Respiratory syncytial virus-related outcomes from an abbreviated palivizumab dose regimen in children with congenital heart disease: A descriptive analysis

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ABSTRACT (250 words)

Background: It has been hypothesized that 4 doses of palivizumab, a neutralizing monoclonal antibody against respiratory syncytial virus (RSV), administered within fixed season dates may reduce hospitalizations comparably to the standard 5-dose schedule. Here, we report outcomes in children with congenital heart disease approved to receive this 4-dose fixed-dates schedule in British Columbia.

Method: Population-based descriptive cohort analysis of all 406 approved palivizumab courses over four seasons (2012-2016) in 325 children with hemodynamically significant congenital heart disease enrolled in the British Columbia RSV Immunoprophylaxis Program. Primary outcome was in-season hospitalization for potential RSV-related lower respiratory tract infection. Secondary outcomes include timing of hospitalization in relation to dosing. Analysis was by intention-to-treat.

Results: Of 406 approved palivizumab courses, 391 were administered. In 33 cases (8.4%) an additional dose was given immediately after cardiac bypass surgery. There were 17 RSV-confirmed hospitalizations (median age 5.9; interquartile range 4 to 10 months) and 8 hospitalizations where RSV was not tested, for a maximum of 25 potential RSV-related hospitalizations (6.2 per 100 approvals, 95% confidence interval: 4.0 to 9.0). Twenty-four of 25 hospitalizations (96%) occurred before the fourth palivizumab dose. One RSV-related hospitalization occurred 52 days after the fourth dose, and this was RSV-confirmed. Forty (62%) of 65 hospitalizations were RSV-negative, with baseline clinical characteristics not different from those with RSV-confirmed hospitalizations.

Interpretation: In infants with hemodynamically significant congenital heart disease a 4-dose fixed-dates palivizumab schedule over a 6-month season provided seasonal protection that compares to the only clinical trial involving a standard five-dose schedule.

INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection in young children (1). Infants born prematurely, those with chronic lung or congenital heart diseases are at higher risk (2, 3). Most hospital admissions occur during the winter, so-called "RSV season", which in most jurisdictions lasts six months (4). There is no vaccine against RSV. However, five seasonal doses of palivizumab, a neutralizing monoclonal antibody against RSV, has been shown to reduce hospitalizations in children with congenital heart disease less than two years, from 9.7% in the placebo group (95% confidence interval, 95%CI: 7.7 to 12%) to 5.3% in the palivizumab group (95%CI: 3.8 to 7.3%), based on one randomized controlled trial (5). Thus, contrary to conventional vaccines that are supposed to induce nearly complete protection in a majority of the population, palivizumab is a passive monoclonal antibody that only provides partial (~50%) protection as long as sufficiently elevated serum drug levels persist during the high viral exposure period (6).

A key question then is how many doses are necessary to achieve optimal protection over the typical 6-month RSV season. Several authors have suggested that a 4-dose schedule should perform nearly as well as the established 5-dose schedule in most settings while reducing unnecessary clinic visits for families, drug injections for children and costs to the health care system (4, 7-10). To this date British Columbia is the only jurisdiction that uses abbreviated 4-dose, fixed-date schedules (3, 10). Our group has recently reported outcomes from infants in the British Columbia RSV Immunoprophylaxis Program overall (11). However, children with congenital heart disease constitute a distinct subgroup of patients that tend to have more severe RSV infections, with hospitalization rates as high as 36% in absence of palivizumab (12). We report hospitalizations in children with congenital heart disease, who were approved to receive a 4-dose abbreviated palivizumab schedule in British Columbia.

METHODS

Study design & setting: Descriptive, population-based cohort study of all children with congenital heart disease in the British Columbia RSV Program over 4 consecutive seasons (2012 to 2016) – this defined our sample size. The Program centrally manages all palivizumab administration provincially. Children younger than 12 months with hemodynamically significant congenital heart disease are universally approved to receive 4 doses. Children with congenital heart disease aged 12 to 24 months may also receive 4 palivizumab doses after clinical review by an expert panel, based on best available evidence.

Exposure: Within the Program, palivizumab is administered according to pre-specified fixed season dates starting on the third Monday of November until March 31. This period was defined based on a review of 16 seasons of provincial RSV hospitalization data (1994-2011) (13). After reviewing the pharmacokinetics of palivizumab, the Program concluded that 4 doses would confer sufficient protective serum drug levels over a typical 6-month RSV season (10). The American Academy of Pediatrics and Canadian Pediatric Society both recommend against palivizumab administration in infants who are still in hospital, instead favoring protecting them using infection control principles (2, 3). Accordingly, in British Columbia palivizumab is administered only to ambulatory children or just prior to hospital discharge.

