Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease

A Duppenthal, R A Ammann, M Gorgievski-Hrisoho, J-P Pfammatter, C Aebi


Background: Haemodynamically significant congenital heart disease (CHD) is a risk factor for severe respiratory syncytial virus (RSV) disease in young children. Population based data on the incidence of RSV hospitalisations in CHD patients are needed to estimate the potential usefulness of RSV immunoprophylaxis using palivizumab.

Aims: (1) To obtain population based RSV hospitalisation rates in children <24 months of age with CHD. (2) To compare these rates with non-CHD patients and with previous studies. (3) To determine the number of patients needed to treat (NNT) with palivizumab to prevent one RSV hospitalisation.

Methods: Six year, longitudinal, population based study at an institution, which is the sole provider of primary to tertiary in-patient care for a precisely defined paediatric population.

Results: RSV hospitalisation 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 to 5.6), 2.0 (0.8 to 3.8), 0.5 (0.1 to 1.8), and 1.3 (0.6 to 2.3), respectively, and the relative risk (RR) in comparison with non-CHD patients was 1.4 (0.6 to 3.1), 1.6 (0.8 to 3.2), 2.7 (0.7 to 9.7), and 1.8 (1.0 to 3.3), respectively. NNT was between 80 (35 to 245) and 259 (72 to 2140) for various age groups.

Conclusion: RSV hospitalisation rates in CHD patients were fourfold lower than reported from the USA. Based on these low rates and RR, unrestricted use of palivizumab does not appear to be justified in this study area.

RESPIRATORY SYNCYTIAL VIRUS (RSV)

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory tract infections in infants and toddlers. Up to 70% of children are infected during their first year of life and 1–3% of the annual birth cohort are hospitalised because of RSV infection. The need for hospitalisation is a useful marker of severity, has emerged as the primary endpoint in clinical trials of RSV prophylaxis, and is a major cost driving event. Major host factors associated with an increased risk for hospitalisation associated with RSV are prematurity and congenital heart disease (CHD). Population based RSV hospitalisation rates for infants with prematurity and those with BPD have been established, and provide the rationale for studying and introducing RSV immunoprophylaxis using the monoclonal antibody palivizumab in some countries. Considerably less data are available for CHD and none provide hospitalisation rates for children with haemodynamically significant CHD. This distinction is important because palivizumab was studied exclusively in patients with haemodynamically significant CHD. In recently published national recommendations for Great Britain and the USA, its use was therefore restricted to this indication. The present study reports population based RSV hospitalisation rates in children with haemodynamically significant CHD, taking advantage of a long term surveillance programme of RSV hospitalisations at an institution serving a precisely defined paediatric population.

METHODS

Study design
In a longitudinal, population based study the incidence of RSV hospitalisation in children <24 months of age born with CHD in the Canton (State) of Bern, Switzerland, between 1 July 1997 and 30 June 2003 was determined. Children without CHD served as comparator population. RSV hospitalisation was defined as an RSV positive respiratory tract infection which necessitated hospital admission. CHD, BPD, prematurity, and age <1 year were defined as mutually exclusive risk factors for severe RSV disease in this order of priority. CHD was defined as haemodynamically significant cardiac malformation. Patients with haemodynamically insignificant malformations were assigned to the non-CHD group. The most recent consensus definition was used for BPD. Prematurity was defined as birth at ≤35 weeks of gestation.

RSV hospitalisations
A surveillance programme initiated in 1997 identified all RSV hospitalisations at this institution. Systematic detection of RSV infected patients was achieved by a guideline requiring that children <3 years of age admitted with clinical manifestations compatible with RSV infection (that is, rhinorrhea, tachypnoea, airway obstruction, apnoea, oxygen requirement, or pneumonia) undergo RSV testing. RSV was detected in nasopharyngeal secretions using a direct immunofluorescence assay. A negative test was repeated once. Patients tested positive for the first time >72 hours after admission and those living outside the Canton of Bern were excluded. A standardised set of clinical data, which included the presence and nature of cardiac malformations, was recorded for each patient.

CHD registry
The division of paediatric cardiology maintains a registry of patients with CHD defined by the International Classification of Diseases, 10th revision, codes Q20–Q26. Patients with haemodynamically insignificant ventricular septum defect
(VSD), atrial septum defect (ASD), and persistent ductus arteriosus (PDA) are not registered.

