

Respiratory Tract Infection and Risk of Hospitalization in Children with Congenital Heart Defects During Season and Off-Season: A Swedish National Study

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Abstract Respiratory tract infections (RTI) are common among young children, and congenital heart defect (CHD) is a risk factor for severe illness and hospitalization. This study aims to assess the relative risk of hospitalization due to RTI in winter and summer seasons for different types of CHD. All children born in Sweden and under the age of two, in 2006–2011, were included. Heart defects were grouped according to type. Hospitalization rates for respiratory syncytial virus (RSV) infection and RTI in general were retrieved from the national inpatient registry. The relative risk of hospitalization was calculated by comparing each subgroup to other types of CHD and otherwise healthy children. The relative risk of hospitalization was increased for all CHD subgroups, and there was a greater increase in risk in summer for the most severe CHD. This included RSV infection, as well as RTI in general. The risk of hospitalization due to RTI is greater for CHD children. Prophylactic treatment with palivizumab, given to prevent severe RSV illness, is only recommended during winter. We argue that information to healthcare staff and parents

should include how the risk of severe infectious respiratory tract illnesses, RSV and others, is present all year round for children with CHD.

Keywords Congenital heart defect (CHD) · Immunoprophylaxis · Palivizumab · Respiratory syncytial virus · Respiratory tract infection

Introduction

Respiratory tract infection (RTI) is common in young children, and RSV infection is among the leading causes of hospitalization [1–4]. About 95 % of infants under the age of two have been infected with RSV [2]. RSV is the most common pathogen, but rhinoviruses, influenza and parainfluenza viruses, human metapneumovirus, coronaviruses and bocaviruses can also be detected in young children who are admitted to hospital with respiratory tract symptoms [4, 5]. Other viral infections can present with similar symptoms to RSV [6].

Congenital heart disease (CHD) is a known risk factor for severe illness and hospitalization due to RSV infection [7–9]. Delay in postoperative recovery after cardiac surgery has been reported in RSV-infected children, as well as for other airway infections [10]. Palivizumab is a prophylactic treatment that reduces the severity of RSV infection and hospitalization rates [8, 11, 12]. Palivizumab is administered monthly during the winter in Sweden, as an intramuscular injection to children with hemodynamically significant congenital heart defects.

RSV activity is dependent on a complex interaction of latitude, temperature, humidity and sunlight ultraviolet radiation [13]. Human susceptibility to viral infections might be altered by weather conditions, and indoor

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infections are likely to increase with extreme cold and heavy rainfall [14]. RSV infection is a seasonal disease in temperate climates such as Sweden, with activity peak when the temperature is lower as it is in the winter, but the virus is present all year round [15]. In areas with persistently warm temperatures and high humidity (close to the equator), however, RSV activity is more continuous throughout the year. More continuous RSV activity is also seen in areas with colder temperatures throughout the year [13].

The aim of this study was to calculate the relative risk of hospitalization due to RSV infection and respiratory tract infection (RTI) in general in CHD children and in different subgroups of CHD. The risk estimations were calculated for summer and winter respectively.

Materials and Methods

The five-year study period was defined as November 1, 2006–October 31, 2011. Rates of hospitalization caused by RSV infection (International Classification of Diseases codes J20.5 and J21.0) and RTI in general (International Classification of Diseases codes J21.9, J20.9, J18.9, J12.9 and J22.9) were retrieved for children under the age of two from the Swedish Inpatient Registry [16], held by the Swedish National Board of Health and Welfare (Socialstyrelsen). The Inpatient Registry includes information on dates of admissions to and discharges from hospitals in Sweden, as well as primary and secondary diagnoses (International Classification of Diseases 10 codes) [17]. Information on hospitalization was retrieved for the six-month periods 1 May–31 October (defined as the summer period) and 1 November–30 April (defined as the winter

period). Using the unique 12-digit national registration number assigned to all Swedish residents, additional information about the type of congenital heart defect was retrieved for hospitalized as well as non-hospitalized patients. The registration number makes it possible to identify individuals and collect certain information from different registers in Sweden [18]. The types of congenital heart disorder were divided into eight subgroups (Table 1).

