L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital

Centre universitaire de santé McGill
McGill University Health Centre

Respiratory Syncytial Virus: Preparing for the 2022-23 season in the wake of COVID-19

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Canadian Paediatric Society Grand Rounds

Sept. 15, 2022

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Disclosure Statement

- **Faculty:** Jesse Papenburg

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Merck, MedImmune, AbbVie
  - **Speakers Bureau/Honoraria:** AstraZeneca, AbbVie
  - **Consulting Fees:** Merck

Canadian Paediatric Society
Société canadienne de pédiatrie

Objectives:

- Discuss the impact of the COVID-19 pandemic on the past two RSV seasons
- Recognize the effects of lifting COVID restrictions on the upcoming RSV season
- Describe current and upcoming prophylactic and surveillance strategies for managing RSV in the era of SARS-CoV-2

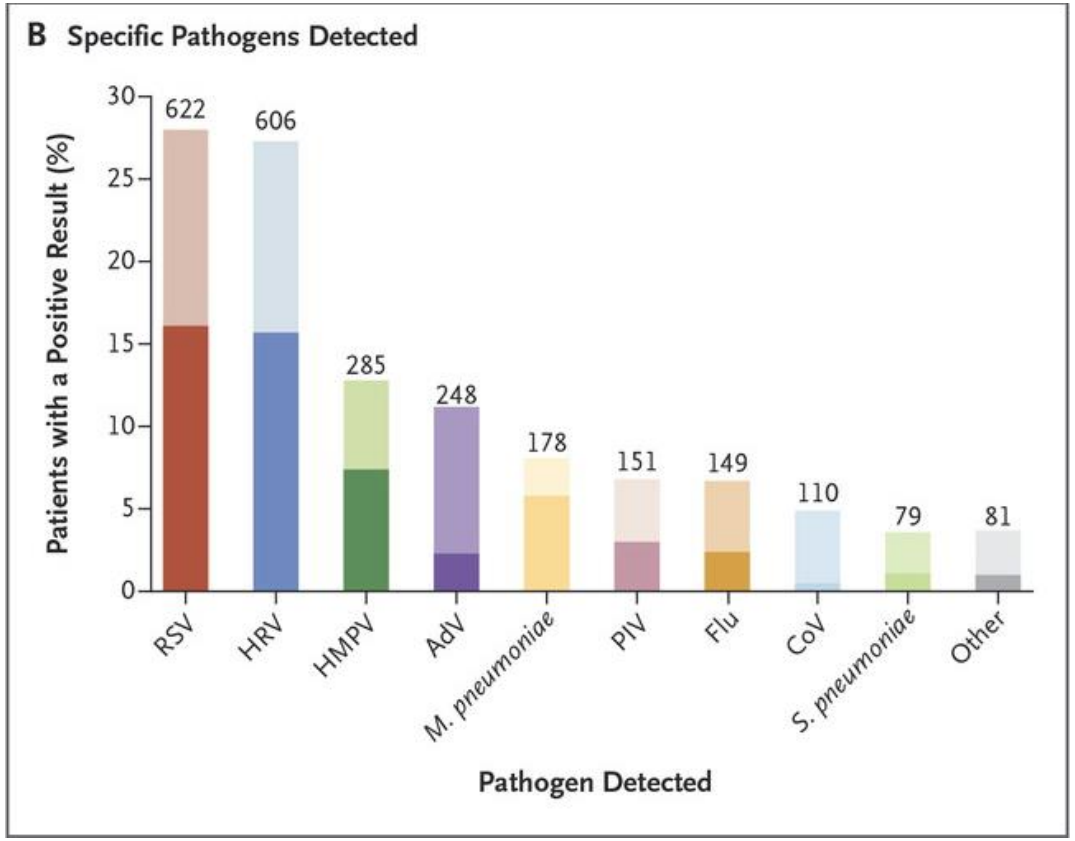
RSV BURDEN OF DISEASE

RSV disease burden in children

- **Most common cause of lower respiratory tract infections among young children in the U.S. and worldwide[1, 2]**
- Each year, in the U.S., RSV leads to[1]:
  - ~ 2.1 million outpatient visits among children < 5 years old
  - > 50,000 hospitalizations among children < 5 years old
- Children with a history of premature birth or chronic medical conditions are at higher risk of severe RSV disease[1]

1- Hall et al. *N Engl J Med* 2009
2- Nair et al. *Lancet* 2010

Pathogens Detected in U.S. Children with Community-Acquired Pneumonia Requiring Hospitalization



Jain et al., *N Engl J Med* 2015

Host risk factors for RSV hospitalisation

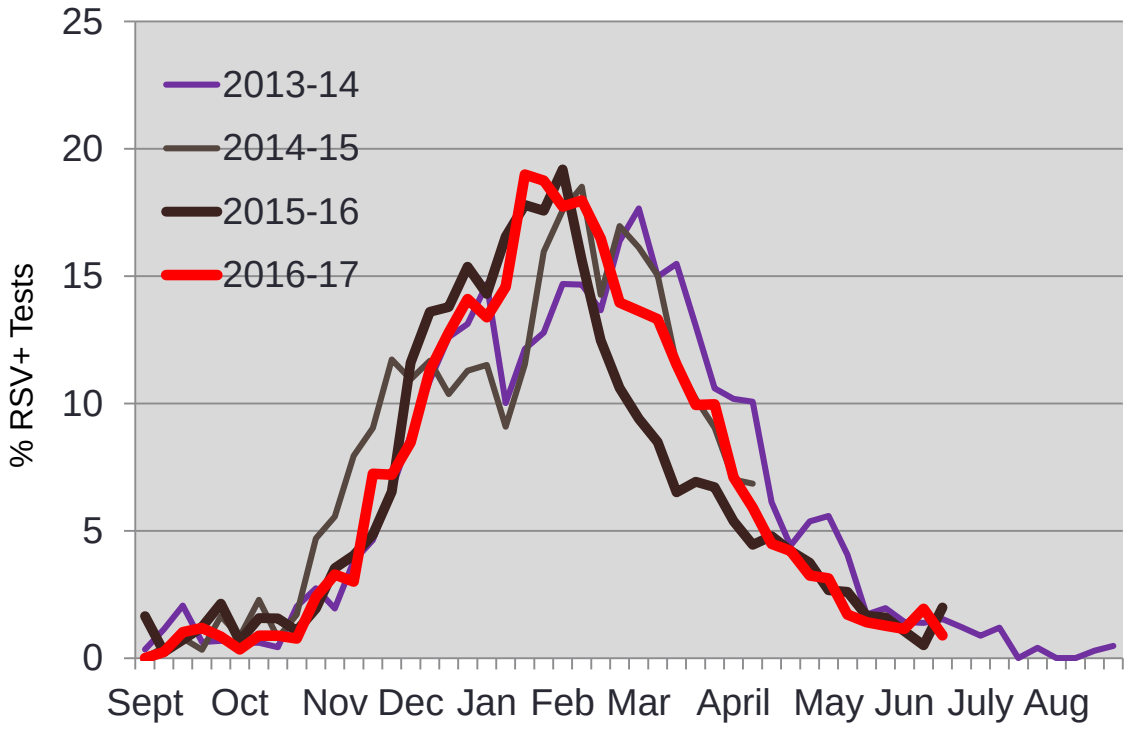
Table I. RSV hospitalizations per 100 child-years by age and risk group

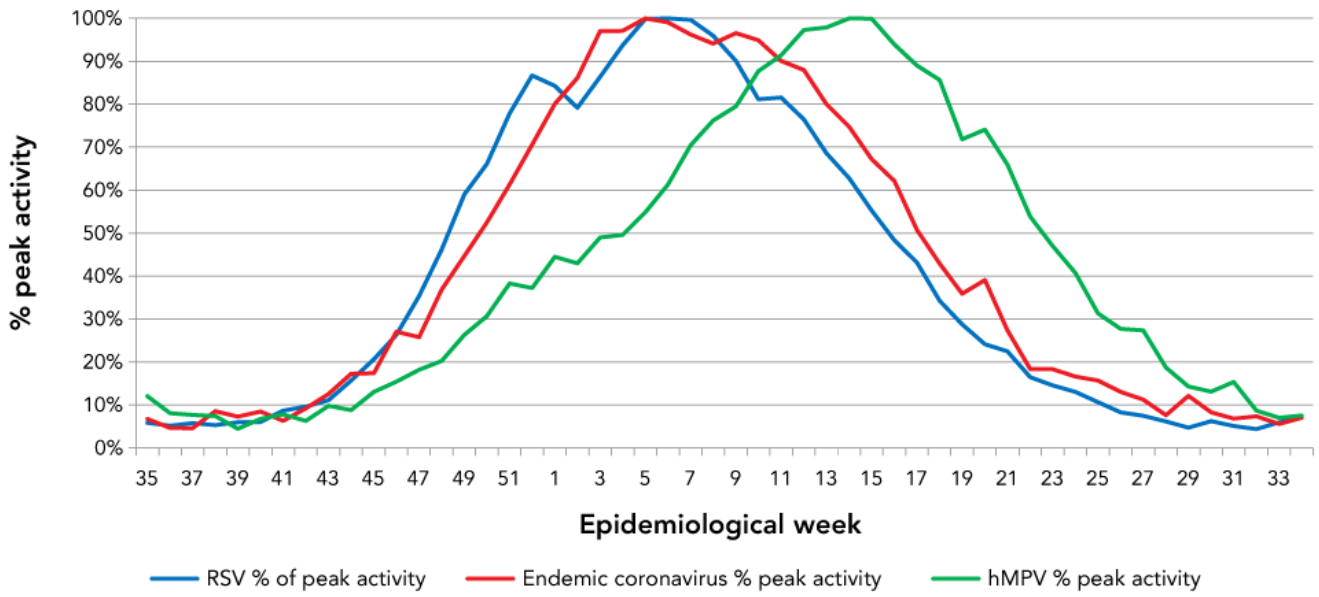
Age (mo)	Normal	CHD	BPD	≤28 wk GA	29–32 wk GA	33–35 wk GA
0–5	4.4	12.1	56.2	9.4	8.2	8.0
6–11	1.5	6.3	21.4	4.6	5.0	3.5
12–23	0.4	1.8	7.3	3.0	0.9	1.1
24–35	0.1	0.5	1.3	0.0	0.2	0.1

Boyce et al. Rates of hospitalization for RSV infection among children in Medicaid. J Pediatr 2000.

