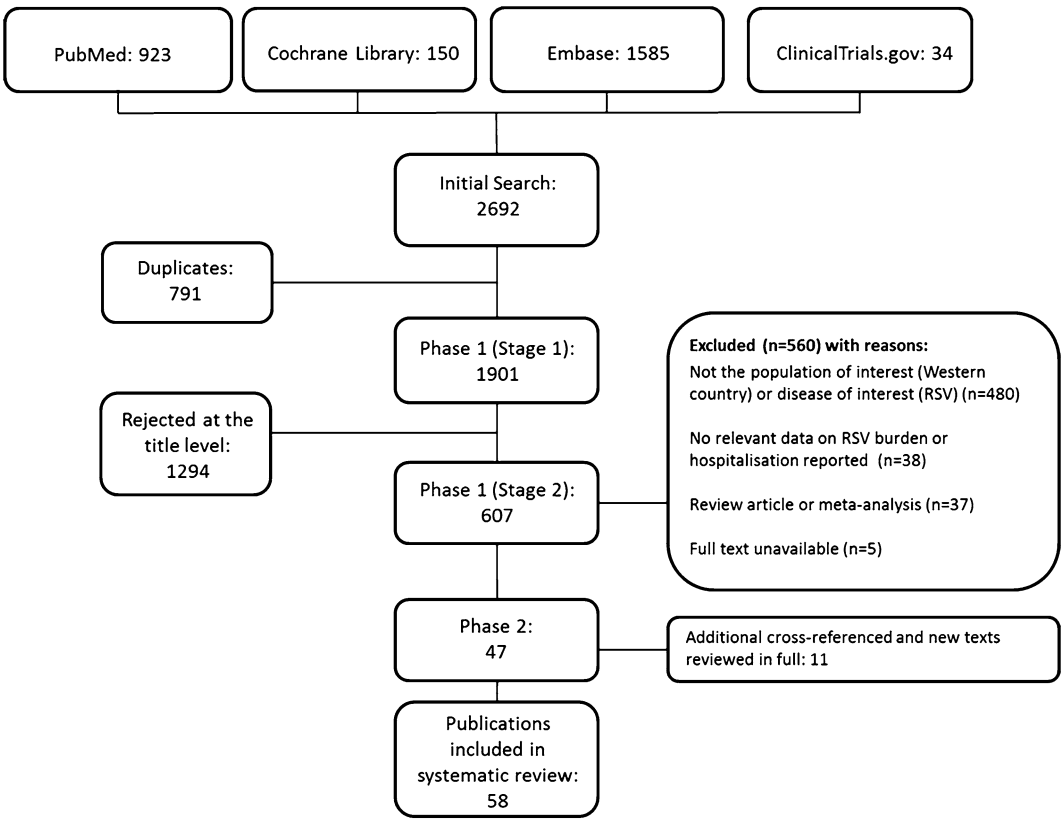

Fig. 1 PRISMA flow diagram: Incidence and burden of RSV in pediatric populations at high risk for RSV infection. *RSV* respiratory syncytial virus. References were screened for inclusion in two Phases. Phase I screening was split into two Stages: Stage 1—based on title and, for those meeting the inclusion criteria, Stage 2—based on abstract. Those references retained after Phase 1 were assessed based on the full paper in Phase 2

Table 1 RSV hospitalization, healthcare resource utilization, and case fatality rates in infants and children with Down syndrome

Study	Country	Design/study population	Incidence RSVH (per 1000)	Hospital LOS, median days (IQR)	Admission to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/ or mechanical ventilation (%)	Case fatality rate (%)
Studies specifically assessing children with Down syndrome								
Sánchez Luna 2017 [29]	Spain	Prospective multicenter study (2012–2013) of 93 term infants aged <12 months with Down syndrome and no risk factors for RSV and 68 matched control infants with no risk factors for RSV; 35.5% Down syndrome cohort received RSV immunoprophylaxis	97[a] (108[b])	7.3	14.3	53.6	3.6	0
Stagliano 2015 [22]	US	Retrospective cohort study of 633 200 children born 2005–2011, 842 of whom had Down syndrome; for children with Down syndrome, 64 of 81 (79%) hospitalized for RSV had ≥1 concomitant risk factor and CHD was present in 50%. Excluded children receiving RSV immunoprophylaxis	96[c]	4 (2–7)	NR	NR	9.3	NR
Zachariah 2012 [27]	US	Population-based study of 630 children aged <2 years with Down syndrome hospitalized for RSV in 2000–2006 [580 (92%) had concurrent underlying conditions]. CHD present (<1 year 31.8%; 1–2 years 15.4%). One child with CLD received RSV immunoprophylaxis	135	<1 year: 4 1–2 years: 5	NR	NR	<1 year: 8.2 1–2 years: 9.6	NR
Gooch 2011 [15]	US	Retrospective study (2001–2007) of 196 children aged <2 years with Down syndrome without concurrent CHD or BPD and 784 matched term controls. Excluded children receiving RSV immunoprophylaxis	36[a]	4.4 (2.7)[d]	NR	NR	NR	NR
Medrano Lopez 2009 [30]	Spain	Prospective study (2006–2007) of 1085 children aged <2 years of whom 279 (25.7%) had Down syndrome (48% with significant CHD). 39.9% of Down syndrome cohort received RSV immunoprophylaxis	78	7[e]	28.4[e]	NR	14.7[e]	NR
Bloemers 2007 [31]	Netherlands	Three groups studied (1) Retrospective observational study of 206 children with Down syndrome born between 1976 and 2005 (2) Prospective birth-cohort study of 241 children with Down syndrome born between 2003 and 2005 followed until 2 years old (45.6% had ≥1 risk factor for severe RSV); (3) unmatched control group of 276 siblings of birth cohort. 36% had hemodynamically significant CHD. No information on RSV immunoprophylaxis	99[f]	10	NR	79.5	12.8	NR

Table 1 continued

Study	Country	Design/study population	Incidence RSVH (per 1000)	Hospital LOS, median days (IQR)	Admission to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/ or mechanical ventilation (%)	Case fatality rate (%)
Studies that included a subset of children with Down syndrome								
Pisesky 2016 [28]	Canada	Retrospective chart review that identified (using ICD10 codes) 19 815 children (<3 years) hospitalized for RSV from 2005 to 2013. 145 RSVHs for children with Down syndrome. No information on RSV immunoprophylaxis	70	NR[g]	NR[g]	NR[g]	NR[g]	NR[g]
Murray 2014 [7]	UK	Retrospective multicenter study (2007–2008) of 7189 children aged <12 months admitted to hospital with bronchiolitis [28 (0.4%) with Down syndrome]. No information on RSV immunoprophylaxis	154	3 (0–9)	NR	NR	NR	NR
Kristensen 2012 [10]	Denmark	Register-based cohort study of 452 205 children aged <2 years of whom 12 498 (2.8%) were hospitalized for RSV from 1997 to 2003. 78/399 RSVHs for children with Down syndrome. During the study period, 118 of total population received RSV immunoprophylaxis	195	1.9 (1.5–2.4)[h]	NR[g]	NR[g]	NR[g]	NR[g]
Fjaerli 2004 [32]	Norway	Population-based retrospective study of 764 children aged ≤2 years hospitalized for RSV between 1993 and 2000 [4 of 7 (57%) children with Down syndrome had CHD]. No information on RSV immunoprophylaxis	135 (154[b])	7.5 (range 2–34)	NR	NR	28.6	14.3[i]

