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Beyond Randomized Controlled Trials: A "Real Life" Experience of Respiratory Syncytial Virus Infection Prevention in Infancy With and Without Palivizumab

Ian Mitchell, MA, MB, FRCPC,[1*†] Suzanne Tough, PhD,[2‡] Lynne Gillis, MSc,[3§] and Carina Majaesic, MD, PhD, FRCPC[4‡]

Summary. A population-based study of the impact of palivizumab on confirmed Respiratory Syncytial Virus (RSV) hospitalizations over a 7-year period within and between two similar health regions.

Clinicians in Calgary implemented palivizumab prophylaxis for high-risk infants during the last four RSV seasons; clinicians in Edmonton did not. The two cities are part of a unified health care system and similar sociodemographics. Infants <36 weeks (wk) of gestational age (GA) were identified. RSV prophylaxis data and RSV-hospitalizations for high-risk infants eligible for prophylaxis were reviewed, as well as that of moderate-risk infants (33–35 weeks GA) for whom RSV prophylaxis was not given a high priority in the recommendations published by the Canadian Paediatric Society (CPS). Prevalence of RSV hospitalization before and after palivizumab was determined (1995–1998 and 1999-2002, respectively).

There were 411 high-risk infants eligible for palivizumab prior to its provision (Pre) and 496 during the prophylaxis program (Post) in Calgary. There were 401 Pre and 425 Post in Edmonton, where no such prophylaxis program was implemented. In Calgary where palivizumab was offered (Post), RSV hospitalization was significantly reduced: 7.3% Pre versus 3.0% Post (OR, 2.53, 95% CI, 1.34, 4.76). No reduction was observed in Edmonton where palivizumab was not offered: 5.0% Pre versus 7.1% Post (OR, 1.45, 95% CI, 0.81, 2.59; $P = 0.212$). RSV hospitalizations did not change for moderate-risk infants not receiving palivizumab in Calgary (OR, 1.26, 95% CI, 0.75, 2.12; $P = 0.389$).

An RSV prevention program with palivizumab for high-risk infants reduced RSV hospitalizations, providing "real life" evidence of the benefits of this prophylaxis strategy. Further research is required to determine if specific sub-sets of moderate-risk infants would also benefit from an RSV prophylaxis program with palivizumab. **Pediatr Pulmonol. 2006; 41:1167–1174.**

Key words: prophylaxis; preterm infants; respiratory syncytial virus; palivizumab; hospitalization; bronchiolitis; chronic lung disease.

[1]Department of Paediatrics, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada.

[2]Departments of Paediatrics and Community Health Sciences, Faculty of Medicine, University of Calgary and Decision Support Research Team, Calgary Health Region, Calgary, Alberta, Canada.

[3]Decision Support Research Team, Calgary Health Region, Calgary, Alberta, Canada.

[4]Department of Paediatrics, Faculty of Medicine, University of Alberta, Alberta, Canada.

[†]Professor.

[‡]Associate Professor.

[§]Research Coordinator.

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*Correspondence to: Ian Mitchell, M.A., M.B., F.R.C.P.C., Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta, Canada, T3B 6A8. E-mail: ian.mitchell@calgaryhealthregion.ca

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INTRODUCTION

Respiratory Syncytial Virus (RSV) is a common disease of childhood with a major impact on health care utilization. Hospitalization accounts for the greatest portion of direct health care costs in RSV infection.[1] Annually, RSV contributes to the majority of over 12,000 bronchiolitis-related hospitalizations in Canada among children under 2 years of age.[2,3] There are no proven disease modifying treatments, and thus prevention with immunization is appropriate. Unfortunately, effective active immunization has not been developed. Palivizumab (Synagis®) is a monoclonal antibody that has been shown to be effective in reducing the impact of RSV infection in those particularly vulnerable to serious outcomes as a result of RSV infection, including those born prematurely with or without chronic lung disease, and those with congenital heart disease.[4] Palivizumab has been demonstrated to reduce the prevalence of RSV hospitalization among high-risk infants in large randomized controlled trials (RCTs).[5] To maintain active protection over the winter when risk of infection is greatest, the drug is given by injection at 28- to 30-day intervals.

