ESTIMATING THE UNDERLYING BURDEN OF RESPIRATORY SYNCYTIAL VIRUS INFECTION AMONG CHILDREN AND ADULTS IN ONTARIO, CANADA: A MODELLING STUDY

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BACKGROUND

- Respiratory syncytial virus (RSV) is the leading cause of lower respiratory infections among children globally.
- Mathematical models can be used to characterize annual RSV seasonal epidemics, investigate underlying disease dynamics and are valuable tools to assess the impact of emerging RSV vaccines.
- Currently, validated RSV transmission models are scarce, and none have been developed for a Canadian population.
- **Objective: we developed a compartmental age-structured model for RSV transmission in Ontario, validated using linked population-based RSV hospitalization records for Ontario infants <2yo**

METHODS

- **Model Structure:** We developed an age-structured, deterministic compartmental mathematical model for RSV transmission, including the following states: susceptible (S), exposed (E), infectious (I), recovered (R).
- Additional S-E-I states were added to distinguish first-time RSV infections from subsequent infections. We also captured maternally derived immunity (M). (Figure 1)
- We included the following 7 age groups: <1, 1-2, 2-4, 5-19, 20-49, 50-64, and 65+
- We assumed a life expectancy of 82 years.
- Mixing between age groups was based on the POLYMOD study, using reported contacts rates for the UK.
- Seasonal transmission was simulated using a cosine forcing function.
- **Model Fitting:** Fitting was performed through Latin hypercube sampling (LHS). Specifically, the top 1% best-fitting parameter sets (based on maximum likelihood) were selected from 10,000 simulated plausible parameter sets to inform the following: latency period, infectious period, duration of natural immunity, and 3 seasonal transmission coefficients.
- **Data**: We fit the model to population-based monthly RSV-related hospitalization (H) data for Ontario infants <2 yo for the period April 2002 through December 2014.
- **Software:** We used the deSolve package in R **v3.6.1** to solve the above set of 56 ordinary differential equations (R Core Team, 2019).

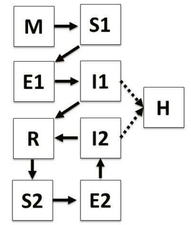

Figure 1. Model schematic

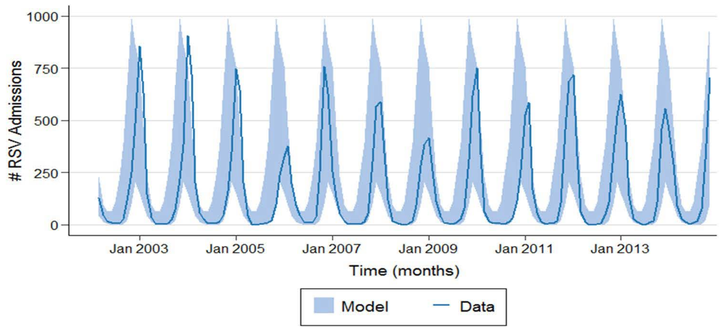

Figure 2. Observed versus predicted number of monthly hospital admissions for RSV among Ontario infants <2yo

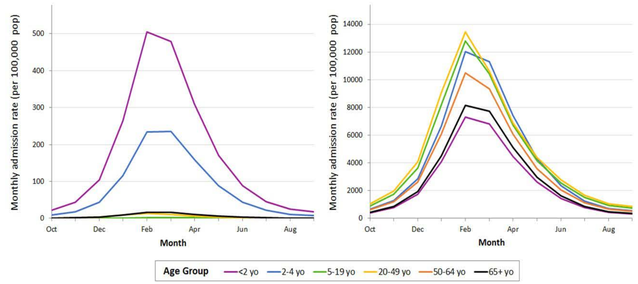

Figure 3. Predicted monthly age-specific RSV admission rate (left) and incidence (right), per 100,000 population, average of top 1% best-fitting parameter sets*
**Figures shown on different scales.*

CONCLUSIONS

Our age-structured model, based on routinely collected population data, accurately captures the observed seasonal RSV epidemic curves.

This validated base model can be further adapted to investigate the potential impacts of emerging RSV vaccination strategies on RSV incidence and admissions across the age continuum.

RESULTS & DISCUSSION

- 19,655 RSV-related admissions were identified over the nearly 13-year study period in this population-based cohort of Ontario infants <2yo.
- Our model accurately reproduced observed patterns in seasonal RSV epidemic peaks; i.e., approximately 600 monthly admissions occurring annually around February among children <2yo.
- Ranges for model parameters that could replicate the patterns in the data were identified based on the top 1% of LHS parameter sets (Fig 2; Table 1).
- Based on this model, we estimate the burden of severe RSV disease to be greatest among children <5yo. We also estimate a large (likely under-diagnosed) burden of RSV among older adults, 65+yo.
- Our model also suggests RSV re-infection is common throughout the life course, particularly among reproductive-aged adults (i.e., 20-49 yrs) (Fig 3).
- Notably, the magnitude of these predicted admission rates are comparable to recently published age-specific estimates for the Canadian population; e.g., 10, 1, 0.05, 0.10, 0.05 and 0.5 per 10,000 pop. for <2, 2-4, 5-16, 17-44, 45-64 and 65+ yos (Reference: Schanzer DL et al. IORV 2018; 12(1):113-21).
- Reliable population-based data on RSV burden among older populations is currently limited; thus, we could not fit our model within older age groups.

TABLE 1. Overview of model parameter values

Parameter	Value	95% CI	Source
Latency period	3.5 d	(2.0, 5.9)	Fitted
Infectious period	14.6 d	(10.7, 19.3)	Fitted
Natural immunity duration	146 d	(102, 268)	Fitted
Maternal derived immunity	106 d	N/A	Lit
Reduced infectiousness, subsequent infection	75%	N/A	Lit
Transmission coefficient	1.5741	(1.0, 3.4)	Fitted
Seasonal oscillation	0.4736	(0.3, 0.8)	Fitted
Seasonal shift (years)	0	N/A	Est
Admission prob., 1st infection	3.5%	N/A	Lit
Admission prob., subsequent	0.35%	N/A	Est
Admission scale factor, adults	0.1	N/A	Lit
Admission scale factor, seniors	1.5	N/A	Lit

CI: Confidence Interval; d: days; Est: Estimated; Lit: Literature

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