Outcome	Number of studies	Number of countries	Population age range and timeframe of studies	Value
Summary				
Incidence of RSVH	10	7	<3 years; 1976–2013	36–195 per 1000 children
LOS	7[j]	5	<3 years; 1976–2013	3–10 days
Admission to ICU/PICU	1[j]	1	<1 year; 2012–2013	14.3%
Supplemental oxygen	2	2	≤2 years; 1976–2013	53.6–79.5%
Intubation and/or mechanical ventilation	3[j]	3	≤2 years; 1976–2013	3.6–28.6%

Table 1 continued

Outcome	Number of studies	Number of countries	Population age range and timeframe of studies	Value
Case fatality rate	2	2	≤2 years; 1993–2013	0–14.3%

BPD bronchopulmonary dysplasia, *CHD* congenital heart disease, *CLD* chronic lung disease, *ICD-10* International Classification of Diseases, 10th revision; *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *NR* not recorded, *PICU* pediatric intensive care unit, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization

[a] Excluded children with CHD, CLD and those born prematurely

[b] Rate based on number of episodes

[c] Also reported an incidence density rate for RSV hospitalization (calculated by diving the number of patients hospitalized for RSV by the person-years at risk) of 195 per 1000 person-years

[d] Mean (standard deviation)

[e] Data for infants with acute respiratory tract infections; no specific data for RSV

[f] Data available for 176 children in retrospective cohort and 219 in prospective cohort

[g] No specific data for children with Down syndrome

[h] Geometric mean ratio (95% confidence interval) for presence of Down syndrome vs. non-presence of condition; $P < 0.001$

[i] Child also had CHD

[j] Excludes study by Medrano Lopez [30], as no specific data on RSV

rates of RSVH ranged from 70 to 195 per 1000 children (<3 years) with Down syndrome, when including those with concurrent CHD and other associated risk factors for severe RSV infection (Table 1) [7, 10, 15, 22, 27–32]. Zachariah et al. [27], using statewide data from Colorado in the US, reported a RSVH rate of 67 per 1000 child-years in children (≤2 years) with Down syndrome compared with 12 per 1000 child-years in matched (by date of admission) children without Down syndrome [odds ratio (OR) 6.0, 95% confidence interval (CI) 5.4–6.7]. RSVHs predominantly occurred in older children (OR 2.4, 95% CI 1.7–3.4), with a higher proportion in boys, and were more commonly associated with CHD and pulmonary hypertension [27]. Similar findings were reported in a UK population-based birth cohort study by Murray et al. [7], which found that admission rates were higher among children aged <12 months with Down syndrome (154 per 1000 infants) compared with those born at term without RSV-associated risk factors (22 per 1000 infants). Down syndrome was found to significantly increase the risk of RSVH in this population [relative risk (RR) 2.5, 95% CI 1.7–3.7] [7]. Down syndrome was also found to be a significant risk factor for RSVH in a national population-based study conducted in Denmark [<2 years; incidence rate ratio (IRR) vs. otherwise healthy children 3.4, 95% CI 2.7–4.4; $P < 0.001$] [10]. In a US retrospective cohort study, it was shown that the risk of severe RSV LRTI remains high through the third year of life in children with Down syndrome versus those without the diagnosis [24–36 months: hazard ratio (HR) 5.1, 95% CI 2.2–11.6] [22].

Down syndrome has also been shown to increase the risk of RSVH in the absence of co-existing risk factors for severe RSV disease [15, 22, 27, 29, 31], in particular CHD, which has been reported in 15–57% of such children [22, 27, 30–32]. A prospective study in Spain by Sánchez-Luna et al. [29] reported a higher rate of RSVH in infants (<12 months) with Down syndrome without other associated risk factors for severe RSV infection (including CHD, BPD, and prematurity) than in matched (by sex and date of birth) infants without Down syndrome and risk factors (97 vs. 15 per 1000 infants,

respectively; $P = 0.03$). In their combined prospective–retrospective study, Bloemers et al. [31] from the Netherlands reported an OR for RSVH of 10.5 (95% CI 2.2–49.5) among term children (≤2 years) with Down syndrome without any CHD in comparison to healthy controls (OR 12.6, 95% CI 2.9–54.5, when including children with hemodynamically insignificant CHD). The study by Zachariah et al. [27] also reported a significantly elevated rate of RSVH in children (≤2 years) with Down syndrome but without risk factors for RSV (including CHD, CLD, prematurity, pulmonary hypertension, and neuromuscular disease; 42 vs. 12 per 1000 child-years in children without Down syndrome; OR 3.5, 95% CI 3.1–4.1), though this rate was lower than that for children with Down syndrome and associated risk factors (67 per 1000 child-years). Another US study, using a medical claims database, found a significantly higher rate of RSVH in children (≤2 years) with Down syndrome than matched control children (by birth, gender and State), when diagnoses of CHD and BPD and those born prematurely were excluded (36 vs. 8 per 1000 children, respectively; OR 4.8, 95% CI 1.6–14.5; $P = 0.005$) [15]. Similarly, the US study by Stagliano et al. [22] reported an incidence density for RSVH of 12.7 per 1000 person-years in children (<3 years) with Down syndrome but without risk factors (CLD, CHD, neuromuscular disease, immunodeficiency, cystic fibrosis, CAA, or prematurity) versus 2.5 per 1000 person-years in healthy children (rate ratio 5.08, 95% CI 3.2–8.2) [22].

Children with Down syndrome spent an average of 3–10 days in hospital for RSV LRTI [7, 15, 22, 27, 29, 31, 32]. Comparative studies have shown that children with Down syndrome have a longer hospital stay than those without the condition, irrespective of the presence of other risk factors for severe RSV disease [22, 27]. In the US study by Stagliano et al. [22], children with Down syndrome had a median LOS of 4 days (5 days for those without risk factors) compared with 2 days in children without Down syndrome ($P < 0.001$ for both). There was also a greater risk of requiring respiratory support, including respiratory intubation and/or mechanical ventilation, with Down syndrome (RR 5.6, 95% CI 2.5–12.3, $P < 0.001$). Zachariah et al. [27] also reported a significantly longer LOS for children with Down syndrome aged 1–2 years compared to those without the condition (median 5 vs. 2 days, respectively; $P < 0.001$), as well as an increased severity of disease (severity scores >2 on the 3M Health Information Systems All Patient Refined Diagnosis Related Groups severity coding scale; <1 year: 50.6% vs. 10.9%, $P \leq 0.001$; 1–2 years: 36.5% vs. 11.0%, $P \leq 0.001$), and higher rates of mechanical ventilation, particularly in older children (1–2 years: 9.6% vs. 1.7%; $P \leq 0.001$). Importantly, this effect was seen even when hospitalizations with other clinical risk factors for RSV were excluded from the analysis [27].