The total number of residents under the age of two was estimated using the number of live births recorded in the National Statistics Sweden database [19], so that all children born in Sweden and <2 years old during 2006–2011 were included in the study. The relative risk of hospitalization, due to RSV and unspecified RTI, was calculated for CHD children compared to children without CHD, for summer and for winter. The relative risk of hospitalization was also calculated separately for each heart defect subgroup and compared to the other subgroups and to otherwise healthy children. The relative risk was calculated using MedCalc® (www.medcalc.org) and Chi-square test. A result with $p < 0.05$ was considered statistically significant.

Results

The relative risk of hospitalization due to RSV infection among children under the age of two was increased for all children with CHD (Table 2), and for all CHD subgroups (Tables 3, 4). The risk of hospitalization for all CHD children was greater in the summer than in the winter, and the risk was higher for RTI in general than for RSV infection.

Table 1 Congenital heart disorders, eight subgroups

Subgroup	International classification of diseases 10 code
<i>Univentricular heart defects</i> (double inlet ventricle, other congenital malformations of cardiac chambers and connections, tricuspid stenosis, mitral stenosis, hypoplastic left heart syndrome)	Q20.4, Q20.8–9, Q22.4, Q23.2, Q23.4
<i>Systemic-pulmonary shunt defects</i> (atrioventricular septal defect, atrial septal defect, ventricular septal defect, common arterial trunk, patent ductus arteriosus, aortopulmonary septal defect, other arteriovenous malformation)	Q21.0–2, Q21.4–9, Q20.0, Q25.0, Q24.8, Q28.2, Q27.3
<i>Pulmonary hypertension</i>	I27.0, I27.8–9
<i>Other complex CHD</i> (ventricular double outflow, Ebstein's anomaly, congenital anomaly/disorder of aortic or mitral valve, cor triatriatum, malformation of coronary vessels, malformation of great veins)	Q20.1–2, Q22.5, Q23.8, Q24.2, Q24.5, Q24.8, Q26.0–9
<i>Left-side outflow obstructions</i> (congenital aortic valve malformations, coarctation and other malformations of aorta and peripheral vascular system)	Q23.0–1, Q23.9, Q24.4, Q25.1, Q25.3–4, Q27.8
<i>Right-side outflow obstructions</i> (pulmonary valve atresia and stenosis, malformations of pulmonary artery)	Q22.0, Q24.3, Q24.8, Q25.5–7
<i>Tetralogy of Fallot</i>	Q21.3
<i>Cardiomyopathy</i> (dilated, hypertrophic and other forms)	I42.0, I42.2, I42.4–5, I42.8–9

Table 2 Relative risk of hospitalization due to respiratory syncytial virus infection and respiratory tract infection in general in the winter and summer for children with CHD (all subgroups included) compared to children without CHD

	CHD	Non-CHD	RR	CI (95 %)	<i>p</i> value
Winter					
Number of children hospitalized due to respiratory syncytial virus	394	7539			
Number of children non-hospitalized due to respiratory syncytial virus	9084	1,078,644	5.99	5.42–6.61	<0.0001
Summer					
Number of children hospitalized due to respiratory syncytial virus	41	545			
Number of children non-hospitalized due to respiratory syncytial virus	9263	1,095,895	8.87	6.46–12.17	<0.0001
Winter					
Number of children hospitalized due to respiratory tract infection	452	7154			
Number of children non-hospitalized due to respiratory tract infection	9041	1,079,014	7.23	6.59–7.93	<0.0001
Summer					
Number of children hospitalized due to respiratory tract infection	276	3158			
Number of children non-hospitalized due to respiratory tract infection	9064	1,093,246	10.26	9.09–11.58	<0.0001

Table 3 Relative risk of hospitalization due to respiratory syncytial virus infection in the winter for CHD subgroups

