



Effectiveness of palivizumab immunoprophylaxis to prevent respiratory syncytial virus hospitalizations in healthy full-term < 6-month-old infants from the circumpolar region of Nunavik, Quebec, Canada

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ABSTRACT

In Quebec, Canada, eligibility for palivizumab (PVZ) immunoprophylaxis was expanded in fall 2016 to include healthy-full-term (HFT) infants residing in the circumpolar region of Nunavik and aged < 3 months at the start of the RSV season or born during the season. This study assessed the effectiveness of PVZ to prevent RSV hospitalizations in these infants during the 3 seasons following its implementation. Medical and laboratory records of < 1-year-old infants (375 average annual birth cohort) admitted to regional and tertiary hospitals with respiratory infection during 6 years were reviewed. Individual pharmacy data and birth registries were used to estimate adherence to PVZ and direct PVZ effectiveness in 0–5-month-old HFT infants by comparing the incidence of RSV hospitalizations 1) in protected and unprotected infants, and 2) during PVZ-protected and unprotected days. Over six seasons, the RSV hospitalization rate was 50.2/1000 (72.6/1000 adjusted for underdetection) in < 1-year-old infants. PVZ was administered to 73% (469) of eligible HFT infants; 37% (237) received all recommended doses. Overall for the three RSV seasons the incidence of RSV hospitalization in PVZ-protected infants was similar to PVZ-unprotected infants, resulting in PVZ direct effectiveness of –6.7% (95% CI –174.8%, 85.6%). The incidence of RSV hospitalization during PVZ-protected and during PVZ-unprotected days was also similar, resulting in PVZ direct effectiveness of –3.8% (CI –167.6%, 64.9%). Over three RSV seasons, there was no evidence that PVZ reduced RSV hospitalizations in HFT Nunavik infants. In addition, the sub-optimal adherence to the recommended PVZ administration schedule suggests feasibility and acceptability issues.

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of hospitalization for respiratory infection in infants < 1 year. Higher rates of RSV-associated hospitalizations (RSVH) have been reported in infants < 1 year residing in circumpolar regions, including Alaska Natives (seasonal and regional variations from 53 to 249 per 1000 (Karron et al., 1999; Singleton et al., 2006; Holman et al., 2004)) and Canadian Inuit (variations from 37 to 195/1000 (Banerji et al., 2009, 2016) compared to infants from the general population in the United States (23 to 26/1000) (Leader and Kohlhasse, 2003; Stockman et al., 2012; Zhou et al.,

2012) or other industrialized countries (21/1000) (Shi et al., 2017).

Palivizumab (PVZ) is a humanized monoclonal antibody licensed for the prevention of severe RSV infection in infants with high-risk conditions, including prematurity (≤ 35 weeks of gestational age (GA)), bronchopulmonary dysplasia (BPD) and hemodynamically significant congenital heart disease (The IMPACT-RSV Study Group, 1998; Feltes et al., 2003). The American Academy of Pediatrics (AAP) and the Canadian Paediatric Society (CSP) no longer recommend administration of PVZ for children without comorbidities born after 29 weeks GA (AAP, starting in 2014) or after 30 weeks GA (CPS, starting in 2015), based on the lower risk of RSVH and controversies in the effectiveness

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of PVZ in these groups (American Academy of Pediatrics Committee on Infectious Diseases, 2014; Robinson and Le Saux, 2015). In other jurisdictions of the world, recommendations are heterogeneous and the debate about which patients may benefit from PVZ is ongoing (Friedman et al., 2016; Pignotti et al., 2016). Both AAP and CPS nevertheless state that special consideration may be given to administering PVZ to infants living in remote Northern communities. The only available data on the effectiveness of PVZ in these infants are from observational and ecological studies with important methodological limits, and conducted only in high-risk sub-groups (Singleton et al., 2003; Banerji et al., 2014). To our knowledge, the efficacy of PVZ in healthy full-term (HFT) infants has not been evaluated.

In the province of Quebec, Canada, provincial eligibility criteria for PVZ immunoprophylaxis were expanded in fall 2016 to include HFT infants residing in the circumpolar region of Nunavik and aged < 3 months at the start of the RSV season or born during the RSV season (Institut national d'excellence en santé et en services sociaux (INESSS), 2017). In absence of reliable evidence regarding its efficacy and impact, this recommendation relied on contextual and experiential data provided by pediatricians of different subspecialties. According to these experts, RSVH rates were very high in this population and caused substantial costs associated with airborne medical evacuation; the efficacy of PVZ to prevent RSVH in HFT infants was expected to be similar to that found in premature children; and this intervention was considered to be both feasible for the healthcare system and well accepted by the population. More details about the decision-making process leading to this recommendation can be found elsewhere (Lorcy et al., 2020). Following this decision, Quebec Ministry of Health mandated the *Institut national de santé publique du Québec* (INSPQ) to conduct quantitative and qualitative analyses. Results of the qualitative evaluation were published elsewhere (Lorcy et al., 2020).

The objectives of the present study were: 1) to estimate the burden of RSVH in < 1 year infants residing in Nunavik (Quebec, Canada) during six RSV seasons (all infants and HFT infants); 2) to assess the effectiveness of PVZ to prevent RSVH in < 6-month-old HFT infants during the three RSV seasons following the implementation of the new recommendation.

