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REVIEW

Defining the Risk and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Infants with Congenital Heart 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 fourth publication covers the risk and burden of RSV infection in infants with congenital heart disease (CHD).

Methods: A systematic review was undertaken for articles published 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 children with CHD as well as studies reporting RSV-associated morbidity, mortality, and healthcare costs were included. The focus was on children not receiving RSV prophylaxis.

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Study quality and strength of evidence (SOE) were graded using recognized criteria.

Results: A total of 1325 studies were identified of which 38 were included. CHD, in particular hemodynamically significant CHD, is an independent predictor for RSV hospitalization (RSVH) (high SOE). RSVH rates were generally high in young children (<4 years) with CHD (various classifications), varying between 14 and 357/1000 (high SOE). Children (<6 years) with RSV infection spent 4.4–14 days in hospital, with up to 53% requiring intensive care (high SOE). Infants (<2 years) with CHD had a more severe course of RSVH than those without CHD (high SOE). Case fatality rates of up to 3% were associated with RSV infection in children with CHD (high SOE). RSV infection in the perioperative period of corrective surgery and nosocomial RSV infection in intensive care units also represent important causes of morbidity (moderate SOE).

Conclusion: CHD poses a significant risk for RSVH and subsequent morbidity and mortality. RSV infection often complicates corrective heart surgery. To reduce the burden and improve outcomes, further research and specific studies are needed to determine the longer-term effects of severe RSV infection in young children with CHD.

Keywords: Burden; Congenital heart disease; Hemodynamically significant; High risk; Hospitalization; Morbidity; Mortality; Non-hemodynamically significant; Respiratory syncytial virus

INTRODUCTION

Congenital heart disease (CHD) is the most common type of birth defect, accounting for one-third of all major congenital anomalies, and represents a major public health issue [1, 2]. The reported total CHD prevalence has increased substantially over the last century, most likely due to improved diagnostic methods and screening modalities, although prevalence rates vary widely among studies worldwide [2]. It is estimated that CHD affects 9 in 1000 children, although significant geographical differences in prevalence have been reported [2]. A systematic review of the literature found that Europe had the second highest reported total CHD birth prevalence [8.2 per 1000 live births, 95% confidence interval (CI) 8.1–8.3]; this was significantly higher than in North America (6.9 per 1000 live births, 95% CI 6.7–7.1; $P < 0.001$) [2].

Children with CHD are at risk for increased morbidity from viral lower respiratory tract infection (LRTI) because of anatomical cardiovascular lesions, which can cause pulmonary hypertension leading to increased ventilation–perfusion mismatch and, ultimately, hypoxia [3]. Globally, RSV is the most common cause of childhood acute LRTIs, with at least 3.4 million episodes necessitating admission to hospital each year [4]. CHD limits an infant's ability to increase cardiac output, and concurrently oxygen delivery can be severely limited [5]. If an infant develops respiratory syncytial virus (RSV) LRTI, oxygen uptake can be further impaired and the work of breathing in these infants with compromised cardiac reserve is increased [5]. Infants and young children with CHD are especially at risk for severe disease and hospitalization and, in some instances, may require admission to the intensive care unit (ICU), supplemental oxygen therapy and prolonged mechanical ventilation [5, 6]. Furthermore, RSV LRTI can cause mortality in the immediate period

surrounding either palliative or corrective cardiac surgery employing cardiopulmonary bypass [7]. Hemodynamically significant CHD (HS-CHD) in association with RSV infection can lead to prolonged hospitalization [8] and an increased risk of death [9]. RSV infection may also delay corrective cardiac surgery [10], potentially increasing CHD-associated morbidity.

Since treatment is largely supportive and there is no effective vaccine for RSV, prevention is critically important in this vulnerable population. Current guidelines focus on infants at high risk for severe RSV infection and recommend RSV immunoprophylaxis in children with HS-CHD aged <12 months at the start of the RSV season [11–13]. However, since a number of children with residual HS-CHD postoperatively or awaiting cardiac transplant still remain at risk for severe RSV LRTI, some position statements continue to support RSV prophylaxis in the second year of life [14–17].

Identification of risk factors for RSV hospitalization (RSVH) and implementation of targeted prophylaxis are important to reduce the burden of severe RSV disease on inpatient and outpatient services and to improve patient outcomes. A vast amount of literature on RSV has accumulated over the past 20 years, and to review, evaluate and interpret this evidence a panel of experts in RSV from the United States, Canada and Europe formed REGAL (RSV Evidence—a Geographical Archive of the Literature) [18]. REGAL provides a comprehensive understanding on a range of topics on RSV LRTI within Western societies. This, the fourth paper in the REGAL series [18–20], identifies and evaluates the risks and associated morbidity and mortality of severe RSV LRTI in infants and young children with CHD.

METHODS

Study Objective

REGAL encompassed seven specific research questions on RSV related to the following topics: overall epidemiology [18], prematurity [19], chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD) [20], CHD, long-term respiratory morbidity, other high-risk groups (e.g., Down syndrome), and prevention, management and future perspectives. For the purposes of REGAL, Western countries were defined as the United States, Canada, and Europe (including Turkey and the Russian Federation). The overall methodology for REGAL was described in full in the first publication [18]. In summary, to address each question a systematic review of the medical literature electronically indexed in PubMed, EMBASE, and the Cochrane Library was performed. In addition, clinicaltrials.gov was searched for any relevant studies that are currently being conducted.