Patients enrolled in these RCTs must fit strict inclusion and exclusion criteria, and results generated under these controlled circumstances provide evidence of drug efficacy under the specific circumstances of the study. However, randomized controlled studies are only the start of the process of understanding the role and place of new compounds in clinical practice. Formal effectiveness research of ''real life'' use of new pharmaceutical interventions is required to validate their value.

Clinical practice guidelines on the use of palivizumab have been produced in the USA,[6] Canada,[7,8] Europe,[9] Latin America[10] as well as Japan,[11] and limitations on its use are partly due to economic considerations, as well as to ensure this prophylaxis is used in infants who are at greatest risk of contracting RSV and would therefore derive the most benefit.

Alberta is a Canadian province with two tertiary referral pediatric centers. Each city has one Pediatric Department to which all pediatricians belong and neither city has any private pediatric units. The populations served by the health regions are similar: 839,845 (Edmonton) and 958,610 (Calgary). The population density of Edmonton is 974/km^2 and of Calgary is 789.90/km^2. The clinicians in these pediatric centers adopted different approaches to the administration of palivizumab. In Calgary, an RSV prevention program was initiated in 1998 as a pilot study. The indications adopted were broadly in line with the American Academy of Pediatrics recommendations. Based on the results of the pilot study, a program was implemented to include the full Canadian Consensus guidelines in 1999 for the selection of infants eligible for prophylaxis with palivizumab.[7] In contrast, in Edmonton, clinicians chose not to introduce an RSV prevention program until 2003. This difference in the introduction of palivizumab allowed for the implementation of a population-based observational study comparing RSV hospitalization rates between the two cities.

This study examined two objectives with respect to RSV hospitalizations as a measure of health care resource utilization. The first was to assess RSV hospitalizations over time and across two distinct regions for pre-term infants. The second objective of this study was to determine the impact of a prophylaxis program with palivizumab on RSV hospitalizations prior to and following the implementation of an RSV prophylaxis program in Calgary and between the two cities of Calgary and Edmonton.

METHODS

RSV Seasons and Case Definitions in Calgary and Edmonton

The calendar dates of the RSV seasons for the two regions were determined as follows: the start of the RSV season was defined as two or more RSV hospitalizations within a 7-day period, for two consecutive 7-day periods. The end of the RSV season was defined as one or no RSV hospitalization during a 7-day period, for two consecutive 7-day periods. The start and end dates of the RSV seasons in the two cities were determined and are displayed in Figure 1.

RSV Prophylaxis Programs

In Calgary, implementation of prophylaxis with palivizumab to all high-risk infants occurred during the 1999–2000 RSV season. During the previous season (1998–1999), palivizumab was provided to infants as part of a pilot study. It was not possible to accurately evaluate the impact of prophylaxis on the whole population during the 1998–1999 RSV season as the pilot study did not identify all eligible infants and consequently this season was excluded from the comparison analyses. The first three seasons (Pre: 1995–1996, 1996–1997, 1997–1998) prior to palivizumab provision have been compared to the last three RSV seasons (Post: 1999–2000, 2000–2001, 2001–2002) when prophylaxis with palivizumab was potentially available to all high-risk infants in Calgary.

During the time period of this study, Edmonton did not implement a program introducing prophylaxis with palivizumab. However, the investigators discovered ten infants with low GA (average GA, 27.1 weeks) that were provided palivizumab during the last season (2001–2002). None of these 10 infants were hospitalized with RSV. These 10 cases were omitted from the statistical analyses.