Palivizumab is administered by RSV Program clinic nurses distributed across British Columbia in 87% of cases, or in family doctor's offices in 13% of cases. Children receive up to four intramuscular doses of 15 mg/kg/dose: the second dose is given 21 days (maximum 28 days) after the first dose and

subsequent doses are given 28 days (maximum 35 days) apart. One additional dose is administered if an infant undergoes cardiopulmonary bypass during the season (immediately post-procedure). No doses are administered after March 31 of a given season.

Outcomes & follow-up period: The main outcome was potential RSV-related hospitalization, which included RSV-confirmed or RSV-undetermined lower respiratory tract infection, as defined below. Follow-up occurred between November 01 and April 30 for each season.

Data collection & definitions: Hospitalizations were centrally reported by clinic nurses to the RSV Program Provincial Clinic Coordinator (CC). Additionally, hospitalizations for lower respiratory tract infections were extracted from the Canadian Institute of Health Informatics discharge abstract database from health authorities in British Columbia, using 7 International Statistical Classification of Diseases and Related Health Problems-10 diagnostic codes: B97.4-Respiratory syncytial virus as the cause of diseases classified to other chapters; J12.1-Respiratory syncytial virus pneumonia; J12.9-Viral pneumonia, unspecified; J20.5-Acute bronchitis due to respiratory syncytial virus; J20.9-Acute bronchitis, unspecified J21.0-Acute bronchiolitis due to respiratory syncytial virus; J21.9-Acute bronchiolitis, unspecified.

The diagnosis of lower respiratory tract infection was confirmed by a review of medical charts, including viral testing (nasopharyngeal swabs) whenever available (LS, CP, JC, CC). Hospitalizations where children tested positive for RSV were considered *RSV-confirmed*, or children not tested for RSV were considered *RSV-undetermined*. Both categories were included in conservative estimates of RSV-related hospitalizations. Hospitalizations where children tested negative for RSV were considered *RSV-negative*. Data were electronically compiled in a spreadsheet, according to their occurrence before the first dose of palivizumab (either before, or after the season start in the case of "late" referrals), within the dosing period (including up to 35 days after the fourth dose), or more than 35 days after the fourth palivizumab dose. Mortality is reported as of the end of the 2016 follow-up period for all children. All data were manually reviewed for accuracy by two investigators (JC, PML).

In addition, the following baseline demographic data was analyzed: type of congenital heart disease, whether a surgical correction was performed (including date and whether cardiopulmonary bypass was required), palivizumab doses (with dates). Congenital heart diseases were categorized by a Cardiologist (DH), as: cyanotic lesion, left to right shunt lesions, left ventricular obstruction (including coarctation of the aorta), combined lesions, cardiomyopathy or unspecified heart defects. Any missing data was treated as such and reported in the tables.

Statistical analyses: Data was analyzed per child per RSV season, except for data related to children's baseline demographics. This means that if a child received palivizumab for more than one RSV season, each season was counted as a separate event (referred to as *approval*s). Results were analyzed descriptively using 95% confidence intervals calculated using the binomial exact method (http://www.sample-size.net/confidence-interval-proportion/), standard deviations, or interquartile range (depending on expected data distribution). Analysis was by intention-to-treat.

Ethics approval: This study was approved by the Children's and Women's Research Ethics Board (#H11-03424).

RESULTS

Study population: The clinical characteristics of the 325 children in the study are presented in **Table 1**. Most (74%) were born at term (n=236 of 318 children in whom gestational age data were available) or were younger than 6 months at the start of the RSV season (n=242/325). Nearly half (n=151; 46%) had cyanotic heart defects, followed by hemodynamically significant left-right shunt (n=129; 40%), left ventricular outflow tract obstruction (n=18; 6%), cardiomyopathies (n=15; 5%), a combination of complex anomalies (n=9; 3%) or unspecified heart defects (n=3; 1%).

Palivizumab administration: Among 325 children with congenital heart disease, 406 palivizumab courses were approved. The majority of courses were approved during the child's first season (n=288; 71%). One hundred (25%) courses were approved in a child's second season, and 18 (4%) were approved the third season. Seventy-two children (22%) received palivizumab for more than one season.