TYPICAL RSV SEASONALITY

RSV Laboratory Surveillance – Québec & Canada



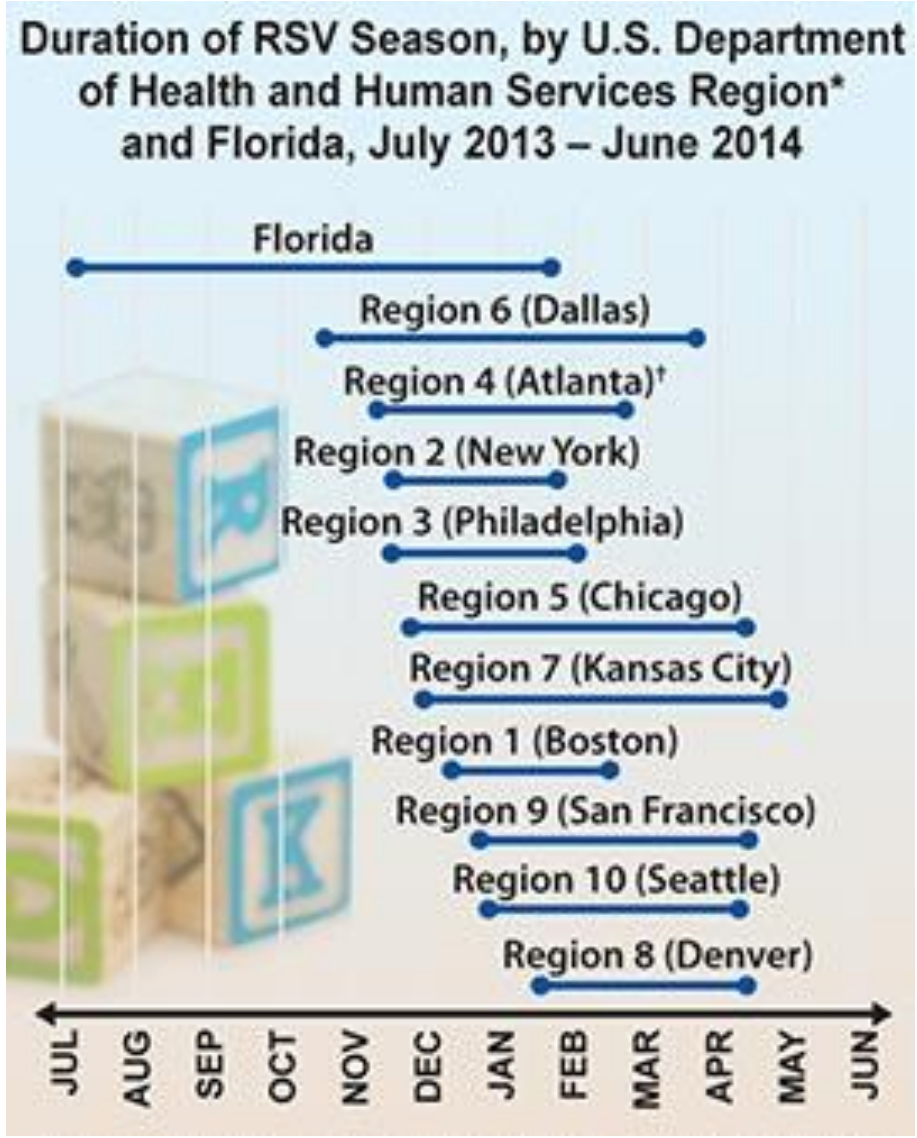


Papenburg et al, J Pediatric Infect Dis Soc. 2021 Apr 3;10(3)

Lagacé-Wiens et al. Can Commun Dis Rep. 2021

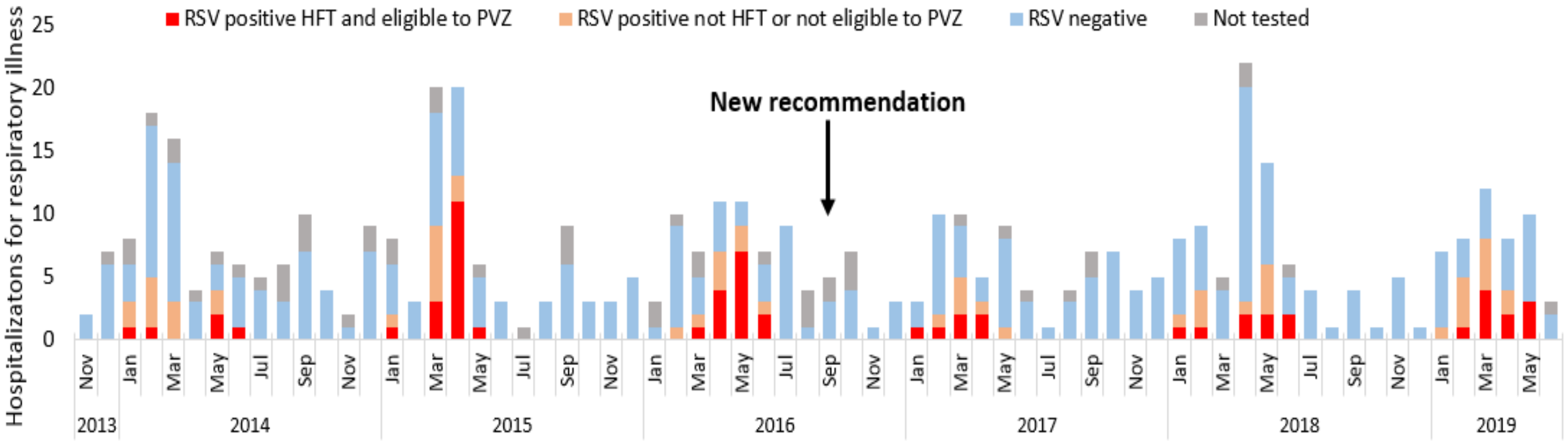
Environmental Drivers of the Spatiotemporal Dynamics of RSV, USA

- Timing of epidemics is associated with a variety of *climatic factors*, including **temperature**, **vapor pressure**, **precipitation**, and **potential evapotranspiration**
- "However, we cannot explain why RSV activity begins in Florida, one of the warmest states, when RSV is a winter-seasonal pathogen…"