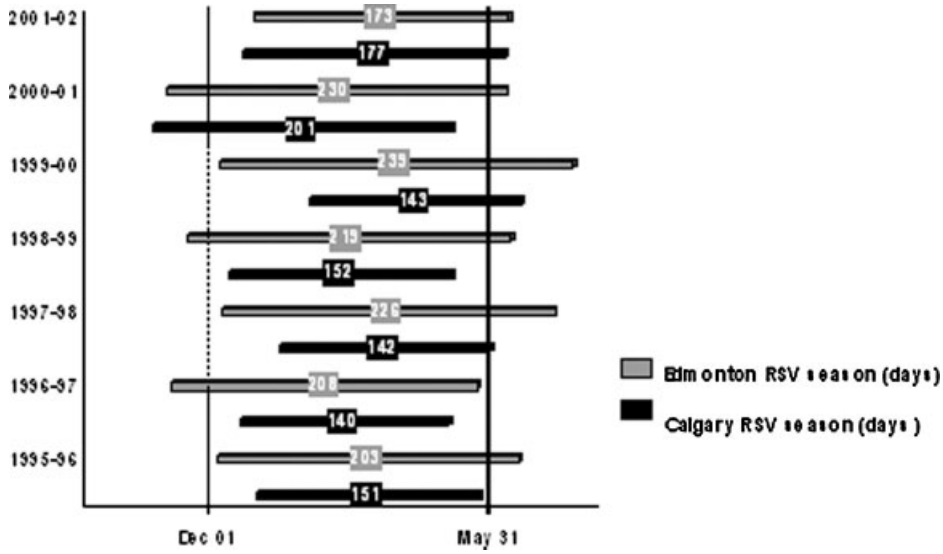

Fig. 1. Duration of RSV seasons in Calgary and Edmonton Health Regions.

Identification of Population at Risk

All premature infants (<36 weeks) born between January 1, 1995 and June 30, 2002 were identified by data analysts using Calgary and Edmonton health region databases. In Edmonton, preterm infants may be admitted to a Level III or one of two Level II NICUs and in Calgary, preterm neonates may be admitted to a Level III NICU or one of three Level II NICUs Data was abstracted from all charts of neonatal survivors who were resident of one or other health region and eligible for the study as moderate or high-risk infants (Table 1). Moderate-risk infants included infants born of GA 33–35 weeks (33 weeks, 0 days up to and including 35 weeks, 6 days) and born within 6 months of the start of the RSV season or during the RSV season. High-risk infants were defined as neonates born of GA < 33 weeks, or born at 33–35 weeks GA with diagnosed chronic lung disease, or born at 33–35 weeks GA and discharged home on oxygen and born within 6 months of the start of the RSV season or during the RSV season. The designations ''moderate risk'' and ''high risk'' follow the designations used in the Canadian guidelines.[7] Infants whose parents resided outside the two cities were excluded, because complete follow-up of these infants could not be assured. Data abstractors were trained and supervised in the use of a standardized data collection form. Data for each infant were manually and electronically traced from the time of birth through until discharge, and charts were obtained from each hospital in cases where infants were transported to a different site prior to initial discharge after birth. Infants of 33–35 weeks GA without chronic lung disease of prematurity (CLD) were excluded when discharge data were absent, as it could not be determined whether these infants were of high or moderate risk. This resulted in one infant in Calgary and 10 infants in Edmonton being excluded.

Identification of RSV Admissions

All RSV admissions in the two cities were identified from the health regions' databases. Children with RSV infection may be admitted in Edmonton to the Stollery Children's Hospital with 123 beds including PICU or a pediatric unit in one of three general hospitals (eight beds in total) and in Calgary to the Alberta Children's Hospital (103 beds, including PICU) or a pediatric unit in one general hospital (15 beds) without PICU. Those infants admitted between January 1, 1995 and June 30, 2002, falling within one of the defined RSV seasons, resident within Calgary or Edmonton, first hospitalization within the first year of life, and confirmation of RSV by positive laboratory documentation were included. The following codes were used (ICD9):