2. Method

2.1. Background

Nunavik is the northernmost region of Quebec, Canada, with a population of $\approx 13,000$ (> 90% Inuit) living in 14 villages scattered along Hudson and Ungava Bays coasts, connected only by airplane and boat. Each village has a nursing station where PVZ (SYNAGIS[®], AbbVie Inc., Saint-Laurent, Quebec, Canada) is administered. For hospitalization, patients require air evacuation to one of the 2 regional hospitals located in Kuujuaq (Hudson) or Puvirnituq (Ungava). If tertiary care is needed, patients are airborne to Montreal (McGill University Health Centre (MUHC)) or (exceptionally) to Quebec City (CHU de Québec-Université Laval).

2.2. Study population

For the burden of RSV during six seasons, the study population consisted of Nunavik infants aged < 1 year hospitalized for a respiratory illness between November 1, 2012 and June 30, 2019, followed up to the age of 1 year or until June 30, 2019. The estimation of PVZ effectiveness was done for the last three RSV seasons (2016–17 to 2018–19) and included only HFT infants who were < 3 months at the start of the RSV season or born during the RSV season (born between October and May of each season) followed up to 6 months or until June 30, 2019. It therefore excluded infants otherwise targeted for PVZ immunoprophylaxis because of high-risk conditions defined as prematurity with GA ≤ 35 weeks or presence of cardiac or pulmonary

comorbidities (The IMPACT-RSV Study Group, 1998; Feltes et al., 2003). These high-risk conditions eligible for PVZ were identified from birth registries, medical records and pharmacy logs. Information on children eligible for PVZ according to prior to 2016 criteria (high-risk) or according to the new recommendation was extracted from pharmacy logs. For infants for whom information for qualifying comorbidities was found in medical records but who were missing from pharmacy registries (< 1%), adjudication of the eligibility for PVZ was achieved by consensus after the review of medical records by two physicians (RG and JP).

2.3. Respiratory illness-related hospitalizations

Medical records of infants admitted to Nunavik hospitals between November 1, 2013 and October 31, 2016 (pre-intervention period) and November 1, 2016 and June 30, 2019 (intervention period) with ICD10 diagnostic codes J00–J22 (acute respiratory diagnoses) at any position (Supplementary text A.1) were extracted by the archivists and reviewed by two research team members (one physician and one research assistant) in order to validate the respiratory diagnosis and to extract additional demographic, clinical and laboratory data. At the annual data collection visit in July, all medical records of recently hospitalized infants where no diagnosis had yet been coded ($\approx 30\%$ of all records) were reviewed to extract respiratory hospitalizations. RSVH was defined as a hospitalization lasting ≥ 24 h with at least one positive RSV test on a specimen collected during hospitalization or within 4 days prior to admission. Repeated hospitalizations for respiratory illness within 14 days were counted as a single episode; hospitalizations lasting < 24 h followed by an air transfer were included in the episode. Air transfers for respiratory illness to regional or tertiary hospitals were extracted from Nunavik hospitals' records and medical evacuations registries. Tertiary care hospital medical records were reviewed for all infants from Nunavik transferred during the study period; eligibility for inclusion in the study (admission for an acute respiratory infection diagnosis) was achieved by consensus between 2 physicians.

2.4. RSV laboratory tests

During the pre-intervention period, nasopharyngeal specimens were collected at the discretion of the treating physician and tested for RSV at the Nunavik hospitals using rapid antigen detection tests (RADT) (BinaxNOW[®] RSV[Alere] in Puvirnituq and in Kuujuaq until January 2015; and BD Veritor[™]RSV[BD Diagnostics] from January 2015 in Kuujuaq). Some specimens were tested at the MUHC using a laboratory-developed multiplex real-time polymerase chain reaction (PCR) assay (Alghounaim et al., 2017) (Supplementary text A.2). Starting on January 1st, 2017, a specimen was collected in all infants admitted for a respiratory illness and tested locally with RADT. Frozen aliquots were sent to the Quebec Public Health Laboratory (LSPQ) and tested with the Luminex[®] NxTAG assay (NxTAG) (Supplementary text A.2).

2.5. Palivizumab administration to HFT infants

Because the new program was recommended in September 2016, the short timeframe for its implementation prompted Nunavik authorities to administer a maximum of 3 doses (up to age 4 months) per infant during the first RSV season. During the next two RSV seasons, up to 5 doses (up to age 5 months) were administered as recommended. Based on RSV circulation, the period of PVZ campaign was from January 1 to April 30 in 2017 and from January 1 to May 31 in 2018 and 2019 (Supplementary Fig. A.1). HFT infants were recommended to receive PVZ every 28 days (Institut national d'excellence en santé et en services sociaux (INESSS), 2017) from January 1 until they reached 4 (2017) or 5 months (2018 and 2019) or until the end of the RSV season, whichever came first, for a total of 1 to 5 doses depending on the date of birth. Information about PVZ doses administered as reported by nursing

stations was extracted from the logs of regional pharmacies or directly from nursing stations for PVZ-eligible infants on the births lists but missing from pharmacies logs.