Immunocompromised Children

Studies undertaken in the United States [20, 33–46], Canada [9, 47], and Europe [7, 10, 17, 48–55] provide compelling evidence that children who are immunocompromised are at high risk for severe RSV infection. The majority of studies focused primarily on HSCT/BMT recipients (16 of 22 studies in Table 2), though data were also available on SOT recipients and cancer patients undergoing chemotherapy and, to a lesser extent, children with primary immunodeficiency, HIV, and those on immunosuppressant therapy and/or corticosteroids. Incidence rates of RSV infection have been reported as high as 200 per 1000 children during an RSV outbreak among pediatric patients hospitalized for various hemato-oncological diseases in Turkey, including those who had undergone HSCT [50]. Of the studies providing information on the incidence of RSV infection in immunocompromised children, 10 of 13 reported rates of between 18 and 72 per 1000 (range 0–200 per 1000) (Table 2). There appeared to be considerable variation in the rates of RSV infection in different patient groups depending on the specific cause(s) of the compromised immune system. For example, a Spanish study by Mendoza Sánchez et al. [17] retrospectively reviewed respiratory viral infections in children aged ≤14 years and found rates of RSV infection were twice as high in patients with HIV than those receiving chemotherapy for cancer (101 vs. 46 per 1000, respectively).

Table 2 RSV hospitalization, healthcare resource utilization and case fatality rate in immunocompromised infants and children

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Studies of children ≤2 years									
Murray 2014 [7]	UK	Retrospective multicenter study (2007–2008) of 7189 children aged <12 months admitted to hospital with bronchiolitis [7 (0.1%) were immunocompromised]. No information on RSV immunoprophylaxis	NA	117	8 (1–58)	NR	NR	NR	NR
Kristensen 2012 [10]	Denmark	Register-based cohort study of 452 205 children aged <2 years of whom 12 498 (2.8%) were hospitalized for RSV from 1997 to 2003. 7/83 RSVHs for children with cancer. During the study period, 118 of total population received RSV immunoprophylaxis	NR	187	1.1 (0.4–2.9)[a]	NR[b]	NR[b]	NR[b]	NR[b]
Simon 2008 [48, 49]	Germany	Prospective, multicenter study of 39 hospitalized infants (<1 year) with cancer who had an RSV infection between 1999 and 2005; no information on RSV immunoprophylaxis	NA (study population)	NA (study population)	7 (2–35)	13	44	3	0
Wang 1995 [42]	US	Multicenter, prospective cohort study of 689 children aged <2 years hospitalized with an RSV infection in 1993 (21 immunocompromised children[c]); no information on RSV immunoprophylaxis	NA (study population)	NA (study population)	10[d]	19.1[d]	NR[d]	14.3[d]	4.8[d]
Studies of children ≤18 years									
Feldman 2015 [35]	US	Retrospective cohort study of 2554 children aged <18 years who had a liver transplant between 2004 and 2013; no information on RSV immunoprophylaxis	72	40[e]	NR	20.9	NR	9.3	4.9[e]

Table 2 continued

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Hutspardol 2015 [9]	Canada	Retrospective study of 844 children [median age 7.5 years (range 1 month–17.8 years)] who underwent HSCT (allogeneic 491, autologous 353) between 2000 and 2012; 1 child (0.1%) received RSV immunoprophylaxis	18	NR	NR	NR	NR	0.2	6.7
Robinson 2015 [8]	Canada	Surveillance study of 24 inpatients and outpatients aged <17 years who had received HSCT or SOT and had an RSV infection within 2 years post-transplant (2010–2013); 2 children (8.3%) had/possibly received RSV immunoprophylaxis	NA (study population)	NA[f]	NR	29	NR	21	8.3
Chemaly 2014 [37]	US	Retrospective study of 59 children aged <18 years with cancer (solid tumor 15%; hematologic malignancy 53%; HSCT 32%) with RSV between 1998 and 2009; no information on RSV immunoprophylaxis	NA (study population)	NA[g] (study population)	6 (2–9)	10	NR	5	5
Lo 2013 [39]	US	Retrospective study of 2375 children who received HSCT or SOT or had cancer at a tertiary center (1993–2006); median age 6.1 and 4.3 years, respectively; no information on RSV immunoprophylaxis	37[h]	NR[i]	NR[i]	NR[i]	NR[i]	NR[i]	NR[i]
Asner 2013 [47]	Canada	Single-center observational study of 117 immunocompromised children aged <18 years (HSCT 13.7%; SOT 16.2%; solid tumors 16.2%; leukemia/lymphoma 28.2%; immunosuppression for chronic condition 1.7%) with positive RSV infection from 2006 to 2011; 15 (12.8%) children received RSV immunoprophylaxis	NA (study population)	NA[j] (study population)	9 (5–24.5)	23.9	NR	17.1	4.3

Table 2 continued

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Tran 2013 [38]	US	Retrospective study of 30 children aged ≤18 years who received an abdominal organ transplant, hospitalized with a positive respiratory illness in 2008–2011; 5 patients (16.7%) with RSV; children <24 months old received immunoprophylaxis	NA (study population)	NA (study population)	NR	NR	NR[i]	NR	40
Anak 2010 [50]	Turkey	Retrospective survey of two RSV outbreaks (2006; 2009) among 30 pediatric patients hospitalized for hemato-oncological diseases treated with or without HSCT; no information on RSV immunoprophylaxis	200	NA	NR	NR	NR[i]	0	0
Sung 2008 [40]	US	Retrospective review of 3 Children's Oncology Group AML trials (2003–2005); 2078 children with de novo AML (median age 8.7 years); no information on RSV immunoprophylaxis	0–22[k]	NR	NR	NR	NR	NR	0.2
Mendoza Sánchez 2006 [17]	Spain	Retrospective study of 347 children aged ≤14 years diagnosed with cancer and receiving anticancer therapy ($n = 218$) or HIV infection ($n = 129$) (1989–2003)	101 (HIV); 46 (cancer)	NR[i]	NR[i]	NR[i]	NR[i]	NR[i]	0 (HIV); 20.0 (cancer)
Small 2002 [45]	US	Single center, retrospective study of 548 allogenic HSCT (including 154 children <19 years) and 394 autologous HSCT recipients from 1994 to 1999; no information on RSV immunoprophylaxis	175[l]	NR	NR	NR	NR	NR	12[m]
Miller 1996 [41]	US	Retrospective study of 173 pediatric recipients of renal transplantation between 1985 and 1993; no information on RSV immunoprophylaxis	30	NR	NR	NR	NR	0	0