Diagnosis	Number of children hospitalized due to respiratory syncytial virus infection	Number of children non-hospitalized due to respiratory syncytial virus infection	RR	CI (95 %)	<i>p</i> value
Univentricular heart defects	7	218			
All children except univentricular heart defects	7926	1,087,510	4.3	2.07–8.92	=0.0001
Systemic-pulmonary shunt defects	272	6614			
All children except shunt defects	7661	1,081,114	5.61	4.99–6.32	<0.0001
Pulmonary hypertension	8	124			
All children except pulmonary hypertension	7925	1,087,604	8.38	4.28–16.41	<0.0001
Other complex CHD	15	362			
All children except complex CHD	7918	1,087,366	5.5	3.35–9.04	<0.0001
Left-side outflow obstructions	45	894			
All children except left-side obstruction	7888	1,086,834	6.65	4.10–8.85	<0.0001
Right-side outflow obstructions	30	524			
All children except right-side obstruction	7903	1,087,204	7.5	5.30–10.63	<0.0001
Fallot's anomaly	13	230			
All children except Fallot's anomaly	7920	1,087,498	7.4	4.36–12.56	<0.0001
Cardiomyopathy	4	118			
All children except cardiomyopathy	7929	1,087,610	4.53	1.73–11.88	=0.0021

Among children with CHD, 394 (4.3 %) were hospitalized due to RSV infection in winter, compared to 7539 (0.7 %) of non-CHD children. During summer time, 41

(0.4 %) children with CHD and 545 (0.05 %) of non-CHD children were hospitalized due to RSV infection. For RTI in general, 452 (5 %) children with CHD were hospitalized

Table 4 Relative risk of hospitalization due to respiratory syncytial virus infection in summer for CHD subgroups

Diagnosis	Number of children hospitalized due to respiratory syncytial virus infection	Number of children non-hospitalized due to respiratory syncytial virus infection.	RR	95 % CI	<i>p</i> value
Univentricular heart defects	2	193			
All children except univentricular heart defects	584	1,104,965	19.42	4.88–77.27	<0.0001
Systemic-pulmonary shunt defects	27	6787			
All children except shunt defects	559	1,098,371	7.79	5.3–11.45	<0.0001
Pulmonary hypertension	0	132			
All children except pulmonary hypertension	586	1,105,026	–	–	–
Other complex CHD	5	342			
All children except complex CHD	581	1,104,816	27.41	11.44–65.7	<0.0001
Left-side outflow obstructions	3	918			
All children except left-side obstruction	583	1,104,240	6.17	1.99–19.16	=0.0016
Right-side outflow obstructions	1	500			
All children except right-side obstruction	585	1,104,658	3.77	0.53–26.76	=0.1843
Fallot's anomaly	3	245			
All children except Fallot's anomaly	583	1,104,913	22.94	7.42–70.84	<0.0001
Cardiomyopathy	0	146			
All children except cardiomyopathy	586	1,105,012	–	–	–

in winter, compared to 7154 (0.7 %) of non-CHD children. During summer time, 276 (3 %) children with CHD and 3158 (0.3 %) of non-CHD children were hospitalized due to RTI in general (Table 2).

During winter, the relative risk of hospitalization was increased for the most severe cases, such as univentricular heart defects. However, cases with less severe types of CHD, such as systemic to pulmonary shunt defects, had an even higher risk of RSV hospitalization in the winter (Table 3).

During summer, the relative risk of RSV hospitalization for the most severely ill cases, such as univentricular heart defects, increased severalfold compared to the risk of RSV hospitalization during the winter. There are few numbers of infected cases in all groups, but the results are statistically significant (Table 4). The same pattern was seen for RTI in general; there was a greater risk of hospitalization in the summer than in the winter for the most severely ill CHD children (Tables 5, 6).

Discussion

This study shows that children with CHD have an increased risk of hospitalization due to RSV infection as well as RTI in general, in summer as well as winter. The risk increased further in summer, especially for the most severe heart conditions.

Respiratory tract infections are common in early childhood, with RSV being the most common pathogen. Influenza viruses, rhinoviruses, human metapneumovirus, human coronaviruses and human bocaviruses can also be detected in young children who are admitted to hospital with respiratory tract symptoms [4, 5]. In this study, we chose to study hospitalization rates for RSV infection and RTI in general, in order to cover all types of viruses that affect young CHD children. The pattern of risk of hospitalization was similar for all types of RTI, with an elevated risk during summer for the most severe cases.

