The real-life effectiveness of palivizumab for reducing hospital admissions for respiratory syncytial virus in infants residing in Nunavut

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BACKGROUND/OBJECTIVE: Nunavut has the highest hospitalization rates for respiratory syncytial virus (RSV) worldwide, with rates of 166 per 1000 live births per year <1 year of age. Palivizumab was implemented in Nunavut primarily for premature infants, or those with hemodynamically significant cardiac or chronic lung disease; however, the effectiveness of the program is unknown. The objective of the present multisite, hospital-based surveillance study was to estimate the effectiveness of palivizumab in infants <6 months of age in Nunavut for the 2009 and 2010 RSV seasons.

METHODS: Infants identified as palivizumab candidates who were <6 months of age were compared with all admissions for lower respiratory tract infection through multisite, hospital-based surveillance documenting the adequacy of palivizumab prophylaxis, admission for lower respiratory tract infection and the results of RSV testing. The OR for RSV admission in unprophylaxed infants was compared with those who were prophylaxed, and the effectiveness of palivizumab was estimated.

RESULTS: Within the study cohort (n=101) during the two RSV seasons, five of the 10 eligible infants who did not receive adequate prophylaxis were admitted with RSV while two of the 91 infants <6 months of age eligible for palivizumab who were adequately prophylaxed were hospitalized with RSV (OR 22.3 [95% CI 3.8 to 130]; P=0.0005). The estimated effectiveness of palivizumab for the cohort was as high as 96%. Eight eligible infants were missed by the program and did not receive prophylaxis.

CONCLUSION: Palivizumab was highly effective in reducing hospitalizations due to RSV infection in Nunavut. Further efforts need to be made to ensure that all eligible infants are identified.

Key Words: Effectiveness; Inuit; Nunavut; Palivizumab; Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTIs) globally (1,2) and is the single most common reason for hospitalizations among infants (1,3). While the development of a safe and effective RSV vaccine remains unrealized, in 1998, palivizumab (Synagis, MedImmune Inc, USA), a monoclonal antibody against RSV, was licensed for the prevention of hospitalization of children considered to be at high risk for severe RSV infection. In the initial multicentre, randomized placebo-controlled trial comparing premature infants ≤35 weeks' gestational age with or without bronchopulmonary dysplasia, overall, there was a 55% reduction in RSV hospitalizations (10.6% versus 4.8%; P<0.001) in the palivizumab arm compared with placebo, with a 78% reduction in RSV hospitalizations in premature infants without bronchopulmonary dysplasia (8.1% versus 1.8%; P<0.001) (4).

L'efficacité du palivizumab en situation réelle pour réduire les hospitalisations causées par le virus respiratoire syncytial chez les nourrissons qui habitent au Nunavut

HISTORIQUE ET OBJECTIF : Le Nunavut présente le plus fort taux d'hospitalisations attribuables au virus respiratoire syncytial (VRS) de par le monde, correspondant à 166 cas sur 1 000 naissances vivantes par année chez les moins d'un an. L'utilisation du palivizumab a été implantée au Nunavut, principalement pour les nourrissons prématurés ou ceux qui sont atteints d'une maladie pulmonaire chronique ou cardiaque significative sur le plan hémodynamique. Cependant, on ne connaît pas l'efficacité de ce programme. La présente étude de surveillance multihospitalière visait à évaluer l'efficacité du palivizumab chez les nourrissons de moins de six mois au Nunavut pendant les saisons du VRS de 2009 et 2010.

MÉTHODOLOGIE : Les chercheurs ont comparé les nourrissons qui étaient déterminés comme candidats au palivizumab et qui avaient moins de six mois à toutes les hospitalisations causées par une infection du système respiratoire inférieur par l'entremise d'une surveillance multihospitalière étayant le caractère pertinent de la prophylaxie au palivizumab, des hospitalisations attribuables à une infection du système respiratoire inférieur et des résultats des tests du VRS. Ils ont comparé le rapport de cotes d'hospitalisations attribuables au VRS chez les nourrissons sans prophylaxie à celui des nourrissons sous prophylaxie et évalué l'efficacité du palivizumab.