Demographic data
Live birth statistics were obtained from the Federal Office of Statistics. The study site is the sole provider of primary to tertiary paediatric in-patient care for an area inhabited by approximately 882 000 with a total birth cohort during the six year study period of 51 346. These figures correspond to 93% of the Canton’s population. The remainder is served by another paediatric hospital. The paediatric cardiology centre serves the entire Canton populated by approximately 944 000 with a six year birth cohort of 54 947. The annual number of patients with newly diagnosed CHD equals the incidence of CHD in the Canton.

Statistical analysis
A study year was defined to last from 1 July to 30 June of the following year. The annual number of live births was assumed to equal the number of child-years with RSV exposure in children <12 months of age. For 12–24 month old children the number of child-years with RSV exposure was defined to equal the number of live births from the previous year. Infant mortality (estimated to be <0.5%) was disregarded for children without CHD, but accounted for in the population of 12–24 month old children with CHD. Hospitalisation rates were calculated by dividing the number of RSV hospitalisations by the corresponding number of child-years. For relative risks (RR), exact unconditional 95% confidence intervals (CI) were calculated according to Chan and Zhang. For proportions, exact Clopper-Pearson 95% CI were calculated. Characteristics of the clinical course of RSV hospitalisations were compared using Fisher’s exact test and the exact Wilcoxon-Mann-Whitney test, where applicable. The number needed to treat (NNT) was calculated using the equation “child-years/(hospitalisations × efficacy)”. Two sided tests were performed throughout. Values of p < 0.05 were considered significant. The StatXact 5.03 software (Cytel Software Corp., Cambridge, MA) was used.

The study was approved by the local ethics committee.

RESULTS
RSV hospitalisations
During six consecutive years, 813 children (456 males) were hospitalised because of RSV infection. Table 1 shows major clinical and outcome variables. Eighty four patients (10%) were >24 months of age and were excluded. CHD, BPD, prematurity, and age <1 month were recorded in 90 (1.4%), 16 (2.1%), 60 (8.2%), and 90 (12.3%) of the remaining 729 patients, respectively. Five (50%) and 462 (64%) children with and without CHD, respectively, were <6 months of age. There was biannual periodicity of RSV hospitalisation frequencies reflecting the pattern of alternating severity of RSV epidemics in this region (fig 1A). There was no correlation between the severity of RSV epidemics and the distribution of risk factors (fig 1B) or the clinical course of RSV hospitalisations (data not shown).

CHD was diagnosed in 407 of 54 947 (0.74%) live born infants during the study period. There were 10 RSV hospitalisations in CHD patients (table 2). Complete surgical correction had already been accomplished at the time of RSV infection in three patients (coarctation, coarctation plus ASD, and ASD plus PDA in one patient each). None of these patients had pulmonary arterial hypertension. The remaining seven children had uncorrected CHD (VSD and complex cyanotic CHD in two patients each; ASD, cor triatriatum with mitral valve stenosis, atroventricular canal, and Epstein’s anomaly in one each). Pulmonary arterial hypertension and cyanosis were present in five and two of these patients, respectively. Haemodynamically insignificant cardiac malformations were recorded in 11 patients (VSD in eight patients; ASD in three; PDA in one) assigned to the non-CHD group.

Course of RSV hospitalisations
Table 1 summarises commonly used clinical criteria for characterisation of the course of RSV hospitalisation in patients with and without risk factor for severe RSV disease. Administration of supplemental oxygen, intensive care unit (ICU) admission, and mechanical ventilation were required in a significantly greater proportion of patients with CHD and for significantly longer periods of time than in those without CHD (table 1). CHD patients were admitted to the ICU significantly more often than children with BPD or prematurity, but not in comparison with otherwise healthy infants <1 month of age. Also, the only death recorded during the study period resulted in a significantly greater case fatality rate for CHD patients. This fatal course occurred in a 19 month old girl, whose cardiac malformation (cor triatriatum with mitral valve stenosis and pulmonary arterial hypertension) was diagnosed only when she was admitted for RSV infection complicated by acute heart failure. Emergency resection of the atrial membrane established mitral valve patency, but the patient died on the first...
postoperative day from intractable pulmonary arterial hypertension and left ventricular decompensation.