Literature Search

The specific research question for this review was: "What is the predisposition and associated morbidity, long-term sequelae and mortality of infants and young children with CHD following severe RSV infection?" The target population for this systematic literature review was infants and young children with CHD/HS-CHD who had 'proven' or 'probable' RSV. CHD as part of syndrome (e.g., Down syndrome) was excluded from this review, as clearly some of the genetic risk factors have an independent impact on RSV acquisition. A separate review on Down syndrome and other special populations will be published in due course. The focus of the current review was children who had not

received RSV immunoprophylaxis; however, to avoid the loss of significant studies, all publications were reviewed regardless of whether prophylaxis was given. Where possible, data for children not receiving prophylaxis were reported, or, if this was not possible, the level of prophylaxis was reported alongside the results.

We performed a literature search in MEDLINE (PubMed), EMBASE and the Cochrane Library from January 1, 1995 to December 31, 2015. The following general terms and limits were used: "RSV" OR "respiratory syncytial virus" AND "congestive heart disease" OR "CHD" AND "hospitalization" OR "predisposition" OR "risk factor" AND "limits: human, infant aged up to 1 year; child (<18 years)''. ''Bronchiolitis'' and ''pneumonia'' were captured as part of the Medical Subject Headings (MeSH) terms. It is recognized that, while some relevant articles might have been missed by the searches, we are confident that the combined Boolean operators ''AND'' and ''OR'' of the key text words and index terms precisely captured the vast majority of relevant citations which were pertinent for this evidence-based review. Additional studies identified through review of bibliographies and as abstracts presented at relevant meetings were also included. To ensure that the review was as contemporary as possible, relevant studies published during the drafting of this paper were also included.

Definition of CHD

The working definitions of CHD have evolved over time and may not be consistent between studies. HS-CHD in relation to RSV has been defined as [21–23]:

- Uncorrected or palliated cyanotic or acyanotic CHD with pulmonary hypertension
- Systolic pulmonary arterial pressure ≥40 mmHg or mean pulmonary arterial pressure ≥25 mmHg, and/or
- Need for medication to manage congestive heart failure.

This definition was not consistently used by all authors and manuscripts, but we suggest that this is a useful definition, and perhaps should be adopted in future manuscripts describing the epidemiology and management of CHD.

For completeness, all reports describing infants with CHD, regardless of definition, were considered for inclusion in this review in order to elucidate the additional risk of RSV infection in children with significant cardiac issues at birth. To facilitate interpretation of the data, the definitions of CHD used in individual studies, where stated, were documented.

Outcomes of Interest

Key outcomes for this review included: hospitalization rates due to severe RSV infection; hospital length of stay (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

All included studies were graded according to 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 (score of 1 = very high risk of bias; score of 12 = very low risk of bias) for observational studies [26]. No quantitative data synthesis was conducted due to heterogeneity 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.

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

Articles Selected

From a total of 1325 publications, 38 studies were included in the final review: 31 identified from the database searches and a further 7 from reference lists/other sources (Fig. 1). Details of all 36 studies, including evidence grades and risk of bias assessments, can be found in the online supplement.

Incidence of RSVH in Infants and Children with CHD

CHD, irrespective of hemodynamic significance, poses a significant risk for severe RSV infection requiring hospitalization [5, 8, 27–47]. RSVH rates ranged from 14 to 357 per 1000 (Table 1), although comparison of these studies is difficult as a result of differences in the study populations, some of which were not specifically CHD patients, methods used and inclusion criteria.