RÉSULTATS : Au sein de la cohorte à l'étude (n=101) pendant les deux saisons de VRS, cinq des dix nourrissons admissibles qui n'avaient pas reçu la prophylaxie pertinente ont été hospitalisés en raison d'un VRS tandis que deux des 91 nourrissons de moins de six mois admissibles au palivizumab qui avaient reçu une prophylaxie pertinente ont été hospitalisés pour la même raison (rapport de cotes 22,3 [95 % IC 3,8 à 130]; P=0,0005). L'efficacité estimative du palivizumab dans la cohorte atteignait 96 %. Le programme a omis huit nourrissons admissibles, qui n'ont pas reçu de prophylaxie.

CONCLUSION : Le palivizumab réduisait le nombre d'hospitalisations causées par l'infection à VRS avec une grande efficacité au Nunavut. D'autres efforts s'imposent pour s'assurer de dépister tous les nourrissons admissibles.

Nunavut is Canada's largest federal territory and has one of the highest rates of hospitalization for RSV globally. RSV causes considerable morbidity in the Arctic regions (5-13) and in Inuit children. The annual rate of admission for RSV was 166 per 1000 live births in the first year of life on Baffin Island in 2001, before the use of palivizumab (5), which is the highest documented rate globally (14). Most of these admissions were in term infants without underlying risk factors (7). For the subset of infants <6 months of age residing in remote communities, the rates of RSV admissions ranged from 328 to 512 per 1000 infant-years (5), and 5.2% of the population born in remote communities on Baffin Island required mechanical ventilation in the first six months of life due to RSV infection (5). In addition to extremely high rates of RSV hospitalizations in Nunavut, severe complications and prolonged mechanical ventilation frequently result (6-9). Palivizumab was

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licensed in Canada in 2002 and the Nunavut program was initiated in 2005. Due to the very high cost of this intervention, palivizumab has been restricted to populations traditionally considered to be at the highest risk for RSV disease, including all infants born up to 35 weeks' gestation, and those with significant cardiac or respiratory conditions (4,15,16).

However, Nunavut presents a unique circumstance, where the extreme morbidity from RSV and the high costs of transporting infants to hospital (5,9,17-20) results in a situation in which even prophylaxis of term Inuit infants in remote communities (without a hospital) was projected to result in cost savings (5). The Canadian Paediatric Society currently recommends that term Inuit infants <6 months of age at the start of the RSV season and residing in remote communities with a persistently high rate of RSV hospitalization be considered for palivizumab prophylaxis (21); however, this has not yet been implemented.

The effectiveness of palivizumab in Nunavut preterm infants has not been established and, currently, there are few published data regarding the use of palivizumab in Inuit or other Aboriginal infants. Introduction of palivizumab in the Yukon Kuskokwim Delta and southwest Alaska region in Alaska (USA) demonstrated a declining trend in RSV hospitalization in premature infants (22,23) while rates remained constant in term infants. The purpose of the present prospective, observational study was to estimate the effectiveness of palivizumab in the population of Nunavut infants through hospital-based surveillance of LRTIs over two consecutive RSV seasons.

METHODS

Nunavut is divided into three geographical regions: Kitikmeot (Western), Kivalliq (Central) and Qikiqtani (or Baffin) (Eastern), with estimated (2006 figures) populations of 5361, 8348 and 15,764, respectively, of whom nearly 85% are Inuit (24). The number of births in Nunavut in 2009 and 2010 were 812 and 835, respectively (25). The Qikiqtani General Hospital in Iqaluit is the only regional hospital in Nunavut and services most of the Qikiqtani region. Typically, infants who require tertiary care from this region are referred to the Children's Hospital of Eastern Ontario in Ottawa, Ontario. Infants from the Kitikmeot region are admitted to Stanton Regional Hospital in Yellowknife (Northwest Territories) and transferred to Stollery Children's Hospital (Edmonton, Alberta) if they require tertiary care, while infants from the Kivalliq region are admitted to Churchill Health Centre (Churchill Manitoba) or transferred to Children's Hospital of Winnipeg (Winnipeg, Manitoba) for tertiary care. All hospitals above were included in this surveillance.