Table 5 Relative risk of hospitalization due to respiratory tract infection in general in winter for CHD subgroups

Diagnosis	Number of children hospitalized due to respiratory tract infection	Number of children non-hospitalized due to respiratory tract infection	RR	95 % CI	P value
Univentricular heart defects	13	210			
All children except univentricular heart defects	7593	1,087,845	8.41	4.96–14.26	<0.0001
Systemic-pulmonary shunt defects	290	6610			
All children except shunt defects	7316	1,081,445	6.25	5.58–7.02	<0.0001
Pulmonary hypertension	17	115			
All children except pulmonary hypertension	7598	1,087,940	18.59	11.92–28.99	<0.0001
Other complex CHD	26	350			
All children except complex CHD	7580	1,087,705	9.99	6.89–14.49	<0.0001
Left-side outflow obstructions	49	889			
All children except left-side obstruction	7557	1,087,166	7.57	5.76–9.95	<0.0001
Right-side outflow obstructions	30	526			
All children except right-side obstruction	7576	1,087,529	7.8	5.5–11.05	<0.0001
Fallot's anomaly	16	229			
All children except Fallot's anomaly	7590	1,087,826	9.43	5.87–15.14	<0.0001
Cardiomyopathy	11	112			
All children except cardiomyopathy	7595	1,087,943	12.9	7.34–22.68	<0.0001

In our study, 4.3 % of children with CHD who were infected by RSV during the winter were hospitalized, while only 0.7 % of RSV-infected children without CHD were hospitalized. In summer, 0.4 % of RSV-infected children with CHD were hospitalized, compared to 0.05 % of RSV-infected children without CHD. These figures were similar for RTI in general. Among children with CHD who were infected with general RTI, hospitalization rates were 5.0 % in the winter and 3.0 % in the summer; children without CHD who were infected by RTI in general had hospitalization rates of 0.7 % in the winter and 0.3 % in the summer. The individual risk of any child being hospitalized for RSV was approximately 17.2/1000 (1.7 %) during the first year of life, according to a recent Swedish study [20]. Our study presents lower risk estimations for non-CHD children, but greatly increased risk for children with CHD.

Prophylactic treatment with palivizumab reduces hospitalization rates and the severity of RSV infection in children with congenital heart defects [9, 11, 21]. This prophylactic treatment is only recommended during the winter, according to the Swedish national guidelines for the

study period, and includes children less than six months of age with congenital heart defects, such as Down syndrome with non-operated shunt defects, and shunt defects with heart failure. Children 1 year of age with univentricular heart defects in status post-bidirectional Glenn-operation, children with additional lung disease and pulmonary hypertension and those waiting for transplantation were also included. Prophylaxis with palivizumab is individually prescribed to each child with CHD who fulfills the indications for prophylactic treatment according to the guidelines. The overall risk of RSV hospitalization for CHD children during winter was lower than the risk hospitalization due to RTI in general. Thus, one can argue that the prophylactic treatment for RSV was effective. Additionally, according to our results, the strategy of RSV prophylactic treatment seems to lower the risk of hospitalization among the most severe cases during the winter. Perhaps, these children are less likely to be missed in the prophylactic treatment program by the pediatric cardiologist. In a previous study, we found that almost half the CHD patients had delays to the start of prophylactic

Table 6 Relative risk of hospitalization due to respiratory tract infection in general in summer for CHD subgroups

Diagnosis	Number of children hospitalized due to respiratory tract infection	Number of children non-hospitalized due to respiratory tract infection	RR	CI (95 %)	P value
Univentricular heart defects	13	184			
All children except univentricular heart defects	3421	1,102,126	21.33	12.6–36.1	<0.0001
Systemic-pulmonary shunt defects	163	6672			
All children except shunt defects	3271	1,095,638	8.01	6.86–9.36	<0.0001
Pulmonary hypertension	10	122			
All children except pulmonary hypertension	3424	1,102,188	24.46	13.47–44.43	<0.0001
Other complex CHD	14	335			
All children except complex CHD	3420	1,101,975	12.97	7.75–21.68	<0.0001
Left-side outflow obstructions	39	887			
All children except left-side obstruction	3395	1,101,423	13.71	10.06–18.67	<0.0001
Right-side outflow obstructions	19	485			
All children except right-side obstruction	3415	1,101,825	12.20	7.84–18.99	<0.0001
Fallot's anomaly	12	239			
All children except Fallot's anomaly	3422	1,102,071	15.44	8.88–26.85	<0.0001
Cardiomyopathy	6	140			
All children except cardiomyopathy	3428	1,102,170	13.25	6.05–29.04	<0.0001

treatment, but this accounted mainly for children with systemic-pulmonary shunt defects [22]. Since children with less severe forms of CHD have a higher risk of RSV hospitalization in the winter than the more severe cases of CHD, the present study indicates that even the less severe forms of CHD carry a substantial risk of hospitalization.