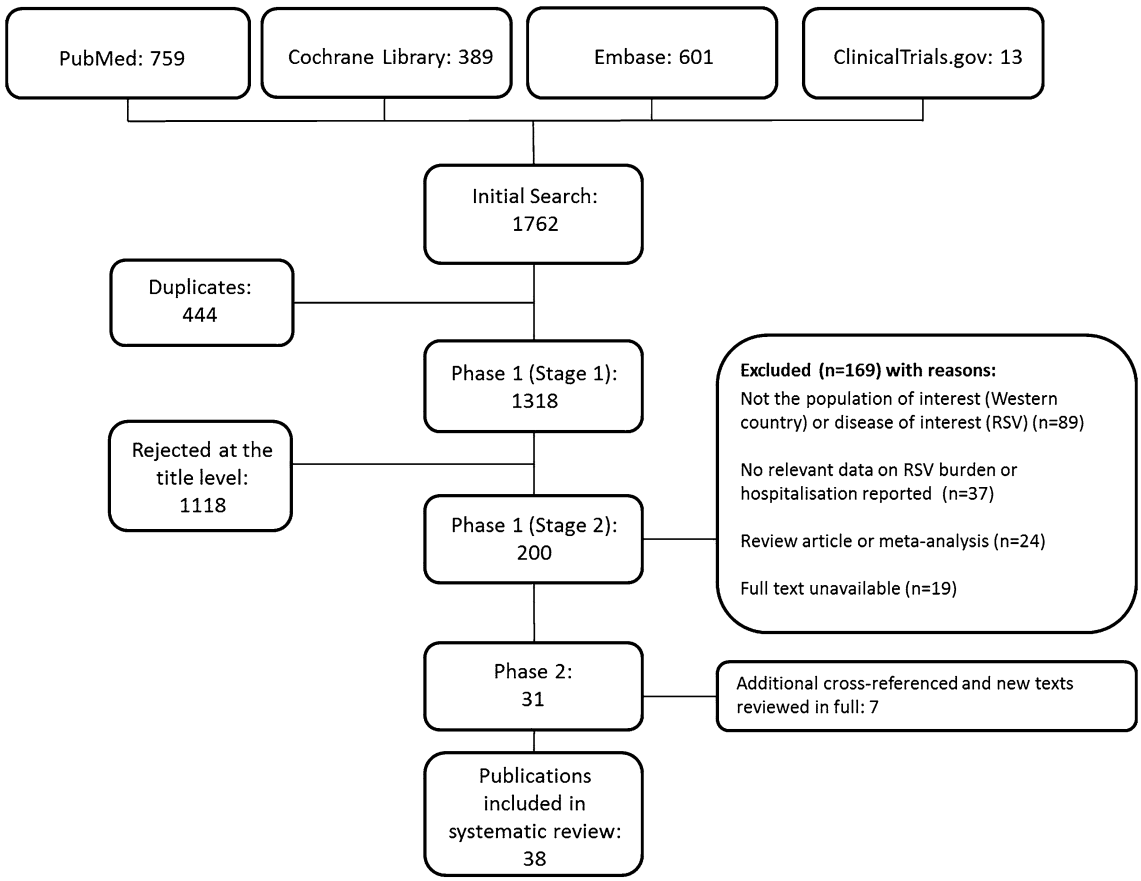

Fig. 1 PRISMA flow diagram: epidemiology and burden of RSVH in infants with CHD

Table 1 RSVH rates among children with and without CHD

Study	Country	Study design	Study definition of CHD/HS-CHD	RSVH rate/1000 children		Risk ratio (95% CI)
				CHD	Non-CHD	
RSVH rates for studies of infants and children with CHD						
Resch 2016 [27]	Austria	3-year retrospective study (2004–2008) of 602 children <3 years with HS-CHD or non-*hs*CHD; RSV immunoprophylaxis recommendation documented in 27.2% with HS-CHD and 2.2% with non-*hs*CHD	CHD classified as being HS-CHD or non-*hs*CHD according to definition of authors (pediatric cardiologists)	CHD: 96.0 HS-CHD: 73.0 Non-*hs*CHD: 104.0	NR	NR
Resch 2011 [28]	Austria	6-year retrospective study (2004–2009) of 433 infants <12 months hospitalized for RSV (388 [89.6%]) or influenza at tertiary care center; 50 children with CHD	Not defined	129.0	NR	NR
Wang 1997 [36]	Canada	2-year prospective study (1993–1995) of 427 children <3 years (253 complex CHD and 14 heart/lung disease); eight tertiary centers; no data on RSV immunoprophylaxis	Complex CHD defined as congenital heart abnormality needing cardiac surgery or dependence on cardiac medication. Patients who were digoxin-dependent or had not received corrective cardiac surgery were included	Overall: 30.0 0–3 months: 360.0 3–6 months: 60.0 6–12 months: 0.0 12–24 months: 10.0 24–36 months: 10.0	NR	NR
Kristensen 2012 [37]	Denmark	6-year retrospective study (1997–2003) of 452,205 children <2 years; 2720 with CHD; 118 received ≥1 dose RSV immunoprophylaxis	CHD not defined. Cardiac diagnoses included only if established at 1 of the 3 centres for pediatric cardiology	107.0	NR	1.70 (1.45–1.99)
Kristensen 2009 [38]	Denmark	7-year retrospective, multicenter study (1996–2003) of 3239 children <2 years with heart disease; no child received RSV immunoprophylaxis	Categorized as HS-CHD in all patients who were cyanotic, decompensated or required anti-congestive therapy. In other patients hemodynamic significance categorized as determined by the attending pediatric cardiologist	CHD/HS-CHD: 102.0 0–5 months: 71.3[a,b] 6–11 months: 73.2[a,b] 12–17 months: 43.4[a,b] 18–23 months: 29.6[a,b] 0–23 months: 56.5[a,b]	NA	HS-CHD: 1.53 (1.04–2.26)[c] Cardiomyopathy: 5.84 (1.26–27.16)[c]
Medrano López 2010 [5]	Spain	4-year prospective, multicenter study (2004–2008) of 2613 children <2 years with HS-CHD hospitalized for ARI (3.8% diagnosed RSV); 90.5% received RSV prophylaxis	Definition of HS-CHD stipulated by the Spanish Society of Pediatric Cardiology	HS-CHD: 38.0	NR	NR