(1) Bronchiolitis or lower respiratory infection codes 4661, 51889, 5198, 07989 (January 1995–March 1997)
(2) RSV bronchiolitis code 46611 (April 1997–March 2002)
(3) RSV pneumonia code 4801 (January 1995–March 2002)
(4) RSV organism, unspecified infection code 0796 (April 1997–March 2002)
(5) RSV bronchiolitis, bronchitis, pneumonia, site unspecified codes J210, J205, J121, B974 (April 2002–June 2002)

TABLE 1— Population Characteristics of Calgary and Edmonton infants Eligible for Study

	Calgary		Edmonton	
	Frequency	Total percentage	Frequency	Total percentage
Total births	2,876	100.0	2,467	100.0
High-risk[a]	907	31.5	826	33.5
Pre[b]	411		401	
Post[c]	496		425	
Moderate-risk[d]	1,969	68.5	1,641	66.5
Pre[b]	907		787	
Post[c]	842		834	
Male	1,536	53.4	1,323	53.6
Female	1,340	46.6	1,144	46.4
Mean GA (week) ± sd	33.0 ± 2.5		32.8 ± 2.6	
Mean BW[e] (g ± SD)	2,070 ± 608		2,067 ± 615	
Mean stay[f] ± SD	24.1 ± 27.6		25.2 ± 29.3	

[a]High-risk, <33 weeks GA or 33–35 weeks GA with either CLD or home oxygen.
[b]Pre 1995–1998.
[c]Post 1999–2002.
[d]Moderate-risk, 33–35 weeks GA without CLD or home oxygen.
[e]BW (Birth Weight), in grams (g).
[f]Mean stay, number of days in hospital following delivery.

Ethics

The study had approval from the appropriate Research Ethics Boards in Calgary and Edmonton and access to health records complied with provincial legislation (Health Information Act).

Statistics

All data were imported or collected onto data abstraction forms and entered into a Microsoft Access database. Upon completion of the study, data were exported from Microsoft Access to Microsoft Excel where they were coded and partially cleaned. Data were then imported into SPSS, version 11.5 for final data cleaning and analysis. Categorical data comparisons such as sex, GA categories, and RSV hospitalizations were conducted using a Pearson chi-square analysis or Fischer's Exact Test (where expected cell values were less than five). Continuous data comparisons such as GA, birth weight and age at time of RSV admission were examined using *t*-tests for independent samples. P values of <0.05 were considered statistically significant.

Bivariate analysis prior to and following the implementation of prophylaxis in Calgary was performed to determine if infant characteristics changed over time. Comparisons were also made between regions and included sex, GA (mean and categorical), birth weight, diagnosis of CLD, and discharged home on oxygen.

The impact of RSV prophylaxis on hospitalization was initially determined with bivariate analysis. Comparisons were made between a pre-prophylaxis period and a post-prophylaxis period within each city and then between the two cities for both moderate and high-risk infants. Secondly, among those hospitalized, differences between prophylaxis and non-prophylaxis periods were described to determine if hospitalization practices had changed over time. Again this occurred within each region and between regions for the moderate and high-risk infants. Analysis examined sex, GA, birth weight, age at time of admission for RSV, treatment of RSV with oxygen and ventilator, admission and time spent in ICU and re-hospitalization for RSV within 6 months following discharge from initial RSV hospitalization.

Data were analyzed on an intent-to-treat basis, thus all infants eligible for prophylaxis were considered in the denominator, regardless of whether or not they were included in the program and whether or not they attended all scheduled injections. Subsequently, multivariate analyses were conducted to evaluate whether the RSV Prevention Program in Calgary successfully identified and prophylaxed infants at high-risk of being hospitalized for RSV.

RESULTS

Eligible infants and their characteristics are provided in Table 1. There was no difference between health regions in the proportion of high- and moderate-risk infants over the study period. The background characteristics of infants did not differ by region, except GA ($P = 0.005$), which was on average 1 day longer in Calgary, a difference unlikely to be of any clinical relevance.

