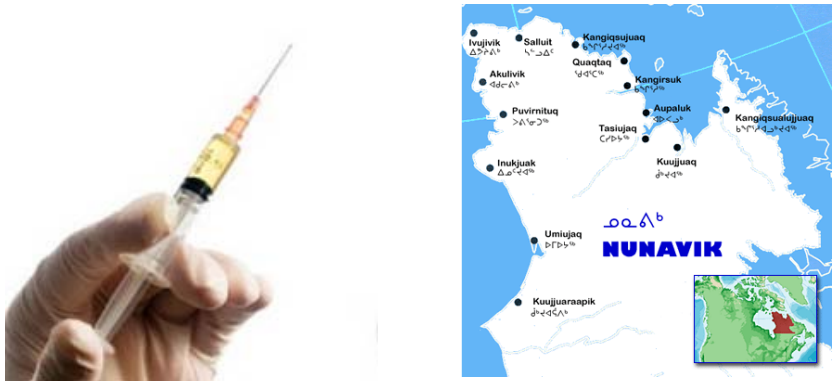




LA PRÉVENTION DU VRS AU QUÉBEC: Saison 2017 - 2018

Marc H. Lebel, MD Décembre 2017



**RSV Prevention in Québec
2017–2018 Season**

 **CHU Sainte-Justine**
Le centre hospitalier
universitaire mère-enfant

 **Marc H. Lebel, MD, FRCPC**
Infectious-Diseases Service

Dr. Marc Lebel

- Pediatrician-infectiologist at the Sainte-Justine Hospital since 1989
- Founded the infectious-diseases service at Ste-Justine
- Synagis consultant at Héma-Québec for nearly 20 years
- Synagis consultant at the *INESSS* for usage criteria
- Representative of the *Association des pédiatres* on the *CIQ*
- Member of the Infectious Diseases and Immunization Committee of the Canadian Paediatric Society
- Impact (Immunization Monitoring Active) investigator of the Canadian Paediatric Society and Health Canada

Learning objectives



At the end of the presentation, the participant will be able to:

- Describe the impact of RSV infections on normal and high-risk children, including children in the Far North
- Understand the eligibility criteria for Palivizumab for at-risk patients in 2017-2018



Effects of Palivizumab as prophylaxis on the reduction of complications linked to the respiratory syncytial virus in children

Sent to the Minister: July 29, 2016

Official publication: August 9, 2016

A production of the *Institut national d'excellence en santé et en services sociaux*

3. Lack of information & exchanges

► More information about RSV and Synagis

► For health professionals:

- Nurses
- Midwives **and also**
- **Family education workers, wellness workers and maybe some interpreters**

NB: Although palivizumab was previously administrated in Nunavik, it is not (well) known by all health workers (some permanent nurses and midwives, staff turnover) or by those not involved in the palivizumab administration before the last RSV season

► Concerns about the recommendation:

- The **safety** of palivizumab
- A **lack of evidence** justifying the need for palivizumab administration to all newborns during the RSV season
- A concern that **Inuit babies are used as experimentation subjects**
- **An informed consent with too little information for parents**
- **A misunderstanding among the Inuits:** some parents in different villages are afraid the DYP will go after them if they do not accept the palivizumab

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3. Some questions

How was the **Synagis** tested before its administration to newborns?

Does anybody know if the **Synagis** will have any **side effects later on in life**, as it is given very early to children (eczema, immunodeficiency, mental health problems, heart deficiency, etc.)?

What is the **impact of the Synagis on RSV and hospitalizations** during the last season?

Why is it recommended to administer the **Synagis to a baby over 2 months old** when he is supposed to be less vulnerable?

Do you know the **effects of Synagis** given at large on all the full-term babies, when it seems that there aren't many studies on this issue? Is this **recommendation relevant for full-term babies**?

Has any **cost-benefit analysis** been done on this recommendation?

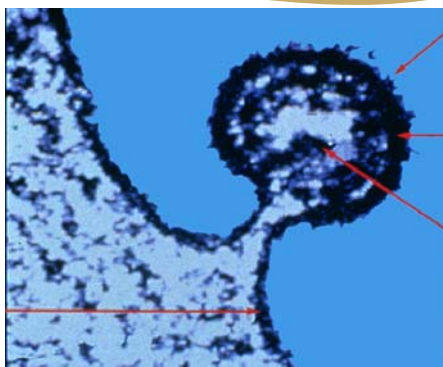
Is it **legal and/or ethical** to send a list of pregnant women?



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Respiratory syncytial virus

- Paramyxovirus
- Infects only humans
- 2 serotypes: A & B
- November to April
- Highly contagious



Question 1

What percentage of young children are hospitalized for an RSV infection?