Of the 406 approved courses of palivizumab, 391 were administered (**Figure 1**). Twelve were never administered because of parent/legal guardian refusal (n=10) or prolonged hospitalization during the season (n=2). In three courses, the number of palivizumab doses could not be determined.

Of the 391 palivizumab courses administered, 351 (90%) included up to 4 doses, and 38 (9.7%) included an additional fifth doses received: in 33 cases (8.4%) immediately after cardiac bypass surgery and in 5 cases (1.3%) at physicians' discretion. Two courses (0.5%) included six doses, at physicians' discretion. Another 30 courses (7.7%) were not completed: seven due to non-compliance during the season, three as a result of hospital admission, four due to the child's death, two at the treating physician's discretion and 14 for unspecified reasons.

Outcomes: Of 406 approvals there was one hospitalization in 64 approvals and more than one hospitalization in 17 approvals, for a total of 89 hospitalizations (21.9%) over 4 seasons (**Figure 2**).

In 17 hospitalizations children tested positive for RSV, for a rate of RSV-confirmed hospitalizations of 4.2 per 100 season-approvals (95%CI: 2.5 to 6.6%). In 8 cases children were not tested for RSV, for a maximum rate of potential RSV-related hospitalizations of 6.2 per 100 approvals (95%CI: 4.0 to 9.0%). Sixty-four children (64 of 406 = 16%) tested positive for non-RSV pathogens.

Among 25 children with RSV-confirmed or RSV-undetermined hospitalization, 20 were in their first RSV season, 5 in their second season and none in their third RSV season. Twenty-three of these 25 children (92%) were 12 months or younger, and the other two children were 21 and 22 months, respectively. One had a corrected transposition of the great arteries with atrio-ventricular discordance and significant residual systemic (left) outflow tract obstruction, and the other had Down syndrome.

Among the 17 RSV-confirmed hospitalizations, two occurred after the start of the season, on November 19 and November 27, but before a Program application had been received. Fourteen occurred within the dosing period. The one remaining admission presented 52 days after the fourth dose. Among the 7 RSV-undetermined hospitalizations, 1 occurred before a Program application had been received on November 30, 6 occurred within the dosing period: 2 of which were non-adherent with the dosing schedule and 1 occurred 29 days after the fourth palivizumab dose.

The clinical characteristics of children hospitalized for RSV-confirmed hospitalizations were similar to those hospitalized for RSV-negative lower respiratory tract infection (**Table 2**). No deaths were

attributable to lower respiratory tract infection in this cohort. None of the 10 children with parent/legal guardian refusal of palivizumab or of the 3 children whose number of doses could not be determined had a lower respiratory tract infection-related hospitalization.

INTERPRETATION

In this study, we report RSV-related hospitalizations in children with congenital heart disease who were approved to receive British Columbia's 4-dose fixed-season abbreviated palivizumab schedule. We show that in a geographical area where the RSV season consistently spans from early November to late April, all but one (96%) RSV-related hospitalizations occurred before the fourth dose, and not as a result of starting immunoprophylaxis late in the season. So these cases were also not the result of a schedule failure. This result is consistent with the fact that the vast majority of RSV infections occur in December and January in North America and Europe, months during which coverage with palivizumab is expected to be no different between 4- and 5-dose schedules, and with the fact that palivizumab only prevents about 50% of RSV-related hospitalizations (5, 14).

These data support analyses by Weinberger indicating that elimination of one of five monthly doses, and initiating a reduced-dose schedule based on the averaged season onset would not result in a substantial decline in protection (4). Our data is also in keeping with American Academy of Pediatrics and Canadian Pediatric Society's most recent guidelines suggesting that less than five palivizumab doses may provide sufficient seasonal protection in infants discharged after the start of the RSV season (2, 3). However, up until now there had been no real-life direct clinical evidence to support this contention. To the best of our knowledge, British Columbia is the only jurisdiction that has universally adopted this abbreviated schedule. A major strength of our study is its population-based nature with high follow-up rates (>99%) under the centralized RSV Program, the cross-referencing of our RSV Program data with a provincial hospitalization database, intention-to-treat analysis, and inclusion of a 6-month fixed-date observation (November 01 to April 30), which spans before and after the drug administration periods. Further robustness is achieved by reporting data over multiple years, facilitating generalization across seasons, considering the biennial pattern of RSV epidemics (15).

