✉ RSV-P? ✉

Inviting New Products for Infant Respiratory Syncytial Virus Prevention to Canadian Practice

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Introduction

- Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infection (ALRI) in young children[1].
- Children in the Canadian Arctic are more vulnerable to severe RSV infection:
  - Northern Canada: 176/1000 infants hospitalized[2]
  - Southern Canada: 11/1000 infants hospitalized[3]
- Transporting northern infants for hospitalization presents a large economic burden.

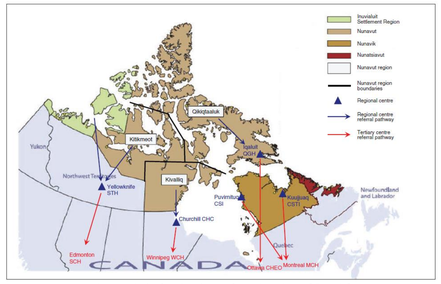


Fig 1: Typical referral pathways for Inuit regions of Canada[2]

- Previously, the only available product for preventing RSV infections in infants was palivizumab, a monoclonal antibody. This product is expensive, requires monthly administration during the RSV season, and is only available for infants with the highest risk of RSV complications.

- New products for RSV infection prevention in infants:
  - **Nirsevimab:** a long-acting monoclonal antibody approved in Canada in April 2023. One dose lasts an entire RSV season.
  - **Abrysvo™:** a vaccine that can be given to pregnant women in their third trimester to protect their infants after birth. Health Canada accepted Abrysvo™ for review in April 2023. It was approved in the U.S. in August 2023.
  - *(Note: the Arexvy™ vaccine was approved in Canada this year; this vaccine is only indicated for older adults.)*

- The questions of cost-effectiveness:
  - Which product is more cost-effective?
  - Is it cost-effective to administer these products universally?
  - If not, who should receive these products?
  - Who is at highest risk of severe RSV infection?
  - Who uses the most resources once infected?

- Properly evaluating an infectious disease requires considering the complexities of disease spread. For example:
  - Vaccinating mothers with **Abrysvo™** theoretically doubles the number of additional people with immunity compared to administering **nirsevimab** to babies only. How might this impact the overall spread of RSV?
  - Older adults also experience higher risk of severe RSV infection. Can reducing infection in younger populations indirectly affect infection rates and resource use in older adults?

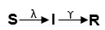
- We will address these questions using a dynamic transmission model of RSV within a cost-effectiveness framework.
- Nourbakhsh et al (2021)[4] evaluated these new strategies for Nunavik, Quebec.
- **No published studies have evaluated the cost-effectiveness of these new products in the wider Canadian context.**

Methodology - Overview

- Modelling infectious diseases can be done using static or dynamic methods[5].
  - Static models assume a constant infection risk (λ). They can only assess the direct effects of vaccination.

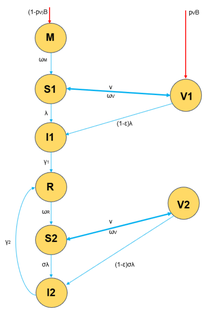
  - Dynamic models allow the infection risk (λ) to vary (more infected individuals = higher infection risk). They can assess the indirect effects of vaccination.

- In a basic dynamic transmission model:
  - The population is divided into disease "compartments".
    - S: Susceptible
    - I: Infected
    - R: Recovered



  - The number of people in each compartment varies over time as people become infected and recover. Differential equations describe these rates of change.

- **A dynamic transmission model for RSV[6]:**
  - Immunity is incomplete; reinfection is possible.
  - Repeat infections have reduced duration and severity; the model should differentiate between first and subsequent infections.
  - Infants are born with protection from natural maternal antibodies.
  - The model must capture our intervention strategies; a "vaccinated" compartment should be introduced.



M: maternally protected
S1: susceptible, naïve
I1: experiencing first infection
R: recovered, temporarily immune
S2: susceptible, non-naïve
I2: experiencing second or greater infection

V1: "vaccinated", naïve
V2: "vaccinated", non-naïve

Fig 2: Model design without age strata

- As well, RSV severity is age-dependent. The model must be age-stratified with individuals able to transition through age strata.

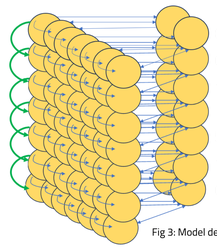


Fig 3: Model design with age strata

- The entire population is divided into 7 age strata. At each age level, individuals move through the disease compartments. Every compartment includes an "aging rate" at which individuals age into the equivalent compartment, one age group older.