- a) 1-3/10,000
- b) 1-3/1,000
- c) 1-3/100
- d) 1-3/10

RSV infections

- RSV: causes URTI, such as colds, or LRTI, such as bronchiolitis and pneumonia
- Among children < 1 year, RSV is the most frequent cause of bronchiolitis
- Nearly all children are infected with RSV during the first two years of life

RSV infections

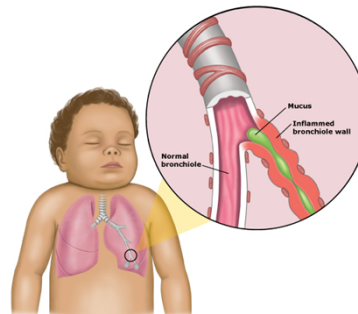
- At the initial exposure to RSV, 25 to 50% of children will come down with symptoms of bronchiolitis or pneumonia
- 0.5 to 3% will be hospitalized
- Majority of hospitalized children: < 6 months

One case of bronchiolitis

- Two-month old infant
- Premature at 34 weeks
- Contact with his three-year-old brother who had a cold
- Onset of nasal congestion, cough, followed by diminished thirst, wheezing and breathing difficulties
- Retraction, tachypnea, ↓ mv

Bronchiolitis

- Obstructive respiratory disease



Arch Pediatr Adolesc Med. 2009;163(11):1072-1072

http://raisingelle.files.wordpress.com/2011/04/bronchiolitis_anatomy_pi.jpg

Complications

- Dehydration
- Apnea
- Cyanosis
- O₂, suction
- Respiratory failure, intubation, ventilator
- Pneumothorax
- Pulmonary superinfection
- Death

Bronchiolitis

- **Most frequent pathogens:**
 - RSV ++++
 - Metapneumovirus ++
 - Parainfluenza 3 ++
 - Parainfluenza 1 +
 - Adenovirus +
 - Influenza +

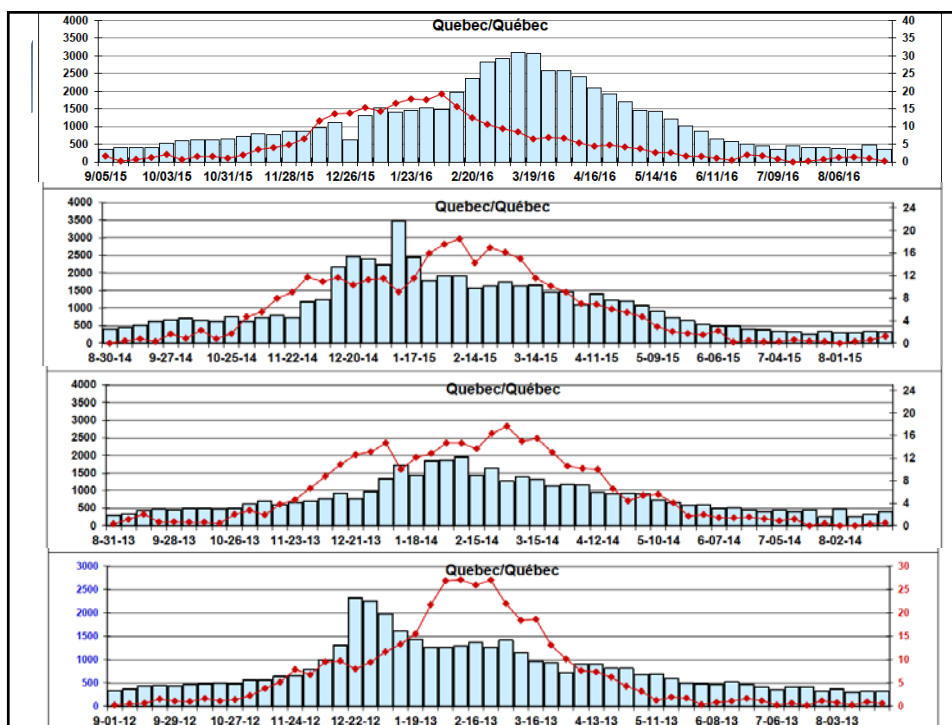
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Question 2