Table 2 continued

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Studies of mixed populations of children and adults									
Chu 2016 [33]	US	Single-center retrospective cohort study of 15 children and young adults aged <21 years with HSCT, SOT or hematologic malignancy with RSV diagnosed as an outpatient between 2008 and 2013; no patient received RSV immunoprophylaxis	NA (study population)	NA[n]	NR	2	6	0	0
Campbell 2015 [34]	US	Prospective study of 458 patients (52 children aged <18 years) who underwent allogeneic HSCT between 2005 and 2010; no information on RSV immunoprophylaxis	19[o]	NA	NR	NR	NR	NR	0[o]
El-Bietar 2015 [36]	US	Prospective study of 349 consecutive patients aged 6 months–25 years who underwent BMT between 2008 and 2013; no information on RSV immunoprophylaxis	52[p]	NR	NR	NR	NR	NR	0
Liu 2009 [44]	US and Europe[q]	Multicenter, retrospective study of 576 lung transplant recipients (≤21 years) from 1988 to 2005; no information on RSV immunoprophylaxis	36[e,h]	NR	NR	NR	NR	NR	NR
El Saleeby 2008 [20]	US	Retrospective study of 58 cases of RSV in immunocompromised pediatric patients aged <21 years (40% ALL, 19% solid tumors, 41% HSCT recipients, AML, or SCID) between 1997 and 2005; no information on RSV immunoprophylaxis	NA (study population)	NA (study population)[p,r]	7 (3–51)[p]	NR	22[p]	9[p]	8.6[p,s]

Table 2 continued

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Luján-Zilbermann 2001 [43]	US	Single center, retrospective review of 281 HSCT recipients (including hematological malignancies, solid tumors, sickle cell disease, metabolic disorders, primary immunodeficiencies) from 1994 to 1997; mean age 9.28 (0.2–22) years; no information on RSV immunoprophylaxis	17[e]	11	NR	NR	NR	NR	0
McCarthy 1999 [51]	UK	Single-center retrospective study of 336 patients [median age 10.6 years (range 0.5–31.1)] who received BMT between 1993 and 1998; no information on RSV immunoprophylaxis	63[t]	NA	NR	NR	NR	NR	19.2

Outcome	Number of studies	Number of countries	Population age and timeframe of studies[u]	Value
Summary				
Incidence of RSV infection	13	7	≤31 years; 1985–2013	0–200 per 1000 population
Incidence of RSVH	4	3	≤22 years; 1994–2013	11–187 per 1000 population
LOS, median	6	4	<21 years; 1993–2011	6–10 days
Admission to ICU/PICU	7	3	<21 years; 1993–2013	2–29%
Supplemental oxygen	4	2	<21 years; 1993–2013	6–44%
Intubation and/or mechanical ventilation	10	4	<21 years; 1993–2013	0–21%

Table 2 continued

Outcome	Number of studies	Number of countries	Population age and timeframe of studies[u]	Value
Case fatality rate	17	6	≤31 years; 1985–2013	0–40%

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia; *HIV* human immunodeficiency syndrome, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *LOS* length of stay, *LRTI* lower respiratory tract infection, *NA* not applicable, *NR* not recorded, *PICU* pediatric intensive care unit, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization, *SCID* severe combined immunodeficiency syndrome, *SOT* solid organ transplant, *URTI* upper respiratory tract infection

[a] Geometric mean ratio (95% confidence interval) for presence of cancer vs. non-presence of condition; $P = 0.814$

[b] No specific data for children with cancer

[c] Includes immunodeficiency, immunosuppressant therapy and use of corticosteroids

[d] Data for immunocompromised cohort

[e] RSV rate during first year post-transplant

[f] 11 of 24 (45.8%) children with RSV hospitalized

[g] 34 of 59 (57.6%) children with RSV infection were hospitalized

[h] Rate based on number of episodes

[i] No specific data for infants/children with RSV infection

[j] 64.1% patients admitted due to RSV; 35.9% nosocomial acquisition of RSV

[k] Prevalence based on children in induction and consolidation for AML

[l] Data for pediatric population aged <19 years who underwent allogenic HSCT

[m] Mortality in patients with LRTI from pooled allogenic and autologous group including children and adults

[n] 15 of 54 (27.8%) children with RSV infection were hospitalized

[o] Data for pediatric population aged <18 years

[p] Data for pediatric and young adult patients

[q] European counties include UK, Germany and Austria

[r] 36% of children with RSV infection were hospitalized

[s] Overall mortality rate

[t] RSV identified during 5-year study period

[u] Includes studies whose populations contain patients up to 21 years old [44], 22 years old [43], 25 years old [36], and 31 years old (median age 10.6 years) [51]

Table 3 RSV hospitalization, healthcare resource utilization and case fatality rate in infants and children with cystic fibrosis

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Deschamp 2015 [61]	US	Interim analysis of multicenter, prospective study estimated to enroll 90 infants (<4 months at recruitment) with CF. Analysis included 13 infants with CF who had 59 nasopharyngeal samples collected and tested using viral PCR analysis over 11 months. No information on RSV immunoprophylaxis	77[a]	NR	NR	NR	NR	NR	NR
Murray 2014 [7]	UK	Retrospective, multicenter study (2007–2008) of 7189 children aged <12 months admitted to hospital with bronchiolitis [11 (0.2%) with CF]. No information on RSV immunoprophylaxis	NA	64	2 (0–14)	NR	NR	NR	NR
Kristensen 2012 [10]	Denmark	Register-based cohort study of 452 205 children aged <2 years of whom 12 498 (2.8%) were hospitalized for RSV from 1997 to 2003. Included 72 children with CF of whom 13 were hospitalized for RSV infection. During the study period, 118 of the total population received RSV immunoprophylaxis	NR	181	1.3 (0.8–2.1)[b]	NR[c]	NR[c]	NR[c]	NR[c]

Table 3 continued

Study	Country	Design/study population	Incidence RSV (per 1000)	Incidence RSVH (per 1000)	LOS, median days (range)	Admitted to ICU/ PICU (%)	Supplemental oxygen (%)	Intubation and/or mechanical ventilation (%)	Case fatality rate (%)
Garcia 2007 [62]	US	Single center, prospective study of 44 children with CF (7–18 years) during the 1998–1999 RSV season. No information on RSV immunoprophylaxis	364[d]	NR[e]	NR	NR	NR	NR	NR
Arnold 1999 [60]	Canada	Secondary analysis of a prospective cohort (1993–1995) including 159 children with underlying lung disease, 8 of whom had CF (mean age 33 weeks). No information on RSV immunoprophylaxis	NR	NA (study population)	11 (4–13)	12.5	NR	0	0

Outcome	Number of studies	Number of countries	Population age and timeframe of studies	Value
Summary				
Incidence of RSV infection	2	1	≤18 years; 1998–2015	77–364 per 1000 children
Incidence of RSVH	2	2	<2 years; 1997–2008	64–181 per 1000 children
LOS, median	2	2	<1 year; 1993–2008	2–11 days
Admission to ICU/PICU	1	1	<2 years; 1993–1995	12.5%
Supplemental oxygen	–	–	–	–
Intubation and/or mechanical ventilation	–	–	–	–

Table 3 continued

Outcome	Number of studies	Number of countries	Population age and timeframe of studies	Value
Case fatality rate	1	1	<1 years; 1993–1995	0%

CF cystic fibrosis, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *NA* not applicable, *NR* not recorded, *PCR* polymerase chain reaction, *PICU* pediatric intensive care unit, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization

[a] 1 of 10 subjects tested positive for a respiratory viral infection (including RSV, human rhinovirus, human metapneumovirus, parainfluenza 3, parainfluenza 4, and influenza B) was symptomatic at the time of testing (no information on virus identified in the symptomatic infant)

[b] Geometric mean ratio (95% confidence interval) for presence of cystic fibrosis vs. non-presence of condition; $P = 0.279$

[c] No specific data for children with cystic fibrosis

[d] 8 of 16 children with RSV infection had co-infection with human metapneumovirus

[e] No specific data for children with RSV infection

For patients undergoing HSCT or SOT, RSV infections typically occur within the first 2 years following transplant [35, 37]. Increased disease severity has been associated with prolonged shedding of RSV and with higher viral loads maintained for longer periods [56].