2.6. Statistical analyses

In order to better estimate the RSVH burden, sensitivity and specificity of the local RADT were calculated using NxTAG results as the reference standard (Chartrand et al., 2015). This sensitivity was used to estimate the number of RSVH potentially missed due to the imperfect sensitivity of the local RADT. We also attributed to infants who had no specimen collected the average positivity rate observed in infants tested by PCR (Supplementary Table A.1).

Similar to vaccine effectiveness estimation (Orenstein et al., 1985), the direct effectiveness of PVZ against RSV-confirmed hospitalizations in HFT infants was estimated as $(1 - \text{relative risk (RR) protected/unprotected}) \times 100\%$ during the PVZ campaign. This was first estimated comparing infants who received no dose (not protected) and those who got all required doses (protected) in a timely way (excluding children with delayed doses). A second analysis used all infants taking into consideration their individual contribution to time at risk into “protected” and “unprotected” periods. Infants were considered “protected” during the 28 days following PVZ administration. The following 15 days (day 29 to 44) belonged to the wash-out period and were excluded from the analysis. The days outside the protected and wash-out periods were classified as “unprotected”. Incidence rates of RSVH during PVZ-protected and unprotected days were used to calculate incidence rate ratios (IRR) for the estimation of PVZ effectiveness. The main analysis was in 0–2-month-olds; secondary analysis included 3–5-month-olds who were partially targeted by the recommendation. Sensitivity analyses were done by: 1) considering the wash-out period as days with PVZ protection; 2) considering the wash-out period as days without PVZ protection.

Quantitative variables were compared using Wilcoxon or Student t-tests when appropriate; 95% confidence intervals (CI) around PVZ effectiveness were calculated with a logbinomial model for the RR and an exact Poisson method for the IRR. A p-value < 0.05 was considered significant. Statistical analyses were performed using SAS 9.4.

2.7. Ethics

This project was an evaluation of a public health intervention legally mandated by the Nunavik director of public health and did not require research ethics committee review. Authorizations to access medical, laboratory and PVZ administration records were granted by the directors of professional services from the regional and tertiary health centers as required by the Act respecting health services and social services (LégisQuébec).

3. Results

3.1. Study population

A total of 2503 infants were born between November 1, 2012 and June 30, 2019 (average 382 per year pre-intervention and 365 during the intervention period) including 156 (6.2%) who were preterm or with other high-risk conditions qualifying for PVZ immunoprophylaxis, leaving a cohort of 2347 HFT newborns, nearly all (> 99%) Inuit.

3.2. Hospitalization for respiratory illness and RSV

Between November 2013 and June 2019, 354 infants < 1 year were admitted with a respiratory illness for a total of 458 episodes including 113 (25%) with RSV (Fig. 1) (annual average 81 (19 RSV-positive)). Of these 354 infants, 67 were considered high-risk (98 episodes) and 287 were HFT infants (360 episodes). The annual average was 17 (2.5 RSV-

positive) in high risk infants and 64 (16 RSV-positive) in HFT. The overall hospitalization rate per 1000 live births for respiratory illness was 83.3 in high-risk infants, 46.4 in HFT infants, and 50.2 in all infants. All RSV-positive hospitalizations occurred between January and June. This period is thereafter defined as the RSV season (Fig. 2).

The number of RSV-positive hospitalizations in HFT infants varied greatly between seasons, especially in 0–2-month-olds (from 2 in 2014 to 10 in 2016) (Table 1, Supplementary Table A.2). In the pre-intervention period, there were 7 RSV-positive transfers to tertiary care hospitals (including 4 ICU admissions) in 0–2-month-old infants (0 to 5 per season) and 2 in 6–11-month-old infants. In the intervention period, all 3 RSV-positive tertiary care transfers (including 3 ICU admissions) occurred in 0–2-month-old infants (Supplementary Table A.2).

During the pre-intervention period, RSV testing by at least one assay was done for 83% of respiratory episodes (97% by RADT and 24% by MUHC multiplex PCR test). During the intervention period, specimens were tested in 95% of respiratory hospitalizations: 97% by RADT and 73% by PCR (92% NxTAG). Using the 123 specimens collected during the intervention period and tested by both NxTAG and RADT, RADT compared to NxTAG had a sensitivity of 60% (95%CI, 44%–75%) and a specificity of 100% (95%CI, 96%–100%). With adjustment for potentially missed RSV cases due to lack of testing and imperfect sensitivity of the RADT (Supplementary Table A.1), the overall RSVH rate per 1000 live births in < 1-year-old infants was 147.6 in high-risk infants, 64.8 in HFT infants and 72.6 in the overall population < 1 year.

Among the 124 infants tested by NxTAG, 96% (119) had at least one virus detected: 35% (43) had RSV (24 RSV with at least one other virus; 19 RSV alone) and 61% (76) had other respiratory viruses (ORV) without RSV. Coinfections with several viruses were frequent and up to 4 viruses were detected simultaneously in one infant (Supplementary Table A.3). Enteroviruses were more frequent (45%, n = 56) than RSV.