Table 1 continued

Study	Country	Study design	Study definition of CHD/HS-CHD	RSVH rate/1000 children		Risk ratio (95% CI)
				CHD	Non-CHD	
Erikkson 2002 [40]	Sweden	12-year retrospective study (1987–1998) of 1503 episodes of RSVH in children <2 years; infants with cardiac malformation (2.9% catchment area; 13% from other areas); no data on RSV immunoprophylaxis	Cardiac malformation/lesion—not defined	CHD: 28.0–64.0[d]	NR	NR
Simoes 1998 [44]	US	3-year prospective, multicenter, randomized, controlled study of 416 children <4 years with CHD or cardiomyopathy (214 control group—no RSV immunoprophylaxis)	Not defined	CHD: 150.0 (control group) <6 months: 240.0 (control group) >6 months: 90.0 (control group)	NR	NR
RSVH rates for studies with mixed populations of infants and children						
Lanari 2004 [45]	Italy	6-month retrospective study (1999–2000) of 1214 children <2 years hospitalized for LRTI or developed RSV LRTI whilst hospitalized in 32 tertiary centers (3.5% non-surgically corrected CHD)	Not defined	CHD: 357.0 Nosocomially acquired RSV: 98.0	NR	NR
Pezzotti 2009 [43]	Italy	6-year retrospective cohort study (2000–2006) of 2407 preterm infants (<36 wGA) followed to 3 years but analyzed at <18 months (34 [1.4%] CHD); 13.5% received ≥1 dose RSV immunoprophylaxis	ICD-9 codes used to classify children. SIO also used to identify infants with diagnosis of CHD	Overall: 47.0 CHD data not presented <18 months: 75.8[b]	<18 months: 46.6[b]	CHD: 1.64 (0.52–5.19)
Meberg 2006 [8]	Norway	18-year retrospective, population-based study (1987–2004) of 43,470 live births (527 [1.2%] CHD; all RSVH ≤2 years); no data on RSV immunoprophylaxis	CHDs defined based on previously published criterion [51] HS-CHD defined as those in need of surgery or catheter intervention	All CHD: 48.0[e] HS-CHD: 92.0[f] HNS-CHD: 33.0	NR	NR
Tatachenko 2010 [46]	Russian Federation	6-month prospective, multicenter, observational study (2008–2009) of 519 children ≤2 years admitted with LRTI (18 [3.5%] high-risk RSV + children, including CHD); No RSV immunoprophylaxis	Not defined	Overall: 380.0 CHD data not presented	NR	NR
Hervás 2012 [47]	Spain	2-year retrospective, single center study (2005–2006) of 2384 children ≤2 years hospitalized for acute bronchiolitis (62.7% RSV)	Not defined	CHD: 23.0	Overall: 55	NR
Bonillo-Perales 2000 [35]	Spain	3-year retrospective study (1997–2000) of 12,895 newborn infants hospitalized for bronchiolitis in region	Presence of CHD with pulmonary obstruction, demonstrated by Doppler echocardiography	CHD: 58.8	NR	NR

Table 1 continued

Study	Country	Study design	Study definition of CHD/HS-CHD	RSVH rate/1000 children		Risk ratio (95% CI)
				CHD	Non-CHD	
Duppenthaler 2004 [30]	Switzerland	6-year prospective, population-based study (1997–2003) of 729 children <2 years hospitalized for RSV (10 [1.4%] with CHD). No RSV immunoprophylaxis.	CHD defined as hemodynamically significant cardiac malformation	CHD: 14.0 <12 months: 20.0[b] 12–24 months: 5.0[b]	<12 months: 12.0[b] 12–24 months: 2.0[b]	NR
Baysal 2013 [42]	Turkey	Prospective study of 419 children <2 years with LRTI (241 [57%] HS-CHD); no data on RSV immunoprophylaxis	Not defined	CHD: 14.0	NR	NR
Boyce 2000 [29]	US	3-year retrospective study (1989–1993) of all children <3 years (enrolled in Medicaid program; included children with CHD)	ICD-9 codes used to classify children	CHD: 50.0 0–6 months: 120.8 6–<12 months: 63.5 12–24 months: 18.2 24–36 months: 4.8	0–6 months: 44.1[g] 6 to <12 months: 15.0[g] 12–24 months: 3.7[g] 24–36 months: 1.0[g]	≤12 months: 2.8 (2.3–3.3)

Summary

Number of studies	Number of countries	Population age range and timeframe of studies	RSVH per 1000 (all CHD)
15	11	<4 years; 1979–2009	14–357

ARI acute respiratory infection, *CHD* congenital heart disease, *CI* confidence interval, *HS-CHD* hemodynamically significant congenital heart disease, *ICD* International Classification of Diseases, Clinical Modification codes, *LRTI* lower respiratory tract infection, *non-hsCHD* non-hemodynamically significant congenital heart disease, *NR* not recorded, *OR* odds ratio, *RSVH* respiratory syncytial virus hospitalization, *SIO* Sistema Informativo Ospedaliero della Regione Laziow, *wGA* weeks' gestational age

[a] Children with heart disease (any cardiac diagnosis)

[b] Per 1000 child–person years

[c] Adjusted OR for HS-CHD

[d] RSVH rate depending on 'early' or 'late' season

[e] $P = 0.002$ vs. non-CHD cases

[f] $P = 0.01$ vs. remaining CHDs

[g] Low risk group

Several studies reported a higher RSVH rate in infants aged <12 months [29, 30, 36, 38]. In a retrospective study by Boyce et al. [29], the estimated number of hospitalizations per 1000 children with CHD aged 6 to <12 months and 12 to <24 months were 63.5 and 18.2, respectively. In another retrospective study performed in Switzerland [30], RSVH rates (per 100 child–years) in CHD patients aged <6, <12, 12–24, and <24 months of age were 2.5 (95% CI: 0.8–5.6), 2.0 (0.8–3.8), 0.5 (0.1–1.8), and 1.3 (0.6–2.3), respectively. The relative risk in comparison with non-CHD patients was 1.4 (0.6–3.1), 1.6 (0.8–3.2), 2.7 (0.7–9.7), and 1.8 (1.0-3.3), respectively [30]. A significant decrease in frequency of RSV LRTI and RSVH was also observed with increasing age in the Canadian PICNIC study [36]. The RSVH rates in children with CHD aged 0–3, 3–6, 6–12 and 12–24 months were 360, 60, 0 and 10 per 1000, respectively [36]. In contrast, Altman et al. [10] found that RSV disease necessitating hospitalization occurred in children with CHD well into the second year of life. The average age at admission for RSV infection in children with CHD was 16 ± 12 months, with children >12 months of age accounting for 61% (34/56) of the cohort [10]. The aforementioned studies included data from 1989–2003 [10, 29, 30, 36, 38]. It might be expected that, with corrective surgery now mostly occurring in the first few months of life, rates of RSVH in the second year of life would be lower than what has been reported here. However, we were unable to identify any data to support this assertion. There is recently published evidence from the US and Canada which indicates that infants with complex cardiac conditions remain at substantial risk of RSVH in the second year of life [48, 49].