Outbreaks of RSV have been reported to occur in cancer care outpatient departments where many pediatric patients with malignancy or those undergoing transplantation are managed [33, 50, 57]. In a retrospective study of all RSV infections in children with cancer from 1998 to 2009 at the MD Anderson Cancer Centre in Texas, Chemaly et al. [37] found that, whilst the majority of cases (43/59; 73%) were community-acquired, over one-quarter (27%) were nosocomial. Since many HSCT and SOT recipients and children with malignancies are frequently seen in clinics, this could explain in part the high rates of RSV infection reported among this patient group. Children mechanically ventilated for reasons other than the actual RSV infection have also been shown to face an increased risk of a severe course of disease [58]. These findings highlight the importance of infection control interventions in outpatient as well as inpatient hospital settings to reduce the spread of RSV infection.

Progression from a generally self-limiting upper respiratory tract infection (URTI) to a more severe LRTI has been shown to occur in 18–28% of RSV-infected, immune-compromised patients [20, 37, 59]. Kim et al. [59] in the US (Seattle, WA) retrospectively evaluated 181 HSCT recipients (median age 40 years; 6 children aged <2 years of age, 20 children aged 2–-14 years) who presented with a RSV URTI. Twenty-four percent of patients (43/181) progressed to RSV LRTI, although no progression was observed in the 6 children aged <2 years. In multivariable models, smoking history ($P = 0.03$; NB study included adult patients), receipt of high-dose total body irradiation ($P = 0.03$), and an absolute lymphocyte count $\leq 100/mm^3$ ($P = 0.002$) at the time of URTI onset were significantly associated with disease progression [59]. In another retrospective study from the US (Memphis, TN) by El Saleeby et al. [20], 16 of 58 children (median age 4.3 years) with cancer (27.6%) and a RSV URTI developed

Table 4 Incidence rate ratios (IRR) for RSVH and geometric mean ratios for duration of RSVH in children with chronic conditions from the Danish RSV database [10]

Condition[a]	RSV/ Total (%)	IRR (95% CI); *P* value	GMR for LOS[b] (95% CI); *P* value
Congenital			
Malformations of respiratory system			
Cleft lip and palate	50/855 (6.4)	1.5 (1.1–2.0); 0.004	1.0 (0.8–1.3); NS
Malformations of the larynx; trachea and bronchi	41/440 (9.3)	1.5 (1.1–2.1); 0.009	1.1 (0.8–1.5); NS
Malformation of the lungs	7/51 (13.7)	2.2 (1.0–4.8); 0.049	1.5 (0.7–3.2); NS
Other conditions associated with respiratory symptoms			
Esophageal atresia	26/115 (22.6)	2.8 (1.6–4.9); <0.001	1.8 (1.1–3.1); 0.022
Neuromuscular disease			
Encephalocele	58/542 (10.7)	1.5 (1.1–2.1); 0.005	1.1 (0.8–1.4); NS
Spina bifida and malformations of the spinal cord	17/172 (9.9)	2.2 (1.3–3.6); 0.002	2.1 (1.3–3.3); 0.003
Muscular dystrophy	13/82 (15.9)	2.5 (1.4–4.6); 0.003	1.5 (0.9–2.4); NS
Cerebral palsy	93/905 (10.3)	1.6 (1.3–2.0); <0.001	1.3 (1.1–1.6); 0.005
Congenital diseases, chromosomal abnormalities, and others			
Malformations of the urinary system[c]	82/1232 (6.7)	1.5 (1.2–1.9); <0.001	1.0 (0.8–1.2); NS
Other chromosomal abnormalities	4/17 (23.5)	5.1 (1.7–15.5); 0.004	1.6 (0.7–3.8); NS
Malformations of the GI tract, liver, biliary system, pancreas, and abdominal wall	94/1078 (8.7)	1.6 (1.3–2.0); <0.001	1.2 (1.0–1.5); NS
Congenital immunodeficiencies	26/122 (21.3)	2.4 (1.6–3.5); <0.001	1.2 (0.9–1.8); NS
Inborn errors of metabolism	29/276 (10.5)	2.4 (1.6–3.5); <0.001	1.1 (0.8–1.5); NS
Acquired			
Interstitial lung disease	3/11 (27.3)	6.5 (1.7–23.9); 0.005	1.3 (0.4–4.1); NS
Gastroesophageal reflux	40/610 (6.6)	1.5 (1.1–2.1); 0.019	1.0 (0.7–1.3); NS
Epilepsy	75/713 (10.5)	2.6 (2.1–3.4); <0.001	1.6 (1.3–2.0); <0.001
Acquired heart disease	53/427 (12.4)	2.0 (1.5–2.7); <0.001	1.1 (0.8–1.4); NS
Liver disease	9/48 (18.7)	4.0 (2.0–8.2); <0.001	1.0 (0.6–1.9); NS

CI confidence interval, *GI* gastrointestinal, *GMR* geometric mean ratio, *LOS* length of stay for RSVH, *IRR* incidence rate ratio, *NS* not significant, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization

[a] Excludes the following conditions all of which were identified as significant risk factors for RSVH: CLD, CHD (both out with remit of review), Down syndrome, cancer and cystic fibrosis (data presented in relevant sections of this paper and Tables 1, 2 and 3, respectively)

[b] Presence vs. no presence of condition

[c] Including vesicoureteral reflux and obstructive renal disease

symptoms of LRTI. Age ≤2 years (OR 9.8, 95% CI 2.0–49.8) and profound lymphopenia (counts of <100 cells/mm^3) (OR 7.2, 95% CI 1.2–44.0) at RSV diagnosis were independent predictors of the development of LRTI and of increased risk for RSV-related mortality in univariate analysis [20]. In their retrospective study undertaken in the US (Houston, TX), Chemaly et al. [37] observed that 11 of 59 (18.6%) children (median age 5 years) with cancer progressed from RSV URTI to LRTI. In contrast to the studies by Kim et al. [59] and El Saleeby et al. [20], no significant risk factors for progression to LRTI were identified [37]. However, a trend of higher rate of RSV LRTI was observed for male sex (OR 2.6, 95% CI 0.9–7.6; $P = 0.09$) and children with lymphocytopenia (counts of <200 cells/mL; OR 3.0, 95% CI 0.9–10.1; $P = 0.085$), though they did not study profound lymphopenia [37].