**RSV hospitalisation rates**

Table 2 lists annual hospitalisation frequencies and rates. In CHD patients, hospitalisation rates for the <12 month old and 12–24 month old children were 2.0 (95% CI 0.9 to 3.8) and 0.5 (0.1 to 1.8) per 100 child-years, respectively. The corresponding numbers for children without CHD were 1.2 (1.1 to 1.3) and 0.2 (0.16 to 0.23), respectively. The RR for RSV hospitalisation in children with CHD was calculated (1.1 to 1.3) and 0.2 (0.16 to 0.23), respectively. The RR for 12–24 month old children were 2.0 (95% CI 0.9 to 3.8)

In this six year study we established that in the Canton of Bern, Switzerland, RSV hospitalisation rates in children <24 months of age with CHD (tables 2 and 3) were markedly lower than previously reported figures from the USA (table 3) and from Sweden. These discrepancies warrant comparative analysis of the methods used for case catchment and ascertainment in these studies. The method used in our study is likely to yield reliable RSV hospitalisation rates, because (1) cases were identified prospectively using a standardised diagnostic algorithm at a single study site, which (2) served a precisely defined geographical area, which permitted generation of accurate data on both the incidence of CHD and the live birth cohort, and (3) the six year observation period eliminated the effect of year to year fluctuation of hospitalisation rates. In addition, both the incidence of CHD (0.74%) in the general population, 19 20 and the overall infant RSV hospitalisation rate of 1.2% are consistent with established figures, lending further support to the accuracy of data acquisition.

Comparison of the present study with the report by Boyce and co-workers, who found approximately fourfold greater hospitalisation rates in CHD patients (table 3), yields a number of possible explanations for discrepant results. In their retrospective analysis of a large Medicaid population in

### Table 1: Clinical course of RSV hospitalisations in 729 children less than 24 months of age stratified according to risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-CHD patients</th>
<th>CHD patients</th>
<th>p value†</th>
<th>Total</th>
<th>BPD</th>
<th>Prematurity &lt; 35 wk</th>
<th>Age &lt; 1 mth</th>
<th>No risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>5</td>
<td>0.098</td>
<td>3.7</td>
<td>5.6</td>
<td>0.6</td>
<td>90</td>
<td>554</td>
</tr>
<tr>
<td>Age (mths)</td>
<td>5 [2.1 to 19.4]</td>
<td>2.3 [0.2 to 23.6]</td>
<td>8.7 [4.0 to 20.8]</td>
<td>5.6 [0.5 to 20.2]</td>
<td>0.6 [0.2 to 1.0]</td>
<td>5.3 [1.1 to 23.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td>6.5 [2.41]</td>
<td>0.265</td>
<td>5 [1 to 30]</td>
<td>11 [4 to 23]</td>
<td>6 [2 to 23]</td>
<td>8 [1 to 27]</td>
<td>5 [1 to 30]</td>
<td></td>
</tr>
<tr>
<td>Supplemental O2 (%)</td>
<td>10 (100)</td>
<td>0.037</td>
<td>496 (69)</td>
<td>12 (80)</td>
<td>44 (73)</td>
<td>77 (86)</td>
<td>363 (66)</td>
<td></td>
</tr>
<tr>
<td>Duration of supplemental O2*</td>
<td>0.6 [1 to 5]</td>
<td>0.023</td>
<td>4 [0 to 21]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td></td>
</tr>
<tr>
<td>Duration of ICU stay*</td>
<td>1.2 [0.25]</td>
<td>0.001</td>
<td>0 [0 to 10]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>5 (50)</td>
<td>0.003</td>
<td>81 (11)</td>
<td>12 (20)</td>
<td>29 (32)</td>
<td>39 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>0 [0 to 18]</td>
<td>0.009</td>
<td>0 [0 to 12]</td>
<td>0 [0]</td>
<td>0 [0 to 12]</td>
<td>0 [0 to 12]</td>
<td>0 [0 to 12]</td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>1 [10]</td>
<td>0.014</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In days, unless indicated otherwise; median [range] are given.
†p values indicate the level of significance for differences between CHD patients and the total of non-CHD patients (two adjacent columns).
‡ICU admission rate: CHD v BPD, p = 0.01; CHD v prematurity, p = 0.045; CHD v age < 1 month, p = 0.144; CHD v no risk factor, p < 0.001.