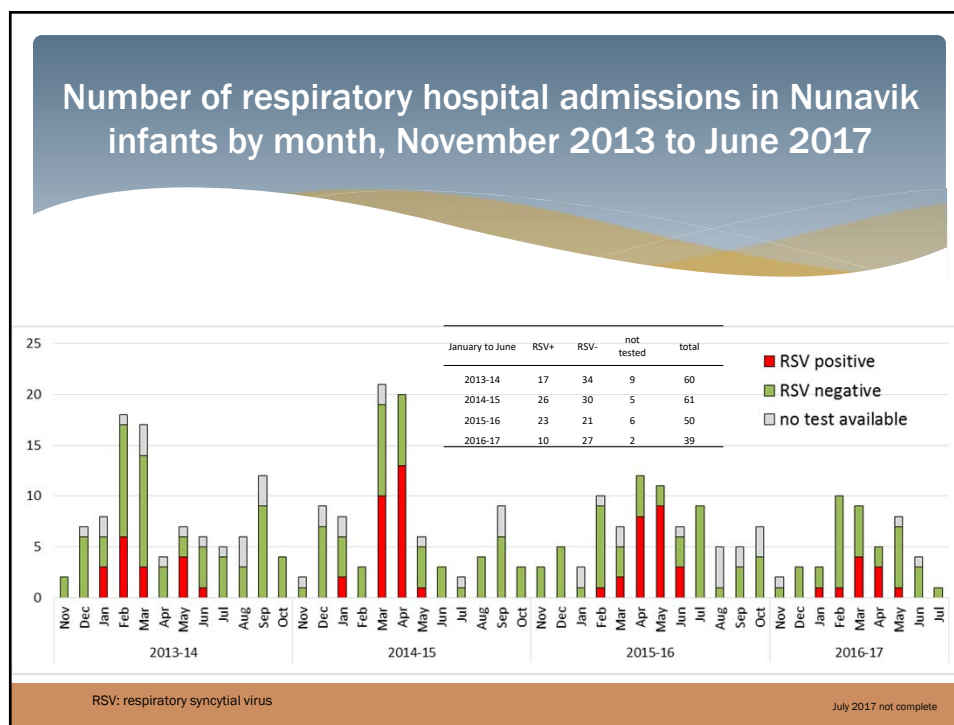
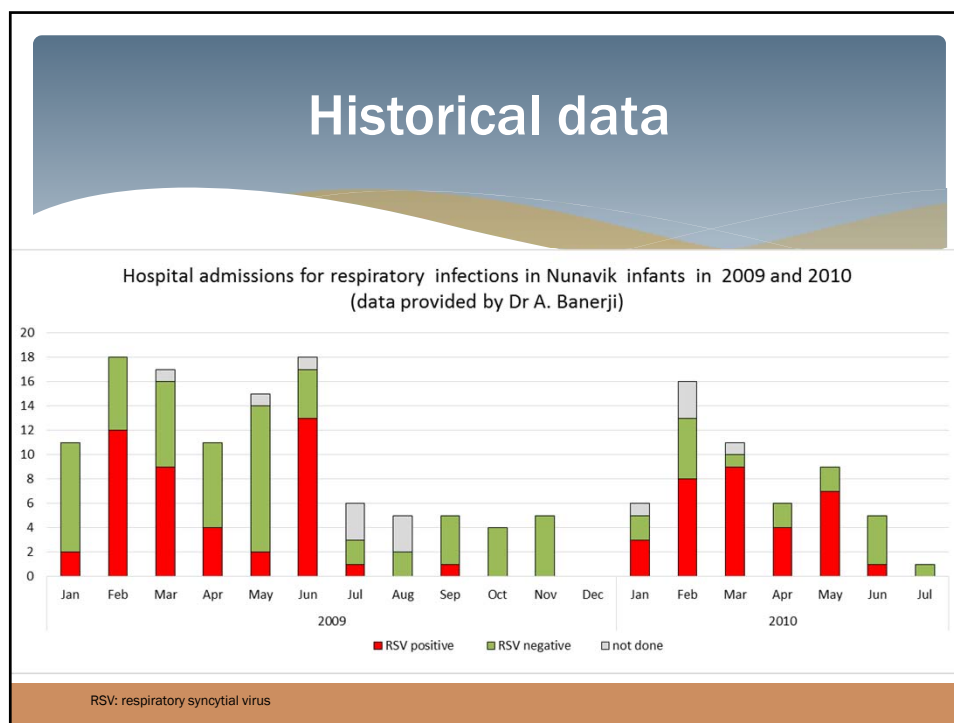
Does the peak viral activity of RSV occur in the fall?

- a) Yes
- b) No
- c) Maybe



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Question 3

Does the beginning of RSV prophylaxis vary from year to year?

- a) Yes
- b) No
- c) It depends

Question 4

Does RSV spread only by air?