For children not already hospitalized due to their underlying condition or its treatment, RSV infections were severe enough to warrant admission to hospital in 28–58% of cases [8, 20, 33, 37, 47]. Four studies were identified describing RSVH rates in immunocompromised children [7, 10, 35, 43]. Feldman et al. [35] in the US undertook a retrospective cohort study of 2554 children aged <18 years who had liver transplants between 2004 and 2013 and reported an RSVH rate in the first year post-transplant of 40 per 1000 children. Another US study, by Luján-Zilbermann et al. [43], retrospectively reviewed 281 patients (mean age 9.28 years) receiving HSCT from 1994 to 1997 and found a rate of RSVH of 11 per 1000; this study included patients with hematological malignancies, solid tumors, sickle cell disease, metabolic disorders, and primary immunodeficiencies. A higher rate of RSVH of 117 per 1000 was reported by Murray et al. [7] among infants (<1 year) with immunodeficiencies. The highest rate of RSVH was reported in the Danish national study of 187 per 1000 in children with cancer <2 years old [10].

Studies have shown that immunocompromised children spend an average of 6–10 days in hospital for RSV infections, with up to 29% requiring admission to the ICU and up to 21% intubation and/or mechanical intervention [7–9, 20, 33, 35, 37, 42, 47–50]. Asner et al. [47] from Canada, in a single-center observational study of 117 immunocompromised children aged <18 years presenting with an LRTI or URTI, identified the following independent predictors for a prolonged hospital stay: nosocomial RSV infection ($P < 0.001$) and the presence of high-risk underlying comorbidities (HSCT and SOT recipients, and congenital immunodeficiencies; $P = 0.008$).

Cystic Fibrosis

Cystic fibrosis has been found to be a significant risk factor for severe RSV infection [7, 10, 60–63] (Table 3). In the population-based, cohort study by Murray et al. [7], admission rates for RSV LRTI during the first year of life were found to be significantly higher among infants with cystic fibrosis (64 per 1000 infants, 95% CI 32.1–115.1) compared with otherwise healthy infants born at term (22 per 1000 infants, 95% CI 21.8–22.9; RR 2.5, 95% CI 1.4–4.4). In contrast to the previous study, a considerably higher rate of RSVH of 181 per 1000 in children (<2 years) with cystic fibrosis was reported in the Danish national RSV cohort [10]. Cystic fibrosis was a significant risk factor for RSVH in this study (IRR 4.3, 95% CI 2.4–7.7; $P < 0.001$ [10].

In a subgroup analysis of the Canadian PICNIC RSV database, the morbidity of RSV infection in children ($n = 68$) with various causes of underlying lung disease (including cystic fibrosis, recurrent aspiration pneumonitis, pulmonary malformation, neurogenic disorders, and tracheoesophageal fistula) was found to be similar to those with BPD ($n = 91$) [60]. Median hospitalization varied from 5 to 13 days and was similar between groups. The proportions of children admitted to ICU and mechanically ventilated were also similar among the different groups [60]. Across studies, the median LOS in hospital for RSV infection for infants (<1 year) with cystic fibrosis was 2–11 days [7, 60].

Importantly, Hiatt et al. [63] observed that the decline in lung function caused by a RSV LRTI among children (<2 years) with cystic fibrosis can persist for several months (mean 3.2 months) after resolution of the infection.

This finding is of great interest, and might be consistent with recently published findings from a large cohort study from the US including 12,702 children with cystic fibrosis, which reported that RSV activity was significantly associated with an increased risk of pulmonary exacerbations (RR 1.05, 95% CI 1.02–1.07, for a 10% increase in the proportion of surveillance tests positive for RSV; $P < 0.001$) [64]. Experimental reports have also implicated RSV in facilitating lung disease in cystic fibrosis caused by *Pseudomonas aeruginosa* [65, 66]. RSV infection has been shown to increase adherence of *P. aeruginosa* to epithelial monolayers in vitro by up to 16-fold [65], and to increase colonization in lung homogenates by 2000 times and impact lung function changes in mice [66].

Neurological and Neuromuscular Disorders, Congenital Malformations, and Other Chronic Conditions

There are a number of other diseases and conditions, both congenital and acquired, that have been reported to increase the vulnerability of infants and children to severe RSV infection [7, 10, 11, 16, 18, 19, 21, 67–69]. The national, population-based study conducted in Denmark analyzed chronic conditions in groups based on anatomy and physiology and some single disease entities amongst a study population of 452 205 children aged 0–23 months [10]. Of the 12 498 children hospitalized for RSV infection, 930 (8.8%) had a diagnosis of chronic disease; these children were older than otherwise healthy children at the time of admission (median, 7.9 vs. 6.2 months, respectively; $P = 0.001$). Adjusted incidence rate ratios for RSVH were 2.2 (95% CI 2.0–2.4) for children with any congenital condition and 2.3 (95% CI 1.9–2.6) for children with an acquired chronic condition. Cleft lip and palate, malformations of the respiratory system and esophagus, neuromuscular disease, malformations of the urinary system (including vesicoureteral reflux and obstructive renal disease), other intra-abdominal malformations (including malformations of the abdominal wall), chromosomal abnormalities other than Down syndrome, congenital immunodeficiencies, and inborn errors of metabolism were each independently associated with an increased risk of RSVH (Table 4). Among acquired conditions, the adjusted rates of RSVH were sixfold higher in patients with interstitial lung disease, fourfold higher in those with liver disease, and at least twofold higher in those with epilepsy, acquired heart disease, and cancer, than in those without the said condition. The duration of RSVH was also significantly increased in infants and children with malformations of the esophagus, some neuromuscular diseases, and epilepsy [10].

Another large, retrospective study by Zachariah et al. [16] identified 77 RSVHs in 3417 children born with major congenital malformations between 1997 and 2004 in Colorado, US (incidence 22 per 1000). When compared to those without malformations, children with spina bifida without anencephaly (RR 2.7, 95% CI 2.0–3.7), agenesis, hypoplasia, or dysplasia of the lung (RR 1.4, 95% CI 1.0–2.0), cleft palate alone (RR 1.4, 95% CI 1.0–2.0), and biliary atresia (RR 3.4, 95% CI 2.2–5.4) had statistically higher risks of being hospitalized with RSV LRTI in the first 2 years of life. Microcephaly, anomalies of the diaphragm, and choanal atresia were not associated with an elevated risk, whereas hypertrophic pyloric stenosis and cleft lip were associated with a lower risk of being hospitalized with RSV LRTI [16].