In multivariate analyses, CHD has been found to be an independent risk factor for RSVH [27, 34, 38, 50]. Data on a population of Danish children with heart disease revealed that cardiomyopathy [odds ratio (OR) 5.84, 95% CI 1.26–27.16] and HS-CHD (OR 1.53, 95% CI 1.04–2.26) were both significant predictors of RSVH [38]. In a retrospective study by Boyce et al. [29], CHD was found to be an independent risk factor for RSVH in the first year of life with an incidence rate ratio of 2.8 (95% CI 2.3–3.3) versus children born at term with no underlying medical condition (low-risk group). While HS-CHD has been shown to have a significantly higher RSVH rate compared to other CHDs (92 vs. 33 per 1000; $P = 0.01$) [8], recent data from the PONI study [50] suggest that children diagnosed with CHD that is not hemodynamically significant (non-*hs*CHD) suffer a substantial burden of RSV disease that seems to be underestimated and underreported in the literature. During the 2013–2014 RSV season, 2390 preterm infants (33 weeks + 0 days to 35 weeks + 6 days) aged ≤6 months were prospectively followed across 23 countries in Western Europe. RSVH rates (per 1000 infant–years) for the study cohort were 41 and 61 during the study period and RSV season, respectively. Non-*hs*CHD diagnosis in this premature population was associated with an increased risk of RSV-related LRTI hospitalization in multivariable analyses ($P = 0.0077$) [50]. Verification of non-*hs*CHD as an independently significant risk factor for RSVH in non-premature populations is required.

Morbidity and Healthcare Resource Utilization

The disease burden associated with RSVH in infants and young children (<6 years) with CHD is considerable (Table 2). Length of stay in hospital and ICU admissions vary among

Table 2 Hospital/ICU LOS for severe RSV infection among infants and children with and without CHD

Study	Country	Study participants	Hospital LOS (days)	Admitted intensive care (%)	ICU LOS (days)	Mechanical ventilation or respiratory support (%)	Oxygen therapy (%)	Case fatality rate (%)
Rates for studies of infants and children with CHD								
Resch 2016 [27]	Austria	602 children <3 years with HS-CHD and non-*hs*CHD	HS-CHD: 14 (median, SD 2–39) Non-*hs*CHD: 7 (median, SD 1–70)	HS-CHD: 46 Non-*hs*CHD: 17	HS-CHD: 10 (median, SD 0–27) Non-*hs*CHD: 9.5 (SD, 0–70)	NR	HS-CHD: 64 Non-*hs*CHD:47	0
Butt 2014 [6]	Canada	30 children <6 years with CHD (40% HS-CHD)	10 (median, 1–65)	53.3	11 (median, 1–43)	50 (30 mechanical ventilation; 20 CPAP or non-invasive positive pressure	33.3	3.3
Kristensen 2009 [38]	Denmark	3239 infants < 2 years with heart disease	6 (mean 0–74)	NR	NR	Mechanically ventilated: 3.9 CPAP: 25.8	27.5	0
Medrano López 2010 [5]	Spain	2613 infants aged <2 years with HS-CHD	7 (median) (IQR 5–7)	30.4[a]	10 (median) (IQR 5–18)[a]	NR	NR	1.98[b]
Medrano 2007 [39]	Spain	760 infants <2 years with HS-CHD	9.7 (mean, 1–56)	NR	NR	NR	NR	0.8[b]
Friedman 2016 [48]	US	4468 infants 12–23 months with various CHD diagnoses	4.4 (mean)	NR	NR	Mechanically ventilated: 11.4	NR	1.6
Altman 2000 [10]	US	63 children with CHD ≤28 months (52% >12 months)	7.4 (mean)	25	9.7 (mean)	Mechanically ventilated: 11	NR	3.12
Simoes 1998 [44]	US	416 children <4 years with CHD or cardiomyopathy	107 days/100 children[c]	5[c]	68 days/100 children[c]	Mechanically ventilated: 3[c]	NR	1.4
Rates for studies with mixed populations of infants and children								
Lanari 2004 [45]	Italy	1214 infants <2 years hospitalized for LRTI or developed RSV LRTI whilst hospitalized in 32 tertiary centers (3.5% non-surgically corrected CHD)	9.2 (mean)	NR	NR	NR	NR	NR
Meberg 2006 [8]	Norway	43 470 live births [527 (1.2%) CHD]	7.6 (mean)	2	NR	0	NR	0.2
Fjaerli 2004 [52]	Norway	764 infants < 2 years hospitalized for RSV bronchiolitis [20 (2.6%) CHD: 12 CHD; 4 CHD and prematurity; 4 CHD and Down syndrome]	6 (median, 2–14)[d]	NR	NR	NR	NR	0.3
Tatachenko 2010 [46]	Russian Federation	519 infants ≤2 years admitted with LRTI [18 (3.5%) high-risk RSV + children, including CHD]	4–13 (range)[e]	NR	NR	0[e]	28[e]	0