Comparison of High-Risk Infants Between Time Periods and Regions

The pre-study population characteristics are similar, but not identical (Table 2). For example, a greater proportion of infants in Calgary were 33–35 weeks gestation and a greater proportion were sent home on oxygen or diagnosed with CLD.

Comparison of Moderate-Risk Infants Between Time Periods and Regions

Characteristics of moderate-risk infants in Calgary, eligible for the study during the time when palivizumab was not available, were compared to infants eligible after implementation of the palivizumab program. Although there was a statistically significant increase (59 g) in the birth weight of moderate-risk infants in Calgary, this is not likely to be clinically relevant. No difference was observed over time for Edmonton. The regions did not differ from each other in sex ratio or GA.

RSV Hospitalizations

Changes Within Cities

In Calgary, high-risk infants born during the last three seasons when the palivizumab program was in place were less than half as likely to be hospitalized with RSV (3.0%) than high-risk infants born during the first three seasons (7.1%), $P = 0.003$. In Edmonton, no such reduction in RSV hospitalization rate was seen. There was no difference in RSV hospitalization for moderate-risk infants in Calgary. (Table 3) Moderate-risk infants in Edmonton were more likely to be hospitalized with RSV during the Pre study period (4.1%) compared to the Post study period (2.1%), $P = 0.02$. (Table 3).

Changes Between Cities

Rates of RSV hospitalizations did not differ between regions for either high-risk or moderate-risk infants during the first three seasons of the study (Pre), when palivizumab prophylaxis was not provided. Post-implementation of palivizumab in Calgary, there was no difference in RSV hospitalization rates between the regions for moderate-risk infants, who were not eligible for palivizumab in either region. However, high-risk infants in Edmonton were 2.4 (95% CI, 1.24–4.82) times more likely to be hospitalized with RSV than high-risk infants in Calgary subsequent to implementation of the palivizumab program in Calgary (7.1% vs. 3.0%). There were more infants born 33–35 weeks GA diagnosed with CLD or discharged home on oxygen in Calgary (n = 48, 9.7%) compared with Edmonton (n = 3, 0.7%). Therefore, data were further analyzed for high-risk infants of <33-week GA only. When the high-risk 33–35 weeks GA infants were removed from comparison, the rate of RSV hospitalization remained significantly higher in Edmonton (7.1%) compared to Calgary (2.9%), $P = 0.004$.

Hospitalization of High-Risk Infants

Fifteen high-risk infants were hospitalized for RSV between the two health regions post-implementation of the Palivizumab program (Table 4). Those not provided palivizumab were 2.61 times more likely to be hospitalized with RSV than those given at least one dose of palivizumab ($P = 0.07$). High-risk infants that were not first born children were 1.6 times (95% CI) more likely to be hospitalized than infants first born (data not tabled). Sex, month of birth, diagnosis of CLD, discharge with home oxygen, mean birth weight, and multiple births versus single births were not risk factors for RSV hospitalization among high-risk infants.

TABLE 2— Pre Study Period Comparison of Characteristics of High-Risk Infants Between Calgary and Edmonton

	Calgary (n = 411)			Edmonton (n = 401)			
Characteristic	Frequency	%	Mean	Frequency	%	Mean	*P*-value
Males	236	57.4		228	56.9		0.871
Female	175	42.6		173	43.1		0.871
Mean GA (week ± SD)			30.0 ± 2.3			29.5 ± 2.6	0.002
<29 weeks GA	104	25.3		116	28.9		0.245
29–32 weeks GA	289	70.3		282	70.3		0.998
33–35 weeks GA	18	4.4		3	0.7		0.001
CLD	105	25.5		26	6.5		<0.001
Home oxygen	72	17.5		21	5.3		<0.001
BW (g ± SD)			1,436 ± 471			1,438 ± 482	0.967

33–35 weeks GA, 33–35 weeks GA with CLD or discharged home on oxygen.
CLD, chronic lung disease.
P-value, Pearson chi-square for sex, GA categories, CLD and Home oxygen: independent *t*-tests for mean GA and birth weight.