Nearly 1,500 children are newly diagnosed with critical congenital heart disease each year in Canada (16). For some of these families the logistics of travel to clinics during the winter can be considerable, particularly in the geographical context of British Columbia. In our cohort, 42 palivizumab courses were either not (n = 12) or partially received (n = 30). Of those, 31 palivizumab courses were missed essentially because parents declined or were not able to attend Program clinics. Reducing the need for unnecessary treatments can help families focus on other visits that may truly benefit their child in addition to the direct drug cost and other savings conferred by an abbreviated palivizumab schedule.

The decision of the BC RSV Program to administer an abbreviated course of palivizumab was largely based on pharmacokinetic data. However, the pharmacokinetics of palivizumab may not be the only reason why fewer doses appear to be effective. Indeed, we previously suggested that neutralizing RSV antibodies persist in children beyond what would be expected on the sole basis of drug pharmacokinetics (17). Therefore, it appears that palivizumab serum levels are not the only factor conferring protection against RSV towards the end of the season and that antibodies naturally acquired from a subclinical exposure to the virus at the peak of the season might provide substantial additional protection towards the end of the season (17).

Limitations: First, our data from a single province mandates confirmation in other jurisdictions. Second, in the absence of a direct comparison group, it is impossible to ascertain the number of RSV hospitalizations that might have been prevented should a standard 5-dose palivizumab regimen been used. Regarding this latter point, with only one hospitalization that occurred after the 4th palivizumab dosing period, it is extremely unlikely that additional palivizumab doses would have statistically significantly changed our Program's outcomes. Moreover, our outcomes are comparable to the only RCT done in children with congenital heart disease (5). The Canadian Registry of Palivizumab (CARESS) reports 260 hospitalizations, including 35 cases where RSV testing was positive, in 1909 children over a 10-year study period (2005-2015) elsewhere in Canada where five doses are offered (18). However, in 31 hospitalized CARESS children (15% cases), RSV testing was not done. Moreover, CARESS is not a truly population-based registry. We combined both RSV-confirmed and RSV-undetermined hospitalizations, which may overestimate RSV-related hospitalization rates in our study. When we consider these factors, RSV hospitalization rates in children with congenital heart diseases in British Columbia do not appear different than in the rest of Canada, or in other populations (**Supplemental Table 1**). Finally, our experience may not apply to areas where RSV epidemics occur in a non-seasonal manner such as Florida and Alaska, and in other tropical or sub-tropical areas (19).

Conclusions: Our experience in British Columbia demonstrates the protection achieved by a fixed-date Program with an abbreviated 4-dose schedule in children with congenital heart disease. These data has a strong theoretical underpinning and warrants consideration in jurisdictions with seasonal RSV. Nonetheless, it is also important to point out that RSV was responsible for only about 19% of lower respiratory tract infection-related admissions in our cohort. Therefore, it is critical to continue to emphasize other preventive measures, including family education towards proper hand hygiene, breastfeeding and limiting infectious exposures in high risk children.

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TABLES & FIGURE LEGENDS

Characteristic	n = 325 children	Number of children with data
Gestational age, weeks (mean ± SD)	36.9 ± 6.2	318
Birth weight, g (mean ± SD)	2870 ± 871	319
Gender (%; 95%CI)	52 [46 – 57]	324
Age at start of first season, months (median; [IQR])	2.2 [0 – 6.0]	325
Surgical correction* (%; [95%CI])	51 [45 – 57]	315
Required bypass procedure (%; [95%CI])	34 [29 – 40]	288
Mortality (%; [95%CI])	4.0 [2.1 – 6.7]	325

Table 1: Clinical characteristics of children with congenital heart disease

*Indicates a surgical correction for the congenital heart defect during the period of follow-up; 95%CI: 95% confidence interval; SD: standard deviation; IQR: interquartile range.

Clinical characteristics	RSV-confirmed (n = 17)	Number of children with data	RSV-negative (n = 40)	Number of children with data
Gestational age, weeks (mean ± SD)	37.7 ± 2.5	17	37.8 ± 2.3	40
Birth weight, g (mean ± SD)	2939 ± 748	17	2778 ± 651	40
Gender (% male; [95%CI])	47 [23 – 72]	17	50 [34 – 66]	40
Age at first in-season admission, months (median [IQR])	5 [4 – 10]	17	6 [4 – 13]	40
Type of congenital heart disease* (%; [95%CI])		17		40
Cyanotic	47 [23 – 72]		50 [34 – 66]	
L-R shunt	35 [14 – 62]		33 [19 – 49]	
Obstructive lesion	12 [1.5 – 36]		5.0 [0.6 – 17]	
Cardiomyopathy	5.9 [0.0 – 29]		2.5 [0.0 – 13]	
Combination	0		10 [2.8 – 24]	
Unspecified	0		0	
Surgical correction (%; [95%CI])	47 [23 – 72]	17	48 [32 – 64][£]	39
Required bypass procedure (%; [95%CI])	25 [7.3 – 52][£]	16	40 [24 – 58][&]	34
Mortality (%; [95%CI])	12 [1.5 – 36]	17	7.3 [1.5 – 20]	40