Spitzer et al. PLoS Pathogens 2015 | Volume 11 | Issue 1

Respiratory hospitalizations, infants, Nunavik, Québec

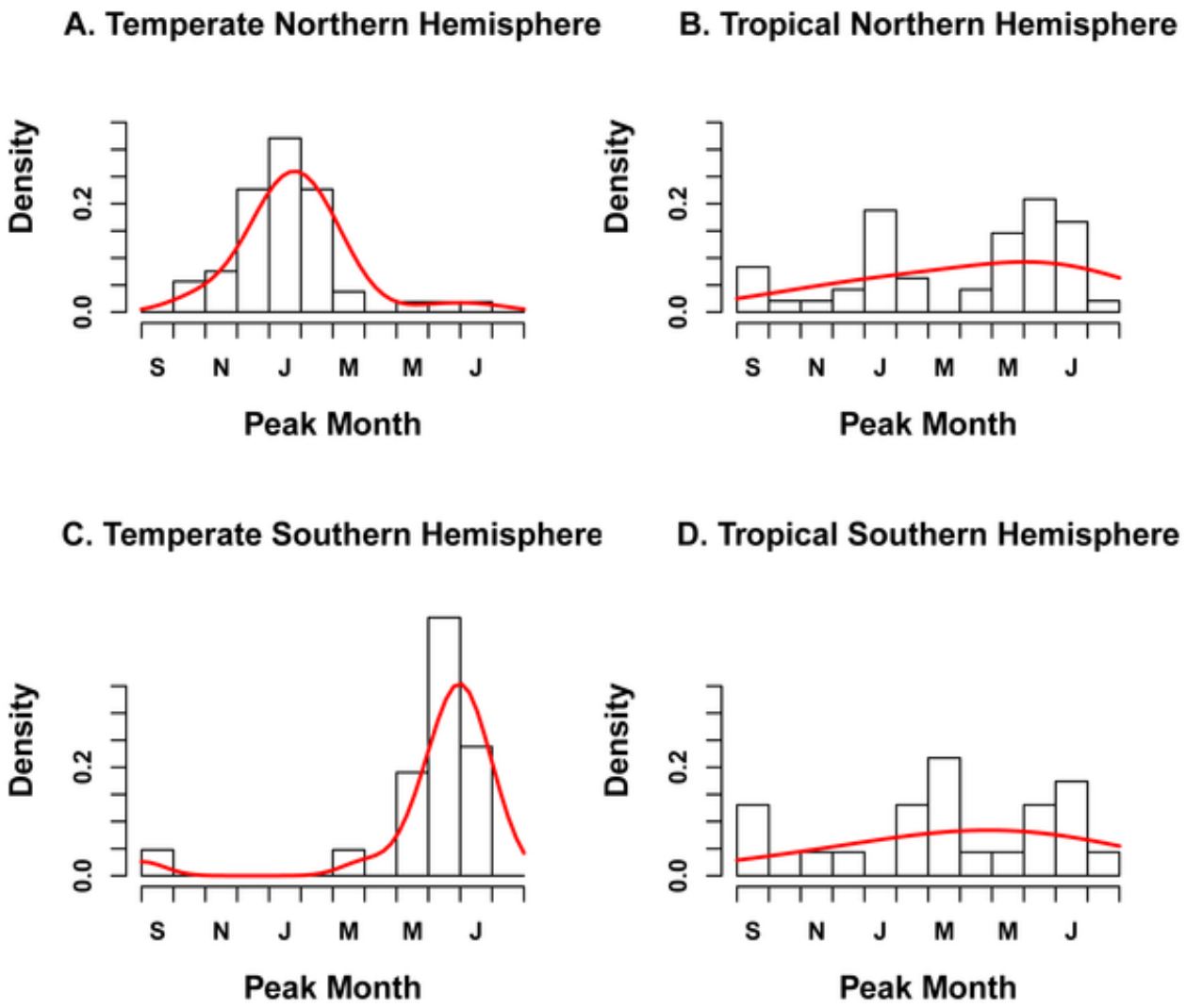


RSV Circulation **: January to June**

Gilca et al. Prev Med Rep. 2020

Slide courtesy of Dr. Rodica Gilca, INSPQ

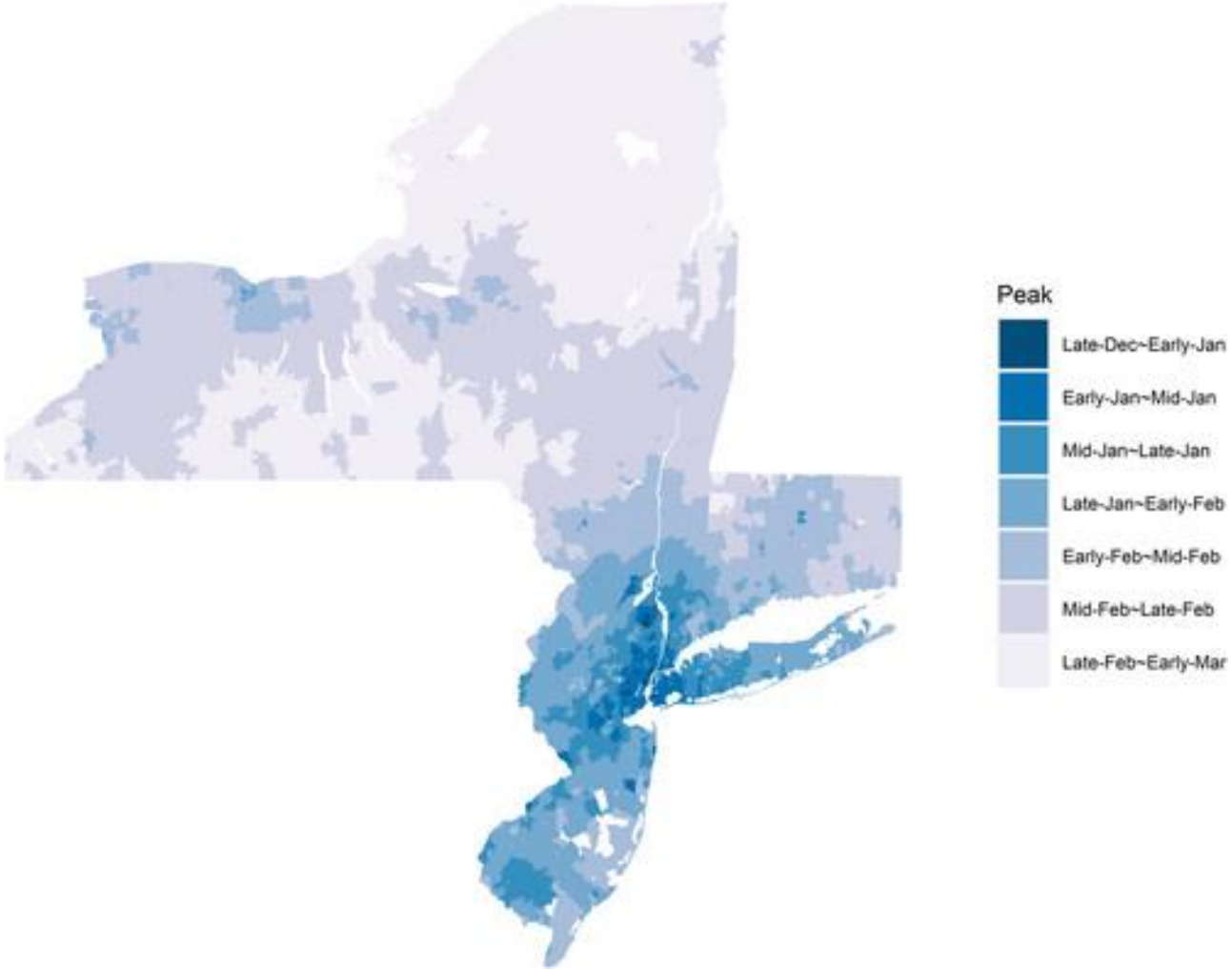
Distribution of RSV peak month by geographic zone



Bloom-Feshbach K et al. (2013) Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV). PLOS ONE 8(2): e54445

Community-based transmission

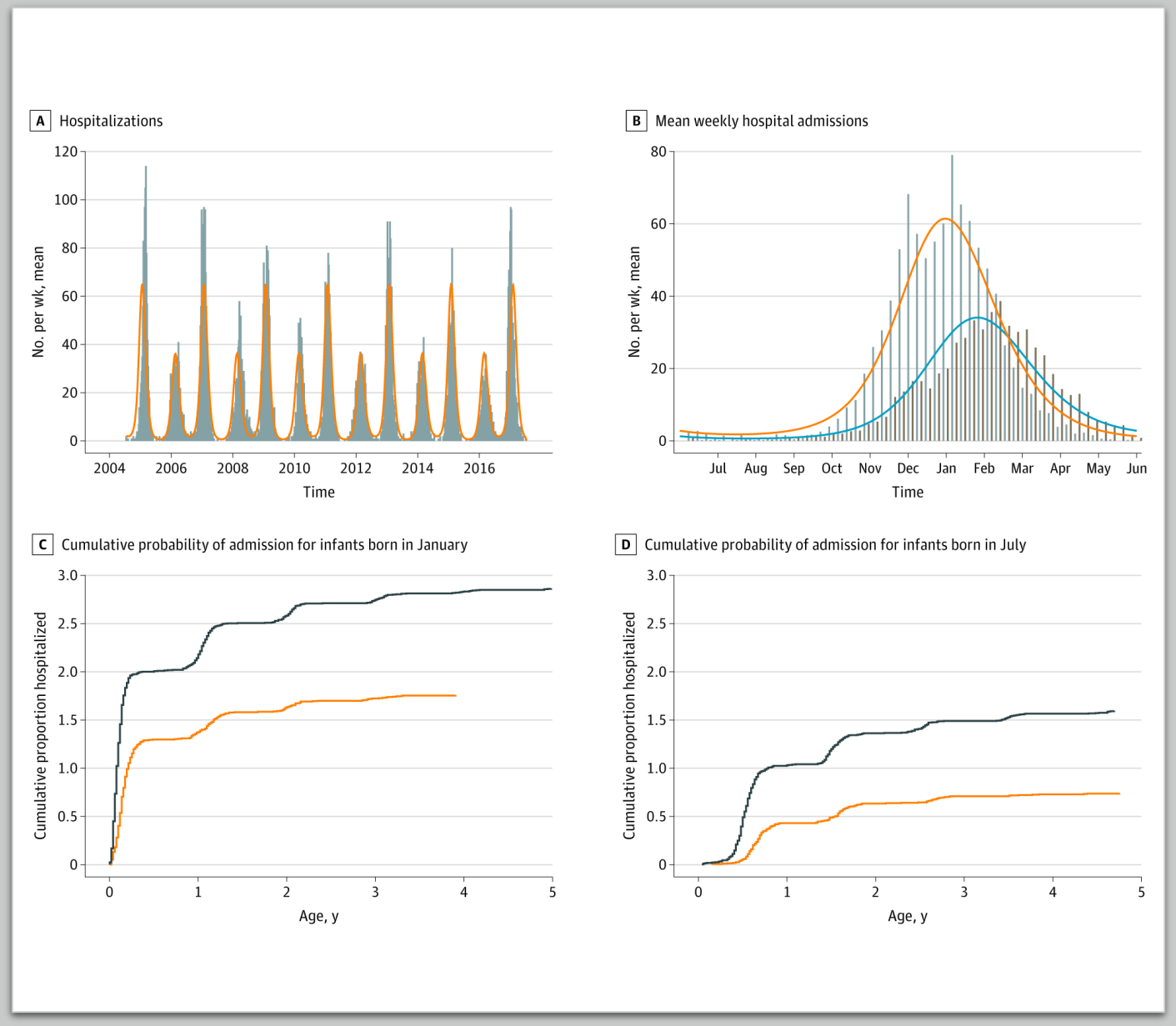
Earlier RSV onset in large cities, with subsequent spread



Zhe Zheng et al. SCIENCE ADVANCES• 23 Jun 2021• Vol 7, Issue 26

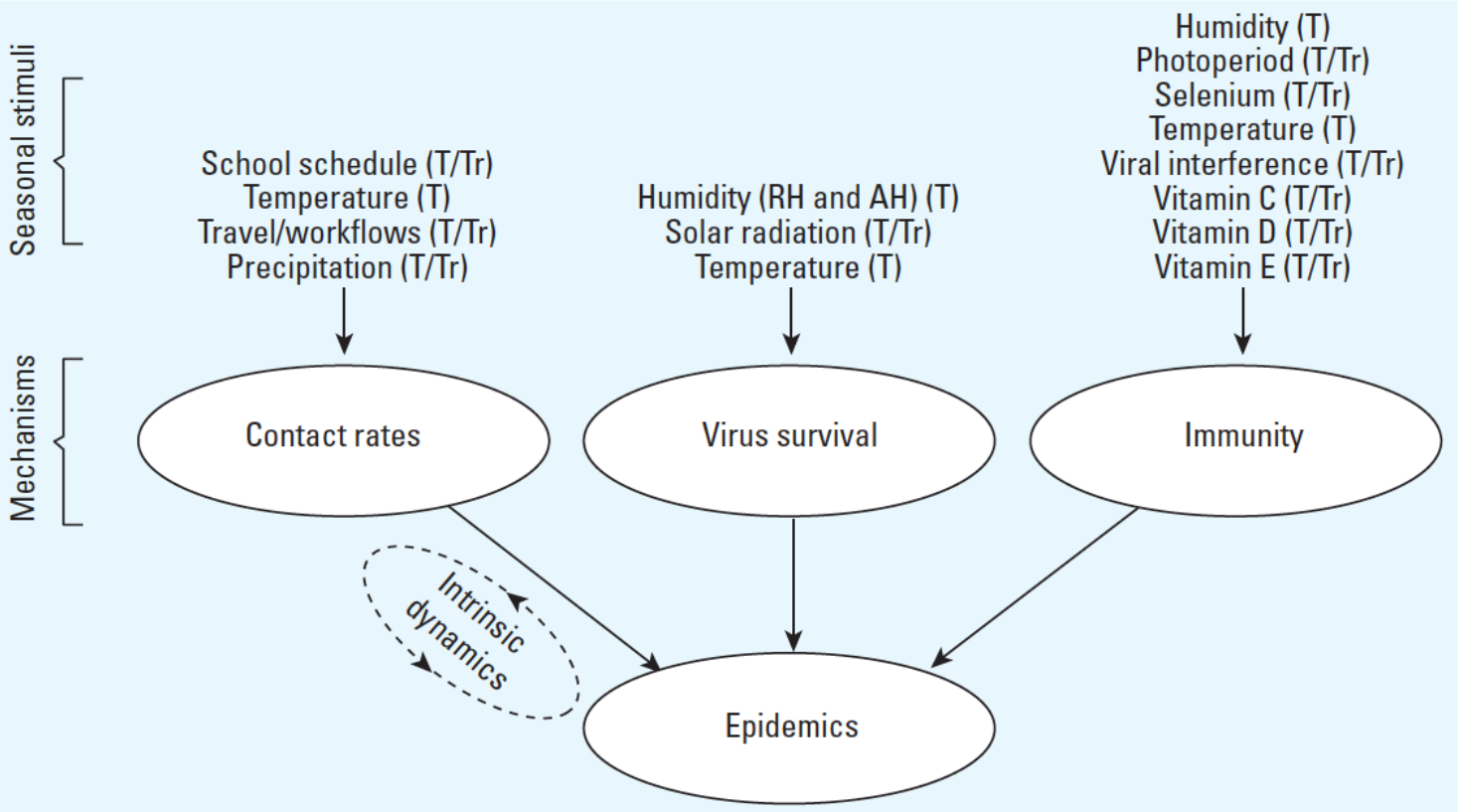
[Community factors associated with local epidemic timing of RSV: A spatiotemporal modeling study]

RSV hospitalizations in young children: Biennial Pattern in Alberta?



[Hawkes et al. JAMA Netw Open. 2021;4(9):e2124650](#).