- a) Yes
- b) No
- c) It depends

RSV transmission methods

- Percentage of volunteers infected with RSV
- Absence of contact
(volunteers seated at 2 m distance) 0%
- Indirect manual contact
(contact with contaminated objects) 40%
- Close contact
(children in volunteers' arms) 71%

Hall CB. *J Pediatr* 1980;141:100

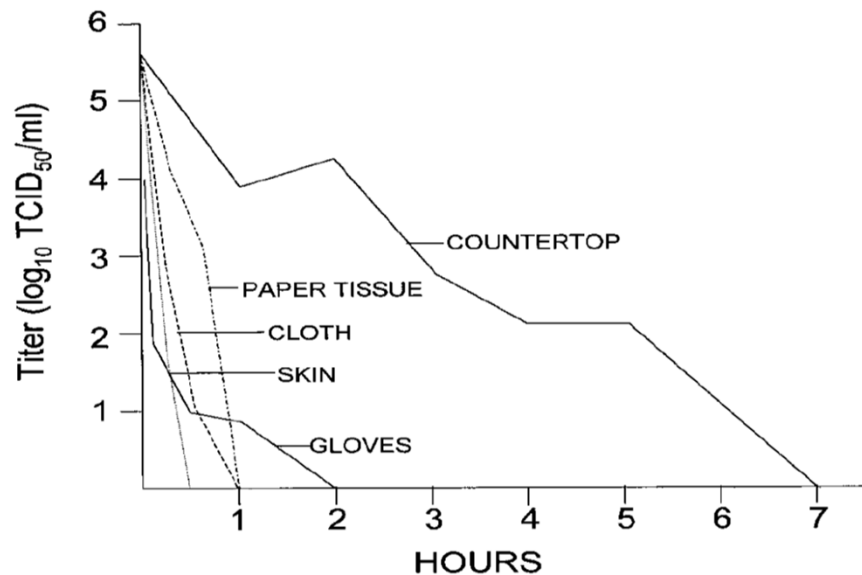


FIG. 2. Survival of respiratory syncytial virus on surfaces. TCID₅₀, 50% tissue culture-infectious doses.⁴

Vol. 19, No. 10, Oct., 2000

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

Transmission of RSV

- Viral excretion persists up to 21 days in infants with pneumonia
- The virus survives several hours on surfaces
 - counters, bed rails 6 - 7 hours
 - porous surfaces (clothing) 1 - 4 hours
 - skin 0.5 - 1 hour
- RSV can penetrate through conjunctive, nasal and oral mucosa

Hall CB, et al. J Pediatr 1976;89:11 Hall CB, et al. J Infect Dis 1980;140:98

Predisposing factors for increased incidence

- Smoking
- Day-cares
- Overcrowded housing
- Boys > girls
- Atopy
- Aboriginal origins
- Absence of breast-feeding

Aujard Y, Fauroux B. Respiratory Medicine 2002;96:suppl. B: S9-S14

Predisposing factors for a more severe form of the disease

- Premature birth
- Chronic lung disease (CLD-BD)
- Congenital heart disease
- Young age (under 6 weeks)
- Immunodeficiency
- Cystic fibrosis

Aujard Y, Fauroux B. Respiratory Medicine 2002;96:suppl. B: S9-S14

Role of RSV antibodies

- Maternal antibodies pass through the placenta from the 28th week of gestation
- RSV infections are less severe in children born at term, who have higher levels of maternal antibodies

de Sierra TM, et al. J Pediatr 1993;122:787-791

Question 5

Is Palivizumab an active vaccine?

- a) Yes
- b) No

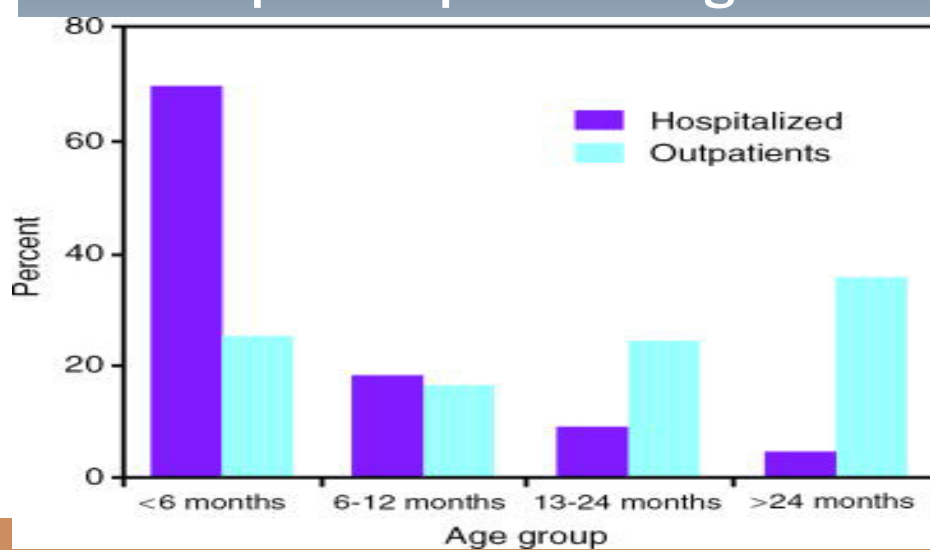
Passive immunity: monoclonal antibodies

- Humanized monoclonal antibody IgG1: Palivizumab
- Recombinant product
- Targets antigens (epitope of f-protein of RSV)