Table 2: Clinical characteristics of infants with RSV-confirmed versus RSV-negative lower respiratory tract infection

*Before surgical correction.

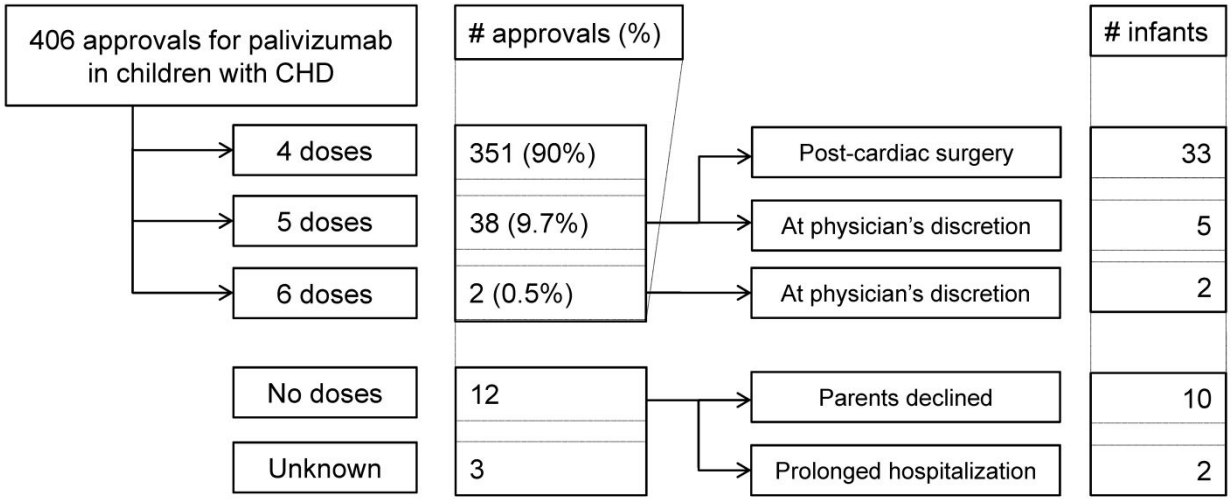

Figure 1: Intention-to-treat distribution of palivizumab doses administered to young children with congenital heart disease in British Columbia between November 2012 and April 2016.

