Evaluation of new palivizumab immunoprophylaxis recommendations in Nunavik infants : results for 2014 to 2017

REPORT

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Direction des risques biologiques et de la santé au travail

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Institut national de santé publique Québec

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Summary

An immunoprophylaxis program with palivizumab, a monoclonal antibody against the respiratory syncytial virus (RSV), has been in place in Quebec since 2005. The program targets pediatric populations considered to be at greatest risk for developing serious respiratory illness due to RSV such as premature infants (<33 weeks of gestation) and children with a chronic respiratory disease or a congenital heart disease. These children at risk are eligible to receive up to 5 monthly doses of palivizumab during the RSV season.

Following a request from the Ministry of Health (Ministère de la Santé et des Services sociaux (MSSS)) to review the eligibility criteria for Québec's palivizumab immunoprophylaxis program, the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) updated the eligibility criteria for palivizumab immunoprophylaxis in 2016. The most important modification was the inclusion of healthy Nunavik children born at term and younger than 3 months of age to the list of eligible children. This decision was based mainly on experts' opinion as there was scarce data regarding the RSV burden and no direct evidence about the efficacy of palivizumab in this population. Experts considered that the RSV burden was important in healthy <3-month-old Nunavik infants born at term causing substantial costs associated predominantly with tertiary air transportation, that efficacy of palivizumab to prevent hospitalisation would likely be as good as it is in premature children and that this intervention would be feasible and acceptable in the population. The MSSS approved this new recommendation in the autumn 2016 and the Nunavik region had to implement it for the 2016-2017 season.

The Institut national de santé publique du Québec (INSPQ) was mandated by the Nunavik Public Health authorities to evaluate the impact of the new recommendations. This report presents the results of the evaluation done at the end of the first RSV season (2016-2017).

For logistical reasons, the implementation of the new recommendation for the 2016-2017 season by Nunavik Public Health authorities consisted in administering up to 3 doses to eligible term healthy infants; the rest of eligible children (premature or with pulmonary/cardiac diseases) were to receive the recommended 5 doses. The great majority (95%) of eligible infants were reached and half of them received all recommended doses. A total of 12 RSV-associated hospitalizations occurred in <12-month-old infants. This number is lower than in the previous three seasons but the decrease affected not only the targeted age group but also infants 4-11 months who did not receive palivizumab and in whom no benefit was expected. This decrease therefore more likely reflects the variability of RSV seasons than the impact of new recommendation. The majority (80%) of infants with RSV-associated hospitalizations were also infected with up to 4 other respiratory viruses.

A qualitative evaluation was conducted to evaluate the impact of the new recommendation on the organisation of services and on perceptions and practices of Nunavik health workers. This evaluation identified significant issues both in terms of feasibility and acceptability. Regarding feasibility, the healthcare system received no additional resources (financial, material or human) to implement the program and had to shift resources previously dedicated to other activities. This shift of resources triggered serious concerns regarding the priority given to palivizumab over other activities for which the priority was obvious (e.g. control of sexually transmissible diseases, tuberculosis, etc). In terms of acceptability, some nurses and midwives were unsatisfied with the information they received or gathered. They wanted good evidence that full-term healthy Inuit babies are at high risk for RSV infection and that palivizumab is effective enough in this group to justify their inclusion in the program. Some healthcare workers underscored that the Inuit population and their leaders were not consulted and involved in the decision or implementation processes. The evaluation also showed that

some nurses and midwives have concerns that the information given to Inuit parents was incomplete and/or misunderstood. According to these healthcare workers, they also perceived that some parents felt under pressure and did not dare to refuse the palivizumab administration. This raises ethical concerns regarding the guarantee of a free and informed consent from parents. Unfortunately, the qualitative evaluation in the first season did not involve the Inuit population.

In conclusion, given the small population and the variability of RSV seasons, the results of the first year are not conclusive; a longer period of follow-up is necessary for a more precise evaluation of the impact and effectiveness of palivizumab. The qualitative evaluation highlighted the need to involve the Inuit population at various stages of the implementation. In order to validate the concerns raised by the health-care workers, we recommend a direct assessment of the perception and opinion of the Inuit population regarding this program.

1 Background

The respiratory syncytial virus (RSV) is a major cause of hospital admissions for lower respiratory tract infections, mostly bronchiolitis and pneumonia, in young children(1,2). A substantial proportion of the RSV-associated morbidity occurs in the first year of life(2). Inuit children who reside in circumpolar regions have higher hospital admission rates for respiratory illness compared to southern regions. The estimated rate of admission for lower respiratory tract infection due to RSV during the first year of life from a cohort study conducted in the Canadian Arctic was 66.9 per 1000 live births in 2009, with variations from 19.7 to 195.1 per 1000 live births per year in different regions(3). This is considerably higher than the global estimate in the same age group of 5,5 per 1000 in industrialized countries based on a meta-analysis of studies between 1995 and 2009(2), that of 27,1 per 1000 in 0-5-month-old infants and 9,8 per 1000 in 6-11-month-old infants in a recent update by the same group of authors(1), and the estimate of 26 in infants <1 year of age per 1000 derived from a hospital discharge database from 1997 to 2006 in the US(4). In Nunavik, the northern part of the province of Quebec, Canada, the only available estimate of the incidence of RSV-associated hospital admissions among infants < 1 year of age per 1000 live births per year is that of 176 in 2009 from the cohort study in the Canadian Arctic(3). This is almost 6 times higher than the estimates in infants born at term with no underlying medical condition (30/1000) obtained in a retrospective cohort study from 1989 to 1993 in the US(5), and more comparable to the incidence measured in high-risk populations (57-70/1000 in premature infants, 92/1000 in those with congenital heart disease, and 388/1000 in those with bronchopulmonary dysplasia) obtained in the same study(5).

The only product currently approved for prevention of severe RSV disease is palivizumab (Synagis®, Abbvie), a humanized monoclonal antibody, marketed as an intramuscular injection to be administered once monthly during the RSV season. An immunoprophylaxis program has been in place in Quebec since June 2005 targeting pediatric populations considered to be at greatest risk for developing serious respiratory illness due to RSV. Prior to the 2016-17 season, the main groups eligible to receive palivizumab during the RSV season were premature infants (<33 weeks of gestation) younger than six months of age and children with a chronic respiratory disease or a congenital heart disease younger than 24 months at the start of the RSV season or born during the RSV season (Appendix A).

Following a request from the Ministry of Health (Ministère de la Santé et des Services sociaux (MSSS)) to review the eligibility criteria for Québec's palivizumab immunoprophylaxis program, the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) updated the eligibility criteria for palivizumab immunoprophylaxis based on a selected assessment framework and submitted new recommendations to the Minister in July 2016(6). The most important modification to the eligibility criteria to the Quebec palivizumab immunoprophylaxis program was for healthy Nunavik children born at term and <3 months of age at the start of the RSV season or born during the RSV season. There was a scarcity of RSV data for this group. The decision to recommend palivizumab was therefore based mainly on experts' opinion who considered that the RSV burden was important in healthy <3-month-old Nunavik infants born at term causing substantial costs associated mainly with tertiary air transportation. They also thought that the new recommendation was feasible and would be well accepted both by the population and the health-care workers. The updated recommendations targeted also the much smaller group of children born at ≤36 weeks' gestational age who are <6 months at the start of the RSV season or born during the RSV season. The MSSS approved both recommendations in the autumn 2016 and Nunavik region had to implement them for the 2016-2017 season.

While some pediatricians working in Nunavik were consulted by the INESSS, neither public health nor other Nunavik healthcare professionals and Inuit leaders were involved during the decision-making process. Nunavik Public Health authorities felt ill-equipped to inform health-care professionals and the Inuit population about the rationale for the new recommendation in this expanded segment of the population and faced real challenges to implement it. For logistical reasons due mainly to the short delay before the start of the RSV season, the implementation of the new recommendation for the 2016-17 season by Nunavik Public Health authorities consisted in administering up to 3 doses to eligible term healthy infants; the rest of eligible children were to receive the recommended 5 doses. In addition, because of the differences in RSV seasonality in Northern regions compared to the Southern regions (season starts later and finishes later in the North); the RSV season was defined from January 1, 2017 to April 30, 2017, instead of that defined for the south from November to March. Children born in tertiary hospitals in the south (mainly children with underlying conditions) received palivizumab starting in November.

The Institut national de santé publique du Québec (INSPQ) was mandated by the Nunavik Regional Board of Health and Social Services to evaluate the impact of the new recommendation on infants <3 months of age born at term. This report presents both the quantitative findings regarding the impact of the recommendation on the burden of disease (quantitative component) and on the organisation of services (qualitative component).

2 Quantitative evaluation

2.1 Objectives

The general objective was to evaluate the impact of the new palivizumab recommendations (designated "intervention" in this report) implemented during the 2016-17 RSV season, specifically:

- To estimate the reduction of the burden of regional (Nunavik) and tertiary (referral centres in the south) RSV-associated hospitalizations among healthy full term Nunavik infants aged <3 month between the three seasons before the implementation of the recommendation (3 retrospective RSV seasons, 2013-14 to 2015-16) and after the implementation of the recommendation (4 prospective RSV seasons, 2016-17 to 2019-20).
- To describe the palivizumab prescription and adherence to recommended doses in Nunavik infants during the retrospective and prospective periods.
- To conduct an economic analysis of the costs and benefits of the new recommendations.

This report presents the results of the first RSV season of implementation of the recommendation (6 months, i.e. January 1 to June 30, 2017) compared to those of the 3 previous seasons (2013-14 to 2015-16).

The results of the economic analysis will be reported later.

2.2 Methods

2.2.1 Nunavik population and organization of health care services

Health care services in Nunavik are divided in two sub-regions. The Inuulitsivik Health Centre (Centre de santé Inuulitsivik, CSI), serving the Hudson Bay population (≈60% of Nunavik population), consists of Puvirnituq Hospital with maternity services and nursing stations in each of the 6 other villages, including two with maternity services. The Tulattavik Health Centre (Centre de santé Tulattavik de l'Ungava, CSTU), serving the Ungava Bay population (≈40% of Nunavik population), consists of the Kuujjuaq Hospital and nursing centres in each of the 6 other villages; maternity services are offered only at Kuujjuaq.

Patients who need to consult a medical specialist or to be hospitalized are transferred to their regional hospitals (CSI or CSTU). Those requiring more specialized care not available locally are transferred to the Montreal Children's Hospital of the McGill University Health Centre (MUHC) in Montreal, where the region manages a patient services unit (Northern Quebec Module, NQM), or exceptionally to Laval University Health Centre in Québec City (CHUL). As villages are isolated, individuals travel exclusively by air between villages or to Montreal or Quebec City. Patients can be transferred by regular flights or evacuated urgently by air ambulance (MedEvac, propeller-engine aircraft or Challenger) with a trained medical professional (nurse, physician, or midwife).

Study population

The burden of RSV-associated hospitalizations was estimated in infants < 1 year of age residing in Nunavik for the period from November 1, 2013 to June 30, 2017. In order to be younger than 12 months of age at admission, children had to be born between November 1, 2012 and June 30, 2017.

To describe palivizumab prescription practices and its adherence, all children who were prescribed palivizumab during the study period (up to 24 months of age) were considered, regardless of age at administration.

Birth Lists

The list of live births between November 1, 2012 and June 30, 2017 for whom a medical chart opening request was registered locally were extracted by the 2 regional health centres from eClinibase in August 2017. Since the two sub-regions operate independently, children who had lived in villages located on both coasts may have medical file opening requests registered at both health centers. In order to find double entries, birth dates that corresponded to more than one medical record number were identified and if names and sexes matched, one line was deleted.

2.2.2 HOSPITAL CHARTS REVIEW

Data for eligible children who were hospitalized locally at least once during their first year of life with a diagnostic code for respiratory infections were extracted from the Quebec hospital admissions administrative database (MED-ECHO) by the two regional hospitals by using diagnostic codes ICD10 J00-J22 at any position (Appendix B). The medical charts of these children were reviewed by two members of the team. Data about hospitalizations for respiratory infections during the first year of life were extracted from hospital charts using a standardized data extraction form and entered in the database. Transfers to a tertiary hospital were entered as separate hospitalizations and to ensure completeness, were compared with the list of <1-year-old infants admitted at MUHC for a respiratory infection between November 1, 2013 and June 30 2017 from the MNQ. The data extraction form collected information on demographics (name, sex, village of residence, place of birth, gestational week at birth, birth weight, and ethnicity), relevant medical history (e.g. congenital heart disease, chronic lung disease, bronchopulmonary dysplasia), information regarding the hospitalization (mode of transportation to hospital, complications, admission to the intensive care unit); laboratory tests for RSV and influenza done at the regional hospital at admission +/- three days, and other relevant laboratory tests if judged relevant, e.g. occasional PCR tests for respiratory viruses sent to MUHC and tests for other suspected infections (e.g. *Streptococcus pneumoniae, Bordetella pertussis or Neisseria meningitidis*).