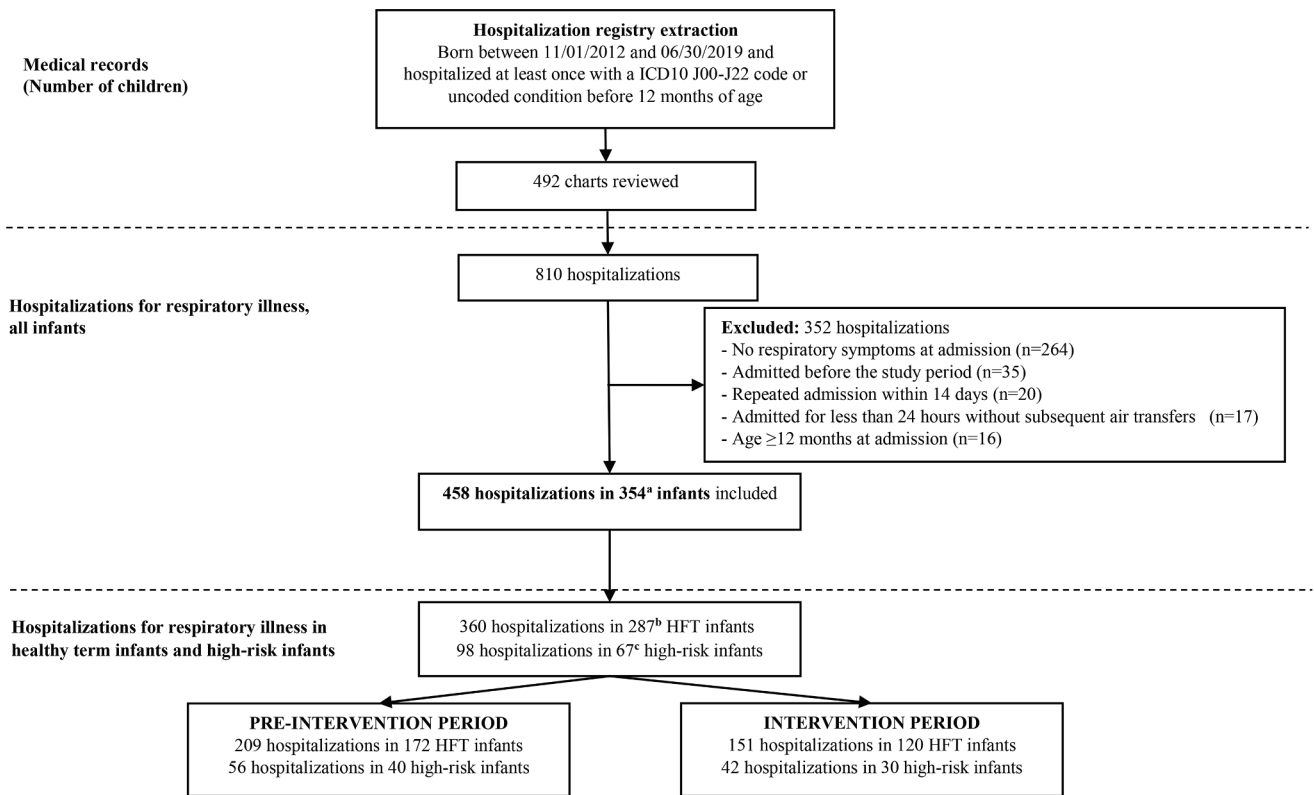
The line list of 0–5-month-old HFT infants eligible to receive PVZ and hospitalized with laboratory-confirmed RSV during the intervention period is presented in Supplementary Table A.4.

3.3. Palivizumab administration and direct effectiveness

During the three intervention seasons, 646 HFT infants were eligible to receive PVZ: 73% received at least one dose but only 37% received all recommended doses (Table 2). While 1926 doses of PVZ should have been administered if all eligible infants had received all recommended PVZ doses (1–4 in 2017; 1–5 in 2018 and 2019) in a timely manner, 1091 doses (57%) were actually administered. More than half (55%) of unprotected days were among children who received no dose, 25% were days before the first dose was received and 19% were days related to interrupted or delayed administration (Table 3). The distribution of infant-days with protection and without protection was similar across the RSV season, except for a greater proportion of unprotected infant-days compared to protected infant-days during the first 3 weeks of the season (Fig. 3). Protected/unprotected cases were evenly distributed throughout each of the 3 RSV seasons (Fig. 3).

In 0–2-month-old infants, 8 RSVH occurred among the 214 infants (3.7%) who received all required doses in a timely manner (protected) and 6 among the 225 infants (2.7%) who received no dose (unprotected) over the three seasons. The higher cumulative incidence in protected infants resulted in a negative effectiveness of -40.2% (95%CI, -297.3% – 50.5%). Up to the age of 5 months, there were 2 additional cases among protected (10/237, 4.2%) and 1 additional case in unprotected infants (7/177, 4.0%), for an effectiveness of -6.7% (95%CI, -174.8% – 58.6%).

Overall for the three seasons the RSVH incidence in 0–2-month-old infants was higher during protected days (45.6/100,000 or 8 RSV hospitalizations for 17,530 PVZ-protected infant-days) than during unprotected days (42.2/100,000 infant-days or 6 RSV hospitalizations for 14,203 PVZ-unprotected infant-days), resulting in a negative



^a 8 infants hospitalized during both pre-intervention and intervention period

^b 5 HFT infants hospitalized during both pre-intervention and intervention period; ^c 3 high-risk infants hospitalized during both pre-intervention and intervention period

High-risk infants: born < 36 weeks GA or with high-risk conditions qualifying for standard PVZ immunoprophylaxis; HFT: healthy-full term (not high-risk) See text for more details

Fig. 1. Flow chart of hospitalizations of Nunavik infants < 1 year included in the analysis.