### Table 2: RSV hospitalisation rates in children with and without CHD

<table>
<thead>
<tr>
<th>Study year</th>
<th>1997/98</th>
<th>1998/99</th>
<th>1999/00</th>
<th>2000/01</th>
<th>2001/02</th>
<th>2002/03</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of hospitalisations</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>0–12 mth of age</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>12–24 mth age</td>
<td>74</td>
<td>70</td>
<td>71</td>
<td>72</td>
<td>64</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Child-years</td>
<td>68</td>
<td>69</td>
<td>64</td>
<td>66</td>
<td>67</td>
<td>58</td>
<td>39</td>
</tr>
<tr>
<td>Hospitalisation rate (per 100 child-years)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.6</td>
<td>5.3</td>
<td>2.0 (0.9 to 3.8)*</td>
</tr>
<tr>
<td>0–12 mth of age</td>
<td>1.5</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>0.5 (0.1 to 1.8)*</td>
<td></td>
</tr>
<tr>
<td>12–24 mth of age</td>
<td>43</td>
<td>139</td>
<td>52</td>
<td>153</td>
<td>60</td>
<td>171</td>
<td>618</td>
</tr>
<tr>
<td>Non-CHD patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>5</td>
<td>14</td>
<td>15</td>
<td>22</td>
<td>12</td>
<td>33</td>
<td>101</td>
</tr>
<tr>
<td>0–12 mth of age</td>
<td>0.5</td>
<td>1.6</td>
<td>0.6</td>
<td>1.8</td>
<td>0.7</td>
<td>2.2</td>
<td>1.2 (1.1 to 1.3)*</td>
</tr>
<tr>
<td>12–24 mth of age</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.4</td>
<td>0.2 (0.16 to 0.23)*</td>
</tr>
</tbody>
</table>

*95% confidence interval in parentheses.
Tennessee, these authors identified CHD patients using the ICD-9 codes 745, 746, and 747. This approach did not allow them to distinguish between haemodynamically significant and non-significant heart disease. Because haemodynamically significant CHD alone is a risk factor for RSV hospitalisation, the accuracy of reported incidence rates may have been affected. Furthermore, the number of RSV hospitalisations in patients with and without CHD (that is, the denominators) may have been overestimated, because episodes coded specifically for “RSV infection” accounted for 6.3% of cases only. The remainder were coded for the diagnosis of “bronchiolitis”. Although corrections were made for influenza, other viruses such as parainfluenza virus, adenovirus, and human metapneumovirus may have accounted for an unknown proportion of cases.

Regardless of the methodological differences between these two studies, CHD patients of all age groups had an RR for RSV hospitalisation of approximately 2 compared with non-CHD patients (table 3). It is thus conceivable that the differences in RSV hospitalisation rates are real and reflect true epidemiological differences. This notion is supported by the results from the two placebo controlled trials of RSV immunoprophylaxis. For instance, hospitalisation rates among CHD patients <6 months of age assigned to the placebo arm were 24% and 12.2%, respectively. These figures are substantially greater than those found in the present study (2.5%), even if we take into account that hospitalisation rates established in our study must be corrected by a factor of 2 for comparison. This adjustment is necessary because patients participating in these trials were observed prospectively during a six month period in winter, during which essentially all RSV infections occur. Thus, true exposure occurs during approximately half of the number of child-years used as denominator in our study. Several reasons for these widely divergent RSV hospitalisation rates are conceivable. It has been shown that the severity of both RSV epidemics and RSV disease varies according to geographical location. Small family size and low rates of day care attendance in Switzerland may reduce exposure to RSV during the first year of life. Also, different criteria for hospital admission may play a role.

Eriksson and co-workers reported the only currently available estimates on RSV hospitalisation rates in CHD patients from a European country. These investigators found hospitalisation rates between 2.8% and 6.4% depending on the severity of the annual RSV epidemic. Comparison with our data is hampered, however, because stratifications according to age and haemodynamic significance of CHD were not made.

The present study has several limitations. (1) We were unable to define the subpopulation of CHD patients who had not had corrective surgery at the time of RSV exposure. Thus, the number of children with CHD at increased risk of RSV hospitalisation may have been smaller, although surgical correction does not necessarily reduce the risk of RSV infection to baseline. This shortcoming, however, does not invalidate comparison of data (table 3), because it was noted also in the two comparator studies. (2) Catchment of RSV infections was incomplete because of less than optimal coverage. (3) Calculation of RSV hospitalisation rates in premature infants and children with BPD was not feasible, because reliable data on the respective birth cohorts were not available. (4) The number of RSV hospitalisations among CHD patients was so small that confidence intervals for hospitalisation rates were wide. (5) The study was conducted in a static, predominantly small family size and low rates of day care attendance in Switzerland may reduce exposure to RSV during the first year of life. Also, different criteria for hospital admission may play a role.