2.2.3 LABORATORY TESTS FOR RSV

Nasopharyngeal specimens in Nunavik are tested for RSV and influenza locally using a rapid antigenic tests (Binax® at CSI and Veritor® at CSTU). Prior to the 2016-17 season, patients were tested for RSV as per physician request. RSV tests were performed locally or occasionally sent to MUHC where specimens were tested by PCR. As part of the prospective evaluation for 2016-17, all <1-year-old infants admitted with a respiratory infection were systematically swabbed. Specimens were 1) tested for RSV at the local laboratories, and 2) aliquots were frozen and sent to the Public Health Laboratory of Quebec (Laboratoire de santé publique du Québec, LSPQ), in order to be tested using a multiplex PCR.

Each hospital laboratory provided a list of RSV rapid antigenic tests done locally between November 1, 2013 and June 30, 2017. Tests results were linked to a hospitalization using medical chart numbers and sample dates or sample numbers. The lists were also verified manually to prevent missing laboratory data because of entry errors or missing information in medical records.

Specimens collected prospectively were sent to LSPQ in June 2017 and tested in July 2017 by Luminex NxTAG Respiratory Pathogen Panel (RPP), which detects the following respiratory viruses: human RSV, influenza A (H1 and N3) and B, coronavirus (229E, OC43, NL63, HKU1); parainfluenza viruses 1, 2, 3, et 4; human metapneumovirus (hMPV), adenovirus, entero/rhinovirus (not differentiated), and bocavirus, as well as bacteria *M. pneumoniae, C. pneumoniae et L. pneumophila*.

2.2.4 PALIVIZUMAB PRESCRIPTION AND ADMINISTRATION

Palivizumab prescriptions during the three seasons before the implementation of the new recommendation were recorded by the regional hospitals pharmacists. Details of distributed doses per child were available for all 3 retrospective seasons in CSI; in CSTU the information was not available for the 2014-15 season.

For the 2016-17 season, a standardized palivizumab administration form containing the child's eligibility criteria, palivizumab prescription and administration dates was implemented in January 2017. Upon administration of each dose, the form was completed then faxed to the CSI or the CSTU pharmacy by the health professional in charge in each village. The two pharmacists provided to the project team this information in paper (CSI) or electronic (CSTU) formats in July 2017. Information contained on printed copies from CSI was entered in the electronic database by the project team in August-September 2017.

2.2.5 STATISTICAL ANALYSIS

RSV seasons were defined from November 1 to October 31 of the following year. For the 2016-17 season, data collected up to June 30 2017 were available for inclusion in this report. Results for the pre-intervention period (2013-14, 2014-15 and 2015-16 RSV seasons) were compared to those of the first season of implementation (2016-17 RSV season).

For infants with respiratory infections who had multiple (2 to 3) hospitalizations occurring within 14 days, all hospitalizations (tertiary hospitalizations included) were considered related to the same health event and merged into one single episode. RSV-associated hospitalizations were defined as hospitalization where the patient had at least one positive RSV test regardless of the laboratory test used. Rapid antigenic tests sensibility and specificity were calculated in comparison with PCR results in specimens where both tests have been performed (available for the 2016-17 season).

Palivizumab doses were considered administered only if there was a prescription date (for 2013-14 to 2015-16 RSV seasons) or an administration date (for 2016-17 RSV season) in the medical/pharmacy chart.

Proportions were compared using Chi-square or Fisher tests when appropriate; 95% confidence intervals (CI) around proportions were calculated with an exact binomial method. A p-value <0.05 was considered significant. Statistical analyses were performed using SAS 9. 4.

2.2.6 Ethics

This project is an evaluation of a public health intervention requested by Nunavik Regional Board of Health and Social services and the Ministry of Health of Quebec and did not require review by a research ethics committee.

The authorization to access the medical records and medical evacuation files of infants <1 year of age hospitalized with respiratory problems at the 2 regional hospitals, laboratory tests results, as well as palivizumab administration records for children of all ages, was granted to the evaluation team by the Directors of Professional Services of Inuulitsivik Health Centre and Ungava Tulattavik Health Center. The authorization to access the medical records of infants <1 year of age residing in Nunavik and hospitalised at the MUHC for respiratory infection was provided by the MUHC Director of Professional Services (Pediatrics).

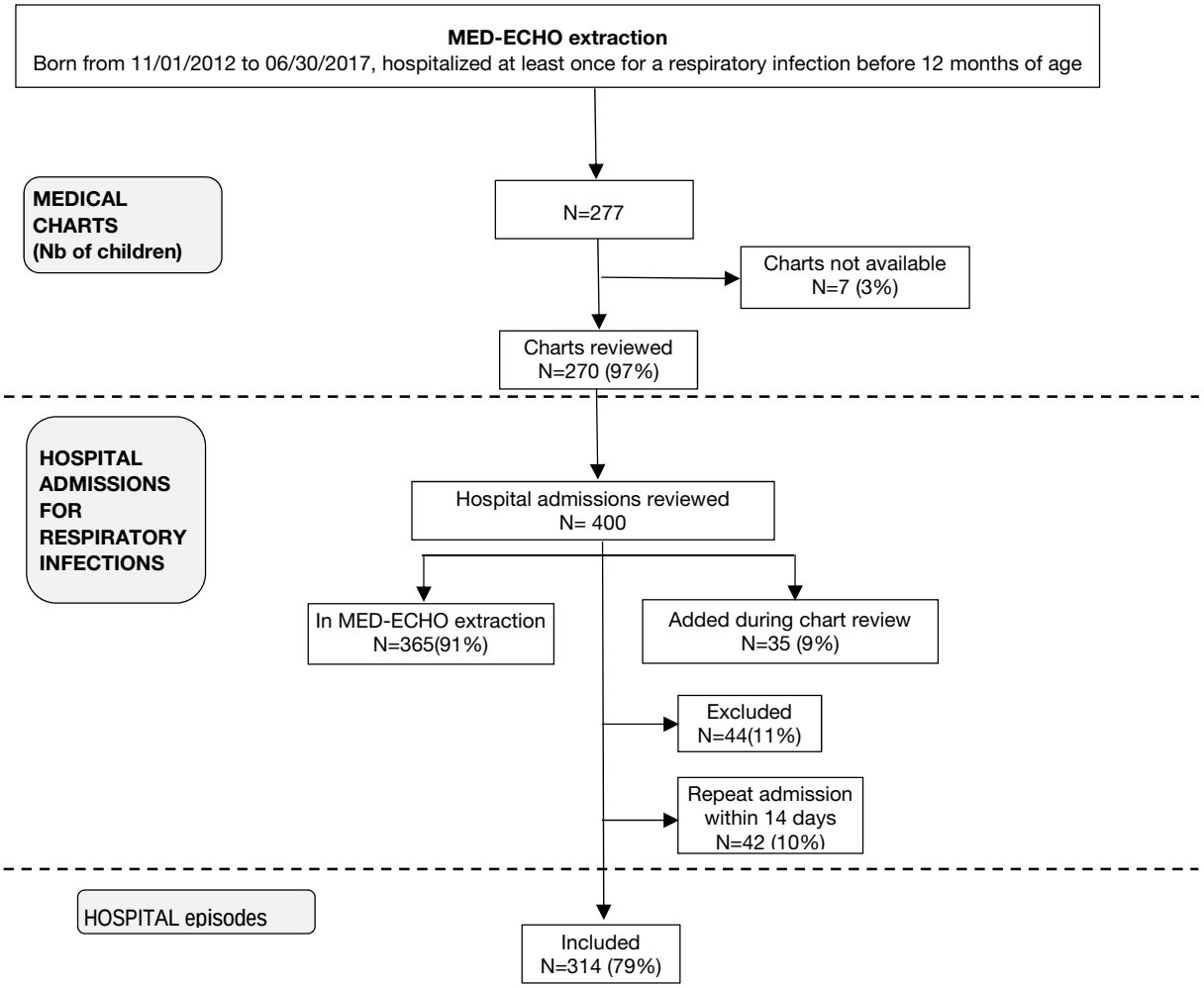
2.3 Results

2.3.1 Review of hospitalization records

Between November 1 2013 and June 30 2017, a total of 277 Nunavik children hospitalized for a respiratory infection before their first birthday were identified from MED-ECHO (Figure 1). The medical charts of 270 (97%) were available for review in July 2017. While MED-ECHO recorded 359 hospitalizations for respiratory infections, 35 additional hospitalizations were identified during the review process including 27 transfers from Nunavik to a tertiary hospital in Montreal or Quebec City, and 8 were not captured initially because of erroneous diagnostic codes entered in MEDECHO but found eligible during medical chart review. A total of 44 (11%) reviewed hospitalizations (35 (14%) at CSI and 9 (6%) at CSTU) were excluded because these children were admitted before November 1 2013 (respectively n=31 and n=4), were aged 12 months or older at admission (n=1 and n=0) or were admitted for a reason other than a respiratory infection (n=3 and n=5) (see Appendix C for more details by coast). A total of 42 (10%) hospitalizations (31 (12%) at CSI and 11 (7%) at CSTU) occurred within 14 days of the first hospital admission, including 27 (21 at CSI and 6 at CSTU) transfers to tertiary hospitals, and were considered related to the same health event.

The analysis included 314 (79% from the 400 reviewed) hospital episodes for respiratory infection (183 (73% from the 249) at CSI and 131 (87% from the 151) at CSTU) in Nunavik infants meeting the inclusion criteria.

Figure 1 Flow chart of hospital admissions included in the analysis

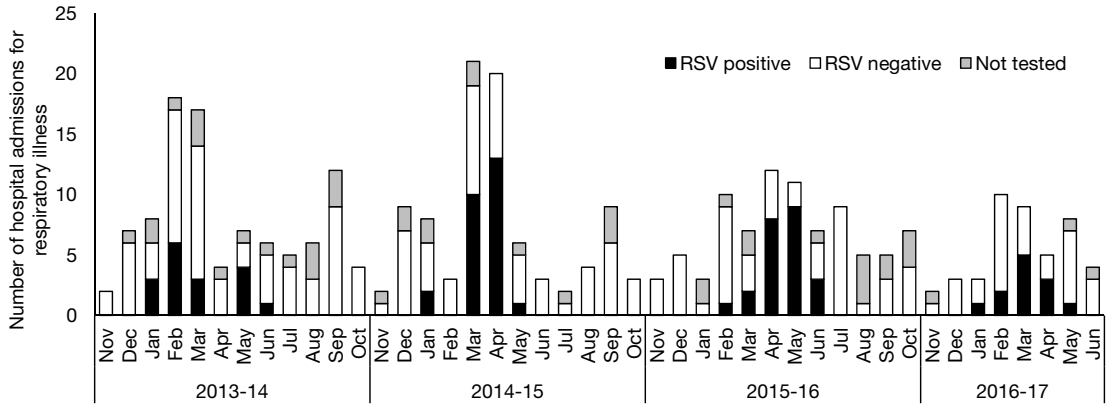


2.3.2 NUMBER OF RSV-ASSOCIATED HOSPITAL ADMISSIONS AND RSV SEASONALITY

During the study period

Between November 1 2012 and June 30 2017, a total of 1,752 children were born in Nunavik. Among them, 270 (15%) were hospitalized at least once for a respiratory infection before 12 months of age, during the study period, for a total of 314 hospitalizations and a rate of 179 per 1000 child-year (Figure 2). At least one RSV test was done for 85% (n=267) of hospitalizations; 78 (29%) of them were positive. All RSV-associated hospitalizations occurred between January and June during these 4 seasons (Figure 2).

Figure 2 Number of hospitalizations for respiratory infections in infants less than one year of age admitted between November 1 2013 and June 30 2017



For the retrospective period, the overall number of respiratory admissions from November to October was 96 in 2013-14, 90 in 2014-15, and 84 in 2015-16; respectively 18%, 29% and 27% of them were associated with RSV. Among those with an available laboratory test (88% from those admitted), the proportion of RSV positive was 22% in 2013-14, 33% in 2014-15 and 33% in 2015-16.

For the period between January and June of each season, the number of respiratory admissions varied from 50 to 61 for retrospective years compared to 39 in 2016-17 (Table 1); the number of RSV-confirmed admissions varied from 17 to 26 (average 22, for an annual incidence of 58.6/1000) for the retrospective period compared to 12 (incidence 32.0/1000) in 2016-17. The 2014-15 season was the season with the highest number of respiratory admissions (n=61), and of RSV-associated admissions (n=26). The number of respiratory admissions was lowest in 2015-16 (n=50) whereas RSV-associated admissions was lowest in 2013-14 (n=17).

Among the 0-2-month-olds, the number of yearly admissions for respiratory illness between January and June varied from 15 to 22 during the retrospective period compared to 15 in 2016-17; there was an average of 7.7 (range 4 to 10) RSV-associated admissions during the retrospective period (incidence 81.7/1000) compared to 4 (incidence 42.6/1000) in 2016-17. However, the reduction of RSV in 2016-17 was also seen in older age groups not targeted by the palivizumab.

Among the 3-5-month-olds, there was an average of 6 admissions for RSV-during the retrospective period compared to 2 in 2016-17 (incidence respectively 67.5/1000 and 21.3/1000) and for 6-11-month-olds there was an average of 8 RSV-admissions during retrospective seasons compared to 6 in 2016-17 (incidence respectively 42.6/1000 and 32.0/1000).