In Nunavut, infants were eligible for palivizumab if they were <6 months of age at the beginning of the RSV season, with a gestational age of <36 weeks and/or had significant cardiac or respiratory disease (21). Eligible infants were identified by nurses in the communities, which was then verified and confirmed by the government of Nunavut (GN) (personal communication, Dr Geraldine Osborne). In Nunavut, the RSV season typically spans January through June, with peaks between March and June (26,27). The GN protocol for the 2009 and 2010 seasons included initiating palivizumab 15 mg/kg/dose the week of December 15, followed by a second dose after three weeks and, subsequently, every four weeks until the end of the RSV season (personal communication, GN). The final dose was given during the week of June 22, for a maximum of seven doses, due to prolonged RSV seasons. For the purposes of the present study, the 2009 and 2010 RSV seasons were defined as January 1 to June 30. The GN provided a data set of all identified palivizumab candidates, with the reasons for eligibility, timing and dosage of palivizumab received.

The present study was nested in a larger cohort surveillance of LRTI admissions in Arctic Canada over an 18-month period for infants <1 year of age (6,7,17). The present study was observational because it would be unethical to offer placebo to infants at high risk for serious RSV infection. A hospital-based surveillance was conducted for all LRTI admissions in Nunavut regional and tertiary care centres for

infants who were <6 months of age at the beginning of the 2009 or 2010 RSV seasons. Inclusion criteria included an infant who resided in Nunavut who was <6 months of age during the RSV season and met the GN eligibility criteria for palivizumab in 2009 and 2010. Exclusion criteria included any infant who was not tested for RSV by enzyme-linked immunoassay (EIA) or polymerase chain reaction (PCR).

Infants from the Kitikmeot and Kivalliq regions were prospectively enrolled while infants from the Qikiqtani region were retrospectively enrolled due to an unanticipated delay in obtaining administrative approval. In addition, a chart review at all sites of infants who were <6 months of age during the study period were reviewed to include missed cases. Data regarding gestational age and underlying cardiac or pulmonary disease that would meet the criteria for inclusion for palivizumab were collected. Infants identified in the surveillance study were cross-referenced against the GN palivizumab dataset over the 2009 and 2010 RSV seasons, by comparing date of birth, community, sex and risk factors.

Viral testing of nasopharyngeal aspirate for clinical purposes was performed at the Provincial Public Health Laboratory in Edmonton, Alberta, Cadham Provincial Laboratories in Winnipeg, Manitoba or at the Montreal Children's Hospital in Montreal, Quebec. In addition, some regional laboratories performed rapid RSV testing using EIA. To enhance viral diagnostics, residual nasopharyngeal aspirate collected from the majority of prospectively enrolled infants were frozen at -70°C, transferred in batches and processed at the Regional Virology Laboratory, McMaster University (Hamilton, Ontario) using the xTAG Respiratory Viral Panel (RVP) assay (Luminex Molecular Diagnostics, Canada), a multiplex PCR test for RSV and 19 other viruses.

Ethics approval was obtained from all hospitals. The study was administrated through the Applied Health Research Centre, St Michael's Hospital (Toronto, Ontario) and was licensed through the Nunavut Research Institute.

Data analysis

For all infants <6 months of age at the start of RSV season who were eligible for palivizumab, RSV hospitalization rates were compared for those who did and did not receive palivizumab as per protocol. The OR for RSV hospitalization in infants who received no/inadequate prophylaxis versus those who were adequately prophylaxed with palivizumab was calculated (Fisher's exact test [two-tailed; PASW Statistics version 17.0]). In addition, an estimation of the effectiveness of palivizumab over the two RSV seasons was calculated as follows (28):

$$(\text{rate in eligible unprophylaxed group} - \text{rate in infants who received palivizumab}) / (\text{rate in eligible unprophylaxed group}) \times 100$$