Explanatory mechanisms for seasonality of respiratory viruses



Tamerius J et al. Global influenza seasonality: reconciling patterns across temperate and tropical regions.
Environ Health Perspect. 2011 Apr;119(4):439-45

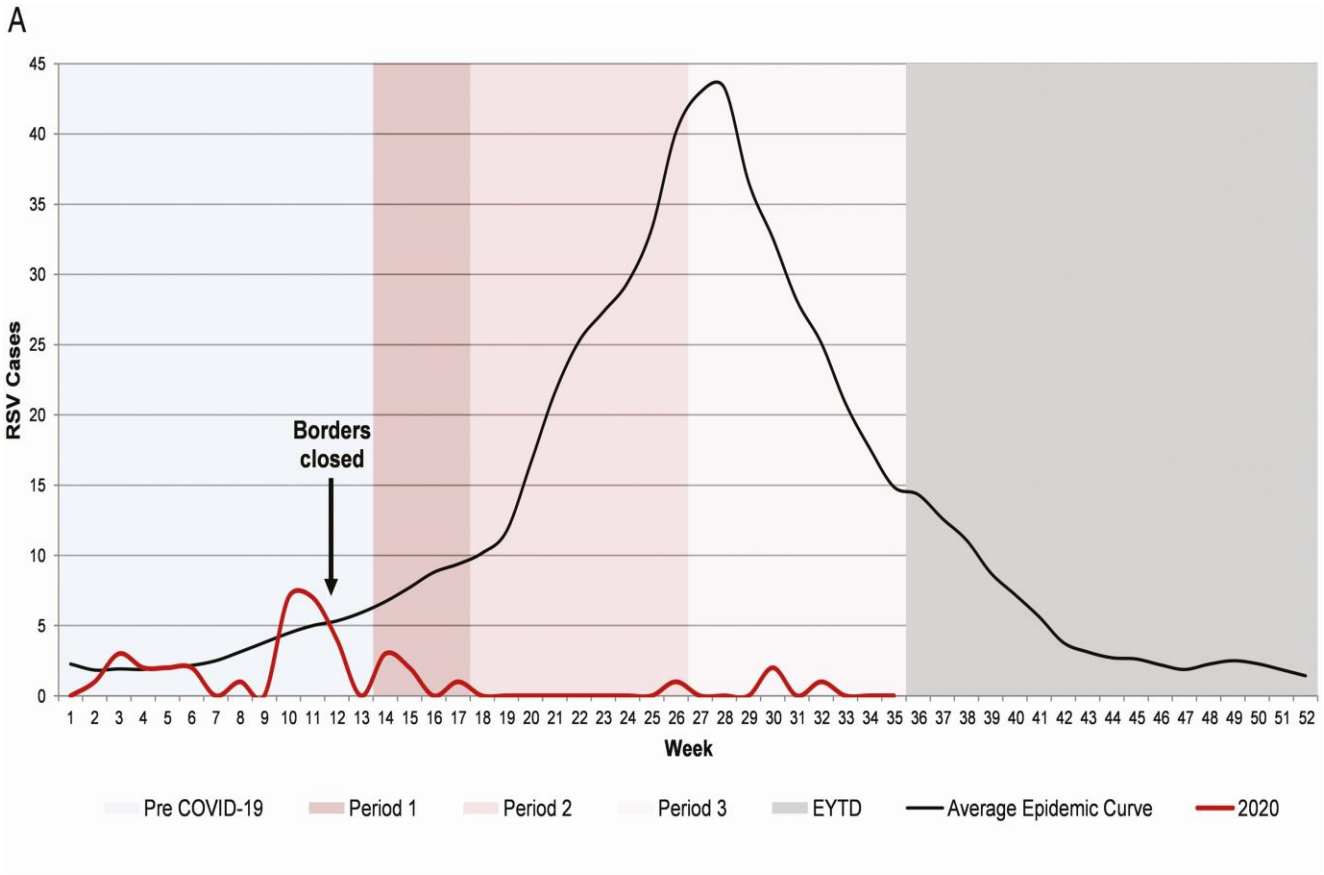
COVID-19 PANDEMIC IMPACT: CIRCULATION OF RSV

Clinical Infectious Diseases

BRIEF REPORT

Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children During the 2020 Australian Winter

Daniel K. Yeoh,[1,2,3,a] David A. Foley,[1,a] Cara A. Minney-Smith,[4] Andrew C. Martin,[5] Ariel O. Mace,[5,6,7] Chisha T. Sikazwe,[4,6] Huong Le,[7] Avram Levy,[4,8] Christopher C. Blyth,[1,4,7,9] and Hannah C. Moore[7]

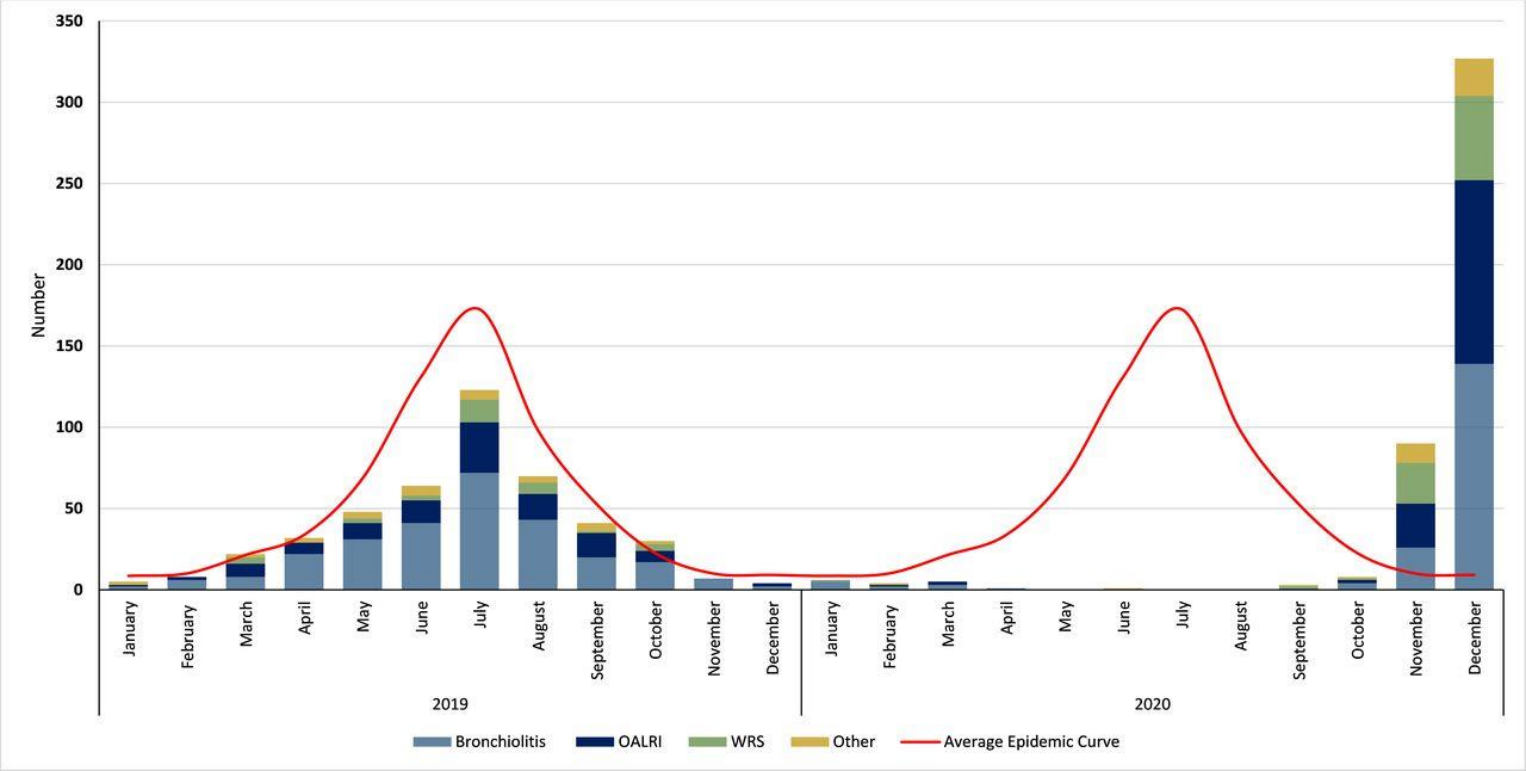


Clin Infect Dis. 2021 Jun 15;72(12):2199-2202.

Interseasonal resurgence of RSV in Western Australia

- RSV-positive admissions peaked in early **summer** 2020, following an absent winter season
- 2.5 times > 2019 peak
- Median age in 2020: 2 times that observed in 2019
  - 16.4 vs 8.1 months, p<0.001
- Increase in RSV-positive non-bronchiolitis admissions
- No clinically meaningful differences in LoS or severity