TABLE 3— Comparison of Hospitalization Rates Between Time Periods for Moderate and High-Risk Infants in Calgary and Edmonton

		RSV hospitalization rate					
Risk category	City	Pre %	Post %	Odds ratio	CI upper	CI lower	*P*-value
High	Edmonton	5.0	7.1	1.45	0.81	2.60	0.212
	Calgary	7.3	3.0	2.53	1.34	4.76	0.003
Moderate	Edmonton	4.1	2.1	1.97	1.10	3.54	0.021
	Calgary	3.3	2.7	1.26	0.75	2.12	0.389

Hospitalization of Moderate-Risk Infants

There were no differences in infant characteristics or hospitalization practices between regions for moderate-risk infants hospitalized with RSV during both the first three RSV seasons and the last three seasons. The hospitalization practices (admission to PICU, days in ICU) were similar between the two regions during this time period.

DISCUSSION

This population-based study demonstrated a reduction in hospitalizations for RSV among high-risk infants treated with palivizumab prophylaxis. The results of this study are important given the increased frequency of RSV hospitalization in preterm infants in the absence of palivizumab, and the high incidence of PICU admission in this high-risk population, compared to full term infants.[12,13] These hospitalizations impose costs on the health care system, considered in most studies; however, the additional emotional and financial impact of re-hospitalization on parents also bears consideration.[14,15] This study was carried out in one advanced health care system where the option of palivizumab was chosen by a whole community and not chosen by another similar community.

The populations of infants were similar in terms of numbers, sex ratio, birth weight, and proportions in high-risk and moderate-risk categories. Although some statistical differences in mean GA were noted between the two cities, based on clinical expertise, these are not believed to be clinically important. There were more infants in Calgary discharged home on oxygen which may reflect the higher elevation of Calgary (1,048 m) compared with Edmonton (670 m) and hence, lower ambient partial pressure of oxygen. There are no studies of the effect of this modest increase in elevation on oxygen therapy and prematurity, however, it has been shown that infants discharged home at elevations greater than 1,310.6 m were more likely to be on oxygen than those living at lower elevations.[16] Although both groups in that study were at higher elevations than infants in this study, it seems reasonable to conclude that ambient partial pressure of oxygen will affect the likelihood of supplementary oxygen therapy being used. Infants admitted with bronchiolitis in Calgary were more likely to be given oxygen, which may indicate different patterns of clinical practice between regions Also it has recently been shown that RSV hospitalizations in infancy increase by 25% for every 1,000 m increase in altitude.[17]

Although the study has the advantage of being ''real life,'' it has a number of disadvantages, some noted above. For example, ICD codes changed during the 7 years of the study. However, by including all possible codes, and by manually reviewing each chart to confirm coding, we are confident we identified all relevant information. Also, as an observational study, we did not impose management practices, diagnostic criteria or tests; we recorded and accepted real life variability. Given the consistency of practice over the 7 years within the cities, it is unlikely that there was a systematic change that would affect the results. We expected baseline differences. Those identified included a longer RSV season in Edmonton and apparent greater severity of RSV in Calgary. Nevertheless, the differences, while unexplained in this study, were small and unlikely to have affected our results. The longer RSV season in Edmonton may be due to the climate difference of a longer, colder winter there.

As a real-life, observational study, all preterm infants in the geographic area of Calgary, in the specified time period were included whether or not immunized. There were no other inclusion/exclusion criteria; consequently, a few infants who fitted the criteria for immunization, but were not immunized, were included as would occur in a clinical situation, and included in intent-to-treat analysis. The inclusion of the population of infants who should have been immunized but were not, highlights the important