The palivizumab eligibility list provided by the GN was assumed to be a complete list of all eligible palivizumab candidates; however, on preliminary analysis, infants who met the criteria for prophylaxis but were not included on the GN list were identified. The effectiveness of palivizumab would be overestimated if there was a large number of infants eligible for palivizumab who were neither identified nor admitted with an LRTI. Because it was not practical to review the entire birth cohort of Nunavut to search for other eligible infants who were not admitted, a sensitivity analysis was conducted for the most extreme situation in which the maximum numbers of eligible infants were missed assuming the upper limit of potentially eligible infants was 8% of the birth population (based on a large study in the Qikiqtani region [19]), and that all additional eligible infants were not identified in the surveillance (neither admitted nor prophylaxed) were recalculated for the lowest limit of effectiveness. The primary data from a case control study conducted on Baffin Island, which enrolled >50% of the birth cohort (19), 15% of the LRTI admissions and 4% of the controls were born <36 weeks' gestation. When adjusting for repeat admissions and then extrapolated to the entire population, the percentage of infants born before 36 weeks' gestation was estimated to not exceed 8%.

Figure 1) Respiratory syncytial virus-positive hospitalizations in infants <6 months of age in Nunavut

RESULTS

There were 210 admissions for LRTI in Nunavut for infants <6 months of age during the 18-month surveillance period; 65 of the 68 (96%) RSV admissions occurred between January and June, affirming the delayed RSV season (Figure 1). Ninety-four infants were identified by the GN as palivizumab candidates ($n=46$ in 2009, $n=48$ in 2010) and were cross-referenced with all LRTI admissions that occurred in the respective RSV seasons (Figure 2). One infant who was admitted with an LRTI was excluded due to the lack of viral testing. This study identified 26 hospital admissions of the 93 remaining infants. Ninety-one of these 93 infants received palivizumab according to the GN guidelines (Figure 2), and two were hospitalized with RSV and were considered to be palivizumab failures. Case 13 (Table 1) had RSV, rhinovirus/enterovirus and influenza A subtype H1N1, and case 28 (Table 2) had RSV alone.

Two of the 93 infants (case 14 [Table 1] and case 29 [Table 2]) were admitted with RSV after incomplete or no palivizumab prophylaxis. Case 14 received palivizumab until March 2009 at a tertiary centre that was not continued on return to Nunavut; the infant was hospitalized with RSV 10 weeks after the final dose (ie, incomplete prophylaxis). Case 29 was only identified by the GN and prophylaxed as an eligible infant after an RSV admission. The present study also identified eight additional infants admitted with LRTIs who met the criteria for prophylaxis but were not on the GN eligibility list, yielding a total of 34 eligible infants admitted with LRTI (Figure 2, Tables 1 and 2). Three of these eight unprophylaxed infants were admitted with RSV.

TABLE 1

Infants born July 1, 2008 to June 30, 2009 who were admitted during the 2009 respiratory syncytial virus (RSV) season and eligible for palivizumab in Nunavut

Infant	Age at admission, months	Gestational age, weeks	Comorbidity	Identified by GN	Received palivizumab	Laboratory result	Laboratory testing method
1	<3	29	No	Yes	Yes	RV/EV, human coronavirus OC43	PCR
2	<9	29	No	Yes	Yes	RV/EV	PCR
3	<6	29	No	Yes	Yes	Negative	EIA
4	<3	35	No	Yes	Yes	RV/EV	PCR
5	<12	35	Cardiac	Yes	Yes	Negative	EIA
6	<6	34	No	Yes	Yes	RV/EV, HMPV	PCR
7	<6	33	No	Yes	Yes	RV/EV	PCR
8	<3	26	No	Yes	Yes	RV/EV, adenovirus	PCR
9	<6	26	No	Yes	Yes	RV/EV	PCR
10	<3	34	No	Yes	Yes	RV/EV	PCR
11	<6	32	No	Yes	Yes	Negative	PCR
12	<6	30	No	Yes	Yes	Negative	EIA
13*	<6	31	Cardiac	Yes	Yes	RSV, RV/EV, influenza A (H1N1)	PCR
14†	<6	31	No	Yes	No	RSV, parainfluenza	PCR
15	<3	33	No	No	No	RSV	PCR
16	<6	31	No	No	No	RSV	PCR
17	<3	35	No	No	No	RSV, <i>Bordetella pertussis</i>	PCR