Clinical phenotype of RSV-positive admissions per month

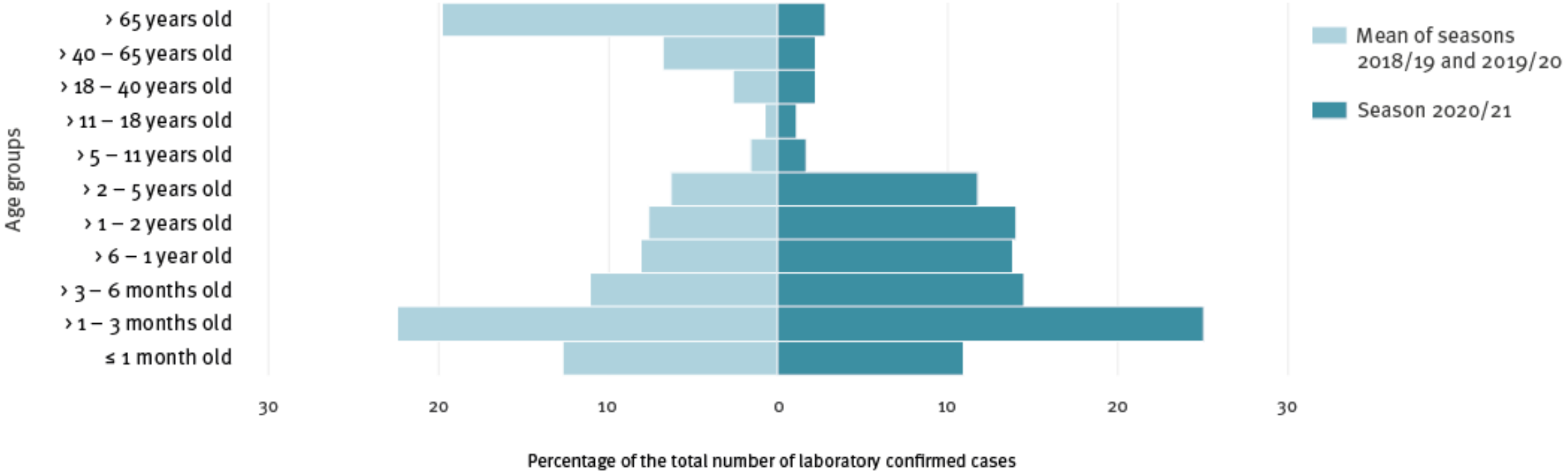


Foley et al. Arch Dis Child 2021

RAPID COMMUNICATIONS

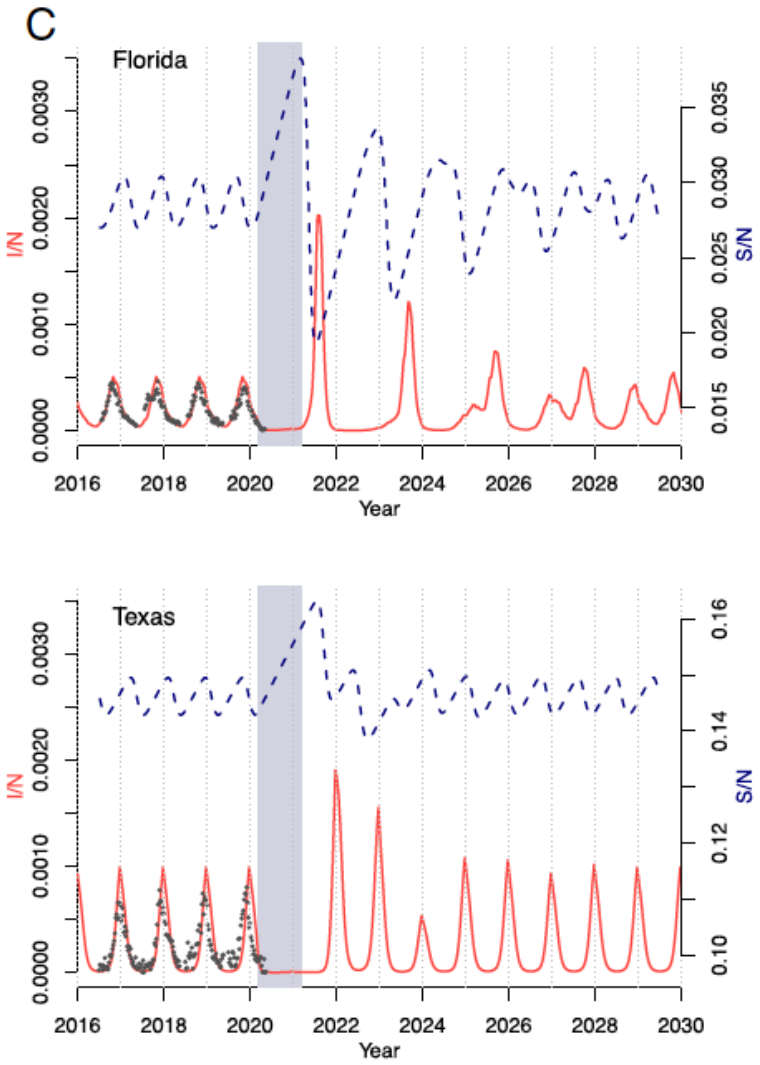
Characteristics of the delayed respiratory syncytial virus epidemic, 2020/2021, Rhône Loire, France

Figure 2. Age pyramid of RSV cases by epidemiological season, university hospitals of Lyon and Saint-Etienne, France, epidemiological seasons 2018/19−2020/21



Casalegno and VRS study group in Lyon. Euro Surveill. 2021;26(29):pii=2100630.

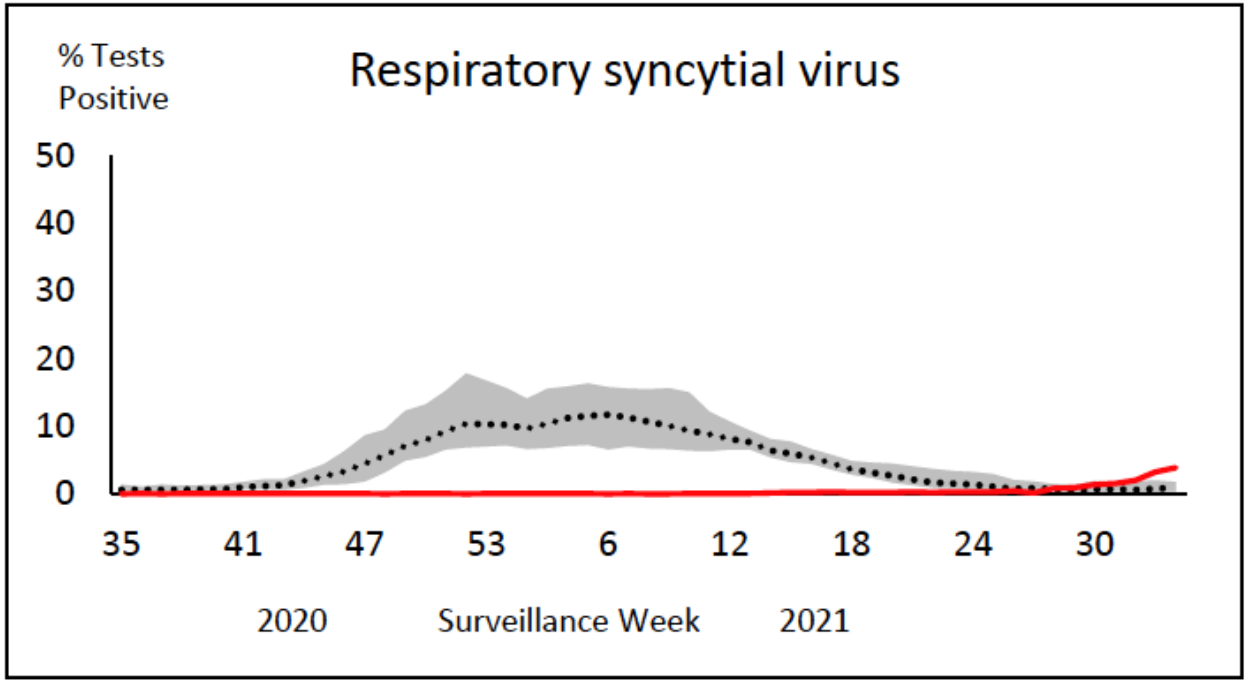
The impact of COVID-19 nonpharmaceutical interventions (NPI) on the future dynamics of endemic RSV

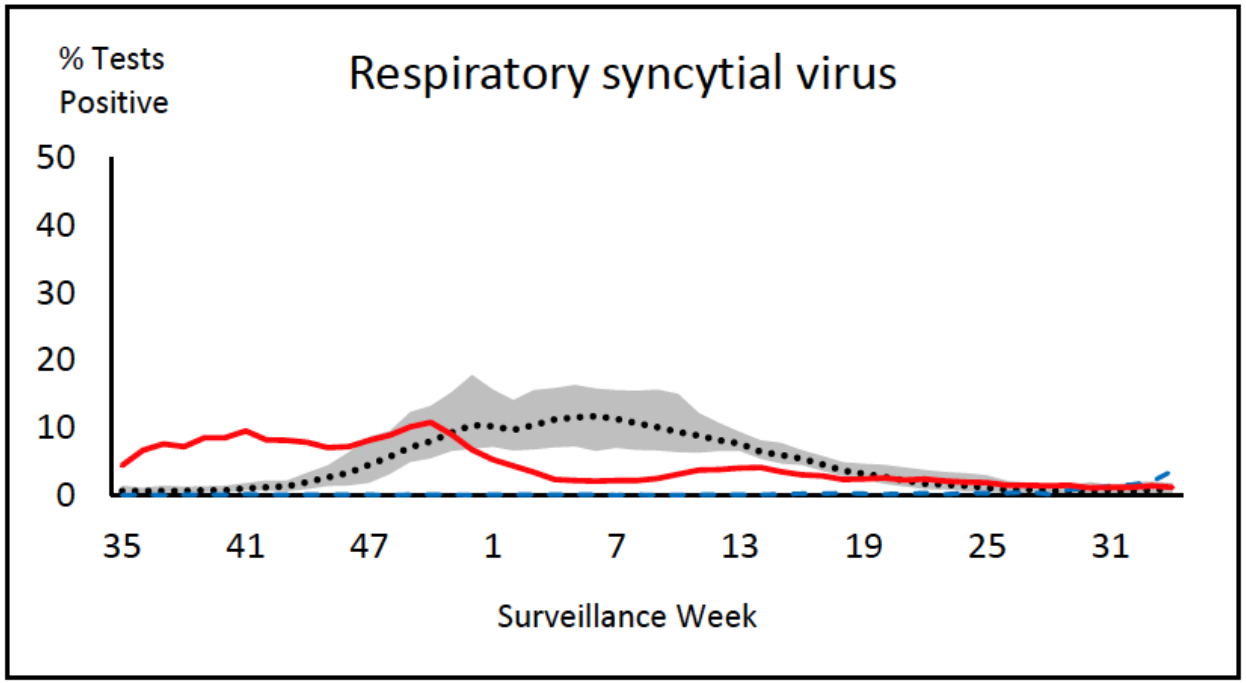


- **The RSV-susceptible population increases while NPIs in place.**
- **Using models fit to historic cases of RSV, they project large future outbreaks may occur following a period of extended NPIs.**
- **Peak outbreaks likely occurring in the winter of 2021–2022**
- **These outbreaks, which may reach peak numbers in the winter, could increase the burden to healthcare systems.**