Criteria for free access to Palivizumab, Québec

- Children born before the 33rd week of pregnancy and aged under six months at the start of RSV season

RSV infections Impact of patient's age



Mortality: RSV

- Review of 34 articles on infants hospitalized for RSV infection
- Mortality:
 - Child not at risk 0-0.2%
 - Premature 1.2%
 - Heart disease 5.2%
 - Bronchopulmonary dysplasia 4.1%

Paediatric Respiratory Reviews 2012;13(S2):S1-S8

IMpact study: RSV

- Prospective study, multi-centre, random distribution, double blind, on prophylaxis for RSV infections
- 139 centres in the U.S., Canada, U.K.
- 1500 patients – randomized 2:1

The IMpact - RSV study group. Pediatrics 1998;102:531

IMpact study: methodology

- Patients

- aged ≤ 6 months and premature (≤ 35 weeks)
- aged ≤ 24 months and with bronchopulmonary dysplasia

Rate of hospitalization due to RSV

	Number	Placebo (%)
All babies	1502	10.8
Child with BD	762	12.8
Child born before 32 weeks	740	11.0
Child without BD	740	8.1
Premature 32-35 weeks	373	9.8
Premature 32-35 weeks without BD	335	10.8

The Impact-RSV Study Group. Pediatrics 1999;102(3):531-7.

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Rate of hospitalization due to RSV

	Number	Placebo (%)	Palivizumab (%)	Reduction %
All babies	1502	10.8	4.8	55
Child with BD	762	12.8	7.9	39
Child born before 32 weeks	740	11.0	5.8	47
Child without BD	740	8.1	1.8	78
Premature 32-35 weeks	373	9.8	2.0	80
Premature 32-35 weeks without BD	335	10.8	1.8	82

The Impact-RSV Study Group. Pediatrics 1999;102(3):531-7.

Question 6

Does Palivizumab prevent RSV infection?

- a) Yes
- b) No

Classification of RSV infections

- Mild infection: URTI
- Moderate infection: LRTI
- Severe infection: hospitalization

Criteria for free access to Palivizumab, Québec

- Babies born at term or near term, aged under 24 months at the start of RSV season, with newborn chronic lung disease, defined by a need for oxygen therapy at birth or which persisted due to a chronic lung problem other than those designated in other criteria, OR

Criteria for free access to Palivizumab, Québec

- premature babies, aged under 24 months at the start of RSV season, with bronchopulmonary dysplasia shortly after birth, defined by a need for oxygen therapy at birth and which persisted up to at least 28 days and up to a gestational age of at least 36 weeks, and this in the presence of antecedents for the disease, AND

Criteria for free access to Palivizumab, Québec

- who needed persistent oxygen therapy during the six months preceding the start of the season or who need oxygen therapy during RSV season

Adverse effects

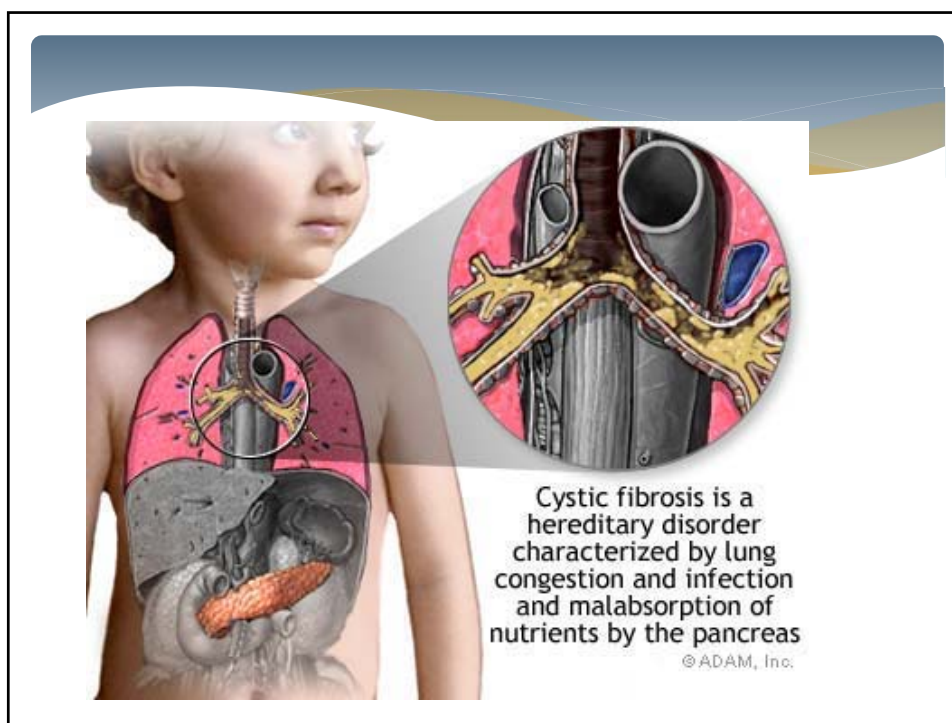
- The rate of undesirable effects linked to treatment was similar between the placebo group and the treatment group:
 - placebo: 10%
 - Palivizumab: 11%

The Impact-RSV study Group Pediatrics 1998;102(3):531-7

Question 7

Are patients with cystic fibrosis of the pancreas (CFP) eligible for Synagis?