Table 1 **Number of respiratory admissions in <12-month-old infants residing in Nunavik for January to June 2013-14 to 2016-17**

January to June	RSV positive	RSV negative	Not tested	Overall respiratory admissions
		0-2 months*		
2013-14	4	8	3	15
2014-15	9	6	3	18
2015-16	10	9	3	22
2016-17	**4**	**11**	**0**	**15**
		3-5 months		
2013-14	5	14	1	20
2014-15	7	9	0	16
2015-16	7	7	1	15
2016-17	**2**	**4**	**0**	**6**
		6-11 months		
2013-14	8	12	5	25
2014-15	10	15	2	27
2015-16	6	5	2	13
2016-17	**6**	**10**	**2**	**18**
		Total < 12 months		
2013-14	17	34	9	60
2014-15	26	30	5	61
2015-16	23	21	6	50
2016-17	**12**	**25**	**2**	**39**

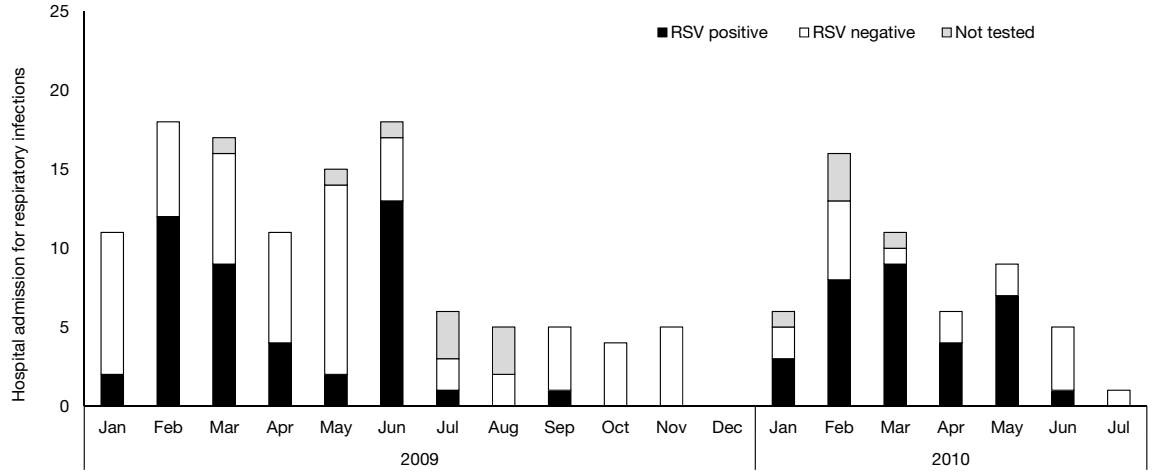
* Age group targeted by the new recommendations

Historical data

In 2009 and 2010, Nunavik participated in a prospective multicentre surveillance study where infants less than 1 year of age admitted for lower respiratory tract infection in all hospitals in the Northwest Territories, Nunavut and Nunavik, had nasopharyngeal aspirates tested by multiplex PCR(3,6). The principal investigator of this study, Anna Banerji, provided us data for Nunavik for historical comparison.

Between January 2009 and July 2010, all but two (3%) of the 74 RSV were detected between January and June (Figure 3). For both seasons, the number of RSV-associated hospital admissions from January to June was much higher overall and in all 3 examined age groups compared to the 4 seasons included in this evaluation (Table 2).

Figure 3 Number of RSV-associated hospital admissions in Nunavik infants less than one year of age admitted between January 1, 2009 and July 31, 2010*



Dr Johanne Morell from MUHC provided us information on tertiary transfers for Nunavik infants for the last 11 years (2005-06 to 2015-16). One additional transfer in a 0-2-month-old infant to CHUL (Centre hospitalier de l'Université Laval) in Quebec City occurred in 2015-16 and was not accounted for in MUHC data. During this period 51 infants had a RSV-associated tertiary transfer (annual range 2-10) for an average of 4.6 per year (Table 2). Two thirds (34/51) of transfers were for 0-2-month-old infants.

* Courtesy of Dr Anna Banerji

Table 2 Number of RSV-confirmed regional and tertiary admissions in Nunavik infants less than one year of age, January to June 2005-06 to 2016-17

January to June of each season	Regional admissions				Tertiary admissions			
	0-2 months	3-5 months	6-11 months	overall	0-2 months	3-5 months	6-11 months	overall
2005-06					4			4
2006-07					5		2	7
2007-08					1	1		2
2008-09	17	7	18	42	4			4
2009-10	11	8	13	32	3	4	3	10
2010-11					2		2	4
2011-12					1	2		3
2012-13					6	1		7
2013-14	4	5	8	17	1		2	3
2014-15	9	7	10	26	2			2
2015-16	10	7	6	23	5*			5
2016-17	**4**	**2**	**6**	**12**	**0**			**0**

* 4 transfers to MUHC, 1 transfer to CHUL not included in Dr Johanne Morel data

2016-17: new recommendations implemented

Dr Johanne Morel data (2005-06 to 2015-16)
Dr Anna Banerji data
Present evaluation

2.3.3 LABORATORY TESTING FOR RSV IN CHILDREN HOSPITALIZED FOR RESPIRATORY ILLNESS

With the systematic testing of all <12-month-old infants admitted with respiratory symptoms since January 1, 2017, 95% of infants were tested compared to 88% during the previous seasons (Table 3).

During the pre-intervention period, 87% of specimens were tested by an antigen detection test and 20% by PCR; both tests were done in 19%. Of the 7 hospitalizations with no PCR test results available in 2016-17, in four the specimens were not collected; three infants were admitted in June after the samples were sent to the LSPQ. These samples will be sent with the second year batch to be tested at LSPQ.

The proportion of RSV-positivity with at least one laboratory test for the period from January to June during pre-intervention was of 44% overall (with variations from 33% in 2013-14 to 52% in 2015-16); post-intervention it was 32%. Proportion of antigen detection test positivity was 41% in pre-intervention and 19% in post-intervention implementation; proportion of PCR positivity was 37% in pre-intervention and 38% in post-intervention implementation.

Using results from 32 children tested in 2016-17 with both antigen detection tests performed locally and PCR tests performed at LSPQ, the sensitivity of the RSV antigen detection tests was 58% (7/12, 95% CI 28%-85%) with a 100% specificity (20/20, 95% CI 83%-100%).

Table 3 Rapid antigen detection and PCR testing among infants younger than 12 months of age admitted for respiratory illness between January and June, 2013-14 to 2016-17

Laboratory tests	Pre-intervention				Intervention
	2013-14 N= 60	2014-15 N= 61	2015-16 N= 50	Overall N= 171	2016-17 N= 39
At least one test done (% among admissions)	51 (85%)	56 (92%)	44 (88%)	151 (88%)	37 (95%)
RSV+ [1]	**17 (33%)**	**26 (46%)**	**23 (52%)**	**66 (44%)**	**12 (32%)**
Antigen detection test (% among admissions)	50 (83%)	54 (89%)	44 (88%)	148 (87%)	37 (95%)
RSV+	**13 (26%)**	**25 (46%)**	**23 (52%)**	**61 (41%)**	**7 (19%)**
PCR (% among admissions)	24 (40%)	6 (10%)	5 (10%)	35 (20%)	32 (82%)
RSV+ [1]	**8 (33%)**	**2 (33%)**	**3 (60%)**	**13 (37%)**	**12 (38%)**
Antigen detection test and PCR (% among admissions)	23 (38%)	4 (7%)	5 (10%)	32 (19%)	32 (82%)
RSV+ by antigen detection test	**5 (22%)**	**1 (25%)**	**3 (60%)**	**9 (28%)**	**7 (22%)**
RSV+ by PCR	**7 (30%)**	**2 (50%)**	**3 (60%)**	**12 (38%)**	**12 (38%)**

[1] % among those with an available test

2.3.4 CHARACTERISTICS OF HOSPITALIZATIONS FOR RESPIRATORY INFECTIONS

Over the study period, among the 210 hospitalizations for respiratory infections that occurred between January and June, 208 (99%) were admissions to a regional hospital (17 patients subsequently transferred to tertiary hospitals). Only 2 (1%) were direct admissions to a tertiary hospital (one during the 2013-14 season and another during the 2014-2015 season) (Appendix D) and occurred because these children were already in Montreal for a follow-up of their medical condition when their health had deteriorated and they were hospitalized. No intensive care unit admission or intubation was reported in these 2 children; one RSV-positive 11-month-old infant who also had social problems was hospitalized for 15 days, another RSV-negative 1-month-old infant was hospitalized for 4 days. We cannot exclude the possibility that a transfer to Montreal would not have occurred if these infants were in their home villages when their respiratory illness started.

There were no significant differences in age distribution between the pre- and post-intervention period among hospitalized, RSV-positive, and RSV-negative infants (Table 4). The length of stay in regional hospitals was somewhat shorter (not significantly) in infants admitted with a confirmed RSV infection in 2016-17 than during pre-intervention period, in 0-2-months and 6-11-months. Length of stay was longer for tertiary hospitalisations compared to regional hospitalizations, both for RSV-negative and RSV-positive hospitalizations ($p<0.05$).

During the 3 pre-intervention seasons, 16 infants (5 to 6 per year) were transferred to a tertiary hospital with a respiratory condition; 9 of them (2 to 5 per year) had an RSV infection confirmed. No transfer for RSV occurred in 2016-17; there was one transfer for a confirmed rhinovirus infection in a 3-month-old infant (Table 4, Appendix D). Infants younger than 3 months represented 67% (12/18) of overall transfers and 80% (8/10) of RSV-associated transfers during pre-intervention period.

Table 4 Number of hospitalizations, RSV tests, and length of stay at regional and tertiary hospitals among infants younger than 12 months of age hospitalized for respiratory illness between January and June

	Regional hospitalizations		Tertiary Hospitalizations	
	pre-intervention	intervention	pre-intervention	intervention
	2013-14 to 2015-16	2016-17	2013-14 to 2015-16	2016-17
Hospitalized	169	39	18	1
0-2 months	54 (32%)	15 (38%)	12 (67%)	0 (0%)
3-5 months	51 (30%)	6 (15%)	4 (22%)	1 (100%)
6-11 months	64 (38%)	18 (46%)	2 (11%)	0 (0%)
Tested for RSV	149	37	18	1
0-2 months	45 (30%)	15 (41%)	12 (67%)	0 (0%)
3-5 months	49 (33%)	6 (16%)	4 (22%)	1 (100%)
6-11 months	55 (37%)	16 (43%)	2 (11%)	0 (0%)
RSV positive	65	12	10	0 (0%)
0-2 months	23 (35%)	4 (33%)	8 (80%)	0 (0%)
3-5 months	19 (29%)	2 (17%)	0 (0%)	0 (0%)
6-11 months	23 (35%)	6 (50%)	2 (20%)	0 (0%)
Length of stay, median/mean [range]	3/3.62 [0.5-10][1]	2/2.83 [1-5]	12.5/11.9 [2-25]	NA
0-2 months	3/3.09 [0.5-8][1]	2.5/2.75 [1-5]	12.5/12.5 [2-25]	NA
3-5 months	3/3.5 [0.5-7]	3/3 [2-4]	0/0 [0-0]	9/9
6-11 months	4/4.26 [1-10]	2/2.83 [2-5]	9.5/9.5 [4-15]	NA
RSV negative	84	25	8	1*
0-2 months	22 (26%)	11 (44%)	4 (50%)	0 (0%)
3-5 months	30 (36%)	4 (16%)	4 (50%)	1 (100%)
6-11 months	32 (38%)	10 (40%)	0 (0%)	0 (0%)
Length of stay, median/mean [range]	2/2.92 [0.5-11][1]	2/2.62 [0.5-6]	7/8.13 [2-14]	NA
0-2 months	2/2.16 [0.5-5][1]	2/2.32 [0.5-4]	11/10.25 [5-14]	NA
3-5 months	3/3.33 [0.5-8]	2.5/2.25 [1-3]	4/6 [2-14]	9/9
6-11 months	2.5/3.06 [1-11]	2.5/3.1 [1-6]	0/0 [0-0]	NA

* Rhinovirus detected

[1] $P<0.05$ for comparison between regional and tertiary hospitalisations during the pre-intervention period

More than ¾ of RSV positive hospitalized infants had a diagnosis of bronchiolitis compared to half in those RSV-negative. Bronchiolitis was more frequent among RSV-positive hospitalizations than among RSV-negative hospitalizations, both during pre- and post-intervention implementation periods (Table 5). A diagnosis of pneumonia was confirmed radiographically in 1/3-1/2 of RSV-positive and RSV-negative infants. No significant differences between pre- and post-intervention periods for the diagnoses of bronchiolitis and pneumonia were detected.

In RSV positive patients younger than 12 months of age, a documented underlying condition was present in 18% during the pre-intervention seasons and 8% during the post-intervention period. The two most frequent underlying conditions were prematurity and heart disease. In RSV positive patients younger than 3 months of age, an underlying condition was documented in 22% (5/23) during the pre-intervention period and in 0% (0/4) during the post-intervention period. Prematurity was present in 13% (3/23) of them (two <33 weeks of gestation and one 33-36 weeks of gestation).