Baker et al. PNAS December 1, 2020 117 (48) 30547-30553

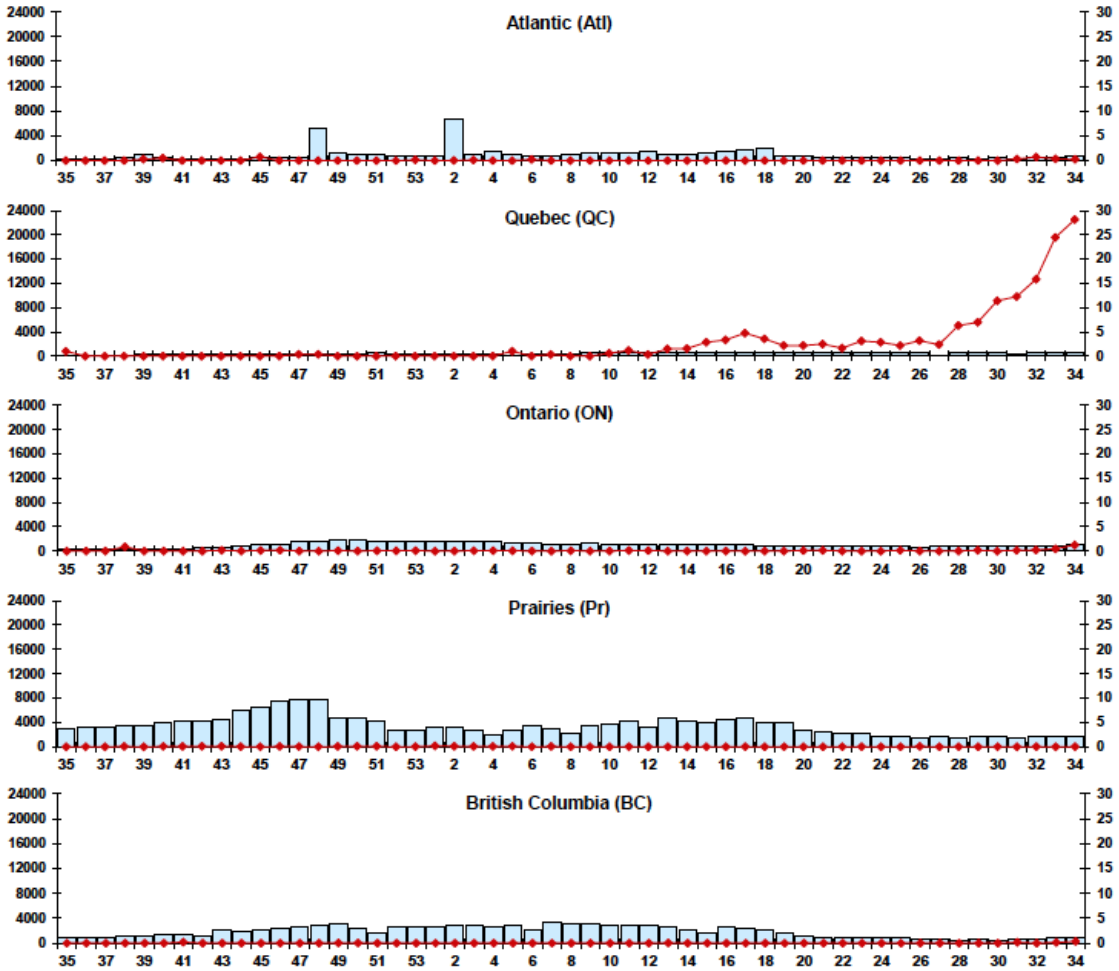
RSV in Canada: 2020-21 vs. 2021-22



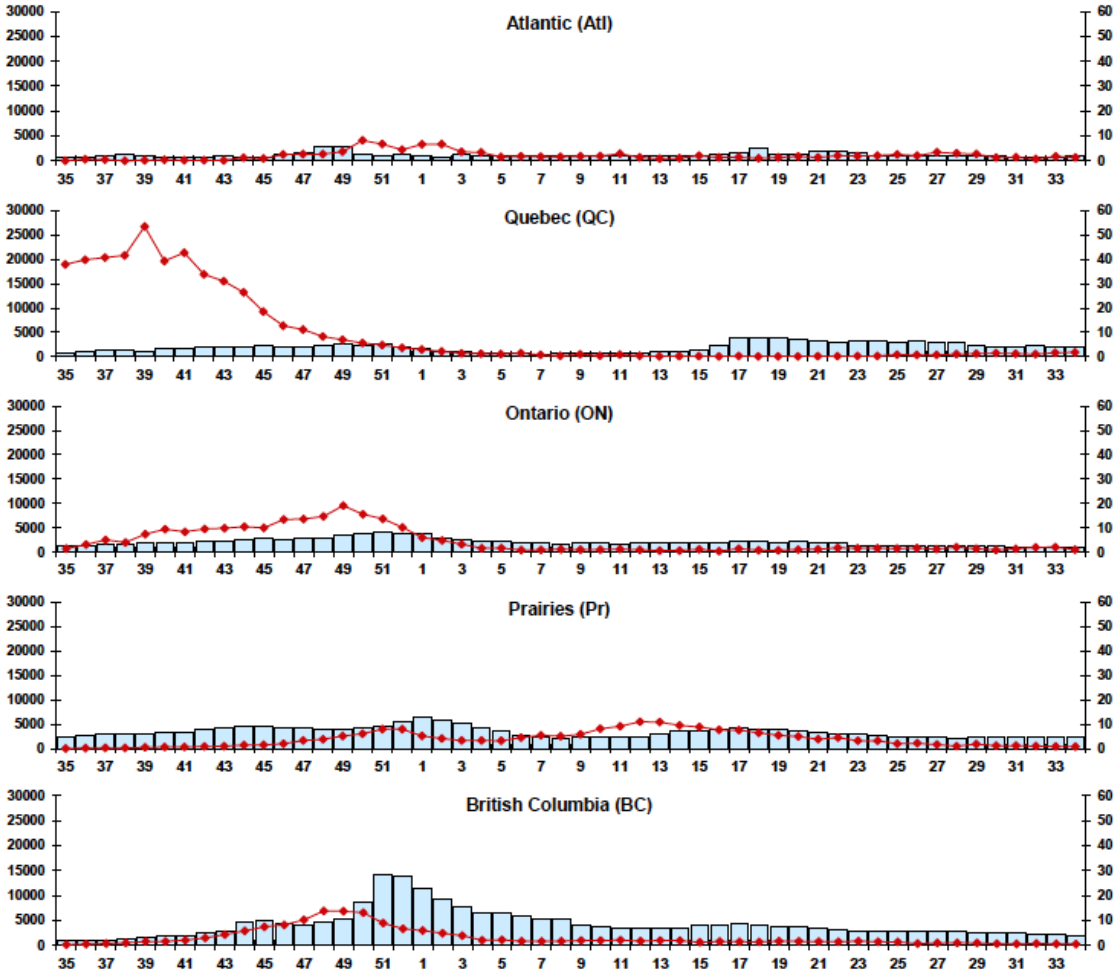


https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/respiratory-virus-detections-canada/2021-2022/week-34-ending-august-27-2022/week-34-ending-august-27-2022.pdf

RSV 2021-22: Quebec led the way!



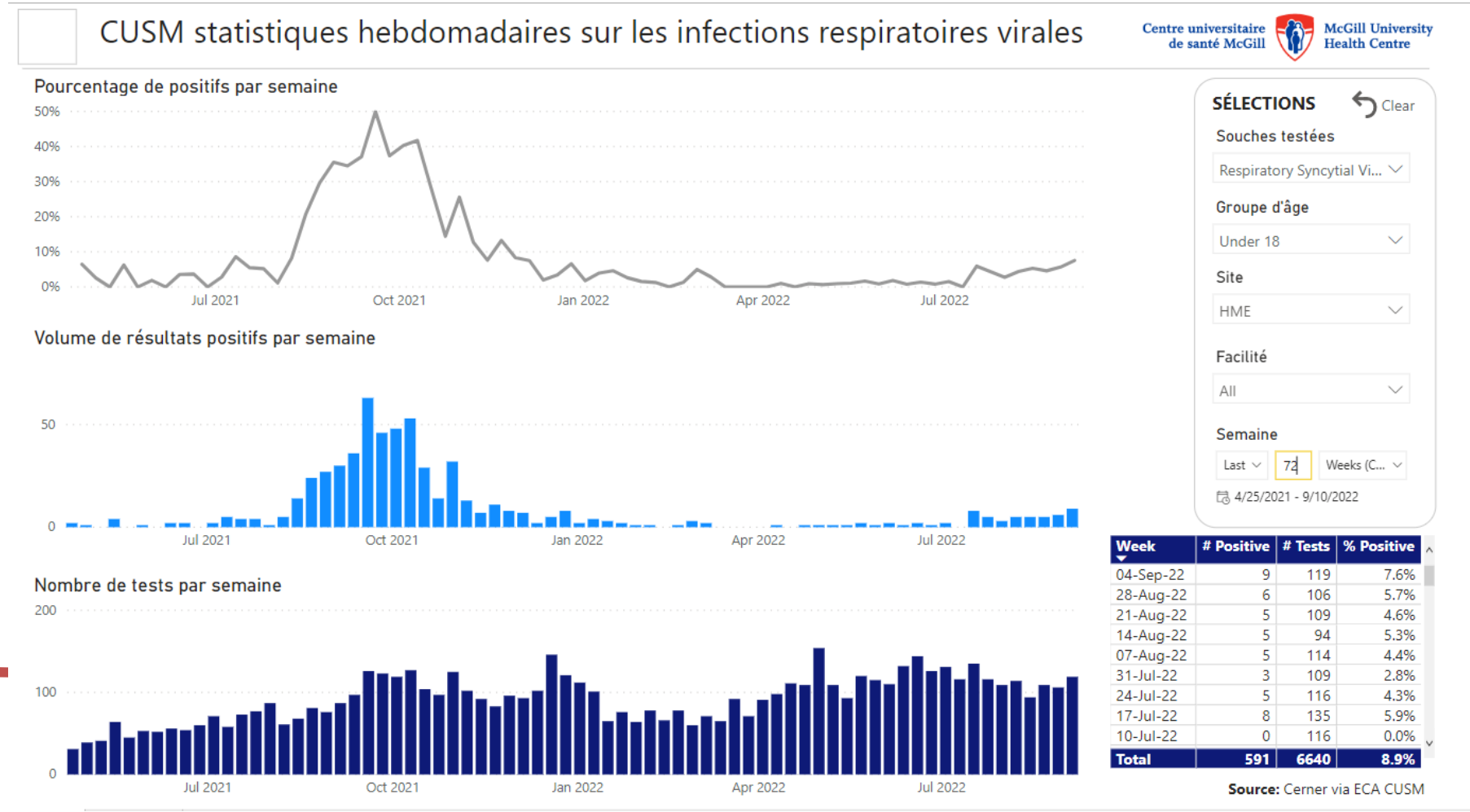
2020-2021



2021-2022

https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/respiratory-virus-detections-canada/2021-2022/week-34-ending-august-27-2022/week-34-ending-august-27-2022.pdf

RSV positivity in Montreal ~5% since mid-July: **Early start to 2022-23 palivizumab prophylaxis Sept. 19th**



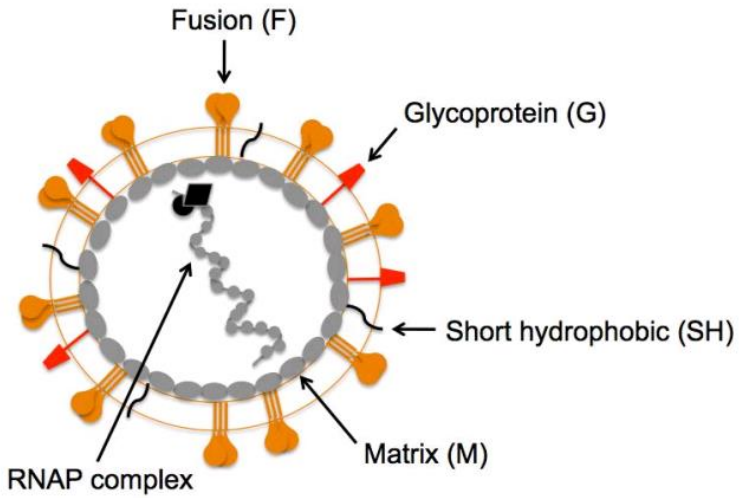
Week	# Positive	# Tests	% Positive
04-Sep-22	9	119	7.6%
28-Aug-22	6	106	5.7%
21-Aug-22	5	109	4.6%
14-Aug-22	5	94	5.3%
07-Aug-22	5	114	4.4%
31-Jul-22	3	109	2.8%
24-Jul-22	5	116	4.3%
17-Jul-22	8	135	5.9%
10-Jul-22	0	116	0.0%
Total	**591**	**6640**	**8.9%**