Table 2 continued

Study	Country	Study participants	Hospital LOS (days)	Admitted intensive care (%)	ICU LOS (days)	Mechanical ventilation or respiratory support (%)	Oxygen therapy (%)	Case fatality rate (%)
Hervás 2012 [47]	Spain	2384 infants ≤2 years hospitalized for acute bronchiolitis (62.7% RSV of which 2.3% had CHD)	6 (median, IQR 3–8)	NR	NR	NR	NR	0.13[f]
Erikkson 2002 [40]	Sweden	1503 episodes of RSVH in infants <2 years; infants with cardiac malformation (2.9% catchment area; 13% from other areas)	17.1 (mean, IQR 3–11)	22	NR	12	NR	0.3
Duppenthaler 2004 [30]	Switzerland	729 infants <2 years hospitalized for RSV (10 [1.4%] with CHD)	6.5 (median, 2–41)	50	1.5 (median, 0–25)	20	100	10[g]
Baysal 2013 [42]	Turkey	419 infants <2 years with LRTI [241 (57%) HS-CHD]	9.9 (5–17)	30[h]	NR	18[h]	NR	2
Willson 2003 [33]	US	684 infants ≤1 year hospitalized for bronchiolitis or RSV pneumonia	6.0 (median)	NR	4.1 (median)	31.7	NR	0.15

Summary for studies infants and children with CHD

Outcome	Number of studies	Number of countries	Population age range and timeframe of studies	Value
Hospital LOS	7	5	<6 years; 1994–2012	4.4–14[j]
ICU admission	5	4	<6 years; 1992–2009	5–53.3 [k]
ICU LOS	4	4	<6 years; 1994–2009	9.5–11[i]
Oxygen therapy	3	3	<6 years; 1996–2009	27.5–64[k]
Invasive mechanical ventilation	5	3	<6 years; 1992–2012	3–30[k]
CPAP or non-invasive positive pressure ventilation	2	2	<6 years; 1996–2003	20–25.8[k]
Case fatality rate	8	5	<6 years; 1992–2009	0–3.3[k]

CHD congenital heart disease, *CLD/BPD* chronic lung disease/bronchopulmonary dysplasia, *CHF* congestive heart failure, *CPAP* continuous positive airway pressure, *HS-CHD* hemodynamically significant congenital heart disease, *ICD* International Classification of Diseases, Clinical Modification codes, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *LRTI* lower respiratory tract infection, non-*hs*CHD non-hemodynamically significant congenital heart disease, *NR* not reported, *NSCHD* non-surgically corrected congenital heart disease, *RSVH* respiratory syncytial virus hospitalization

[a] 2366 children received RSV immunoprophylaxis
[b] Case fatality rate due to respiratory infection
[c] Data for control group ($n = 214$) who did not receive RSV immunoprophylaxis
[d] Group of children with only CHD as risk factor
[e] Data for all high-risk children in study, defined as prematurity, CLD/BPD or CHD
[f] Case fatality rate for all children enrolled
[g] One patient
[h] Percentage of children admitted to hospital due to RSV
[i] Median days
[j] Average (mean/median) days
[k] Percentage

Table 3 Clinical course of RSVH in children aged <2 years with CHD compared to other risk populations [30]

Parameter	CHD ($n = 10$)	BPD ($n = 15$)	Prematurity ≤35 wGA ($n = 60$)	Age <1 month ($n = 90$)	No risk factor ($n = 554$)
Hospital LOS[a]	6.5 (2–41)	11 (4–23)	6 (2–23)	8 (1–27)	5 (1–30)
Supplemental oxygen[b]	100	80	73	86	66
ICU admission[b,c]	50	6.7	20	32	7.0
ICU LOS[a]	1.5 (0–25)	0 (0–5)	0 (0–16)	0 (0–17)	0 (0–18)
Mechanical ventilation[b]	20	0	1.7	5.6	1.3

BPD bronchopulmonary dysplasia, *CHD* congenital heart disease, *ICU* intensive care unit, *LOS* length of stay, *wGA* weeks' gestational age

[a] Median days (range)

[b] Percentage

[c] CHD vs. BPD, $P = 0.01$; CHD vs. prematurity, $P = 0.045$; CHD vs. age <1 month, $P = 0.144$; CHD vs. no risk factor, $P < 0.001$

studies, but, on average, children with CHD and severe RSV infection spent an average of 4.4–14 days in hospital [5, 6, 8, 10, 27, 30, 33, 38–40, 42, 45, 47, 48, 52]. Up to 53% were admitted to ICU with a median stay of 9.5–11 days [5, 6, 10, 27, 30, 44]. A retrospective, single-center study of 30 children with CHD and severe RSV infection reported that more than half (53.3%) were admitted to PICU for treatment [6]. The majority (87.5%) of PICU admissions were in infants ≤2 years of age and the median number of days spent in PICU was 11 days (range 1–43 days). The majority (87.7%) of these children had not received RSV immunoprophylaxis. During hospitalization, 15 children (50%) required respiratory support: 9 required mechanical ventilation and 6 required continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation. In addition, a third (33.3%) of the children required supplemental oxygen. Of the 24 infants in the study aged ≤2 years, 14 had non-*hs*CHD. The overall hospital LOS for all patients was 10 days (range: 1–65 days). Hospitalized children were susceptible to major complications following RSV infection: 20% were found to have concurrent bacterial sepsis, 16.7% electrolyte abnormalities, and 13.3% worsening of pulmonary hypertension [6].