*Vaccine failure; †Missed two doses of palivizumab before being admitted with RSV, counted as unvaccinated. EIA Enzyme-linked immunoassay; GN Government of Nunavut; HMPV Human metapneumovirus; PCR Polymerase chain reaction; RV/EV Rhinovirus/enterovirus

Figure 2) Palivizumab prophylaxis and respiratory syncytial virus (RSV) status for Inuit infants identified by surveillance as palivizumab candidates in Nunavut, admitted to hospital during the 2009 and 2010 RSV seasons

Within the study cohort ($n=101$) during the two RSV seasons, two of the 91 infants <6 months of age eligible for palivizumab who were adequately prophylaxed were hospitalized for RSV, while five of the 10 eligible infants who did not receive adequate prophylaxis were admitted with RSV (Figure 2). The rate of RSV hospitalization for the infants not or inadequately prophylaxed with palivizumab (50%) was significantly higher than the rate for the infants who had received RSV prophylaxis (2.2%) OR 22.3 (95% CI 3.8 to 130; $P=0.0005$). The estimated effectiveness of palivizumab for the cohort was 96%.

A 'worst case scenario', in which 8% of the Nunavut population was eligible for palivizumab (approximately 65 infants per year) was assumed and that all infants not identified in the present study were missed. In

TABLE 2
Infants born July 1, 2009 to June 30, 2010 who were admitted during the 2010 respiratory syncytial virus (RSV) season and eligible for palivizumab in Nunavut

Infant	Age at admission, months	Gestational age, weeks	Other comorbidity	Identified by GN	Received palivizumab	Laboratory result	Laboratory testing method
18	<3	31	No	Yes	Yes	Parainfluenza	PCR
19	<6	34	No	Yes	Yes	RV/EV, parainfluenza	PCR
20	<9	28	No	Yes	Yes	RV/EV	PCR
21	<6	35	No	Yes	Yes	Negative	PCR
22	<3	33	No	Yes	Yes	Negative	PCR
23	<9	29	No	Yes	Yes	Negative	EIA
24	<6	35	No	Yes	Yes	Negative	EIA
25	<9	>37	Cardiac	Yes	Yes	Negative	EIA
26	<12	29	No	Yes	Yes	Negative	EIA
27	<6	35	No	Yes	Yes	Negative	EIA
28*	<6	28	No	Yes	Yes	RSV	PCR
29†	<6	36	No	Yes	No	RSV	PCR
30	<3	35	Cardiac	No	No	Adenovirus	PCR
31	<3	35	No	No	No	Negative	PCR
32	<6	26	No	No	No	Negative	PCR
33	<3	34	No	No	No	Negative	EIA
34	<3	34	No	No	No	Negative	EIA

*Vaccine failure; †Only given palivizumab after hospital admission for RSV, classified as unvaccinated. EIA Enzyme-linked immunoassay; GN Government of Nunavut; PCR Polymerase chain reaction; RV/EV Rhinovirus/enterovirus

TABLE 3
Effectiveness of palivizumab in Nunavut 2009/2010 for infants <6 months of age who were eligible for respiratory syncytial virus (RSV) prophylaxis according to Government of Nunavut criteria*

RSV season	Total eligible, n	Prophylaxed			Unprophylaxed			Effectiveness†
		n	RSV positive, n	Attack rate	n	RSV positive, n	Attack rate	
2009	49	45	1	0.021	4	4	1.0	0.979
2010	52‡	46	1	0.019	6	1	0.167	0.887
2009/2010	101	91	2	0.022	10	5	0.5	0.956

*Eligible population born between January 1, 2008 and June 30, 2009, and between January 1, 2009 and June 30, 2010; †Palivizumab effectiveness = (attack rate in unprophylaxed – attack rate in prophylaxed) / attack rate in unprophylaxed; ‡53 were prophylaxed but one was not tested for viruses and was excluded from the analysis

addition to the 49 and 53 infants identified by the GN in 2009 and 2010, respectively, there would be 16 unidentified eligible infants in 2009 and 12 in 2010, resulting in a lower limit of palivizumab effectiveness of 83% ($[5/38 - 2/91] \div 5/38 = 83\%$) (Table 3).