The study by Murray et al. [7] observed higher rates of RSVH in infants <1 year with cerebral palsy (107 per 1000 infants, 95% CI 61.4–174.4; RR 2.4, 95% CI 1.5–4.0) and nervous system congenital abnormalities (86 per 1000 infants, 95% CI 61.9–116.1; RR 1.7, 95% CI 1.3–2.4) than otherwise healthy infants born at term (22 per 1000 infants, 95% CI 21.8–22.9). A neurological disorder [defined as the presence of one or more of the following diagnoses: Intracranial hemorrhage grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia, cerebral infarction, hydrocephalus or other symptomatic neurological conditions] has also been found to be an independent risk factor for RSVH in a multivariate analysis of 1158 children born preterm at 29-35 weeks' gestational age in Germany and Austria (OR 3.6, 95% CI 1.3–9.9; $P = 0.01$) [67].

Findings from a prospective, multicenter study by Wilkesmann et al. [11], covering 6 consecutive RSV seasons (1999–2005), illustrated that children with neuromuscular impairment have more severe RSV LRTI, since they have a longer median LOS in hospital (11 days vs. 7 days; $P < 0.001$) and higher requirement for mechanical ventilation (9.6% vs. 1.9%; $P < 0.001$), compared to children without neuromuscular impairment. Furthermore, multivariate logistic regression confirmed that neuromuscular impairment was independently associated with PICU admission (OR 4.94, 95% CI 2.7–8.9; $P < 0.001$) and mechanical ventilation (OR 3.9, 95% CI 1.3–10.2; $P = 0.017$) [11]. These findings were confirmed by a second retrospective study by Purcell et al. [69] in the US who found that infants and young children with neurologic disease ($n = 38$) had significantly longer LOS in hospital (5.4 ± 3.3 vs. 3.9 ± 2.2 days; $P < 0.05$), admittance to PICU (23.7% vs. 3.2%; $P < 0.001$), and requirement for mechanical ventilation (18.4% vs. 1.5%; $P < 0.001$) for RSV LRTI, than children without risk factors ($n = 2287$).

Data are available for a few other diseases and conditions associated with increased morbidity from RSV infection. Data from a prospective, multicenter study conducted in Spain showed that children (<5 years) with inborn errors of metabolism required significantly more frequent admission to PICU (OR 6.7, 95% CI 1.2–38.0; $P < 0.05$) and requirement for mechanical ventilation (OR 12.3, 95% CI 2.1–71.5) for RSV infection than previously healthy children [21, 70]. Pockett et al. [19], using nationwide data for England from 2001 to 2008, found that children (mean age 1 year) with chronic diseases including insulin-dependent diabetes mellitus, epilepsy, cancer, or cystic fibrosis, hospitalized with RSV infection had greater LOS [mean 10.1 days, standard deviation (SD) 22.5] than otherwise healthy children (mean age 0.1 years) hospitalized with RSV infection (mean 1.9 days, SD 3.2).

Incidence of RSVH Over Time in Children Affected by Underlying Comorbidities

A recently published study from the US has reported that RSVH rates have not declined in Down syndrome without CHD, CAA, and a number of other conditions (cystic fibrosis with pulmonary manifestations, neuromuscular disease, HIV, immunodeficiency, and other genetic metabolic musculoskeletal conditions) [18]. This 15-year (1997–2012) historical cohort study, using data from the nationwide Kids' Inpatient Database, found that RSVH rates increased by 7.6% for Down syndrome without CHD ($P = 0.09$), by 4.3% for CAA ($P = 0.41$), and by 9.3% for other high risk conditions ($P = 0.62$) [18].

Case Fatality Rates

There are relatively few studies that have reported RSV-related mortality in infants and children with underlying medical conditions or chronic diseases. Infections are well known to make an important contribution to mortality in children with cancer [71, 72], and RSV-attributable case fatality rates have been reported as high as 19% in children undergoing bone marrow transplant, primarily for hematological malignancies [51]. Case fatality rates as high as 40% have also been reported in SOT recipients [38]. The majority (13/18) of studies, however, report rates of RSV-related mortality in immunocompromised children and young adults at below 10% (includes seven studies with no RSV-attributable mortality) [8, 9, 17, 33–38, 40–43, 45, 47, 49–51]. In the study by Wilkesmann et al. [11] RSV-attributable mortality was significantly higher in the neuromuscular impairment group than those without the condition (5.5% vs. 0.2%, respectively; $P < 0.001$). Individual studies in Down syndrome and cystic fibrosis provide few insights into RSV-related mortality in these patient groups.

Two studies were identified that specifically investigated RSV-related mortality in children, including those with underlying medical conditions [73, 74]. Thorburn et al. [73] in the UK undertook a study of 406 children (median age 5.1 months) admitted to the PICU over an 8-year period (1999–2007) and found 18 deaths (4.4%) directly related to RSV infections. All of these children had pre-existing medical conditions: chromosomal abnormalities (29%); cardiac lesions (27%); neuromuscular (15%); CLD (12%);

large airway abnormality (9%); and immunodeficiency (9%). Predisposing risk factors for death were pre-existing disease (RR 2.4, 95% CI 2.0–2.8), cardiac anomaly (RR 3.0, 95% CI 2.2–4.1), and nosocomial/hospital-acquired RSV infection (RR 2.9, 95% CI 1.3–6.6) [73]. A more recent analysis of RSV mortality rates in hospitalized infants and children aged <2 years was undertaken in the US using the Kids' Inpatient Database and the Pediatric Health Information System [74]. Both datasets indicated that RSVH-associated mortality was uncommon, occurring in 3–4 per 10 000 admissions, and had decreased over the last 20 years. Of these deaths, 20–26% had neuromuscular conditions and 13–19% had congenital or genetic conditions. Nearly 40% of the deaths in both datasets occurred in medically fragile infants and children with ≥2 complex chronic conditions [74].

Limitations

The rarity of the vast majority of the conditions, diseases and disorders covered in this review inevitably results in studies with often small populations of particular interest, data captured retrospectively over many years using various methodologies, and different diagnoses reported together sometimes in combination. This is perhaps most evident when considering immunocompromised children, where HSCT and SOT recipients with various underlying malignancies and treatment regimens were often studied in concert. Also, when looking at underlying conditions that have no direct consequence on the cardio-respiratory system, such as for example, urinary tract malformation, it is not possible to relate the increased incidence of RSV infection to the underlying condition (which seems unlikely) or to the risks and side effects of the medical management (i.e. recurrent hospital visits). Accurate information on RSV-related mortality, in particular, is difficult to obtain clear information on when analyzed retrospectively in the context of significant, life threatening comorbidities, such as cancer. Variation in hospitalization practices both for the conditions of interest and for RSV infections and changes in RSV surveillance over time and between countries (including level and methodology of testing and specimen used) will also have influenced the results and conclusions drawn.