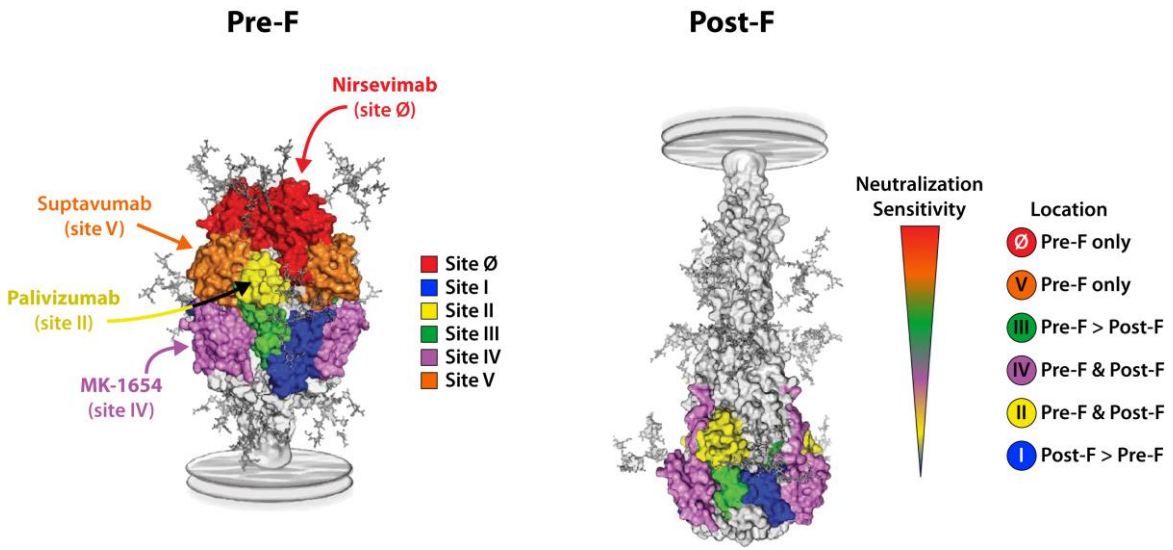
Étant donné l'augmentation de l'activité du VRS au Québec, l'INSPQ a émis une recommandation afin de devancer la saison 2022-2023 (voir calendrier à la page 2). Un suivi serré de l'épidémiologie sera effectué afin de déterminer la fin de la saison 2022-2023.

PASSIVE IMMUNIZATION AGAINST RSV

Palivizumab

- Palivizumab (Synagis®):
  - Monoclonal antibody that binds the RSV fusion protein (RSV-F), the major antigenic determinant
  - Licensed for prevention of RSV LRTI in high-risk children
- PZB immunoprophylaxis:
  - Monthly administration during RSV season reduces hosp. risk for RSV by **55%** in premature infants with or without CLD[1] and by **45%** in infants with hemodynamically significant CHD[2]
  - Specific recommendations regarding its targeted use: and CPS, AAP and NACI [3,4,5]





Mejias et al. Ann All Asthma Imm 2020

1-IMpact-RSV Study Group. *Pediatrics* 1998; 2-Feltes et al. *J Pediatr* 2003; 3- CPS. *Paediatr Child Health* 2015; 4- AAP. *Pediatrics* 2014

Position statement

Preventing hospitalizations for respiratory syncytial virus infection

Joan L Robinson, Nicole Le Saux; Canadian Paediatric Society
, Infectious Diseases and Immunization Committee
Paediatr Child Health 2015;20(6):321-26
Posted: Sep 8 2015 **Updated:** May 12 2016

Canadian Paediatric Society

- More restrictive indications for palivizumab use
  - Born @ <30 wk GA and <6 months of life at start of season
  - HD significant cardiac disease and <12 months of life
  - BPD / CLD and <12 months of life, or <24 months if recent O2 needs
- Broader indications:
  - Infants in remote communities who would require air transportation for hospitalization born before 36 + 0 weeks' GA and <6 months of age at the start of RSV season
  - Consideration may be given to administering palivizumab during RSV season to **term Inuit infants** until they reach six months of age

http://www.cps.ca/en/documents/position/preventing-hospitalizations-for-rsv-infections

Frist NACI Recommendations on Palivizumab since 2003!!!

Published June 2022

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants

https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/palivizumab-respiratory-syncitial-virus-infection-infants.html

Paediatrics & Child Health, 2021, e115–e120
doi: 10.1093/pch/pxz166
Original Article
Advance Access publication 20 February 2020

Original Article

The palivizumab patchwork: Variation in guidelines for Respiratory Syncytial Virus prevention across Canadian provinces and territories

Matthew Jalink MSc[1], Joanne M. Langley MD MSc[1,2,3,]

Table 1. Eligibility for palivizumab prophylaxis in the 2018 to 2019 season in Canadian provinces and territories compared to CPS recommendations

NACI: *Consider for*
- *<12 months of age with haemodynamically significant chronic cardiopathy other than congenital*
- *12-24 months awaiting heart transplant or having received a heart transplant within 6 months of onset of the RSV season*

	Canadian Paediatric Society Eligibility Criteria:			
	Recommended:			
	Congenital heart disease[1] on treatment[2]	Chronic lung disease[3] on treatment[2]	Prematurity (<30 WGA + 0 days)[4]	Remote Community[5]
	<12 MOA or <24 MOA on oxygen[6]		< 6 MOA at start of RSV season	<36 + 0 WGA and < 6 MOA[7]
Province or Territory				
AL	< 24 MOA	< 24 MOA	≤ 28 6/7 WGA , 29 0/7-32 6/7 WGA + CA; 33 0/7 -35 6/7 + CA + RF; MB	In risk score
BC	< 12 MOA	< 12 MOA	< 29 WGA + CA; 29 0/7 - 34 6/7 WGA + CA + RF	In risk score
MN	<12 MOA; A if 12–23 MOA	< 24 MOA	< 33 WGA; 33–35 WGA + RF	33–35 WGA
NB	< 24 MOA	< 24 MOA	≤ 32 0/7 WGA;32 + 1/7 WGA - 35 WGA + RF	
NL	≤ 12 MOA	< 12 MOA	√	√
NT	< 24 MOA	≤ 24 MOA	< 32 6/7 WGA; 33 0/7 - 35 6/7 WGA + RF	In risk score
NS	< 24 MOA	< 24 MOA	√	
NU	< 12 MOA	< 24 MOA	< 35 + 6/7 WGA	√
ON	<24 MOA	< 24 MOA	< 32 WGA + 0/7; 33–35 WGA +RF	33–35 WGA + CA
PE	< 24 MOA	< 24 MOA	√	
QC	< 12 MOA	< 24 MOA	<33 WGA	and term infants < 3 MOA
SK	< 24 MOA	< 24 MOA	<30 WGA; <33 WGA + CA; < 36 WGA + RF	√
YT	< 12 MOA, < 24 months: A	< 12 MOA, if 13 to < 24 MOA then A	< 29 0/7 WGA + CA; 29 0/7 - 34 6/7 WGA + RF	In risk score

NACI:
Recommended for
- <36wGA in remote northern Inuit communities who would require air transport for hospitalization
Consider for
- *term infants aged <6 months living in remote Inuit communities with very high rates of hospitalization for RSV among term infants*
- *Infants of < 36 wGA and age <6 months living in other remote communities with high rates of hospitalization for RSV and where air transport would be required for hospitalization*

Jalink and Langley. *Paed & Child Health* 2021.

***NACI**: consider if <24 months and recent/ongoing O2 or assisted ventilation*

***NACI**: consider if <24 months and severe immunodeficiency*

	Should not routinely be offered to:				
	Immuno deficiency	**Down syndrome**	**Cystic Fibrosis**	**Upper airway obstruction**	**Other Chronic pulm. disease**
Province or Territory					
AL		< 12 MOA	A	Congenital	MecA or GERD on oxygen, lung anomaly
BC		A	A		Home respiratory support <24 MOA
MN					
NB					
NL					
NT		< 12 MOA	< 24 MOA		
NS					
NU					
ON		< 24 MOA			
PE					
QC			< 24 MOA	< 24 MOA	
SK	A	A	< 12 MOA		
YT		A	A		

Jalink and Langley. *Paed & Child Health* 2021.

Risk scores/criteria for healthy pre-term infants

Table 2. Risk scores used by provinces and territories

PICNIC risk score	Provincial-territorial risk scores											
	AL	BC (and YT)	MB	NB	NL	NT	NS	NU	ON	PEI	QC	SK
Born during Respiratory Syncytial Virus season	Nov–Feb	Nov–April (variable points)	Nov–Mar	Nov–Jan		Nov–Feb			Nov–Jan			Nov–Feb
Male	✓	✓	✓	✓		✓			✓			✓
SGA	✓	✓	✓	✓		✓			✓			✓
Subject or siblings attend daycare	✓ (<4 years of age)	✓ (in first 3 months postdischarge)	✓	✓		✓ (<4 years of age)			✓			✓
Any preschool sibling		✓ (age < 5 years)										--
> 1 smoker in household	✓	≥ 2	≥ 2	≥ 2		✓			✓			≥ 2
> 5 persons in household	✓	≥ 6	✓	✓		✓			✓			≥ 6
No eczema in first-degree relative			✓	✓					✓			✓
Other factors	Remote location Multiple birth of eligible sibling	Remote location Multiple birth of eligible sibling	33 - 35 WGA			Remote location Twin of eligible sibling						
	33 + 0/7 - 35 + 6/7 WGA	29–30 6/7 WGA Female not breastfeeding		32 + 1/6 - 35 WGA + CA		33 + 0/7 - 35 + 6/7 WGA + CA			33 - 35 WGA + CA			33 - 35 +0/7 WGA

Jalink and Langley. *Paed & Child Health* 2021.