Duppenthaler et al. [30] observed that complications leading to ICU admission, supplemental oxygen and ventilation appear to be more common in infants aged <2 years with CHD than in those without CHD. In addition, infants with CHD were significantly more often admitted to the ICU than infants with BPD or prematurity ≤35 weeks gestational age (50% vs. 6.7% and 20%, respectively), but not in comparison with otherwise healthy infants <1 month of age (32%) (Table 3) [30]. Baysal et al. [42] also reported that PICU admission and mechanical ventilation rates were significantly higher for infants with CHD aged <2 years as compared to infants without CHD infected with RSV ($P = 0.01$). In a further study by Kristensen et al. [38], cardiac decompensation (including the need for anticongestive therapy) was identified as a predictor for respiratory support (supplemental oxygen, nasal CPAP or mechanical ventilation) during RSVH [relative risk (RR): 1.81, 95% CI 1.02–3.23].

Recently published data from the US specifically examined the risk of RSVH in the second year of life in infants with CHD [48]. In total, 4468 RSVHs among infants 12–23 months of age with CHD were identified over a 16-year period (1997–2012). The mean LOS for RSVH was 4.4 days, with 11.4% requiring mechanical ventilation. For those without CHD, the comparative rates were 2.3 days and 2.3%, respectively. Several specific CHD diagnoses were associated with a longer LOS and higher rates of mechanical ventilation, with congestive heart failure having the worst overall morbidity (LOS: 8.2 days; mechanical ventilation: 31%) [48].

Nosocomial outbreaks of RSV infection in ICUs also represent an important cause of morbidity in this specific, high-risk population [53, 54]. Children on long-term mechanical ventilation may acquire RSV infection by transmission through droplets or caregivers and face an increased risk of a severe course of RSV infection [53]. A German study prospectively documented 1568 RSV infections in 1541 pediatric patients of whom 20 (1.3%) had acquired the RSV infection while being treated by mechanical intervention for other reasons. Thirty-five percent of the children (median age 4.2 months, range 0.5–97 months) who acquired the RSV infection whilst mechanically ventilated had CHD [53]. In a UK study reporting on a RSV outbreak in a PICU, 27.8% (15/54) of the children acquired the RSV infection whilst in the PICU [54]. In this study, PICU-acquired RSV infection was defined as having occurred when a child admitted to the PICU was RSV-negative or from whom no samples were taken because they did not exhibit signs of bronchiolitis, and who then was found to be RSV-positive $\geq$5 days after the admission [54]. Nosocomially-acquired RSV infection has also been documented during hospitalization in infants aged <2 years in an Italian study [45]. These data confirm the high risk of infants and children developing a severe RSV infection during hospitalization and the importance of adhering to strict infection control measures to prevent further spread of RSV in clinical settings.

Further data from a retrospective study in Canada demonstrated that children with CHD hospitalized for LRTI (0.6% RSV) in infancy had an almost two-fold increase in risk of childhood chronic respiratory morbidity (asthma, chronic bronchitis or chronic lung disease) by age 10 compared to CHD children not hospitalized for LRTI [58.5% (244/417) vs. 31.5% (884/2805), respectively] [55]. Among CHD children, LRTI hospitalization was associated with a 3-fold increase in the risk of childhood chronic respiratory morbidity [adjusted OR 3.0 (2.3–3.9)] and a 6-fold increased risk of hospitalization for chronic respiratory morbidity [adjusted OR 5.7 (4.0–8.1)] [55]. The nature, incidence and impact of long-term respiratory morbidity associated with RSVH in infancy in Western countries will be covered in more detail in a subsequent publication in the REGAL series.

Impact of RSV Infection on Cardiac Surgery for CHD

Surgical outcomes in children with CHD have improved over the past two decades. However, a significant number of children are exposed to RSV, which can result in substantial morbidity and mortality [10, 56–58]. In a post hoc analysis of a multicenter, randomized trial [59], Tulloh et al. [57] included all children who underwent cardiac surgery comparing outcomes for those who acquired RSV infection with those who did not (controls), matched for demographics (age and weight at operation) and physiology of cardiac morphology. It was found that RSV

infection more than 6 weeks before cardiopulmonary bypass caused significant morbidity, but there was no indirect evidence of pulmonary hypertension after RSVH. This analysis also found that the duration of heart failure medication tended to be longer (by 6 months in >50% of children) if the children were hospitalized for RSV than if not [57]. Khongphatthanayothin et al. [56] reported on 25 children with CHD who had cardiac surgery within 6 months after RSV infection. Surgery for CHD performed during the symptomatic period of RSV infection was associated with a higher risk of postoperative complications (particularly pulmonary hypertension) than if surgery was undertaken electively after being discharged following RSV infection [56]. Altman et al. [10] reported that post-operative RSV infection in children with CHD can cause significant morbidity, resulting in prolonged hospital stays (2.1 times longer vs. historical, age-matched controls with comparable cardiac lesions) and time spent in ICU. RSV infection also resulted in delayed cardiac surgery in 35% (12/34) of patients in need of surgery during the RSV season [10]. Any delays in corrective surgery caused by RSV infection may increase cardiac-associated morbidity in children with CHD, though no evidence is available to adequately quantify this impact.