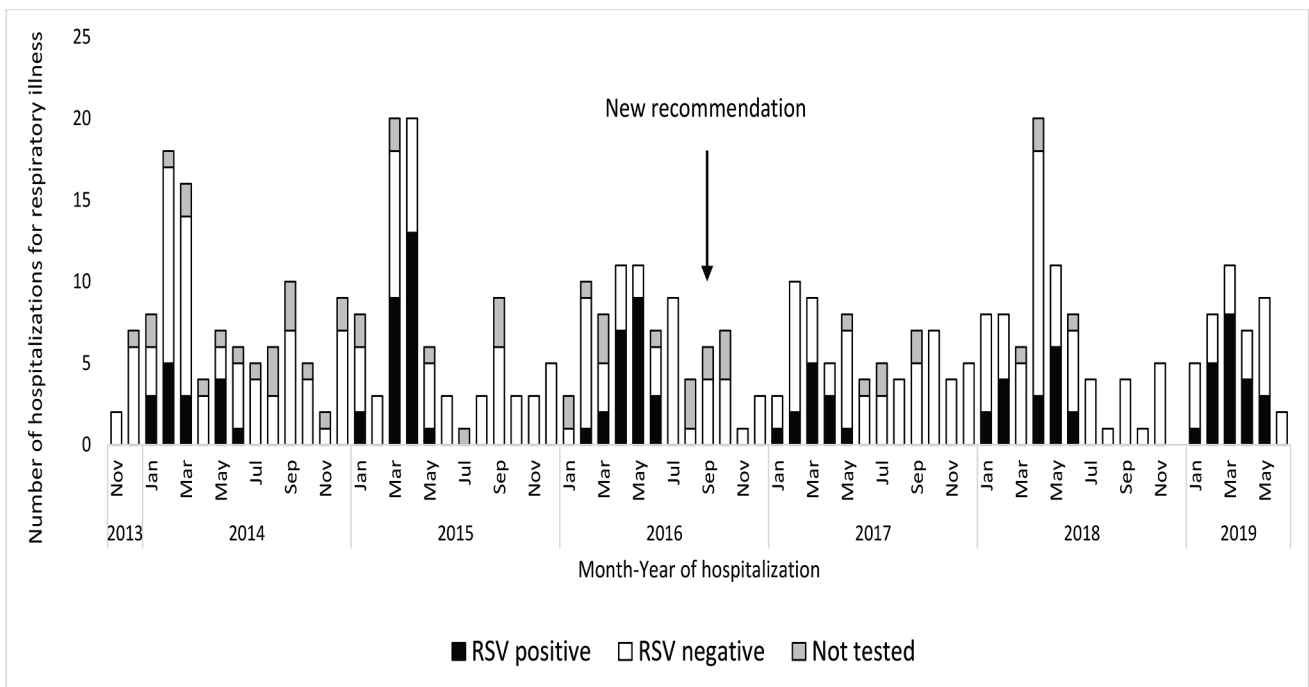


Fig. 2. Hospitalizations* for respiratory illness in Nunavik infants aged < 1 year by month, November 2013 to June 2019 *Up to 5 respiratory hospitalizations per infant. Two infants had more than one RSV hospitalization; one at 7 and 8 months of age during the same RSV season; one at 1 and 11 months of age during different seasons. New recommendation: Palivizumab (PVZ) immunoprophylaxis in healthy full term (HFT) infants residing in Nunavik aged < 3 months at the start of the RSV season or born during the RSV season Healthy full-term infants: born ≥ 36 weeks GA without high-risk conditions qualifying for standard PVZ immunoprophylaxis. See text for more details.

Table 1
Hospitalizations with respiratory infections during the RSV season (between January and June) among healthy full-term Nunavik infants < 1 year.

Age group	Number/rate hospitalized by RSV test result ^a	January–June 2014	January–June 2015	January–June 2016	January–June 2017	January–June 2018	January–June 2019	January–June, overall
0–2 months	RSV Positive, number	2	8	4	3	8	35	
	RSV positive rate per 1000 infants	24.4	93.0	48.8	37.5	95.2	70.4	
	RSV Negative, number	6	5	9	6	4	39	
	Not tested, number	2	3	0	1	0	9	
3–5 months	Total hospitalized	10	16	13	10	12	83	
	RSV Positive, number	4	6	2	4	3	24	
	RSV positive rate per 1000 infants	42.6	65.2	22.7	47.1	32.3	44.4	
	RSV Negative, number	9	6	4	5	5	35	
6–11 months	Not tested, number	1	0	0	0	0	2	
	Total hospitalized	14	12	6	9	8	61	
	RSV Positive, number	6	9	6	7	6	39	
	RSV positive rate per 1000 infants	29.7	52.0	33.0	40.7	35.5	36.3	
< 1 year	RSV Negative, number	11	11	6	17	10	57	
	Not tested, number	4	1	2	3	0	11	
	Total hospitalized	21	21	14	27	16	107	
	RSV Positive, number	12	23	12	14	17	98	
Overall	RSV positive rate per 1000 infants	31.7	65.5	34.1	41.5	49.1	46.4	
	RSV Negative, number	26	22	19	28	19	131	
	Not tested, number	7	4	2	4	0	22	
	Total hospitalized	45	49	33	46	36	251	