Table 5 Respiratory diagnoses and underlying conditions in infants younger than 12 months of age with at least one RSV test available hospitalized between January and June before and after the implementation of new recommendations

	RSV-positive		RSV-negative	
	Pre-intervention 2013-14 to 2015-16	Intervention 2016-17	Pre-intervention 2013-14 to 2015-16	Intervention 2016-17
Respiratory Diagnoses	**N=66**	**N=12**	**N=85**	**N=25**
Bronchiolitis	57 (86%)	9 (75%)	36 (42%)	14 (56%)
Pneumonia	26 (39%)	6 (50%)	43 (51%)	9 (36%)
Radiographically confirmed	15	2	22	5
Bronchiolitis and pneumonia	18 (27%)	3 (25%)	13 (15%)	3 (12%)
Other respiratory diagnoses[1]	1 (2%)	0 (0%)	19 (22%)	5 (20%)
Underlying conditions	12 (18%)	1 (8%)	24 (28%)	6 (25%)
Prematurity	8 (12%)	0 (0%)	14 (16%)	5 (20%)
<33 weeks of gestation	5 (8%)	0 (0%)	4 (5%)	3 (12%)
33-36weeks of gestation	3 (4%)	0 (0%)	10 (12%)	2 (8%)
Chronic Heart Diseases	4 (6%)	0 (0%)	11 (13%)	1 (4%)
Congenital airway anomalies	1 (2%)	1 (8%)	3 (4%)	0 (0%)
Other underlying conditions[2]	5 (8%)	0 (0%)	5 (6%)	2 (8%)

[1] For RSV-associated hospitalizations: cough and rhinorrhea (n=1). For RSV-negative hospitalizations: upper respiratory tract infection (n=15), Flu (n=4), bronchopneumonia (n=3), laryngitis (n=2)

[2] For RSV-associated hospitalizations: metabolic disease (n=1), birth weight <1500g (n=2), severe anemia (n=2). For other hospitalizations: intubated during the last 6 months (n=4), birth weight <1500g (n=2), Hirschsprung disease (n=1), History of multiple organ failure (n=2), Latent tuberculosis (n=1)

2.3.5 DETECTION OF OTHER RESPIRATORY VIRUSES

During the 2016-17 RSV season, 90 specimens from Nunavik infants with respiratory infections were sent to the LSPQ, including 32 hospitalized and 59 who received ambulatory care (Table 6). At least one respiratory virus was detected in most specimens (98%). RSV was detected in 39% (n=12) of hospitalized and 42% (n=25) of ambulatory patients. The majority of infants infected with RSV were also coinfected with another respiratory virus (8/12 hospitalized and 15/25 not hospitalized).

Other respiratory viruses without RSV were identified in more than half of infants (58% hospitalized and 56% not hospitalized). Some viruses (such as human metapneumovirus and parainfluenza virus) were detected as frequently as RSV. Overall, other respiratory viruses were 2 times more frequent than RSV (>80% compared to 39% and 42%). The number of respiratory viruses detected in a single sample varied from 1 to 5.

Table 6 Respiratory viruses detected in infants with respiratory illness between January and June 2017

Detected viruses	Hospitalized N=32	Not hospitalized N=59
At least one respiratory virus	**31 (98%)**	**58 (98%)**
RSV	**12 (39%)**	**25 (42%)**
RSV only	4 (15%)	10 (17%)
Co-infection with other viruses	8 (24%)	15 (25%)
Other respiratory viruses without RSV	**19 (58%)**	**33 (56%)**
Other respiratory viruses, with or without RSV*	27 (82%)	48 (81%)
Human metapneumovirus	10 (33%)	16 (27%)
Rhino/enterovirus	11 (36%)	19 (32%)
Parainfluenza virus	8 (24%)	16 (27%)
Adenovirus	9 (27%)	11 (19%)
Coronavirus	4 (12%)	7 (12%)
Influenza A	1 (3%)	4 (7%)
Bocavirus	1 (3%)	8 (14%)

* Not mutually exclusive, single or in coinfection

2.3.6 USE OF PALIVIZUMAB

Palivizumab prescription and adherence

Pre-intervention period

Palivizumab prescription records were available at both sites for the three pre-intervention seasons, except for the 2014-15 season at CSTU. There were 25 to 29 children per year at CSI and 13 to 20 per year at CSTU who received palivizumab during the pre-intervention period. The most frequent known indication was an underlying condition (29% to 81% depending on site and season). Between 5% and 40% of children had an unknown indication or were prescribed palivizumab outside eligibility criteria. Overall, approximately 10% of the birth cohort received palivizumab immunoprophylaxis during the pre-intervention period.

The majority of children prescribed palivizumab were aged less than 12 months (76% to 100% depending on site and seasons). Among those identified as eligible for palivizumab, a lower proportion was reached during the 2015-16 season than during the two prior seasons (Table 7). During pre-intervention seasons, as most were eligible for up to 6 doses, a majority of those prescribed palivizumab received between 4 and 6 doses. A significant proportion of infants missed at least one dose (43% to 88%), explained by a delayed first dose (11% to 53%) or a late subsequent dose (0% to 71%).

Intervention period

Based on palivizumab administration forms, birth lists and hospital charts, 100 infants at CSI and 79 at CSTU (almost half of the annual birth cohort) were eligible to receive palivizumab at least once during the 2016-17 season (Table 7). Of these, the majority (74% at CSI and 89 % at CSTU) were term infants younger than 3 months at the start of the RSV season or born during the RSV season (e.i. born between October 1 2016 and April 30 2017) and eligible to palivizumab according to new recommendations. There was a significantly greater proportion of premature infants younger than 6 months of age or with an underlying condition at CSI (22%) than at CSTU (6%). One of the reasons for this difference could be the source of information: original palivizumab administration forms with complete information were available at CSI; while only an extraction from the original forms in an excel file where the information on underlying conditions was missing was available at CSTU. The proportion of children born between 33 and 36 weeks of gestation and who were <6 months at the start or during the 2016-17 RSV season is difficult to estimate at this point, but it is expected to be less than 5%.

Nearly all eligible children (97% at CSI and 92% at CSTU) received at least one dose, but about half missed some of the doses they were eligible to receive (table 7). The main reason of missed doses was the delayed administration of the first dose (36% at CSI and 35% at CSTU) or the administration of at least one subsequent dose more than 45 days after the previous one (20% at CSI and 13% at CSTU). This resulted in postponing the due date of the last dose outside the eligibility period (>3 months of age or April 30, 2017) and fewer administered than scheduled doses.

Table 7 Palivizumab indications, prescription and number of doses administered at CSI and CSTU, 2013-14 to 2016-17 RSV seasons

	Pre-intervention period					Post-intervention period	
	2013-14		2014-15	2015-16		2016-17	
	CSI	CSTU	CSI*	CSI	CSTU	CSI	CSTU
Eligible to palivizumab[1]	**25**	**20**	**28**	**29**	**13**	**100**	**79**
Premature and <6 months of age	3 (14%)	1 (7%)	1 (5%)	5 (29%)	(0%)	8 (8%)	2 (3%)
Underlying conditions	17 (81%)	10 (71%)	15 (71%)	5 (29%)	4 (57%)	14 (14%)	2 (3%)
Born at term between October 1 2016 and April 30 2017	NA	NA	NA	NA	NA	74 (74%)	70 (89%)
Unknown/Outside eligibility criteria for the season	1 (5%)	3 (21%)	5 (24%)	7 (41%)	3 (43%)	4 (4%)	5 (6%)
Prescribed Palivizumab	**21 (84%)**	**14 (70%)**	**21 (75%)**	**17 (59%)**	**7 (54%)**	**97 (97%)**	**73 (92%)**
<12 months at first dose	17 (81%)	13 (93%)	16 (76%)	17 (100%)	7 (100%)	95 (98%)	73 (100%)
≥12 months at first dose	4 (19%)	1 (7%)	5 (24%)	(0%)	(0%)	2 (2%)	(0%)
Received palivizumab	**21 (84%)**	**14 (70%)**	**21 (75%)**	**17 (59%)**	**7 (54%)**	**97 (97%)**	**73 (92%)**
1 dose	0 (0%)	0 (0%)	2 (10%)	2 (12%)	1 (14%)	25 (26%)	34 (47%)
2-3 doses	2 (10%)	6 (43%)	3 (14%)	6 (35%)	2 (29%)	63 (65%)	36 (49%)
4-6 doses	19 (90%)	8 (57%)	16 (76%)	9 (53%)	4 (57%)	9 (9%)	3 (4%)
At least one dose missing compared to scheduled doses	**14 (67%)**	**9 (64%)**	**11 (52%)**	**15 (88%)**	**3 (43%)**	**44 (47%)**	**40 (55%)**
First dose delayed[2]	7 (50%)	1 (11%)	5 (45%)	8 (53%)	1 (33%)	16 (36%)	14 (35%)
At least one subsequent dose delayed by >15 days	10 (71%)	3 (33%)	4 (36%)	5 (33%)	0 (0%)	9 (20%)	5 (13%)

[1] Information on eligibility may be missing for children with underlying conditions who did not receive palivizumab and were not hospitalized

[2] Defined as receiving the first dose after November 30 2016 for premature infants and children with underlying conditions and receiving it after January 15 2017 for infants born at term

* Information not available for CSTU

NA: Not applicable

Palivizumab use among infants with RSV-associated hospitalizations during the 2016-17 RSV season

During the 2016-17 season, 12 RSV-associated hospitalizations were identified: four 0-2-month-old infants (Table 8, cases # 1 to 4), two 3-5-month-olds (cases #5 and 6) and six 6-11-month-olds (cases # 7 to 12). Other respiratory viruses were detected in 67% (8/12) of infants, 75% (6/8) of them had at least two other respiratory viruses detected in addition to RSV. The most frequently detected viruses were adenovirus (n=5), human metapneumovirus (n=4) and rhino/enterovirus (n=3). Underlying conditions were detected in only one infant of 9 months (laryngomalacia and a birth weight <1500 g) who was not eligible for palivizumab because of age. Among the six patients aged less than 6 months at admission, all were eligible for palivizumab (when they were <3-month-old), 5 received palivizumab and 4 got all 3 doses.

0-2-month-old infants

Two 0-2-month-old infants (cases # 2 and 3) were hospitalized with a confirmed RSV infection despite three palivizumab doses as recommended and within 28 days of their last dose. One of them was coinfected with a rhino/enterovirus whereas the other was only infected with RSV.

Two other infants (cases # 1 and 4) with a confirmed RSV infection had received their last dose of palivizumab more than 28 days before hospitalization; another respiratory virus was detected in one of them. Case #1 received one dose 49 days before being hospitalized and would have been eligible to two more doses 28 and 56 days after the first dose. Case #4 was eligible to 1 dose early in January 2017 but it was not administered.

3-5-month-old infants

Cases #5 and #6 received 2 doses before 3 months of age as indicated and were hospitalized at 5 and 6 months of age, 50 and 76 days after their last dose respectively. However, since these two infants were also infected with other respiratory viruses, it is not possible to disentangle the independent role of RSV from that of other respiratory viruses in hospitalization.

6-11-month-old infants

Cases #7 to #12 were older than 6 months of age at admission with no underlying condition putting them at high risk for RSV infections, thus they were not eligible to palivizumab.

Table 8 Line listing of RSV-associated hospitalizations during the 2016-17 RSV season

Case #	Age in months at hospital admission	RSV detection		Detection of other respiratory viruses	Underlying conditions	Palivizumab		
		Antigenic test	Multiple x PCR			Eligible	Received	Delay between last dose and day of hospitalization
0-2-month-olds								
1	1	-	+	Metapneumovirus	No	3 doses	1 dose	49 days
2	2	-	+	Rhino/Enterovirus	No	3 doses	3 doses	24 days
3	2	+	+	No	No	3 doses	3 doses	4 days from last dose (33 days from previous dose)
4	2	+	+	Adenovirus + Parainfluenza	No	1 dose	No	NA
3-5-month-olds								
5	3	+	+	Adenovirus + Rhino/enterovirus	No	2 doses	2 doses	50 days
6	5	+	+	Coronavirus + Metapneumovirus	No	2 doses	2 doses	76 days
6-11-month-olds								
7	6	+	+	Adenovirus + Metapneumovirus	No	No	No	NA
8	7	+	+	Adenovirus + Rhino/enterovirus	No	No	No	NA
9	8	-	+	No	No	No	No	NA
10	8	-	+	No	No	No	No	NA
11	8	-	+	Adenovirus + Metapneumovirus	No	No	No	NA
12	9	+	+	No	Laryngomalacia, birth weight (<1.5 Kg)	No (>6months)	No	NA

NA: not applicable

3 Qualitative evaluation

3.1 Objectives

The main objective was to evaluate the impact of the new palivizumab recommendation on services organization and on perceptions and practices of Nunavik health workers during the first season of implementation.

The secondary objectives were:

- To describe the experience and difficulties faced by professionals during the implementation of the recommendation (feasibility)
- To describe their concerns regarding the recommendation (acceptability)
- To share the suggestions and requests expressed by health-care workers.

3.2 Methods

The experience, difficulties and concerns regarding the implementation of the new recommendation was evaluated by interviews with professionals working in Nunavik health services.

3.2.1 Respondents and recruitment

The CSI (Puvirnituq) and the CSTU (Kuujjuaq) provided the contact information of the professionals involved in the implementation of the new recommendation. Each respondent had to give oral consent before being interviewed. Different types of professionals (n=20) were contacted to provide diverse answers and a more global insight into the implementation experience. The respondents included physicians, pharmacists, various nurses, midwives, a coordinator, a family education worker, and laboratory professionals **(Table 9)**. Among the participants, three were Inuit and 17 were non-Inuit. They worked in Puvirnituq, Inukjuak, Salluit on the Hudson Bay, and in Kuujjuaq on the Ungava Bay.