Case Fatality Rates

Few studies have specifically investigated mortality due to RSV in young children with CHD. Available data from the published literature suggest that the case fatality rate for RSV is relatively low among infants and children with CHD in Western countries, ranging from 0 to 3.3% [5, 6, 8, 10, 30, 38–40, 42, 44, 47, 48, 52]. In a retrospective, single-center study of 30 children with CHD by Butt et al. [6], conducted over a period of 7 years, only one death (3.3%) was attributed to RSV. Meberg et al. [8] reported one death related to RSV infection among 500 RSVH children with CHD; a 4-month-old premature, male infant with Down syndrome, suffering from CLD, atrioventricular septal defect and heart failure. In a US study of 4486 RSVHs among infants 12–23 months of age with various CHD diagnoses, the overall case fatality rate was 1.6%; however, certain diagnoses were associated with substantially higher rates (transposition of great vessels: 10.6%; congestive heart failure: 9.6%; cardiomyopathy: 9.5%; Ebstein's anomaly: 8.8%) [48]. A study published in 2009, undertaken to determine the mortality rate and risk factors for death in children with severe RSV infection, found that pre-existing disease/comorbidity, in particular multiple pre-existing diseases and cardiac anomaly, was associated with a significantly higher risk of death from severe RSV infection [9]. All the RSV deaths had pre-existing medical conditions/comorbidity (27% cardiac lesions) [9]. Similar data come from a recently published US study which reported that the majority (76–79%) of RSV-associated deaths occurred in infants with complex chronic conditions [60]. Cardiovascular conditions were the most frequent single chronic condition identified, being associated with 37–45% of all RSV-related deaths [60].

Limitations

It should be recognised that the evolving definitions of CHD over time may have affected comparisons between studies and interpretation of results. Additionally, it is difficult to measure the impact of improved surgical practice in this population on the

subsequent outcome of RSV infection. There were also few studies identified specifically addressing children with CHD, with the majority of studies including mixed populations of children. Other factors, such as improvements over time in both medical and surgical practice and RSV surveillance, will also have influenced interpretation of the results. Future studies should use the current, accepted definition of CHD, as described in "Methods". Research areas of particular interest include studies investigating how delays in surgery caused by RSV impact CHD-related morbidity and studies on the epidemiology and associated morbidity of severe RSV LRTI in infants with CHD in the second year of life.

Summary Box

Key statements/findings	Level of evidence[a]
CHD, in particular HS-CHD, is a significant risk factor for severe RSV infection with RSVH rates ranging from 14–357 per 1000	Level 1 (Level 1 studies: $n = 9$; Risk of bias[b]: very low)
Children with CHD spend an average of 4.4–14 days in hospital for RSV infection, with up to 53% requiring admission to the ICU	Level 1 (Level 1 studies: $n = 8$; Risk of bias[b]: very low)
Children with CHD have a more severe disease course (increased ICU admission and ventilation) than children without CHD	Level 1 (Level 1 studies: $n = 2$; Risk of bias[b]: very low)
RSV infection can delay and impact surgery for CHD, increasing post-operative complications, such that the timing of surgery is an important consideration	Level 2 (Level 1 studies: $n = 1$; Level 2 studies: $n = 1$; Level 3 studies: $n = 2$ Risk of bias[b]: very low)
Case fatality rates associated with RSVH in children with CHD are reported to range from 0–3.3%	Level 1 (Level 1 studies: $n = 6$; Risk of bias[b]: very low)
Key areas for research	
Further research and specific studies are needed to determine the longer-term effects of severe RSV infection in infants and young children with HS-CHD as well as those with CHD that is not hemodynamically significant. Additional data are also required to assess outcomes of HS-CHD and *non-hs*CHD in children, independent of chromosomal/non-chromosomal anomalies and other serious pre-existing medical disorders	

CHD congenital heart disease, *HS-CHD* hemodynamically significant congenital heart disease, *ICU* intensive care unit, *LOS* length of stay, *non-hsCHD* non-hemodynamically significant congenital heart disease, *RSVH* respiratory syncytial virus hospitalization, *OR* odds ratio, *RR* risk ratio

[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]

[b] Average RTI Item Bank Score [26], where ≤ 2 = very high risk of bias and 10–12 = very low risk of bias

CONCLUSIONS

Infants and children with CHD are at high risk for severe RSV infection, particularly in the first year of life. Available data from the published literature suggest that, while the case fatality rate for RSV in this vulnerable population is relatively low, the burden of RSV in terms of hospitalization and the need for ICU admission is high. Nosocomially acquired RSV-infection in CHD children results in substantial morbidity. In addition, cardiac surgery performed during

the symptomatic period of RSV infection has been associated with a high risk of postoperative complications, particularly postoperative pulmonary hypertension. Data suggest that early surgery significantly reduces the risk of RSVH during the first RSV season. Conversely, RSV infection may delay corrective cardiac surgery.

Most studies have focussed on HS-CHD, but the definition across the reviewed studies is not standardized. Recent data suggest that infants with CHD that is not hemodynamically significant are also at increased risk of RSVH and suffer a substantial burden of RSV disease. Moreover, infants with CHD seem to remain at risk for RSVH during their second year of life, particularly those with complex cardiac conditions, although this risk may be diminishing with earlier surgical intervention and improving outcomes. Further research and specific studies are needed to determine the longer-term effects of severe RSV infection in infants and young children with HS-CHD, as well as those with CHD that is not hemodynamically significant, in order to reduce the burden and improve outcomes in this patient population.

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