^a RSV-positive by at least one laboratory test (RADT or PCR).

effectiveness of -8.0% (95%CI, $-277.7\%-67.1\%$) (Table 3). The effectiveness among 0–5-month-old infants was 3.8% (95%CI, $-167.6\%-64.9\%$) over three seasons (Table 3). One additional RSVH occurred in June 2018 (after the end of PVZ campaign) 15 days after the receipt of a 5th dose of PVZ and was not included in the effectiveness analysis. Among infants included in the effectiveness analysis and tested with multiplex PCR, more infants with RSV were coinfecting with ORV during protected days (78% (7/9)) compared to unprotected days (50% (4/8)). In sensitivity analyses where the washout was considered as days with or without PVZ protection, PVZ effectiveness was essentially unchanged (Table 3).

The line-list of 0–5-month-old HFT infants eligible to receive PVZ and hospitalized with RSVH during the intervention period is presented in Supplementary Table 4.

4. Discussion

Over the six-year period, the observed RSVH rate per 1000 live births was high in the overall population of Nunavik infants < 1 year (50.2 observed, 72.6 adjusted for underdetection), with substantial variability between seasons. This is similar to that reported in Canadian circumpolar regions (overall 66.9/1000, varying from 19.7/1000 in Northwest Territories to 195.1/1000 in Kitikmeot Region in 2009) and in infants from the Alaska Yukon-Kuskokwim Delta (YKD) (65/1000 during 2009–2012) (4,18), and much higher than in the general population of infants from the USA or industrialized countries (20.9/1000) (Zhou et al., 2012). The variable intensity of RSV seasons observed in this small population is similar to that reported in Alaska YKD (ranging between 16 and 245/1000 per year from 1994 to 1995 to 2011–2012) (Bruden et al., 2015). This variability of infectious diseases epidemics (more extreme in small isolated populations) is one of the most important threats to the validity of the studies comparing the burden of an infectious disease before and after the implementation of public health interventions in a population (Des Jarlais et al., 2004; Bernal et al., 2017) and the reason why we chose an alternative design to assess the effectiveness of PVZ.

The coverage with PVZ was lower than reported in high-risk Aboriginal children in Canada (Hui et al., 2016), in Alaska (Singleton et al., 2006), and in other vulnerable populations such as Medicaid patients (Frogel et al., 2010). The causes of this low coverage are likely multifactorial. No additional human resources were available to run this program and shifting resources to the PVZ program caused a hidden but real opportunity cost in terms of reduced activities in other important programs like immunization or sexually transmitted diseases control. Even if more resources had been available, the refusal rate and lack of compliance likely reflect limited acceptability or importance of the PVZ program for Inuit families, as highlighted in a qualitative analysis carried out during the first year of implementation (Lorcy et al., 2020).

In this first estimation of PVZ effectiveness in HFT and in Inuit infants, the absence of protection provided by PVZ was unexpected. In the landmark randomized controlled trial (RCT) IMPact-RSV, prophylaxis with PVZ resulted in a 39% reduction of RSVH in children with BPD and 78% in preterm children without it, for an overall 55% reduction (The IMPACT-RSV Study Group, 1998). Subsequent studies in various settings supported a protective effect of PVZ against RSVH in high-risk children, although the size of benefit was generally lower than reported in the IMPact-RSV RCT (Feldes et al., 2003; Robinson and Le Saux, 2015; Homaira et al., 2014; Andabaka et al., 2013; Anderson et al., 2017) and it was inconclusive in infants with cystic fibrosis (Kua and Lee, 2017; Simões et al., 2018). The only study (RCT) in HFT infants was carried out in a different population (Native American infants from southwestern USA) of older age (< 12 months) with another monoclonal anti-RSV antibody, motavizumab, which never received regulatory approval, and therefore its results cannot be generalized (O'Brien et al., 2015). Although numbers are small, RSV-ORV

Table 2
Palivizumab administration and adherence in healthy full-term Nunavik infants.

RSV season	Number of eligible infants ^a	Total number of palivizumab doses recommended	Number of refusals ^b (% of eligible infants)	Number of doses received (% of total recommended number of doses) ^c	% of infants who received at least one dose	% of infants who received all recommended doses
	N	N	%(n)	%(n)	%(n)	%(n)
<i>0–2 months</i>						
2017	198	321 ^d	5%(10)	73% (233)	66% (131)	46% (91)
2018	220	402 ^e	14%(31)	71% (286)	63% (138)	27% (61)
2019	228	437 ^e	11%(25)	60% (263)	66% (152)	27% (62)
2017–2019	646	1160	10%(66)	67% (782)	65% (421)	33% (214)
<i>0–5 months</i>						
2017	198	406	5%(10)	65% (264)	72% (141)	51% (101)
2018	220	732	14%(31)	56% (409)	72% (159)	31% (68)
2019	228	788	11%(25)	54% (426)	74% (169)	30% (68)
2017–2019	646	1926	10%(66)	57% (1099)	73% (469)	37% (237)

^a Born between October 1st, 2016 and April 30th, 2017; October 1st, 2017 and May 31st, 2018 or October 1st, 2018 and May 31st, 2019.