Table 9 Distribution of participants by occupation

Occupation	Number of respondents
Physician (MD)	**2**
Pharmacist	**3**
Nurse*	**7**
Midwife	**4**
Coordinator	**1**
Family education worker	**1**
Laboratory professional	**2**
Total	**20**

* Nurses: Vaccination nurse, Child health nurse, Infection prevention and control nurse, Director of nursing and Public health nurse

3.2.2 DATA COLLECTION AND DATA ANALYSIS

The interview guide (**Appendix E**) investigated several issues related to the impact of implementing the new recommendation on professionals and their work. Topics included the overall experience, the RSV laboratory tests during the 2016-2017 RSV season, the palivizumab administering process before and after the new recommendation in the different villages (with or without a maternity unit), the opinions on the new recommendation and its implementation, and suggestions for improvement for the next season. The interview guide was slightly altered during the data collection process, as the wording and the order of pre-established questions varied according to participant interviews. The interviews were conducted in a flexible way to maintain an inductive approach: the main issues were used as a starting point to prompt discussion, to investigate participants' experience and opinions and to discuss other issues if needed.

Nineteen interviews were conducted in French (n=16) and in English (n=3) between July 17th 2017 and September 11th 2017, by a medical anthropologist. Seventeen face-to-face interviews were conducted in Nunavik (n=16) and in Quebec City (n=1), and two other interviews were conducted by phone or video conference according to participants' availabilities. All were one-on-one interviews except for one interview which was conducted with a group of two professionals. Interviews lasted between 15 minutes and 2 hours and 25 minutes. Seven of the interviews lasted less than 30 minutes, six lasted between 30 and 60 minutes and six lasted over an hour. Interviewees' anonymity was preserved; therefore the names of participants are not reported herein.

All interviews were recorded with participants' consent and were completely transcribed. The verbatim are transcribed in French or English, according to the language spoken during the interviews. A thematic content analysis was performed using the software N'Vivo 10. The thematic content analysis refers to a coding or classification method used to analyze the collected data. This methodology is used to highlight key features and their precise meaning, as well as create conceptual categories. Data codification was performed by the anthropologist of the research team.

For the thematic content analysis, the implementation of the new recommendation has been defined as a process divided into three phases: decision-making phase, organizational phase and implementational phase. The analysis of the implementation process is based here on the health-care workers' perceptions and perspectives in order to better understand the issues they had to face (*i.e.* misunderstandings) and their expectations. The decision-making phase is a pre-implementational phase where the INESSS played a major role alongside the MSSS (see above in Background). However, in general the interviewed health-care workers did not know the specific role of this organization at this stage of the implementation and that public health officials of Nunavik had to implement the new recommendation approved by the MSSS. That is why, according to the majority of the respondents, public health officials, Montreal and Quebec City experts and some physicians who work in Nunavik made the decision themselves and ordered them to implement the new recommendation. Following their perspectives in the analysis, the decision-making phase includes the experts and public health officials. The organizational phase represents the planning and preparation of the program implementation in the main health centres of Puvirnituq and Kuujjuaq. The third phase is the actual implementation of the program in the nursing centres of the 14 villages. The impact of the implementation of the new recommendation on the professionals and their work was analysed by taking into account the whole process while focusing on the organizational and implementational phases where the participants were more involved. The three phases of the process are used to better explain the professionals' experience and difficulties, and their concerns.

3.2.3 ETHICAL CONSIDERATIONS

Participation was completely voluntary; and professionals provided verbal consent to participate. Their participation did not involve any risks, except a minimal risk of unintentional breach of confidentiality. However, we took all necessary precautions: the individual-related data and the interviewed recordings were processed confidentially; access to computers was limited to authorized personnel and protected by passwords. Data and interviewed recordings will be destroyed at the end of the evaluation.

3.3 Results: Perceptions, practices and changes following the implementation of the new recommendation

3.3.1 AN ADDITIONAL WORKLOAD

The new recommendation increased significantly the number of infants eligible to the palivizumab program. This has had an impact on the work organization of the health professionals working in the villages of the Hudson and Ungava Bay. According to the participants, this change represented an additional workload. Significant changes in organizational structure were required in order to involve more workers and redistribute the tasks among them.

The additional workload was greatest for those involved in the organizational and implementational phases (pharmacists, nurses). This additional workload was considered “acceptable” by laboratory professionals, midwives, interpreters, family education workers, and some nurses, especially among the respondents of the Hudson Bay. However it was considered “excessive” by the pharmacists on both coasts and the nurses (especially those working in two villages) involved in both the organizational and implementational phases. At least one worker resigned because of the stress caused by the additional workload related to the new program.

The reasons of the work overload depend on the activities conducted during each phase and on the global context of the new recommendation’s implementation: the Nunavik health context, the health services organization, the palivizumab context. Considering the numerous health problems and priorities in Nunavik and in North of Quebec in general(8–12) such as sexually transmitted infections (STI), tuberculosis, hypertension, obesity, mental health, food security, suicide, cancer, etc., health professionals are generally very busy, particularly during epidemics. The new recommendation was implemented during a very busy period (*i.e*. outbreaks of influenza and tuberculosis). Furthermore, in this region, the organizational context could contribute to the workload. The staff turnover in Nunavik health services is very significant (*i.e.* a large proportion of new staff, and the typical permanent work schedule of two months on, one month off) and communication problems often occur. This context is problematic for health programs such as the palivizumab prophylaxis which depend on key permanent professionals (vaccination nurses, child health and public health nurses, and pharmacists). Finally, some restrictions were due to the palivizumab program context itself and the conditions for implementing the new recommendation. More specifically participants on both coasts criticized the decision-makers for the short delay between the decision and the implementation of the new recommendation, the limited information provided about RSV and palivizumab, and the absence of additional resources (financial, human and material) to support the increased number of infants eligible to the program.

> *Cette année ça a été vraiment une tâche lourde, pénible qui demandait beaucoup de temps, parce qu’il a fallu inventer une façon de faire. Notre façon de faire des années passées n’était plus applicable, parce que trop compliquée pour le volume [d’enfants]*

> *qu'on avait. Ça aurait pris un temps fou. On a inventé un nouveau système. Puis dans ce nouveau système-là, il y a beaucoup plus d'intervenants qu'il y avait avant. Puis comme dans le Nord, il y a un taux de roulement de personnel incroyable. Ça, ça amène qu'il y a toujours quelqu'un qui est pas au courant de comment ça se fait, puis que l'information ne s'est pas transmise à cette personne-là. Fait que là, ça fait un grain de sable dans l'engrenage et puis tout le monde en souffre*. (Pharmacist)

> *J'ai rapidement vu que c'était beaucoup d'ouvrage. Parce que donner la vaccination oui, et donner l'injection, préparer c'est 5-10 minutes. Mais de joindre les parents, s'assurer qu'on donne à tous les enfants, faire la logistique de tout ça, les papiers, faxer les informations avec la pharmacie, ça peut m'enlever 15 à 20 minutes par rendez-vous que j'avais déjà d'autres choses à faire pour cet enfant-là puis qu'en même temps je donne le Synagis*. (Nurse)

In this context, health professionals of the CSI and the CSTU involved in the organizational phase had numerous meetings about the new recommendation (acceptability) and its implementation (feasibility). This took longer than expected due to the preparation of the implementation, the time required to obtain information and make promotional material.

The workers involved in the implementational phase had multiple tasks to undertake. First, they had to identify and contact the parents of children eligible to the program (including the children born in the fall of 2016). This activity was very challenging and time-consuming in the Inuit context with hunting and fishing seasons to consider, trips outside the village, with children name changes, and in a context where traditional adoption(13) and foster placements by the Nunavik Director of Youth Protection (DYP) are frequent. The Inuit interpreters and family education workers helped a lot in this task, working at the interface between the health services and the population. More precisely, they played a key role in facilitating contact and communication between the parents and the nurses (as they are key players in another health context(14)). Midwives provided the parents with the information on RSV and palivizumab and obtained their consent. Nurses were informed by the midwives about every new birth in order to prepare the administration of the first dose of palivizumab. A form was filled and sent to the pharmacy to facilitate the follow-up and the palivizumab order requests. After each dose the health professionals filled out the follow-up forms and sent them back to the pharmacy. Regarding the newborn follow-up, a new appointment is regularly scheduled with the parents and the child one month and two months after birth. The second and the third doses of palivizumab could be administered during these visits. Also, because palivizumab has to be administered by a nurse, in the villages with maternity services where natal care is performed by a midwife, an additional attendance of a nurse is required for the first dose (following birth) and the second dose (one month-visit).

3.3.2 A LACK OF INFORMATION & EXCHANGES ABOUT THE RISKS OF RSV & THE BENEFIT AND SAFETY OF PALIVIZUMAB

Even if palivizumab was administered to some infants in Nunavik before the 2016-2017 RSV season, only the few staff previously involved in the process (pharmacists, some permanent nurses) had information on this product. Despite the information provided at the beginning of the 2016-2017 RSV season, other permanent workers (nurses, midwives) involved more recently stated that they did not have enough relevant information to conduct their work properly. Some used the Internet to update their knowledge on RSV, the administration of palivizumab and the recommendation. Furthermore, many professionals would have liked to ask questions and share their concerns about the new recommendation with the decision-makers and the experts from Montreal and Quebec City. A midwife explained her request:

Do we want to have a discussion with Dr. X? We wanted to have a more complete discussion with public health, just to find out you know, just to explore issues that were not being taken into consideration.

More specifically, nurses and midwives have expressed the following concerns:

1) The safety of palivizumab (*i.e.* side effects later on in life),

2) A lack of evidence justifying the need for palivizumab for all newborns during the RSV season, and for babies older than two months who are supposed to be less vulnerable,

3) Social risks (i.e. tobacco consumption and smoke in the household, violence) and protection factors (i.e. breastfeeding) were not taken into account in the new recommendation,

4) The perception that full-term healthy Inuit babies were used as experimentation subjects because this program had never been implemented elsewhere. A nurse and a midwife shared their concerns:

   Donc le déroulement déjà là, c'est un paquet de professionnels qui se méfient du projet, qui se méfient de l'étude, […] on a l'impression que la population est cobaye. On fait des recherches sur le dos de la population puis nous autres on est des acteurs de ça. On est obligé de faire partie de toute cette magouille-là. (Nurse)

   And again, and in all of these studies and I expressed that they don't know what the effect would be on term kids. So in effect, if they're giving it to term babies, they're doing an experimentation on these babies. (Midwife)

5) The impact of the new recommendation (the time needed to perform the implementation) on the management of other health priorities (*i.e*. tuberculosis, sexually transmitted infections) and more vulnerable people,

6) The lack of information given to the Inuit parents. According to the midwives and some nurses who delivered the information to the parents, the pamphlet and the consent form did not provide complete information and should be improved. Furthermore, it seems that in the Inuit culture, information is in general better understood orally, in their mother tongue, the Inuktitut. However, the information was not systematically given in Inuktitut and could have caused misunderstanding among the parents.

3.3.3 ETHICAL ISSUE

An ethical issue arises from the lack of information and consent in Inuktitut and the confusion expressed by some parents. According to the data collected from the health-care workers in closer contact with the population, some parents did not make an informed and free decision. As an example, some parents did not understand why they had to come back with their infant for a second or a third injection. Nor they understood the pain felt by their crying newborn, or the way he was breathing after each injection. Some of the interviewed participants felt that the misunderstanding could have led to a feeling of mistrust of health-care workers and that some parents signed the consent with confusion and distrust. More specifically, there were concerns regarding the freedom of parents to refuse palivizumab prophylaxis for their babies. According to the respondents, misunderstandings occurred among parents in various villages on both coasts. Some of them feared of being judged as bad parents if they refused the palivizumab for their child. Some parents would

have accepted palivizumab administration because they were afraid that the DYP would pressure them and put them in trouble. According to the nurses and midwives, that is one of the main reasons why few parents refused palivizumab. In this context, the parents feeling under pressure did not make a free decision. That is why the provided information needs to be more comprehensible and complete for Inuit parents to allow them to make an informed and a free choice.