NACI 2022: PVZ may be considered for infants of **30 to 32+6 wGA** aged *< 3 months* at the onset of or during the RSV season if they are at *high risk of exposure* to RSV from day care attendance or presence of another preschool child or children in the home. (Discretionary NACI Recommendation)

Impact of the Withdrawal of Palivizumab Immunoprophylaxis on the Incidence of Respiratory Syncytial Virus (RSV) Hospitalizations Among Infants Born at 33 to 35 Weeks' Gestational Age in the Province of Quebec, Canada: The RSV-Quebec Study

Jesse Papenburg,[1,2,3] Isabelle Defoy,[4] Edith Massé,[5] Georges Caouette,[6] and Marc H. Lebel[7]

Table 1. Incidence of Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations (RSV-H) and Laboratory-Confirmed RSV-H by Season Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

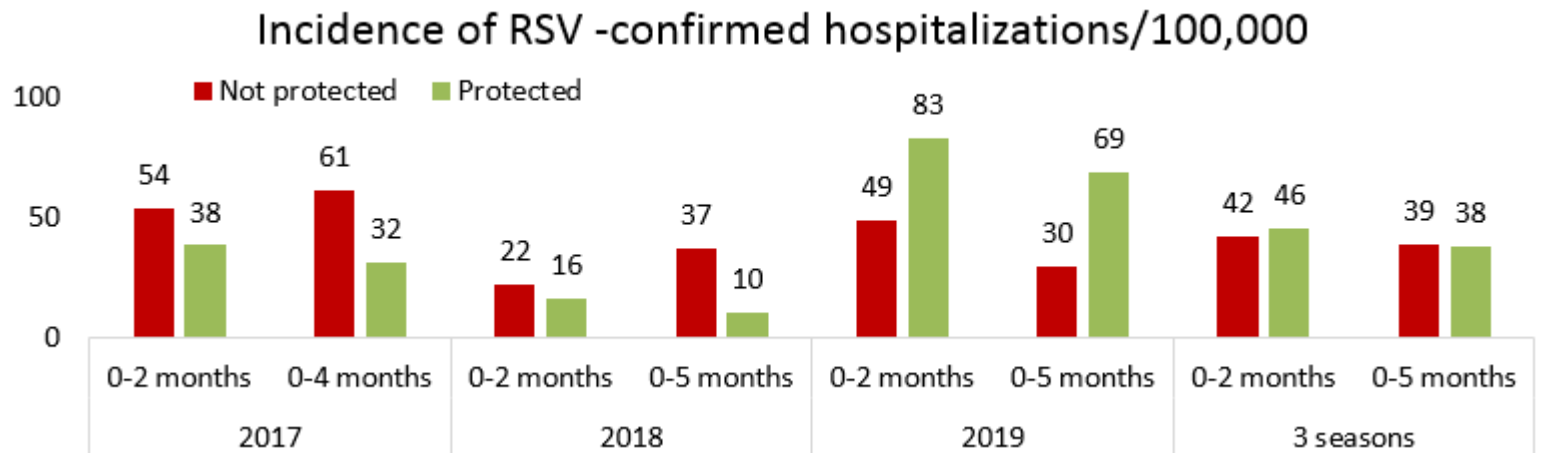
Characteristic	Season 1	Season 2	Season 3	Season 4
Total LRTI/RSV-H	45	60	58	72
Total births (33–35 wGA)	1697	1656	1633	1471
Incidence by season, %	2.65	3.62	3.55	4.89
Incidence by period, %	3.13		4.19	
Total laboratory-confirmed RSV-H	42	55	41	65
Total births (33–35 wGA)	1697	1656	1633	1471
Incidence by season, %	2.47	3.32	2.51	4.42
Incidence by period, %	2.89		3.41	

Table 5. Multivariable Logistic Regression Models for Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations (RSV-H) and for Laboratory-Confirmed RSV-H Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

Covariate	LRTI/RSV-H Primary Model	LRTI/RSV-H Adjustment for Season Intensity	RSV-H	RSV-H Adjustment for Season Intensity
Season intensity in Quebec[a]	NA	4.42 (1.07–18.23)	NA	12.15 (2.47–59.82)
Season group				
Seasons 3 and 4 vs. seasons 1 and 2	1.36 (1.04–1.76)	1.57 (1.18–2.11)	1.19 (0.9–1.58)	1.50 (1.11–2.03)
wGA: 33 vs 35	0.99 (0.69–1.42)	0.98 (0.68–1.41)	0.98 (0.68–1.47)	0.98 (0.67–1.45)
wGA: 34 vs 35	1.05 (0.79–1.41)	1.06 (0.79–1.42)	1.10 (0.81–1.50)	1.11 (0.81–1.52)
Male sex	1.17 (0.90–1.54)	1.18 (0.91–1.54)	1.16 (0.87–1.54)	1.17 (0.88–1.55)
Birth month group of November, December, January vs other months	1.62 (1.23–2.14)	1.62 (1.23–2.14)	1.69 (1.26–2.26)	1.69 (1.26–2.27)

Papenburg et al. *JPIDS* 2021

PVZ effectiveness, **healthy full-term infants**, Nunavik QC, 2017-2019

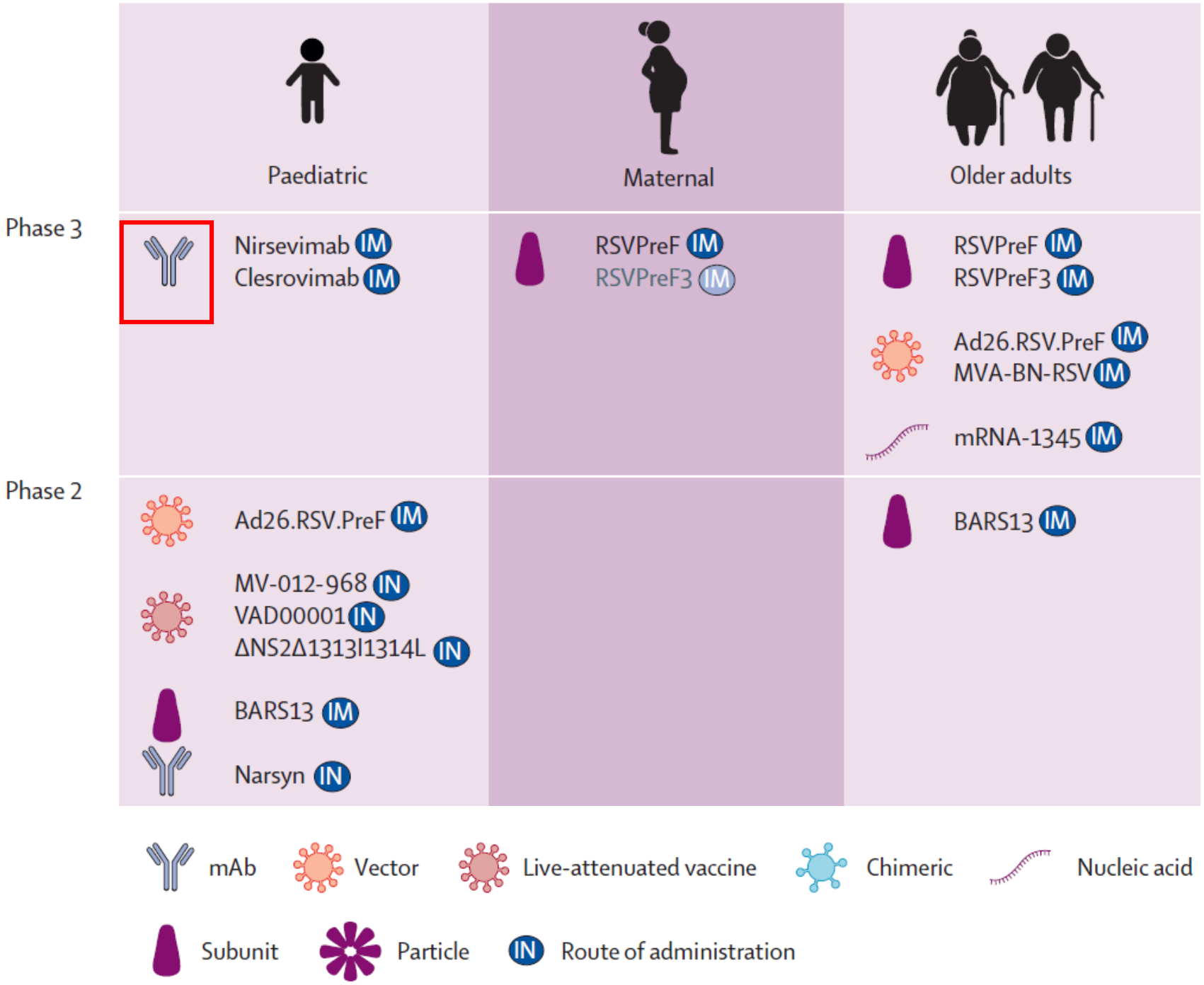


Season	Age	Incidence/100,000 in not protected	Incidence/100,000 in protected	Effectiveness	95% CI
2017	0-2 months	54	38	29%	-882% to 95%
	0-4 months	61	32	48%	-351% to 96%
2018	0-2 months	22	16	28%	-5518% to 99%
	0-5 months	37	10	73%	-234% to 99%
2019	0-2 months	49	83	-70%	-992% to 67%
	0-5 months	30	69	-133%	-1293% to 47%
3 seasons	**0-2 months**	**42**	**46**	**-9%**	**-281% to 67%**
	0-5 months	**39**	**38**	**3%**	**-169% to 65%**

Slide courtesy Dr Rodica Gilca, INSPQ. Prev Med Rep. 2020

UPCOMING PROPHYLACTIC STRATEGY: NIRSEVIMAB

Fast-track evaluation by FDA and EMA underway



Mazur *et al*, Lancet ID 2022

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Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

- RCT Nirsevimab vs placebo
- Healthy, born preterm (29-35 weeks)
- Single i.m. injection at the start RSV season

Table 2. Medically Attended Lower Respiratory Tract Infection and Hospitalization Associated with Respiratory Syncytial Virus (RSV) through 150 Days after Dose.*

End Points and Analyses	Nirsevimab (N=969)	Placebo (N=484)	Relative Difference (95% CI)	P Value
	number (percent)		%	
Medically attended RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			70.1 (52.3–81.2)	<0.001
Observed events	25 (2.6)	46 (9.5)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	25 (2.6)	46 (9.5)	72.9 (56.5–83.1)	<0.001
Hospitalization for RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			78.4 (51.9–90.3)	<0.001
Observed events	8 (0.8)	20 (4.1)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	8 (0.8)	20 (4.1)	80.0 (55.0–91.1)	<0.001

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

N ENGL J MED 386;9 NEJM.ORG MARCH 3, 2022

- RCT Nirsevimab vs placebo
- Healthy, term (>35 w)
- Single i.m. injection at start RSV season
- **NNT to avert one hospital admission >50**

Table 2. Medically Attended Lower Respiratory Tract Infections and Hospitalizations Associated with Respiratory Syncytial Virus (RSV) through 150 Days after the Injection.*

End Point and Analysis	Nirsevimab (N=994)	Placebo (N=496)	Efficacy (95% CI)†	P Value
	no. (%)			
Medically attended RSV-associated lower respiratory tract infection			74.5 (49.6 to 87.1)	<0.001
Poisson regression with robust variance				
Observed events	12 (1.2)	25 (5.0)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		
Hospitalization for RSV-associated lower respiratory tract infection			62.1 (−8.6 to 86.8)	0.07
Poisson regression with robust variance				
Observed events	6 (0.6)	8 (1.6)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		

Conclusions

- Strict non-pharmacological interventions including lockdowns abruptly stopped RSV circulation in Canada starting March 2020 until spring/summer 2021
  - Less global connectivity = less seeding of the virus
  - Less local connectivity = less interregional seeding of the virus
  - Less community contact = slower growth/transmission
- A shorter/milder/earlier 2021-22 season means
  - RSV susceptible population may higher than usual in many regions
  - Many children born in the last 12 months have not been exposed to RSV
- The timing, intensity, and age distribution of the RSV epidemic may not be typical in 2022-23 and may vary across Canadian regions
- It is important to be aware of your province's guidelines/indications for palivizumab immunoprophylaxis