^b Explicit refusal on the consent form (first or subsequent doses).

^c Missed doses are for infants who were not reached or did not show up to scheduled visits.

^d 1 to 4 doses recommended depending on the date of birth.

^e 1 to 5 doses recommended depending on the date of birth.

coinfections occurred more frequently in PVZ protected (78%) than unprotected HFT infants (50%). High frequency of RSV co-infections has also been reported in 9 hospitals in the Canadian Arctic, where 41% of infants < 1 year admitted in 2009 with respiratory infections had RSV co-infections (Banerji et al., 2016). It is not possible to determine the independent causal role of RSV in the hospitalizations of children coinfecting with ORV, and consequently the proportion of these infections that may or may not be prevented by PVZ.

The main limitation of this evaluation was the small number of cases and the ensuing wide confidence intervals. Nevertheless, PVZ effectiveness was very low when using different methods of estimation and under different sensitivity analyses addressing potential biases. The study population is homogenous, had universal access to PVZ and it is unlikely that the propensity to be hospitalized with RSV infection differed between infants who received PVZ versus those who did not. Second, more infants were unprotected than protected at the beginning of the season (first 3 weeks). However, none of the cases occurred during this period and protected/unprotected cases were evenly distributed throughout each of the RSV seasons. Therefore, the validity of the comparison between protected/unprotected periods was not affected. As such, after three years of this program, the likelihood of high level of direct protection of PVZ against RSVH in this population appears low. Third, during the pre-intervention period, treating physicians may have been inclined to order a laboratory test in infants more likely to have RSV infection or with more severe illness. Assuming a similar proportion of RSV positivity in infants who were not tested when adjusting for underdetection, we may have overestimated RSV incidence. Since less tests were done during the pre-intervention period, the overestimation is likely higher during that period as compared to the intervention period. Because of the overestimation, the adjusted RSVH burden should be interpreted as the upper theoretical limit of the real burden.

The strength of this study is the individual follow-up of every infant born during the study period in Nunavik, with thorough review of medical and laboratory records and pharmacy logs, validated against administrative individual data (birth registries and medical evacuation files) to ensure high quality data. Availability of individual information allowed an accurate account of individual contribution to time at risk during PVZ-protected and unprotected periods and valid estimate of PVZ effectiveness. Finally, despite the small size of the population targeted by the new recommendation, our evaluation provides a unique contribution to the evidence needed to inform public health policies in other Northern Inuit communities.

5. Conclusion

After three RSV seasons we found no evidence that PVZ reduced RSV hospitalizations in HFT Inuit infants. In addition, the suboptimal coverage with PVZ doses during the three RSV seasons suggests feasibility challenges in a resource-limited setting and limited acceptability of this program for some Inuit families.

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CRedit authorship contribution statement

Rodica Gilca: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing. **Marie-Noëlle Billard:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Joseline Zafack:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Jesse Papenburg:** Conceptualization, Investigation, Methodology; Writing - review & editing. **François D. Boucher:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Hugues Charest:** Investigation, Methodology, Writing - review & editing. **Marie Rochette:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - review & editing. **Gaston De Serres:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The following authors report specific relationships that could be interpreted as implying a conflict (name author, nature of the relationship, and company or organization): RG has received research grants from Sanofi Pasteur. JP has received consulting/honoraria fees from AbbVie, Cepheid and Seegene, and research grant funding outside of the current work from AbbVie, BD Diagnostics and MedImmune. GDS has received investigator-initiated grants from Pfizer and received paid

Table 3
 Palivizumab effectiveness under an assumed protection of 28 days and wash-out period of 15 days in healthy full term Nunavik infants.
 RSV season and age group

RSV season and age group	Infant-days		Number of RSV hospitalizations ^b		Incidence/100,000 infant-days		Effectiveness		95% CI							
	Overall	Not protected	Protected	Excluded ^a	Total	Not protected	Protected	Effectiveness								
	Infant-days	no dose before 1st dose	between doses/after last dose	Excluded ^a	Protected	Not protected	Protected	Effectiveness								
2017																
0-2 months	9,580	3,712	2,207	1,145	360	5,217	651	4	2	2	0	53.9	38.3	28.8%	-881.6% to 94.8%	
0-4 months	12,339	4,921	2,980	1,330	611	6,349	1,069	5	3	2	0	61.0	31.5	48.3%	-351.1% to 95.7%	
2018																
0-2 months	11,663	4,485	2,456	1,583	446	6,267	911	3	1	1	1	22.3	16.0	28.4%	-5517.7% to 99.1%	
0-5 months	20,129	8,079	4,348	2,025	1,706	10,031	2,019	5	3	1	1	37.1	10.0	73.2%	-234.4% to 99.5%	
2019																
0-2 months	13,107	6,006	3,132	2,208	666	6,046	1,055	8	3	5	0	50.0	82.7	-65.6%	-966.1% to 67.8%	
0-5 months	22,516	10,019	5,372	2,479	2,168	10,208	2,289	10	3	7	0	29.9	68.6	-129.0%	-1272.5% to 47.7%	
3 seasons																
0-2 months	34,350	14,203	7,795	4,936	1,472	17,530	2,617	15	6	8	1	42.2	45.6	-8.0%	-277.7% to 67.1%	
0-5 months	54,984	23,019	12,700	5,834	4,485	26,588	5,377	20	9	10	1	39.1	37.6	3.8%	-167.6% to 64.9%	
Sensitivity analyses, 3 seasons																
Washout period considered as protected																
0-2 months	34,350	14,203	7,795	4,936	1,472	20,147	0	15	6	9	0	42.2	44.7	-5.7%	-261.0% to 66.4%	
0-5 months	54,984	23,019	12,700	5,834	4,485	31,965	0	20	9	11	0	39.1	34.4	12.0%	-140.3% to 66.8%	
Washout period considered as unprotected																
0-2 months	34,350	16,820	7,795	4,936	1,472	17,530	0	15	7	8	0	41.6	45.6	-9.7%	-255.2% to 65.3%	
0-5 months	54,984	28,396	12,700	5,834	4,485	26,588	0	20	10	10	0	35.2	37.6	-6.8%	-185.9% to 60.1%	