TABLE 4— RSV Hospitalization in High-Risk Infants

	Provided palivizumab			Statistics	
	No	Yes	Total	Pearson chi-square	0.07
RSV					
Yes	269	5	274	O.R.	2.61
No	206	10	216	95% CI upper	0.81
Total	475	15	490	95% CI lower	8.92

differences between an RCT and an observational study. If this had been an RCT, infants not recruited into the study would not have been included in the analysis and therefore their RSV admissions would have been excluded. Such use of inclusion/exclusion criteria and the potential for selection bias into the study is important for the conclusions about efficacy required from an RCT. However, in an observational, population-based study all data must be included to justify conclusions about effectiveness. Despite the inclusion of these infants, the benefits of an RSV prevention program were confirmed. We chose to compare two time periods, each of three RSV seasons. RSV seasons were defined a priori and were not consistent from year to year with respect to start/end dates, durations of season, number of hospitalizations and infections by one or other or both RSV strains (A and B). The availability of data over successive time periods allows for more stable estimates of rates between the two health regions. Moderate-risk infants were not offered palivizumab in either city and as the hospitalization rates for these infants did not change over time within Calgary, it rules out a change in RSV hospitalization criteria over time as a source of bias.

It was an objective of this study to investigate changes and differences in RSV admissions for preterm infants over time between Edmonton and Calgary. No differences were observed either between the cities or across time with respect to oxygen supplementation during hospitalization, the number of infants admitted to PICU or the mean number of days spent in ICU. This suggests that changes in practice cannot explain the decrease in RSV hospitalization beyond the use of palivizumab in Calgary. As such, an RSV prevention program with palivizumab reduced the RSV hospitalization rate in high-risk infants, providing evidence of the benefits of this prophylaxis strategy.

The use of palivizumab in Calgary was based on Canadian recommendations produced in 1999.[7] The Canadian statement uses ''priority'' for palivizumab, rather than indications, and designates ''high-risk'' groups which are:

* Children 24 months of age or younger with BPD who require oxygen within the 6 months preceding the RSV season.
* Infants born at 32 weeks gestation or earlier who are 6 months of age or younger at the start of the RSV season.

Prevention of RSV hospitalization in preterm infants may have long-term benefits on health care utilization and child morbidity. Studies on preterm infants hospitalized with RSV-related bronchiolitis or pneumonia within the first year of life suggest these infants may be at increased risk of long-term morbidity.[18–20] Some of the chronic symptoms subsequent to RSV infection include wheezing, asthma and upper respiratory tract infections, resulting in additional health care utilization. One of these studies was specific to infants born 32–35 weeks gestation without bronchopulmonary dysplasia, infants that are not eligible for prophylaxis in Canada.[20] Reviews of the importance of RSV prophylaxis will need to consider the impact of palivizumab on RSV infection beyond the immediate reduction in acute infection. Simoes et al.[21] have presented preliminary evidence of a marked reduction in episodes of respiratory illness in the season after palivizumab was used in infants immunized, compared with a large group of infants not immunized. In a comparison of 193 high-risk infants immunized with palivizumab compared with 231 not immunized, recurrent wheezing in the second year of life occurred in 6.8% of those immunized and 19.1% of those not immunized ($P = 0.0008$).

This study provides evidence that palivizumab reduces RSV hospitalization in high-risk infants when made available as a structured program. Infants who may benefit from immunization have been missed in other areas.[22] Indeed there was incomplete ascertainment of cases in Calgary in the early stages of program development, reinforcing the need for the program to have a rigorous method of identifying cases. Clinicians in Edmonton started to prescribe palivizumab during the final stages of this study and continue to use it.

In that the primary cost to the health care system of RSV infection is hospitalization, cost reductions are likely a positive outcome of palivizumab use. More importantly, the opportunity to reduce infant morbidity, family stress and anxiety and the use of scarce inpatient health care resources is a key benefit of palivizumab prophylaxis. If reductions in acute RSV infection resulted in reductions in acute re-infection as well as reductions in the long-term morbidity associated with RSV infection, including increased lifetime risk of asthma and respiratory morbidity, then the opportunity exists to determine what other infant groups would benefit most from palivizumab prophylaxis.

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