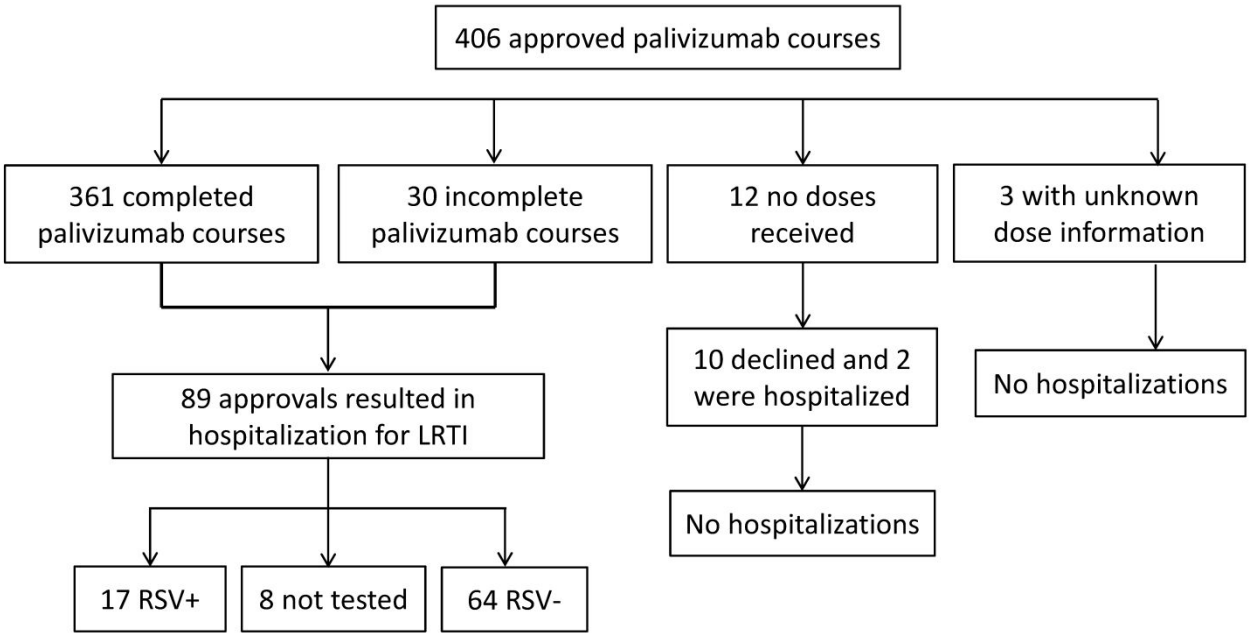

Figure 2: Lower respiratory tract infection hospitalization outcomes in young children with congenital heart disease enrolled in the British Columbia provincial palivizumab program between November 2012 and April 2016. Data is reported as number of children-approvals (i.e. approvals for each season in children who received palivizumab for more than one season is counted separately).

Supplemental Table 1: Population-based study data on rates of RSV hospitalizations in young children with congenital heart disease

Population	Study period	Outcome measure	Estimates	Use of palivizumab	Reference
Tennessee Medicaid Program (USA) (248,652 child-years)	July 1989 – June 1993	RSV-associated hospitalizations (6.3% of were coded specifically for RSV, and 93.7% were coded as bronchiolitis)	Infants < 6 months: 12.08%; 6 to <12 mo: 6.35%; 12 to 24 months: 1.82%; 24 to 36 months: 0.48%	Not specified	Boyce 2000 (20)
Karolinska Hospital, Stockholm (48,715 population catchment area)	1987 – 1998	RSV-confirmed hospitalization (nasopharyngeal swab with direct immunofluorescence ± viral culture)	6.4% and 2.8% during early and late RSV season, respectively	Not specified	Eriksson 2002 (21)
Bern, Switzerland (51,346 births)	July 1997 – June 2003	RSV-confirmed hospitalization per 100 children-years (nasopharyngeal swab with direct immunofluorescence)	Infants <6 months: 2.5% (95%CI: 0.8 to 5.6); <12 months: 2.0% (0.9 to 3.8); 12 to 24 months: 0.5% (0.1 to 1.8); <24 months: 1.3% (0.6 to 2.3)	Not specified	Duppenthaler 2004 (22)
CARESS registry: 27 hospital sites in Canada (508 children prospectively followed)	2005 – 2009 RSV seasons	RSV-confirmed hospitalization	1.99%	Yes (enrollment criteria)	Mitchell 2011(23)
57 hospital in Spain (1,896,426 births)	2004 – 2008 (Oct 1 to Apr 30)	Hospital admission due to acute respiratory tract infection	3.8%	Yes (over 90% of patients)	Medrano Lopez 2010 (24)
Denmark (452,205 children)	Jan 1997 – June 2003	RSV hospitalization defined by the first positive RSV test	Incidence rate ratio (95% CI) 1.7 (1.45–1.99)	Yes (118 patients)	Kristensen 2012 (25)
Tertiary care Centre, Southern Austria (602 infants)	Jan 2004 – Dec 2008	LRTI hospitalization with a positive RSV test result	7.3% for hemodynamically significant and 10.4% for non-hemodynamically significant congenital heart disease (Overall 9.6%)	Yes in 41 children (27%) with HSCHD and 10 children (2%) with HNSCHD	Resch 2016 (26)
County of Vestfol, Norway (43,470 live births)	Jan 1987 – Jul 2 005	Admittances for RSV-infections (but also bronchiolitis in ICD-9)	9.2% for hemodynamically significant and 3.3% for non-hemodynamically significant congenital heart disease (Overall	Not specified	Meberg 2006 (27)

Population	Study period	Outcome measure	Estimates	Use of palivizumab	Reference
			4.8%)		
Taiwan (1,168,866 live births)	1997 – 2013	Hospitalization for RSV-specific ICD-9 codes	Hospitalization OR 3.5 (children 12 to 23 months)	Not specified	Friedman 2017 (28)

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