^a Wash-out period.

^b RSV-positive by at least one laboratory test (RADT or PCR).

^c 0-4 months in 2017.

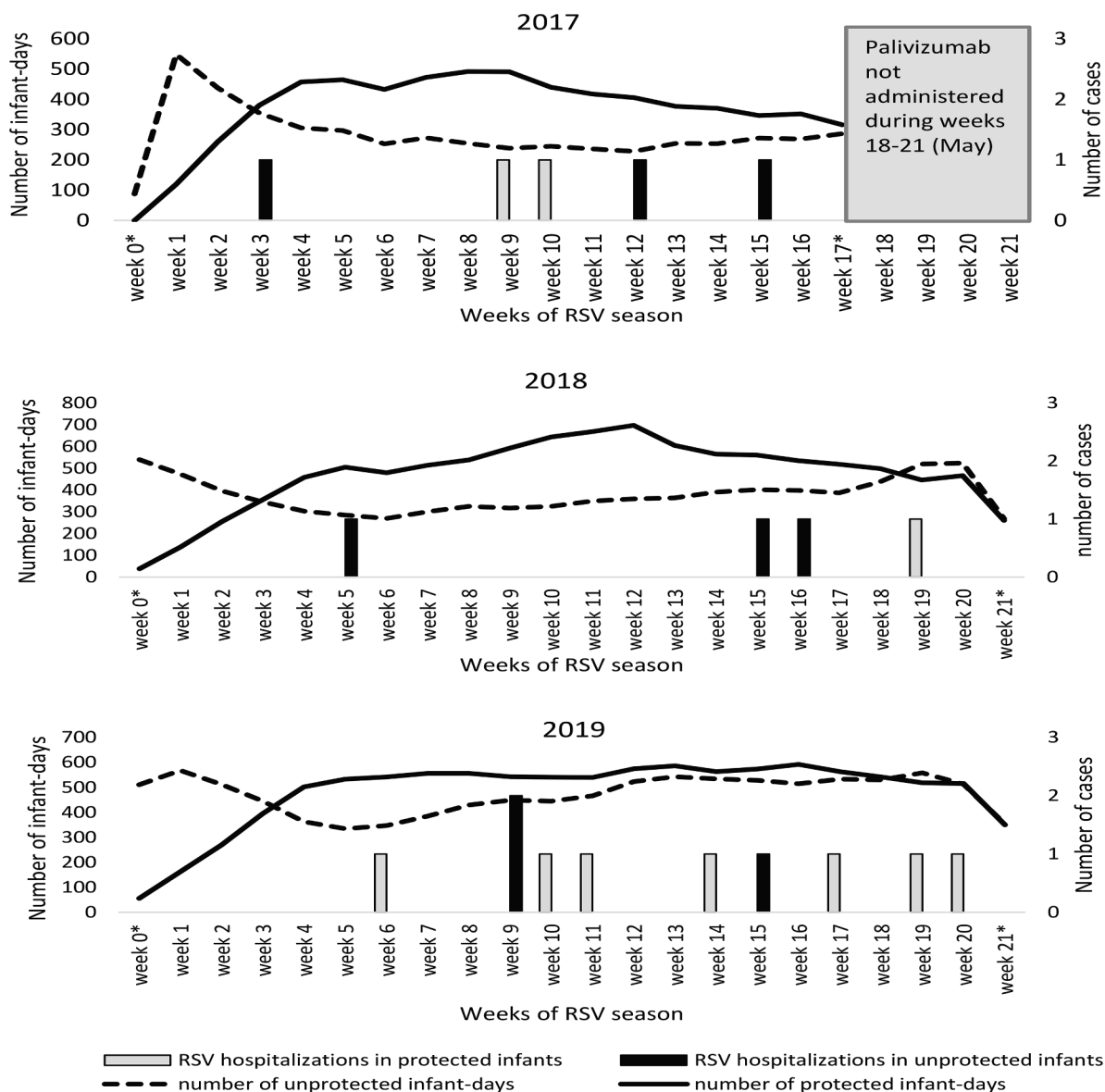


Fig. 3. Distribution of “protected” and “unprotected” infant-days and RSV hospitalizations in palivizumab-protected and unprotected healthy full-term 0–5-month-old Nunavik infants included in the effectiveness analysis, by week of each RSV season.

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Appendix A. Supplementary data

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