> *C'est quand même rare là qu'ils refusent ou ben ils vont dire qu'ils ont l'air réticent, puis là on leur explique, puis là ils comprennent, puis ils acceptent là. Mais pas beaucoup de réticence*. (Nurse)

> *J'ai vu de la confusion avec les vaccins, la vaccination régulière, puis l'injection du Synagis. […] Ça se pouvait très bien que j'appelle pour la vaccination régulière, puis que l'enfant ait reçu une injection du Synagis il y a trois semaines. Le parent me disait : « Ben pas besoin, pas besoin de venir, il vient de recevoir son vaccin »… Je ne suis pas sûre que l'ensemble de la population a compris que c'était une immunité passive, que ce n'est pas un vaccin, puis que surtout qu'ils ont le choix de dire oui ou non. […] La population ne se sent pas confortable de refuser, a peur d'être jugée.* (Nurse)

> *La méfiance, c'est quand tu donnes l'enseignement puis là tu fais signer le consentement. Puis il n'est pas trop sûr de comprendre, puis il signe ça. Il te regarde, puis là tu injectes quatre injections à son enfant puis il te regarde. Mais là je veux dire ayoye là : « Qu'est-ce que tu lui as fait à mon enfant là? Il pleure, il braille pendant deux minutes. Je ne l'ai jamais entendu brailler de même! ». Parce que ça semble assez douloureux. Je veux dire je pense qu'il y a un impact important sur la clientèle c'est la douleur.* (Nurse)

> *Quand les médecins venaient dans le bureau, puis que moi j'essayais de ne pas montrer que je trouvais plus ou moins pertinent que l'enfant de deux mois toute potelée, bien en santé elle était d'une famille fonctionnelle reçoive… [le Synagis]. Ben je le proposais pareil, mais quand le médecin arrivait : « Ben non, il faut donner ça, voyons donc on a… ». Puis tsé je veux dire, c'est nettement imposé*. (Nurse)

> *Parents complaining, like sometimes they say: "What if I refuse and then the DYP comes to my place and says: "Your child needs a vaccine and whatever"?"* (Midwife)

> *And when these parents say that they are afraid because the DYP will go after them, it is not ok*. (Midwife)

3.3.4 COMMUNICATION PROBLEMS

During the decision-making phase, communication between public health officials, experts from Montreal and Quebec City, and some physicians working in Nunavik was not always smooth. Furthermore, physicians, nurses and midwives resented the fact that the Inuit population was not at all included in the decision-making phase and could not contribute to discussions. They wanted the Inuit population to be included in the consultation regarding the program. As a physician emphasized:

> *Ce que je déplore, bien ce que j'aimerais plus voir moi c'est de l'implication justement au niveau Inuit dans ce genre de concertation-là. Parce qu'à part les pédiatres de McGill, la Santé publique et puis nous, j'aurais aimé ça voir plus […] j'aurais aimé ça qu'il y ait plus d'Inuit impliqués.*

Moreover, workers involved in the organizational and implementational phases highlighted communication problems with the decision-makers: the lack of clarity of some instructions at the beginning of the implementation (*i.e.* on the RSV testing in one village), and the lack of clarity of the arrangements used to communicate RSV and palivizumab information to the Inuit population. There were also communication problems between health professionals during the organizational and implementational phases. As an example, some follow-up forms were not sent to the pharmacy or were not sent on time because of problems with the fax machine or forgotten. Omissions can be explained by the global context of workload and important staff turnover in Nunavik which significantly complicated the work for several reasons. Instructions were not always properly shared among health professionals, misunderstandings occurred, some readjustments were needed, and these impacted the workload for key permanent workers. Finally, nurses had problems reaching and scheduling appointments with parents without telephone at home. In this situation, they generally asked Inuit interpreters or family education workers for assistance. They could also send a reminder letter by mail (in some villages) or go directly to the parents' home.

3.3.5 PRACTICAL PROBLEMS

Some practical problems and inconveniences occurred during the implementation of the new recommendation: palivizumab shortage during two weeks in the Ungava Bay, cold chain issues, faxing problems. The time necessary to mix the palivizumab powder and solvent at the beginning (+/- 20 minutes) caused the impatience of some parents. This problem was solved when nurses were provided with pre-mixed vials which were much appreciated. Most of these problems have been resolved over time.

3.4 Suggestions and requests from participants to improve the acceptability and the feasibility of the program

According to the respondents, the implementation of the program could be improved by the following suggestions.

1) The organization of the palivizumab program could be improved by:

- Providing the recommendations for the program well in advance to facilitate the local organization,
- Providing supplementary resources (human, financial, material) during the program, according to the organization of each coast and the local needs,
- Involving directly the Inuit population in the palivizumab program (including in the decision-making phase): leaders, hospital workers, parents,
- Considering the possibility of matching the RSV prevention campaign with the palivizumab program which could be an interesting strategy, as it could facilitate the program implementation,
- Maintaining or putting into practice some steps by hospital professionals themselves (if it is not implemented yet), such as internal reorganization and task distribution among professionals, collective prescription of laboratory test ordering, involvement of interpreters and family education workers to support nurses and contact parents.

2) **Communication (including the transmission of information) should be improved between decision-makers, hospital workers, and the Inuit population.** Some suggestions are more about the Inuit population:

- Inuit parents should be provided easily understandable and complete information on RSV and palivizumab via radio or social networks (*i.e*. Facebook). The information could be given in the late prenatal period so that the parents would have time to reflect,
- Inuit parents and the Inuit population should be consulted to share their opinions on the palivizumab program and bring another perspective to improve the implementation of the new recommendation.

Other suggestions are more about the communication with the health-care workers involved in the program:

- Providing more information on RSV and palivizumab to the health-care workers, including Inuit workers (midwives, family education workers, wellness workers, interpreters) in order for them to be able to answer parents' questions,
- Providing a course on informed choice and consent and how to present information in a neutral fashion,
- Explaining the reasons justifying the necessity of the program compared to other health priorities in Nunavik,
- Discussing the social risk (i.e. violence, drug consumption, smoking environment) and protection factors (i.e. breastfeeding) and the vulnerability of the newborns with health-care workers,
- Including laboratories in the communication (sampling),
- Emphasizing effective and high quality communication in order to avoid misunderstandings and the perception of a lack of transparency.

4 Discussion

This evaluation showed that the RSV season in Nunavik spanned essentially between January and June. There are substantial variations in the burden for RSV between seasons. The estimated average RSV-associated hospitalization rate in <12-month-old infants in Nunavik was 58.6/1000 for the 3 retrospective years. This is 3 times lower than the rate of 176/1000 reported in Nunavik in 2009 (3), and more in the range of rates reported for the same year in other Arctic regions (19.7/100 in Northeast Territories, 36.7 in Qikigtaaluk Region (Nunavut), and 91.2 in Kitikmeot Region (Nunavut))(3).

In the targeted by the new recommendation 0-2-month-old infants, the estimated average RSV-associated hospitalization rate was 81.7/1000 during the retrospective period and 42.6/1000 during the prospective period. While there were only 4 RSV-associated hospitalizations in the 0-2-month-olds in 2017 compared to an average of 7.7 during the three pre-intervention seasons, there were only 4 RSV-associated hospitalizations in 2013-14. Furthermore, RSV-associated hospitalizations were also less frequent in 2017 in age groups not targeted by the intervention (3-5 and 6-11-month-olds). While some residual protection may have been observed in 3-5-month-olds following the administration of palivizumab by the end of the second month of age, there is no expected benefit of the program in 6-11-month-olds. This comparison may underestimate the reduction of RSV-associated hospitalizations provided by palivizumab prophylaxis as most infants hospitalized with respiratory illness were tested for RSV with antigen detection test rather than PCR during the retrospective as compared to the prospective period when a more sensitive PCR test was used.

There was no RSV-associated tertiary transfer in 2017; however it is difficult to conclude if this was attributable to palivizumab as only 1 transfer was reported in the targeted age group during some previous years. This outcome is unlikely underestimated since all transferred patients are tested by PCR.

One of the surprising findings of this evaluation was the large number of other respiratory viruses occurring simultaneously with or without RSV; some of the viruses were as frequent as RSV and globally there were more other respiratory viruses than RSV detected both in hospitalized and not hospitalized children with respiratory infection. In fact, the majority (80%) of infants with RSV-associated hospitalization were also infected with up to 4 other respiratory viruses. It is virtually impossible to determine the independent role of the RSV in these hospitalizations, and consequently the proportion preventable by palivizumab. The small sample size prevents us at this point from performing stratified analyses which would help to clarify the role of single RSV infection vs mixed RSV infection. However, given similar distribution of mixed RSV and other respiratory viruses infections in hospitalized children and in children who consulted but were not hospitalized, it does not seem at this point that other viruses are indicators of greater severity.

One of the main challenges of this project is the small population which limits the capacity to demonstrate significant differences. A power calculation based on historical data estimated that seven years of follow-up of this population would be necessary to demonstrate a significant decrease in RSV-associated hospitalizations in the targeted age group if palivizumab prevented 70% of these hospitalizations. Given the lower RSV-associated hospitalization rates observed in the present evaluation, the number of years needed may be higher.

One of the limits associated to this project are the difficulty to trace the use of health-care resources by Nunavik infants because of adoptions, name changes, placement in foster families, delayed medical record opening, difficulties obtaining denominators for children eligible for palivizumab prophylaxis according to previous recommendations prior to implementation of standardized palivizumab forms, as well as the difficulty to access digital laboratory testing results. Also, the indications for a specific test request during the retrospective period are not known; test ordering practices may vary from year to year or according to the physician. Since the great majority of infants had been tested for RSV during the retrospective period, these variations are not expected to have an important impact on the interpretation of results.

Finally, since the proportion of children born between 33 and 36 weeks of gestation and who were <6 months at the start or during the 2016-17 RSV season is difficult to estimate at this point, we were not able to evaluate this component of the new recommendations. However, because the proportion of these children is expected to be low, and because some of them were already receiving palivizumab during the pre-intervention period as part of pre-approved indications outside eligibility criteria, we do not think that this change in the recommendation had an important impact on RSV-associated hospitalizations.

Although the final report of the INESSS(6) considered the recommendation to be feasible for the healthcare system and acceptable for the population, qualitative evaluation revealed significant issues both for feasibility and acceptability. Regarding feasibility, the healthcare system received no additional resources (financial, material and human) to implement the program. In the Nunavik context where resources are often limited, some nurses directly implicated in the administration of palivizumab became overburdened and/or had to decrease their involvement in existing programs. This shift of resources triggered serious concerns regarding the priority given to palivizumab over other activities for which the priority was obvious (e.g. control of sexually transmissible diseases, tuberculosis, etc). In terms of acceptability, some nurses and midwives were unsatisfied with the information they received or gathered. They wanted good evidence that full-term healthy Inuit babies included in the program are at high risk for RSV infection and the intervention is effective enough in this group to justify their inclusion in the program. They suspected that Inuit infants were used as experimentation subjects. Although 95% of targeted infants received at least one dose of palivizumab, there were problems of acceptability in the Inuit population. The qualitative evaluation drew the attention that the Inuit population and their leaders were not consulted and involved in the implementation process. It also showed that some nurses and midwives have concerns that the information given to Inuit parents was incomplete and/or misunderstood. According to these health-care workers, they also perceived that some parents felt under pressure and did not dare to refuse the palivizumab administration. This raises ethical concerns regarding the guarantee of a free and informed consent from parents. Unfortunately, the qualitative evaluation in the first season did not assess directly the perception and opinion of the Inuit population. This should be done in future seasons.

To facilitate the communication and the dissemination of information among all stakeholders, a meeting could be organized before each RSV season in order to provide up-to-date information, design a system of reminders (*i.e.* palivizumab administration process, swabs collection), invite Inuit leaders, answer professionals' and Inuit leaders' questions, and encourage the exchange of ideas. Documents and relevant discussions about RSV and palivizumab could be saved on the Intranet of the hospital for health-care workers. Some links could be added to provide more information to professionals.

The Inuit population consultation and involvement, the improvement of the communication and of the organization of the implementation are essential factors for the program to succeed. Information provided by the present evaluation such as quantification of the RSV burden and of the use of palivizumab, feasibility and acceptability of the new recommendations, may better equip health-care professionals in their interactions with the Inuit population. In addition to engaging Inuit leaders, hospital workers and parents in the palivizumab program at various stages, Inuit organizations, which work to improve health among their community (e.g. organization of Inuit women Saturviit), could be consulted and involved in the program as well. Furthermore, a member of the organization could be invited to talk to health-care workers about the perception of diseases in general, more specifically child diseases and respiratory illnesses in the Inuit culture to improve mutual understanding.

5 Conclusion

In conclusion, first year evaluation showed that following the adjusted implementation (3 doses instead of the 5 recommended), the majority of eligible infants were reached and half of them received all prescribed palivizumab doses. The number of RSV-associated hospitalizations was lower in 2017 than in most, but not all previous seasons, both in targeted and in older infants. An important proportion of RSV infections (80%) were associated with other respiratory viruses; RSV was identified in 1/3, while other respiratory viruses were identified in 2/3 of respiratory hospitalizations. Given the small population and the variability of RSV seasons, the results of the first year are not conclusive; a longer period of follow-up is necessary for a more precise evaluation of the impact and effectiveness of palivizumab in this population.

Qualitative evaluation revealed significant issues both for feasibility and acceptability. High quality communication and sharing information between decision-makers, health-care workers and parents, as well as the involvement of Inuit population at various stages of the implementation, and providing the resources adapted to the local needs are key factor for the success of palivizumab immunoprophylaxis program. In order to validate the concerns raised by the health-care workers, we recommend a direct assessment of the perception and opinion of the Inuit population regarding this program.