- a) Yes
- b) No
- c) Under certain conditions



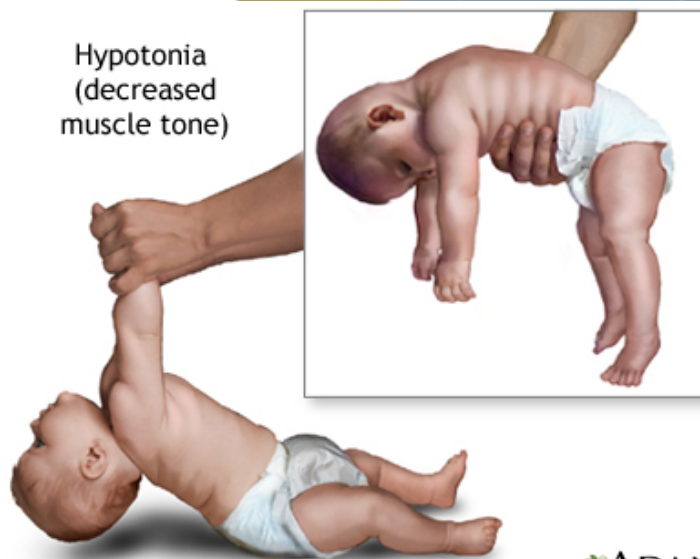
Criteria for free access to Palivizumab, Québec

- Children aged under 24 months at the start of RSV season
- With cystic fibrosis
- With respiratory symptoms or significant failure to thrive

Criteria for free access to Palivizumab, Québec

- Children aged under 24 months at the start of RSV season
- For whom evacuation of secretions from the airways is hindered significantly due to a neuromuscular disorder (diagnosis must be provided on request)

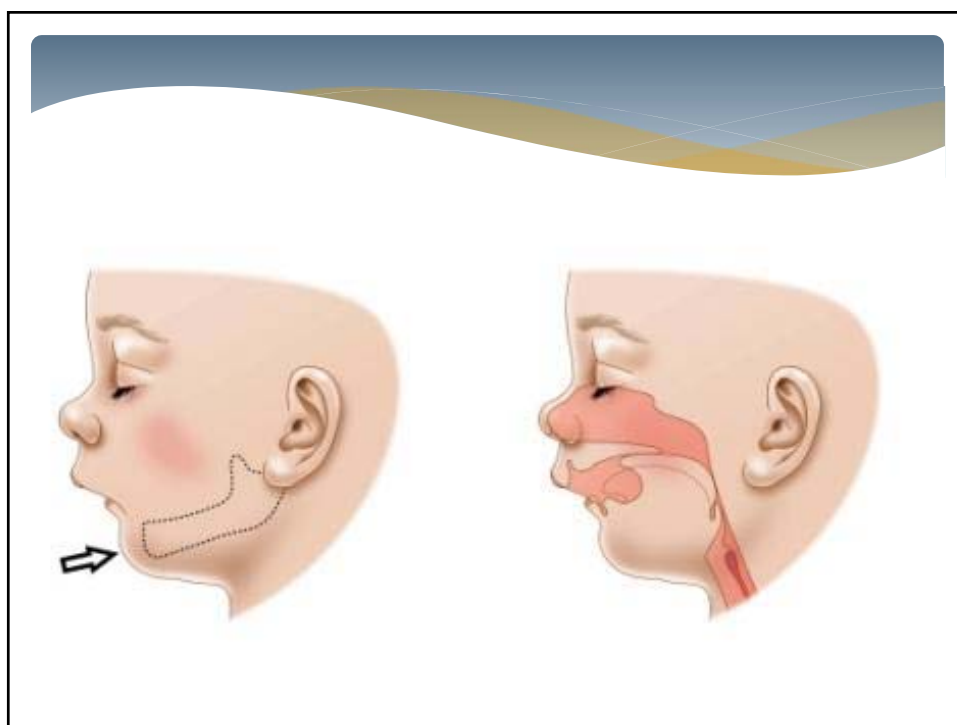
Hypotonia
(decreased
muscle tone)



ADAM.