### Table 3
**Risk comparison for RSV hospitalisation in children with and without CHD as assessed in 2 different studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameter*</th>
<th>Age group</th>
<th>Hospitalisation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>Hospitalisation rate</td>
<td>&lt;6 mth</td>
<td>2.5 (0.8 to 5.6)</td>
</tr>
<tr>
<td></td>
<td>Non-CHD patients</td>
<td>&lt;12 mth</td>
<td>1.8 (1.6 to 2.0)</td>
</tr>
<tr>
<td></td>
<td>Relative risk</td>
<td>12–24 mth</td>
<td>1.4 (0.6 to 3.1)</td>
</tr>
<tr>
<td>Ref. 4†</td>
<td>Hospitalisation rate</td>
<td>&lt;6 mth</td>
<td>12.1 (10.1 to 14.3)</td>
</tr>
<tr>
<td></td>
<td>CHD patients</td>
<td>&lt;12 mth</td>
<td>5.5 (5.3 to 5.7)</td>
</tr>
<tr>
<td></td>
<td>Relative risk</td>
<td>12–24 mth</td>
<td>2.2 (1.8 to 2.6)</td>
</tr>
</tbody>
</table>

*Per 100 child-years, 95% confidence intervals are given in parentheses.
†Hospitalisation rates for non-CHD patients and confidence intervals were calculated using raw data provided in the report.
‡p values for comparison of relative risks between the two study populations for the age groups <6 months, <12 months, 12–24 months, and <24 months were 0.45, 0.43, 0.70, and 0.51, respectively (test for homogeneity).

### Table 4
**Numbers of CHD patients needed to treat (NNT) with palivizumab for prevention of one hospitalisation according to published efficacy data**

<table>
<thead>
<tr>
<th>Age group</th>
<th>RSV hospitalisations</th>
<th>Child-years*</th>
<th>Hospitalisation rate per 100 child-years</th>
<th>Efficacy of palivizumab (risk reduction)</th>
<th>NNT‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mth</td>
<td>5</td>
<td>204</td>
<td>2.5</td>
<td>51%</td>
<td>80 (35 to245)</td>
</tr>
<tr>
<td>&lt;12 mth</td>
<td>8</td>
<td>407</td>
<td>2.0</td>
<td>33%†</td>
<td>154 (78 to356)</td>
</tr>
<tr>
<td>12–24 mth</td>
<td>2</td>
<td>391</td>
<td>0.4</td>
<td>58%‡</td>
<td>259 (72 to2140)</td>
</tr>
<tr>
<td>&lt;24 mth</td>
<td>10</td>
<td>798</td>
<td>1.3</td>
<td>45%‡</td>
<td>177 (97 to369)</td>
</tr>
</tbody>
</table>

*To account for the fact that true RSV exposure exists during approximately six months per year, child-years (see table 2) were divided by a factor of 2 to calculate NNT.
†Risk reduction for this age group is not given in the publication by Feltes and co-workers. Here we used the average of the risk reduction rates reported for the age groups <6 months (51%) and 6–12 months (16%), respectively.
‡NNT; number needed to treat for prevention of one RSV hospitalisation (95% CI are given in parentheses).
Reliable data on RSV hospitalisation rates in CHD patients are needed more than ever before. Feltes and co-workers recently reported the results of a large, placebo controlled trial of RSV prophylaxis using palivizumab in children <24 months of age with haemodynamically significant CHD. Palivizumab was found to cause a risk reduction for RSV hospitalisation of 51% and 45%, respectively, among patients <6 months and <24 months of age. These efficacy data can be used to calculate the number of CHD patients needed to be treated with palivizumab for prevention of one RSV hospitalisation (table 4). Taking into account the fact that palivizumab costs between €3500 and €5000 per patient, it is evident that this intervention would not be cost effective. Considering the low RSV hospitalisation rates and RR, unrestricted use of palivizumab thus appears to be of low priority in our CHD patient population, despite the fact that both the course of RSV hospitalisations and the case fatality rate were significantly less favourable compared with non-CHD patients, including children with BPD and prematurity (table 1). The American Academy of Pediatrics recommends the use of palivizumab in children <24 months of age with haemodynamically significant CHD. The British Paediatric Cardiac Association, however, restricts palivizumab to patients <12 months of age. Our data would support this approach, because the RSV hospitalisation rate among CHD patients 12–24 months of age was lower than that of children <12 months of age without CHD.

In conclusion, RSV hospitalisation rates in patients with CHD were found to be low, and the risk of RSV hospitalisation was only twofold greater compared to non-CHD patients. Recommendations for use of palivizumab in CHD patients will need to weigh these epidemiological findings, which entail costs between €280 000 and >€1 000 000 for prevention of a single RSV hospitalisation, against the more severe course of RSV disease in these patients.

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