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Appendix A:

Quebec palivizumab eligibility criteria for the 2015-16 and the 2016-17 RSV seasons

Criteria for the 2015-2016 season

HÉMA-QUÉBEC
Produits sanguins
Cellules souches
Tissus humains

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Téléphone : 418 780-4362
Télécopieur : 418 780-2093

HQ-15-025

CIRCULAIRE

**INFORMATIONS SUR LA DISPONIBILITÉ DU SYNAGIS®
POUR LA SAISON 2015-2016**

Le 10 septembre 2015

AUX MÉDECINS SPÉCIALISTES EN NÉONATOLOGIE / PÉDIATRIE
AUX MÉDECINS MICROBIOLOGISTES INFECTIOLOGUES
AUX DIRECTEURS DES SERVICES PROFESSIONNELS (CLSC)

c. c. Aux directeurs des banques de sang
Aux chefs technologistes/Coordonnateurs des banques de sang
Aux pharmaciens des établissements

Madame,
Monsieur,

HÉMA-QUÉBEC continue d'offrir, pour la saison 2015-2016, le produit SYNAGIS® qui vise à prévenir les infections au virus respiratoire syncytial (VRS) chez les enfants. Le SYNAGIS® est destiné à la prophylaxie de ce type de virus chez les patients répondant aux critères d'utilisation suivants[1] :

1- les bébés nés à moins de 33 semaines de grossesse et âgés de moins de 6 mois au début de la saison du VRS;

2- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints d'une maladie pulmonaire chronique du nouveau-né (définie par le besoin d'oxygène à 36 semaines d'âge gestationnel) ou de dysplasie bronchopulmonaire (définie par un besoin d'oxygène à 28 jours de vie et jusqu'à au moins 36 semaines d'âge gestationnel) **et**

   ✓ qui ont eu besoin d'oxygène dans les 6 mois qui précèdent la saison du VRS;
   ou
   ✓ qui en ont besoin pendant la saison du VRS;

3- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints de fibrose kystique et qui présentent des symptômes respiratoires ou un retard staturo-pondéral significatifs;

4- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante en raison d'un trouble neuromusculaire;

[1] L'Institut national d'excellence en santé et en services sociaux (INESSS) revoit actuellement les critères d'utilisation. Les travaux ne pouvant se conclure en temps pour la saison 2015-2016 du VRS, le MSSS s'appuie notamment sur les travaux préliminaires du comité d'experts et sur les recommandations des sociétés canadienne et américaine de pédiatrie pour apporter les modifications aux critères précédemment émis par l'INESSS en 2009.

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Télécopieur : 418 780-2093

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5- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante, en raison d'anomalie congénitale des voies aériennes supérieures;

6- les enfants âgés de moins de 12 mois, au début de la saison du VRS, atteints de cardiopathie congénitale, de cardiomyopathie ou de myocardite qui entraîne des conséquences hémodynamiques cliniquement significatives ou souffrant d'hypertension artérielle pulmonaire modérée ou grave (la demande doit être soumise par un cardiologue pédiatrique pour garantir la justesse du diagnostic);

7- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, ayant subi une greffe de moelle osseuse, de cellules souches ou d'organe solide (cœur, foie ou poumon) dans les 6 mois qui précèdent la saison du VRS ou pendant la saison du VRS.

L'immunisation par le palivizumab est recommandée selon une administration aux 4 semaines, débutant à la mi-novembre. Un maximum de 5 doses doit être administré par saison, la dernière dose ne devant pas être administrée au-delà du mois de mars. Par conséquent, la distribution pour la nouvelle saison débutera à compter du 9 novembre 2015.

Finalement, notez que **la prophylaxie devra être cessée dans le cas où une infection à VRS a été confirmée chez l'enfant**. L'éventualité d'un deuxième épisode infectieux est rare, notamment grâce à l'immunité croisée existant entre les génotypes A et B du VRS.

Veuillez compléter le formulaire A pour toutes les demandes rencontrant les critères ci-haut mentionnés. Toutes les demandes ne rencontrant pas les critères ci-haut mentionnés doivent être complétées en utilisant le formulaire B. Toutes les demandes pour les indications non préapprouvées seront évaluées par un des deux médecins spécialistes en maladies infectieuses pédiatriques dont nous avons retenu les services. Une recommandation sera émise relativement à l'usage du SYNAGIS® chez ces patients. Si possible, veuillez faire parvenir vos demandes quelques jours avant l'administration prévue du SYNAGIS®.

Le Palivizumab (SYNAGIS®) est un médicament indiqué pour la prévention des infections sévères dues au VRS. Ce produit est homologué au Canada et est distribué par la Corporation AbbVie. Le SYNAGIS® est un anticorps monoclonal humanisé qui est administré par voie intramusculaire. Pour obtenir des renseignements médicaux ou scientifiques, communiquez avec le département de l'information médicale de la Corporation AbbVie au 1 888 704-8271.

Pour commander le SYNAGIS®, veuillez compléter le formulaire A ou B ci-joints et le faire parvenir par télécopieur (le numéro est indiqué sur les formulaires A et B) ou communiquez avec le Service à la clientèle de la Corporation AbbVie au 1 888 704-8270 ou au 514 906-9770.

Il sera également possible de placer des commandes en ligne à compter du 23 septembre 2015. Des formulaires électroniques seront disponibles sur le site Internet d'AbbVie www.rsvshield.ca, à la section Professionnels de la santé. Veuillez noter que l'accès à la section Professionnels de la santé sera protégé par mot de passe. Veuillez utiliser ce code d'inscription pour y accéder pour la première fois : **562485925**. Par la suite, vous devrez vous enregistrer pour utiliser ce site.

Veuillez noter que dans le but de simplifier le processus de gestion de la distribution du SYNAGIS®, il n'est plus nécessaire de signer et de retourner le bordereau d'envoi émis par la Corporation AbbVie à Héma-Québec. À la réception des produits, la signature du réceptionnaire servira de preuve de livraison.

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Tissus humains

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HQ-15-025

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De plus, nous aimerions porter à votre attention qu'il est **très important de s'assurer que le SYNAGIS® soit réfrigéré dès la réception du produit et conservé entre 2° et 8° celcius.** Il est aussi très important de signaler tout bris ou toute erreur de commande, dans un délai de 24 heures, au Service à la clientèle de la Corporation AbbVie au numéro ci-haut mentionné ainsi qu'à HÉMA-QUÉBEC au 514 832-5000 poste 5339.

Nous vous remercions de votre collaboration.

Original signé par

Dr. Gilles Delage
Vice-président aux affaires médicales en microbiologie

Jean Lapierre
Directeur des produits stables

Pièces jointes : Formulaire de demande A (Indications préapprouvées)
Formulaire de demande B (Indications non préapprouvées)
Annexe A (tableau des contacts et des coordonnées)

c. c. M. Serge Maltais, président et chef de la direction
M. Marco Décelles, vice-président et chef de l'exploitation
Dr Marc Germain, vice-président aux affaires médicales et directeur médical aux tissus humains
Dr André Lebrun, vice-président aux affaires médicales en hématologie

Criteria for the 2016-2017 season

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HQ-16-021

CIRCULAIRE

**INFORMATIONS SUR LA DISPONIBILITÉ DU SYNAGIS®
POUR LA SAISON 2016-2017**

Le 15 septembre 2016

AUX MÉDECINS SPÉCIALISTES EN NÉONATOLOGIE / PÉDIATRIE
AUX MÉDECINS MICROBIOLOGISTES INFECTIOLOGUES
AUX DIRECTEURS DES SERVICES PROFESSIONNELS (CLSC)

c. c. Aux directeurs des banques de sang
Aux chefs technologistes/Coordonnateurs des banques de sang
Aux pharmaciens des établissements

Madame, Monsieur,

HÉMA-QUÉBEC continue d'offrir, pour la saison 2016-2017, le produit SYNAGIS® qui vise à prévenir les infections au virus respiratoire syncytial (VRS) chez les enfants. Le SYNAGIS® est destiné à la prophylaxie de ce type de virus chez les patients répondant aux critères d'utilisation suivants[1] :

1- les bébés nés à moins de 33 semaines de grossesse et âgés de moins de 6 mois au moment du début de la saison du VRS;

2- les bébés nés à terme ou près du terme, âgés de moins de 24 mois au moment du début de la saison du VRS, atteints d'une maladie pulmonaire chronique du nouveau-né, définie par un besoin d'oxygénothérapie à la naissance ou qui a persisté en raison d'une atteinte pulmonaire chronique autre que celles désignées dans les autres critères;
OU
les bébés prématurés, âgés de moins de 24 mois au moment du début de la saison du VRS, atteints de dysplasie bronchopulmonaire, définie par un besoin d'oxygénothérapie peu après la naissance et qui persiste jusqu'à au moins 28 jours de vie et jusqu'à un âge gestationnel d'au moins 36 semaines, et ce, en présence d'antécédents caractéristiques de la maladie;
ET
qui ont eu besoin d'oxygénothérapie persistant dans les 6 mois qui précèdent le début de la saison du VRS ou qui en ont besoin pendant la saison du VRS;

3- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints de fibrose kystique et qui présentent des symptômes respiratoires ou un retard staturo-pondéral significatifs;

4- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante en raison d'un trouble neuromusculaire (le diagnostic doit être fourni sur la demande);

5- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante, en raison d'anomalie congénitale des voies aériennes supérieures (le diagnostic doit être fourni sur la demande);

[1] L'Institut national d'excellence en santé et en services sociaux (INESSS) a revu les critères d'utilisation et déposé son rapport final au Ministère de la Santé et des Services sociaux. Ce rapport est disponible sur le site Internet de l'INESSS (www.inesss.qc.ca/publications).

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6- les enfants âgés de moins de 12 mois au moment du début de la saison du VRS, atteints de cardiopathie congénitale, de cardiomyopathie ou de myocardite qui entraîne des conséquences hémodynamiques cliniquement significatives ou souffrant d'hypertension artérielle pulmonaire modérée ou grave (la demande doit être soumise par un cardiologue pédiatrique pour garantir la justesse du diagnostic);

7- les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, ayant subi une greffe de moelle osseuse, de cellules souches ou d'organe solide (cœur, foie ou poumon) dans les 6 mois qui précèdent la saison du VRS ou pendant la saison du VRS;

8- les enfants nés à 36 semaines de gestation ou moins et âgés de moins de 6 mois au moment du début de la saison du VRS ou nés pendant celle-ci, résidant au Nunavik;

9- les enfants nés à terme, âgés de moins de 3 mois au moment du début de la saison du VRS ou nés pendant celle-ci, résidant au Nunavik.

CRITÈRES NON ADMISSIBLES :

L'administration du palivizumab n'est pas indiquée pour :
- prévenir les infections nosocomiales par le VRS;
- les enfants âgés de 24 mois ou plus au moment du début de la saison du VRS.

AUTRES MODALITÉS D'ADMINISTRATION :

- Le palivizumab devrait être administré aux 4 semaines à raison d'un maximum de quatre (4) doses ou cinq (5) doses par saison, selon la date du début de la prophylaxie propre à l'enfant et celle de la fin de la saison du VRS. Le calendrier d'administration suivant doit être suivi :

	Calendrier d'administration du palivizumab au Québec	
Région	Tout le Québec (sauf Nunavik)	Nunavik
Saison du VRS	1e novembre au 31 mars	1e décembre au 30 avril
*Advenant une prolongation de la saison du VRS, une procédure sera mise en place pour en informer les cliniciens		

- L'administration du palivizumab devrait avoir lieu dans les 48 à 72 heures avant qu'un enfant admissible au palivizumab obtienne son congé de l'hôpital après la naissance;
- Une dose additionnelle au cours de la saison du VRS doit être donnée dans le cas des enfants soumis à un processus de circulation sanguine extracorporelle en raison d'une chirurgie cardiaque;
- La prophylaxie doit être cessée après qu'un enfant ait été hospitalisé en raison d'une infection des voies respiratoires par le VRS dont la présence a été confirmée par un test de dépistage;
- Aucune dose de palivizumab ne devrait être donnée après la date de la fin fixée (voir tableau ci-dessus), sauf dans les circonstances particulières suivantes* :
  - Si le VRS est toujours en plein activité au Nunavik, une dose devrait être administrée en mai aux enfants admissibles au palivizumab qui ont quitté l'hôpital au cours des mois de février à avril après leur naissance*.
  - Pour les autres régions du Québec, une dose devrait être administrée en avril à certains prématurés, si le VRS est toujours en pleine activité dans la collectivité. Il s'agit de ceux qui ont quitté l'hôpital au cours des mois de janvier à mars après leur naissance*.

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Veuillez compléter le formulaire A pour toutes les demandes rencontrant les critères ci-haut mentionnés. Toutes les demandes ne rencontrant pas les critères ci-haut mentionnés doivent être complétées en utilisant le formulaire B. Toutes les demandes pour les indications non préapprouvées seront évaluées par un des deux médecins spécialistes en maladies infectieuses pédiatriques dont nous avons retenu les services. Une recommandation sera émise relativement à l'usage du SYNAGIS® chez ces patients. Si possible, veuillez faire parvenir vos demandes quelques jours avant l'administration prévue du SYNAGIS®.

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Nous vous remercions de votre collaboration.

Original signé par

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Vice-président aux affaires médicales en microbiologie

Jean Lapierre
Directeur des produits stables

Pièces jointes : Formulaire de demande A (Indications préapprouvées)
Formulaire de demande B (Indications non préapprouvées)
Annexe A (tableau des contacts et des coordonnées)
Les versions électroniques des formulaires A et B sont disponibles à www.hema-quebec.qc.ca, à la section Sang/Professionnels de la santé/Circulaires d'information/HQ-16-021).