Prophylactic respiratory syncytial virus treatment with palivizumab is both expensive and painful, and is recommended when RSV incidence is at its highest level [23, 24]. In our study, there were a low number of RSV-infected CHD children during the summer. Rather than suggesting extensive prophylactic treatment, we would like to stress the overall vulnerability for these children, including the risks of RSV infection as well as severe RTI in general, throughout the whole year. Information to parents and healthcare staff must include the risk of severe viral RTI during winter season but also in summer. We also argue that seasonal and regional variations in the onset of the RSV epidemic should indicate when to start treatment, rather than a specific date.

Testing for RSV is possible in all hospitals in Sweden all year round, but there are regional and seasonal variations in RSV testing. As the treatment is similar for all types of RTI, it is of little importance to the clinician whether the child has RSV or not, so not all affected children are tested. Only the tested cases are reported to the Swedish Public Health Agency [25], and the agency only collected data on the numbers of RSV infections during the winter season and published weekly on their Web site. Waiting for this reporting to start may delay prophylactic treatment and RSV protection for children with CHD. We argue for local testing and reporting to pediatric cardiologists, as well as to the Swedish Public Health Agency. Testing for RSV can be less common during summer, so there is a risk of under-reporting. This must account for CHD children as well as non-CHD children. RSV infections can occur sporadically throughout the year, especially in areas with colder weather throughout the year, or areas with small seasonal changes in the climate [13]. However, prophylaxis with palivizumab in the summer, when RSV prevalence is generally low

in Sweden, cannot be recommended. In countries with subtropical climates, the RSV season can last up to ten months, so the period for giving prophylaxis may follow the local epidemiology [26].

The Swedish National Inpatient Registry does not provide information on whether or not a child has received prophylactic treatment, which limits this study. However, the nationwide setting of this study with a large number of cases covering a long period of time is a strength and rules out the difference in testing and decreases the impact of the annual variation of RSV in the study. We chose to study RSV in particular and RTI in general, to eliminate the risk of under-reporting of RSV cases, as they are most likely included in the group of children with general RTI.

This register-based study is limited by its dependence on correctly registered diagnostic codes. The exact number of patients with missing data on primary diagnoses and other diagnostic errors (such as incorrect diagnoses) has not been validated for congenital heart disorders, but this has been done overall for several other diagnoses. The positive predictive values are reported to be approximately 85–95 % in the Inpatient Register [16]. The risk of misclassification among RSV, RTI and CHD can be regarded as limited in our study.

Migration of families in and out of Sweden may have occurred during the study period and may limit the study. However, the risk of hospitalization is calculated from exact numbers retrieved from inpatient register. The hospitalized children were then subgrouped into different congenital cardiac malformations and compared to all other children (other CHD malformations as well as otherwise healthy children). For a large national population, we do not estimate migration to influence the risk estimations.

Relative risk of hospitalization as an estimation of morbidity in RSV among children with CHD is used in several studies [7, 12, 27]. Even though the number of CHD children with a specific heart condition is small in our study, the risk estimation for hospitalization is significant. However, hospitalization rates do not necessarily reflect the current condition of the child. Thresholds for admission may vary between different hospitals with different geographic settings and may also vary on an individual basis between different clinicians who have different experience. Further studies are needed to determine the morbidity and indications for hospitalization in all respiratory tract infections among CHD children in Sweden.

In conclusion, the relative risk of hospitalization was increased for all CHD children in all subgroups, both for RSV infection and RTI in general. However, the risk was found to be even higher for the children with the most severe forms of CHD during the summer, which indicates

that risk of severe infectious illness may be present all year round for CHD children.

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Compliance with Ethical Standards

Conflicts of interest None.

Ethical Standards All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. The study was approved by the Regional Ethical Review Boards in Umeå, Sweden (D-nr 2014/100-31).

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