Criteria for free access to Palivizumab, Québec

- Children aged under 24 months at the start of RSV season
- For whom evacuation of secretions from the airways is hindered significantly
- Due to a congenital anomaly of the upper airways (diagnosis must be provided on request)



Criteria for free access to Palivizumab, Québec

- Children aged under 12 months at the start of RSV season
- With a congenital heart disease, cardiomyopathy or myocarditis with clinically significant hemodynamic consequences or suffering from moderate or severe pulmonary hypertension (application must be made by a pediatric cardiologist to guarantee accuracy of diagnosis)

Tetralogie van Fallot *cyanose*

Children with Tetralogy of Fallot exhibit bluish skin during episodes of crying or feeding.



"Tet spell"

ADAM.

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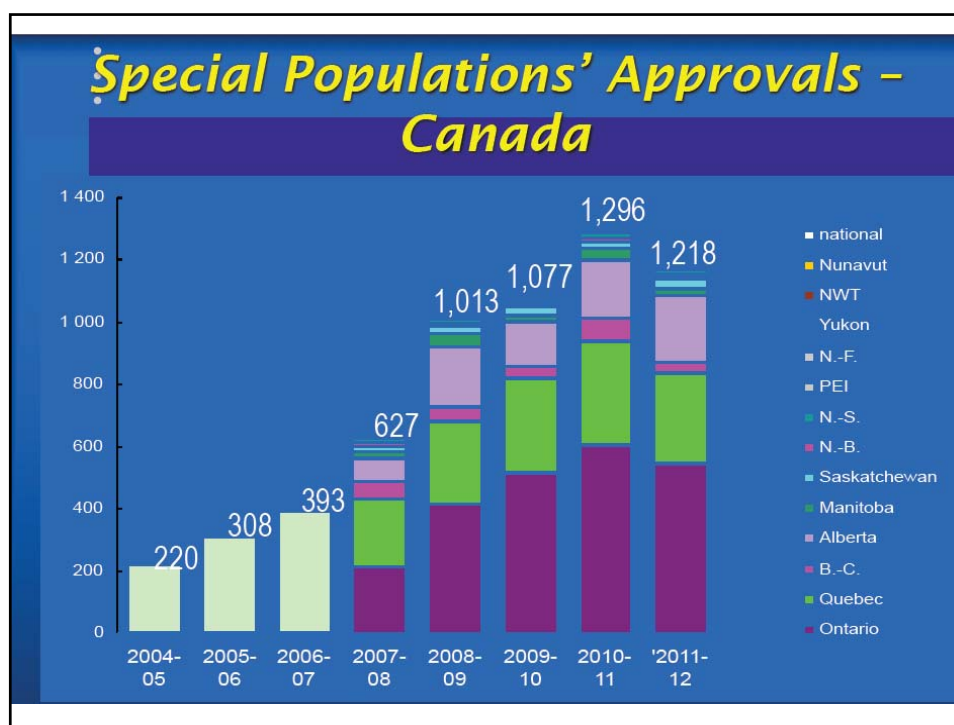
Conclusions: effectiveness

- Prophylaxis with Palivizumab has been linked to a **45% reduction** in hospitalizations caused by RSV among children with a congenital heart disease (p=0.003)
- Consistent results across all heart conditions: 1287 children enrolled in the study
- Serum levels of Palivizumab dropped by 58% after extracorporeal circulation

Statistics: 2014-2015 season at Sainte-Justine Hospital		
	Number identified	Applications at Sainte-Justine
Neonatology		
< 29 weeks	115	78
29 to 32 6/7 weeks	140	108
33 to 35 6/7 weeks	245	44
Other cases, 36 weeks +	3	2
Diaphragmatic hernia	5	4
Cardiology		
1 st season	115	65
2 nd season	76	35
3 rd season and siblings	83	16
Bronchopulmonary dysplasia		
1 st season	6	6
2 nd season	16	16
Pneumology		
Apnea	4	4
ATOE	8	7
CAVD and sleep	0	0
CF	10	10
General pneumology	31	31
Tracheostomy	1	1
Pediatrics		
USIP - PSIC - integrated pediatrics	13	13
Other specialties		
GMO	5	5
ENT	1	1
Neurology	1	1
Dermatology	1	1
	873	4498

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Criteria for free access to Palivizumab, Québec

- Children born at 36 weeks of gestation or earlier and aged six months at the start of RSV season, or born during the season, residing in Nunavik
- Children born at term, aged under three months at the start of RSV season, or born during the season, residing in Nunavik