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Appendix B:

ICD-10 diagnostic codes extracted from the provincial administrative database MED-ECHO

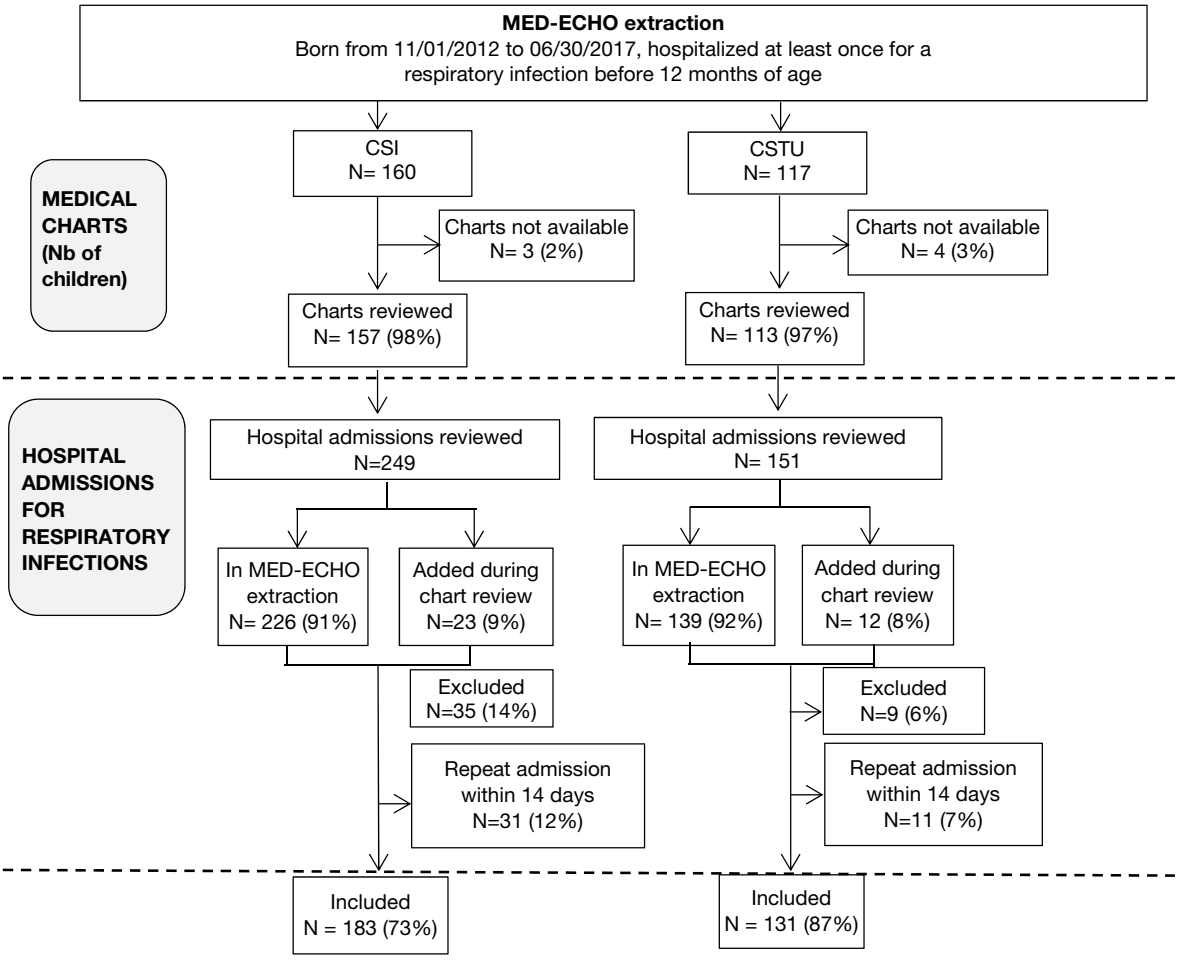
ICD-10 diagnostic codes extracted from the provincial administrative database MED-ECHO

Category	ICD code	Diagnosis
Acute upper respiratory infections	J00	Acute nasopharyngitis [common cold]
	J01	Acute sinusitis
	J02	Acute pharyngitis
	J03	Acute tonsillitis
	J04	Acute laryngitis and tracheitis
	J05	Acute obstructive laryngitis [croup] and epiglottitis
	J06	Acute upper respiratory infections of multiple and unspecified sites
Influenza and Pneumonia	J09	Influenza due to certain identified influenza viruses
	J10	Influenza due to other identified influenza virus
	J11	Influenza due to unidentified influenza virus
	J12	Viral pneumonia, not elsewhere classified
	J13	Pneumonia due to Streptococcus pneumoniae
	J14	Pneumonia due to Hemophilus influenzae
	J15	Bacterial pneumonia, not elsewhere classified
	J16	Pneumonia due to other infectious organisms, not elsewhere classified
	J17	Pneumonia in diseases classified elsewhere
	J18	Pneumonia, unspecified organism
Other acute lower respiratory infection	J20	Acute bronchitis
	J21	Acute bronchiolitis
	J22	Unspecified acute lower respiratory infection

Appendix C:

Details for flow chart of hospital admissions included in the analysis in the two Nunavik sub-regions

Details for flow chart of hospital admissions included in the analysis in the two Nunavik sub-regions



CSI: Inuulitsivik Health Centre (Centre de santé Inuulitsivik, CSI), Hudson Bay
CSTU: Tulattavik Health Centre (Centre de santé Tulattavik de l'Ungava, CSTU), Ungava Bay

Appendix D:

Regional and tertiary hospitalizations according to age at admission and RSV season

Regional and tertiary hospitalisations according to age at admission and RSV season

	Regional hospitalizations				Tertiary hospitalizations			
	2013-14	**2014-15**	**2015-16**	**2016-17**	**2013-14**	**2014-15**	**2015-16**	**2016-17**
Hospitalized	N = 59	N = 60	N = 50	N = 39	N = 6*	N = 5	N = 7*	N = 1
<3 months	15 (25%)	17 (28%)	22 (44%)	15 (38%)	2 (33%)	3 (60%)	7 (100%)	0 (0 %)
3-5 months	20 (34%)	16 (27%)	15 (30%)	6 (15%)	2 (33%)	2 (40%)	0 (0%)	1(100%)
6-11 months	24 (41%)	27 (45%)	13 (26%)	18 (46%)	2 (33%)	0 (0%)	0 (0%)	0 (0%)
Tested for RSV	50	55	44	37	6	5	7	1
<3 months	12 (24%)	14 (25%)	19 (43%)	15 (41%)	2 (33%)	3 (60%)	7 (100%)	0 (0%)
3-5 months	19 (38%)	16 (29%)	14 (32%)	6 (16%)	2 (33%)	2 (40%)	0 (0%)	1(100%)
6-11 months	19 (38%)	25 (45%)	11 (25%)	16 (43%)	2 (33%)	0 (0%)	0 (0%)	0 (0%)
RSV positive	16	26	23	12	3*	2	5	0 (0%)
<3 months	4 (25%)	9 (35%)	10 (43%)	4 (33%)	1 (33%)	2 (100%)	5 (100%)	0 (0%)
3-5 months	5 (31%)	7 (27%)	7 (30%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6-11 months	7 (44%)	10 (38%)	6 (26%)	6 (50%)	2* (67%)	0 (0%)	0 (0%)	0 (0%)
Length of stay *[median-mean (range)]*	3.5/4 [1-8]	4/4 [0.5-8]	3/2.93 [0.5-10]	2/2.83 [1-5]	10/9.67 [4-15]	13.5/13.5 [2-25]	15/12.6 [6-18]	NA
<3 months	5/5 [2-8]	3/2.89 [0.5-8]	2/2.5 [1-6]	2.5/2.75 [1-5]	10/10 [10-10]	13.5/13.5 [2-25]	15/12.6 [6-18]	NA
3-5 months	3/3.4 [2-5]	5/4.57 [2-7]	3/2.5 [0.5-6]	3/3 [2-4]	0/0 [0-0]	0/0 [0-0]	0/0 [0-0]	9/9
6-11 months	3/3.86 [1-7]	5/4.6 [2-8]	3.5/4.17 [1-10]	2/2.83 [2-5]	9.5/9.5 [4-15]	0/0 [0-0]	0/0 [0-0]	NA
RSV negative	34	29	21	25	3	3	2*	1**
<3 months	8 (24%)	5 (17%)	9 (43%)	11 (44%)	1 (33%)	1 (33%)	2* (100%)	0 (0%)
3-5 months	14 (41%)	9 (31%)	7 (33%)	4 (16%)	2 (67%)	2 (67%)	0 (0%)	1 (100%)
6-11 months	12 (35%)	15 (52%)	5 (24%)	10 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Length of stay *[median-mean (range)]*	2/3.1 [0.5-11]	3/2.93 [0.5-11]	2/2.62 [0.5-6]	2/2.62 [0.5-6]	8/9.33 [6-14]	2/3 [2-5]	14/14 [14-14]	NA
<3 months	2/2.06 [0.5-5]	3/2.6 [1-3]	2/2 [0.5-4]	2/2.32 [0.5-4]	8/8 [8-8]	5/5 [5-5]	14/14 [14-14]	NA
3-5 months	3/3.5 [1-8]	3/3.11 [0.5-6]	3/3.29 [2-6]	2.5/2.25 [1-3]	10/10 [6-14]	2/2 [2-2]	0/0 [0-0]	9/9
6-11 months	3/3.33 [1-11]	2/2.93 [1-11]	3/2.8 [1-5]	2.5/3.1 [1-6]	0/0 [0-0]	0/0 [0-0]	0/0 [0-0]	NA

* No transfer occurred, the infant was already in Montreal at the moment of hospitalization

** A rhinovirus was detected

Appendix E:

Qualitative analysis: interview guide

French

Guide d'entrevue – Évaluation qualitative

Professionnels de la santé et de laboratoire (infirmières, pharmaciens, médecins, sages-femmes, assistant-chef de laboratoire)
Puvirnituq – Salluit – Kuujjuaq

Présentation

1. Pourriez-vous vous présenter et rendre compte de votre parcours professionnel?
2. Quelles sont les différentes tâches, activités que vous êtes amené(e) à faire dans le cadre de votre travail?

Administration du Synagis

3. Depuis quand êtes-vous impliqué(e) dans le projet d'administration du Synagis? De quelle manière y êtes-vous impliqué(e)? Quel est votre rôle? Quelles sont les tâches que vous devez faire dans ce projet? Pourriez-vous décrire précisément votre travail par rapport au Synagis? Et comment vous êtes amené(e) à travailler avec vos collaborateurs?

Prélèvements

4. Dans quelle mesure êtes-vous impliqué(e) dans les demandes de prélèvements pour les analyses de laboratoire? Merci de préciser.

Procédure avant/depuis la dernière recommandation

5. Comment se déroulait la procédure (administration/prélèvements) avant la dernière recommandation de l'INESSS? À Puvirnituq ou Kuujjuaq et dans les autres villages?
6. Comment cela se passe-t-il pour vous depuis la mise en application de la dernière recommandation? Et pour vos collaborateurs? À Puvirnituq ou Kuujjuaq et dans les autres villages?
7. Comment cela se passe-t-il avec les parents des nouveau-nés? Comment a-t-on l'information de la naissance d'un enfant?
8. Disposez-vous d'un outil permettant de faire le suivi des doses administrées aux enfants? (doc papier, informatisé…)
9. Que fait-on des produits qui n'ont pas été administrés? Dans quelle mesure l'information est transmise en cas de non administration? Disposez-vous d'un système permettant de faire un rappel pour l'administration des doses suivantes?
10. Auriez-vous rencontré des difficultés dans votre travail suite à la dernière recommandation? Si oui, lesquelles (communication avec les parents; confusion et saturation des parents par rapport aux traitements; roulement de personnel; surcharge de travail; refus d'utilisation d'outils mis à disposition…)? Merci de préciser.

Propositions d'amélioration

11. Suite aux difficultés rencontrées, auriez-vous des suggestions d'améliorations que vous aimeriez partager? Merci de préciser.

English
Interview guide
Synagis – VRS – Nunavik

Health professionals and laboratory personnel (nurses, pharmacists, physicians, midwives, laboratory chief assistant) Puvirnituq – Salluit – Kuujjuaq

Presentation

1. Could you introduce yourself as well as your work experience?
2. What are the different tasks and activities that you are required to do in your current position?

Synagis administration

3. Since when have you been involved in the Synagis administration project? How are you involved? What is your role? What are the tasks that you are required to do for this project? Could you describe your work regarding Synagis in more detail? How do you work with your collaborators?

Sampling

4. How are you involved in collecting sample requests for laboratory analysis? Please specify.

Procedure before/since the last recommendation

5. How was the procedure (administration/sampling) before the last INESSS recommendation? In Puvirnituq or Kuujjuaq and in other villages?
6. Since the implementation of the last recommendation, how have things been for you? And for your collaborators? At Puvirnituq or Kuujjuaq and in other villages?
7. How are things handled with the parents of the newborns? How do we obtain information on when a child is born?
8. Do you have a tool to track the doses administered to children (paper document, computer software…)?
9. What happens to the products that aren't administered? To what extent is information communicated in the case of non-administration? Do you have a system reminding you to administer future doses?
10. Have you encountered any difficulties in your work since the last recommendation? If so, what are these difficulties (*i.e*. communicating with parents; confusion and parent saturation regarding treatments; staff turnover; work overload; refusing to use available tools)? Please specify.

Suggestions for improvement

11. Seeing as you have encountered certain difficulties, do you have any suggestions for improvement that you would like to share? Please specify.