Methodology - Mathematics

The rate of change for each disease compartment is described by differential equations. For example, the S1 (susceptible, naïve) compartments are described by:

$$\frac{dS1_a}{dt} = \underbrace{\omega_M M_a + \omega_V V1_a - (\lambda + \mu + \nu)S1_a}_{\text{Transmission Terms}} \quad \underbrace{- \kappa_a S1_a + \kappa_{a-1} S1_{a-1}}_{\text{Aging Terms}}$$

Entry:

$\omega_M M_a$:	entry from M compartment as maternal immunity wanes
$\omega_V V1_a$:	entry from V1 compartment as vaccination immunity wanes
$\kappa_{a-1} S1_{a-1}$:	entry from S1 compartment in the previous age strata as individuals age

Exit:

$(\lambda + \mu + \nu)S1_a$:	(λ) exit to I1 compartment as individuals become infected (μ) exit to "Death" at a baseline mortality rate (ν) exit to V1 compartment as individuals are vaccinated
$\kappa_a S1_a$:	exit to S1 compartment in the next age strata as individuals age

The infection risk in age group i is:

$$\lambda_i = \underbrace{\beta_o \left(1 + b_1 \cos\left(\frac{2\pi t}{52} + \phi\right)\right)}_{\text{Cosine seasonal forcing term}} \sum_{j=1}^{7} \underbrace{\frac{C_{i,j}(I1_j + I2_j)}{N_j}}_{\text{The average number of daily contacts with age group j (see matrix), multiplied by the probability of each contact being infectious.}}$$

Table 2: Contact Matrix[7]

	0 to 5 mo	6 to 11 mo	12 to 23 mo	2 to 4 y	5 to 17 y	18 to 64 y	65+ y
0 to 5 mo	0.27	0.27	0.27	0.27	0.04	0.04	0.01
6 to 11 mo	0.27	0.27	0.27	0.27	0.04	0.04	0.01
12 to 23 mo	0.56	0.56	0.56	0.56	0.09	0.08	0.02
2 to 4 y	1.78	1.78	1.78	1.78	0.30	0.25	0.07
5 to 17 y	1.41	1.41	1.41	1.41	7.56	1.53	0.43
18 to 64 y	5.09	5.09	5.09	5.09	5.93	11.45	2.27
65+ y	0.42	0.42	0.42	0.42	0.56	0.70	1.36

Table 1: Parameters

$\delta_{i,j}$	Kronecker delta	$\delta_{a,1}$ equals 1 for the first age group, and zero thereafter
p_V	Proportion of infants born vaccinated	Intervention dependent
B	Birth rate	Geography dependent
$1/\omega_M$	Average duration of maternal immunity	112 days[8]
$1/\omega_R$	Average duration of post-infection immunity	202.8 days[9]
μ	Baseline mortality rate	Age dependent
ν	Vaccination rate	Intervention dependent
λ	Infection risk	See equation
κ_a	Aging rate of age group a	1/width of age strata
$1/\gamma_1$	Average duration of first infection	6.16 days[10]
$1/\gamma_2$	Average duration of subsequent infections	5.36 days[10]
σ	Reduced susceptibility to infection after a primary infection	0.757[11]
ε	Intervention efficacy	Intervention dependent
$C_{i,j}$	Contact matrix of average number of daily contacts of an individual in age group i with age group j.	See matrix
Seasonal forcing terms:		
β_o	Average transmission rate	0.121/day[12]
B_1	Amplitude of seasonal fluctuation	0.246[12]
ϕ	Seasonal phase shift	-20 days[12]

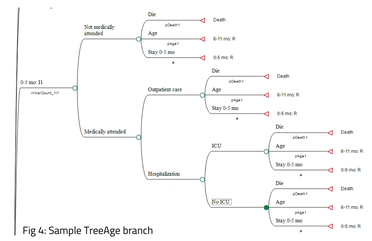


Fig 4: Sample TreeAge branch

The model is run using TreeAge Pro 2023 R 1.2. The disease pathways for an "Infected" compartment are shown. Costs and utilities are incurred within each "Infected" compartment.

Expected Outputs and Significance

- The model will compare the following strategies:
  - Nirsevimab administered to infants under 6 months
  - Nirsevimab administered to infants under 12 months
  - Abrysvo vaccine administered to pregnant women
  - No intervention

- Prevention strategies will be evaluated separately for each geographical region:
  - Nunavut
  - Northwest Territories
  - Nunavik, Quebec
  - Southern Canadian provinces + the Yukon

- Model output for each strategy:
  - Cost ($ CAD)
  - Quality-Adjusted Life Years (QALYs) gained
  - Incremental Cost-Effectiveness Ratio (ICER) compared to the next strategy

$$ICER = \frac{incremental\ cost\ (\$)}{incremental\ effectiveness\ (QALY)}$$

  - # infections averted
  - # hospitalizations averted
  - Cost $/hospitalization averted

  - For products without a listed price (Abrysvo™), the above results can be calculated for a range of likely prices. The model can then be used to calculate a maximum purchasing price per dose for the product at which it remains cost-effective compared to alternative strategies.

- The results of this study should help inform public policy as the landscape of RSV prevention in Canada shifts and decisions must be made regarding coverage for these new products.

- Other products for RSV infection prevention are in various stages of development, including at least 3 other monoclonal antibodies and 10 pediatric vaccines[13]. In addition, the Arexvy™ vaccine was licensed in Canada this year for older adults. While this model is currently designed to evaluate nirsevimab and Abrysvo™ for RSV prevention in infants, it can be adapted with relative ease to evaluate other products and/or populations in the field of RSV infection prevention in the future.

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