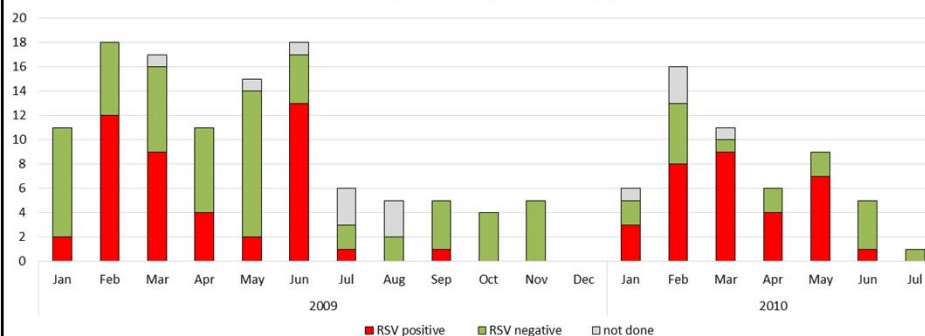
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Historical data

Hospital admissions for respiratory infections in Nunavik infants in 2009 and 2010
(data provided by Dr A. Banerji)



RSV: respiratory syncytial virus

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Hospital charts review

<12-month-old infants hospitalized with respiratory diagnoses	Hudson		Ungava		Nunavik		Overall
	2013-14 to 2015-16*	2016-17**	2013-14 to 2015-16*	2016-17**	2013-14 to 2015-16*	2016-17**	
Admissions identified from MEDECHO¹	209	20	121	16	330	36	366
Added during reviewing process ²	22	1	9	10	31	11	42
Reviewed	231	21	130	26	361	47	408
Excluded ³	68	1	23	1	91	2	93
Admissions included in the analysis	163	20	107	25	270	45	315
Matched with a laboratory test	136	20	90	22	226	42	268
RSV positive	43	5	23	5	66	10	76
RSV negative	93	15	67	17	160	32	192
Number of children with ≥1 admission	125	14	87	21	212	35	247
1 admission	78	10	71	18	149	28	177

*November to October; **November to June

¹ICD10 respiratory Dx codes J00-J22

²Tertiary admissions; occurred after MEDECHO extraction; not detected by used Dx codes J00-J22

³Occurred before November 1, 2013; age ≥12 months; admitted for another reason (trauma, bacteremia, meningitis, epilepsy, febrile convulsions, apnea probably due to neuromuscular disorder, etc.), age ≥12 months; chart not available; repeat admission within 14 days (excluded from the numerator, total number of hospital days included)

Number of regional and tertiary admissions with a confirmed RSV infection in Nunavik infants, according to different sources

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
2008-09	17	7	18	42				
2009-10	11	8	13	32				
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	4	10	0			0

*4 transfers to McGill Health Centre; 1 transfer to CHUL

**new recommendations implemented

Dr. Anna Banerji data
present evaluation

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- In 2016, liquid Palivizumab



Produits sanguins
Cellules souches
Tissus humains

4045, boul. Côte-Vertu
Saint-Laurent (Québec) H4R 2W7
Téléphone : 514 832-5000
Télécopieur : 514 904-1021

1070, avenue des Sciences-de-la-Vie
Québec (Québec) G1V 5C3
Téléphone : 418 780-4362
Télécopieur : 418 780-2093

CIRCULAIRE

HQ-17-026

Information on the Availability of Synagis for the 201-2018 season

July 6th, 2017

To: **Specialists in neonatology/pediatrics**
Microbiologists-infectiologists
Directors of Professional Services (CLSC)

c.c. **Director s of bloods banks**
Chief technologists/coordinators of blood banks
Pharmacists in Institution

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- 8- children born at 36 weeks of gestation or earlier and aged under six months at the start of RSV season or born during the season, residing in Nunavik;
- 9- children born at term, aged under three months at the start of RSV season or born during the season, residing in Nunavik.
 - No Palivizumab doses should be administered after the established end date (see table below), except under the following particular circumstances*:
 - If RSV is still active in Nunavik, one dose should be administered in May to children admissible for Palivizumab who left hospital in the months from February to April after their birth.*
 - For the other regions of Québec, one dose should be administered in April to certain premature babies, if RSV is still active in the community. These are babies who left hospital in the months from January to March after their birth.*



Other Administration Details

- Palivizumab should be administered every four weeks to a maximum of four (4) or five (5) doses per season, depending on the start date of the child's prophylaxis treatment and that of the end of RSV season. The following administration calendar should be followed:

Calendar for administration of Palivizumab in Québec		
Region	All of Québec (except Nunavik)	Nunavik
RSV season	November 1 to March 31	December 1 to April 30
*In case of an extended RSV season, a procedure will be established to inform clinicians.		

- Palivizumab should be administered from 48 to 72 hours before the child admissible for Palivizumab is discharged from hospital after birth.

Conclusions

- Extensive experience with Palivizumab for 20 years
 - premature children and children born at term
 - side effects comparable to placebo
 - no long-term side effects
- Children in the Far North: hospitalization rates equivalent to groups at risk for which prophylaxis is recommended
- Children aged under three months are at greatest risk
- Cost-effective
- Preliminary public-health study: reduction in hospitalization rates