Key statements/findings	Level of evidence[a]
A number of conditions, diseases, and disorders are associated with an increased risk of severe RSV disease and related morbidity and mortality	
Down syndrome	
Down syndrome is a significant risk factor for RSVH in early (<3 years) childhood (rate ratio[b]: 2.5–12.6), even when excluding co-existing risk factors for severe RSV disease, such as CHD and prematurity (rate ratio[b]: 3.5–10.5) [moderate SOE[c]]	Level 1 studies: $n = 1$; Level 2 studies: $n = 8$; Level 3 studies: $n = 1$[d] Risk of bias[e]: very low
RSVH rate of 70–195 per 1000 children [moderate SOE[c]]	
Average of 3–10 days hospitalization [moderate SOE[c]]	
Irrespective of other risk factors, increased severity of disease, longer duration of hospital stay, and greater risk of respiratory support, including intubation and/or mechanical ventilation, versus otherwise healthy children [moderate/low SOE[c]]	

continued

Key statements/findings	Level of evidence[a]
Im munocompromised children (including HSCT/BMT recipients, SOT recipients, cancer patients on chemotherapy, children with SCID/DiGeorge syndrome, and those with HIV)	
RSVH rate of 11–187 per 1000 children and young adults [low SOE[c]]	Level 1 studies: $n = 1$
Average of 6–10 days hospitalization with ≤29% admitted to ICU and ≤21% requiring intubation and/or mechanical intervention [low SOE[c]]	Level 2 studies: $n = 5$
Independent predictors of prolonged hospital stay: nosocomial RSV infection ($P < 0.001$) and presence of HSCT, SOT or congenital immunodeficiencies ($P = 0.008$) [low SOE[c]]	Level 3/4 studies: $n = 21$[f]
	Risk of bias[e]: low[g]
Cystic fibrosis	
Cystic fibrosis is a significant risk factor for RSVH in early (<2 years) childhood (rate ratio[b]: 2.5–4.3) [low SOE[c]]	Level 1 studies: $n = 0$ Level 2 studies: $n = 5$ Level 3 studies: $n = 1$[h]
RSVH rate of 64–181 per 1000 children [low SOE[c]]	Risk of bias[e]: very low
Average of 2–11 days hospitalization [low SOE[c]]	
Morbidity (LOS, ICU, mechanical ventilation) of RSV in children with various forms of underlying lung disease (including cystic fibrosis) similar to those with CLD [low SOE[c]]	
Neurological and neuromuscular disorders, congenital malformations, and other chronic conditions	
Neurological and neuromuscular conditions (including spina bifida, cerebral palsy, and muscular dystrophy[i]) are associated with a significantly ($P < 0.05$) increased risk of RSVH and increased morbidity [low SOE[c]]	Level 1 studies: $n = 0$
	Level 2 studies: $n = 8$
	Level 3 studies: $n = 1$[j]
A number of other congenital malformations and chronic conditions[k] are also associated with a significantly ($P < 0.05$) increased risk of RSVH [low SOE]	Risk of bias[e]: very low
RSV-attributable mortality	
Immunocompromised children, case fatality rates: 0–40% (7/18 studies with 0%) [low SOE[c]]	Level 1 studies: $n = 1$
	Level 2 studies: $n = 6$
Underlying medical conditions, case fatality rates: <1%, with pre-existing disease (RR 2.4, 95% CI 2.0–2.8) a significant risk factor for mortality [low SOE[c]]	Level 3/4 studies: $n = 17$
	Risk of bias[e]: very low[l]

continued

Key statements/findings	Level of evidence[a]
Key areas for research	
Where feasible, larger, prospective, well-designed studies are needed to more fully define the risk and outcomes of RSV infection in these populations	
More data are needed on fatality rates in children with underlying medical conditions or chronic diseases to determine how much is directly attributable to RSV and the true burden of disease	

BMT bone marrow transplant, *CHD* congenital heart disease, *CI* confidence interval, *HR* hazard ratio, *HSCT* hematopoietic stem cell transplant, *ICU* intensive care unit, *LOS* length of stay, *RR* relative risk, *RSV* respiratory syncytial virus, *RSVH* respiratory syncytial virus hospitalization, *SCID* severe combined immunodeficiency, *SOT* solid organ transplant, *HIV* human immunodeficiency virus

[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 [24, 25]. When grading the evidence, in general, we considered prospective, cohort studies as Level 1; prospective, case–control studies or large (e.g. national or multinational), well-designed, retrospective studies as Level 2; well-designed, retrospective studies as Level 3; and small/methodological weak retrospective studies and case series as Level 4

[b] Includes odds ratio, relative risk, incident rate ratio, and hazard ratio

[c] SOE (strength of evidence): high = supported by Level 1 evidence; Moderate: supported by limited Level 1 and/or Level 2 evidence; Low: supported by limited Level 2 and/or Level 3 evidence

[d] Six of the 10 studies specifically investigated children with Down syndrome (one Level 1 study [30] and five Level 2 studies [15, 22, 27, 29, 31]

[e] Average RTI Item Bank Score [26], where 7–9 = low risk of bias and 10–12 = very low risk of bias

[f] 23 of the 27 studies specifically investigated immunocompromised children (one Level 1 study in HSCT recipients [34]; two Level 2 studies in SOT recipients [44] and in a mixed population of immunocompromised children (HSCT, SOT and chemotherapy recipients, and those on long-term immunosuppression) [47]; 15 Level 3 studies in HSCT/BMT [9, 36, 43, 45, 51, 52], chemotherapy [49], SOT [35, 38], and mixed populations of immunocompromised children (including chemotherapy, SOT, HSCT/BMT, severe combined immunodeficiency, and HIV) [17, 20, 33, 37, 39, 40]; and five Level 4 studies in SOT [41, 46], HSCT [54], chemotherapy recipients [55], and chemotherapy and BMT recipients [50])

[g] Six studies could not be scored due to insufficient information provided or case reports

[h] Three of the six studies specifically investigated children with cystic fibrosis (all Level 2 studies [61–63])

[i] Also including: Intracranial hemorrhage grade III or IV (periventricular hemorrhage); cystic periventricular leukomalacia; cerebral infarction; encephalocele; hydrocephalus; malformations of the spinal cord; epilepsy; and other symptomatic neurological conditions

[j] Eight studies included neurological/neuromuscular conditions (seven Level 2 and one Level 3) [7, 10, 11, 16, 67–69], one of which (Level 2 study) was specifically focused on children with neuromuscular impairment [11]

[k] Including [10, 16, 19, 21]: cleft lip and palate; malformations of the larynx, trachea and bronchi; malformation of the lungs; esophageal atresia; malformations of the urinary system; other chromosomal abnormalities; malformations of the GI tract, liver, biliary system, pancreas, and abdominal wall; congenital immunodeficiencies, inborn errors of metabolism; interstitial lung disease; gastroesophageal reflux; acquired heart disease; liver disease; and insulin dependent diabetes mellitus

[l] Three studies could not be scored due to insufficient information provided or case reports

CONCLUSIONS

Respiratory syncytial virus is a major public health concern. Findings from this systematic review provide further evidence that RSV infection may be severe in children with a variety of underlying medical conditions or chronic diseases, leading to hospitalization, prolonged LOS, need for admission to ICU and mechanical ventilation, and even death. Certain high-risk groups, including children with Down syndrome and children immunocompromised through the administration of anticancer chemotherapy, and especially HSCT and SOT recipients, and those with neurological disorders, have increased RSV-related morbidity when hospitalized than otherwise healthy children with RSV infection.

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