DISCUSSION

The results of the present study suggest that, in Nunavut, the use of palivizumab for high-risk infants was highly effective, with a failure rate of only 2%. However, one of the two failures had coinfection with rhinovirus/enterovirus and influenza A (subtype pH1N1) and may not have truly been a palivizumab failure. The effectiveness of palivizumab is higher than that in any other subgroup of at-risk infants in the RSV-Impact study (4) or any Canadian subpopulation currently eligible for prophylaxis (21).

Although the GN list was initially assumed to be complete for eligible infants, we discovered through our analysis that some eligible infants were missed. It is of concern that at least eight preterm infants were never identified as being eligible for palivizumab and three were hospitalized with RSV. However, we believe that there are no systematic selection biases for the missed infants compared with the prophylaxed infants because they are serviced by different nursing stations. The unprophylaxed infants, however, did appear to be younger than the prophylaxed infants, which may be due to palivizumab providing protection in early infancy when the majority of admissions occur (19). Enhancing the awareness of nurses with regard to candidates who qualify for palivizumab may increase the capture of premature and other high-risk infants at birth. Because the RSV season in the Canadian Arctic is delayed compared with the rest of Canada (26,27), it is vital that the local nursing stations identify infants who are

transferred from southern hospitals, where the prophylaxis program has concluded, to avoid any gaps in prophylaxis.

Although the present study was limited by small numbers, the findings are relevant due to the significant impact of RSV in this population. In this cohort of infants, RSV was associated with severe complications, with a substantial number of transfers to tertiary hospitals for mechanical ventilation that was associated with prolonged intubation and secondary bacterial and fungal sepsis, among other complications (6,7,17).

In addition to being extremely common, the costs incurred for RSV hospitalizations of Canadian Inuit infants are substantial (17). A recent budget impact analysis of a cohort on Baffin Island, based on palivizumab efficacy of 78%, projected the number needed to treat to prevent one RSV hospitalization to be 3.9 for rural Inuit infants <6 months of age regardless of gestational age; universal palivizumab prophylaxis in the Baffin Island cohort living in remote communities was projected to result in cost savings (5). Our budget analysis of this cohort demonstrated a cost savings of \$55,000 per admission avoided in the Kitikmeot region in 2009 (29). The lack of effectiveness data from this cohort in the past has been a barrier to expanding the program to term Inuit infants.

Our data demonstrate that palivizumab was associated with a considerable decrease in RSV admissions in Inuit infants with the classic risk factors for severe disease. Because palivizumab is a monoclonal antibody, physiologically, it should be as effective in a term population who should be at a lower risk for severe RSV illness. Because palivizumab is very expensive, active surveillance of RSV in the North to monitor the start and end of the season would optimize its use. In addition, enhancement of public health measures to reduce the risk of RSV transmission is required (19).

Limitations

The present study was limited by its small sample size due to the low birth rate in Nunavut. Additionally, a retrospective chart review was conducted in the Qikiqtani region where RSV testing had been performed at the discretion of the attending physician, which was, at times, suboptimal, and may have underestimated the true burden of RSV, especially because EIA has a sensitivity of 70% compared with PCR (30). Because this was an effectiveness study, it reflects real-life practice in the Arctic, where EIA is commonly performed for RSV detection instead of PCR; PCR testing as performed in our study represents enhanced testing. Because the present study was observational in nature, the number of and other variables for unprophylaxed infants could not be controlled. A study of future RSV seasons with enhanced and systematic identification of eligible infants would provide more information; however, multisite prospective surveillance in the remote Arctic communities can be logistically challenging and prohibitively expensive.

CONCLUSION

Our study demonstrates that RSV prophylaxis with palivizumab was highly effective in protecting high-risk Inuit infants from RSV hospitalization during the 2009 and 2010 RSV seasons. The major weakness in the current program was the lack of identification of all infants at high risk for RSV hospitalization. Efforts to enhance identification of these infants at birth should improve the impact of this program. The very high effectiveness of palivizumab in at-risk infants should be considered for the potential future expansion of prophylaxis to incorporate term infants in regions with high prevalence rates of RSV, as recommended by the Canadian Paediatric Society.

DEDICATION: The authors dedicate this study to the memory of Dr Michael Davis, one of the coinvestigators.

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