Exploring the dynamics of respiratory syncytial virus (RSV) transmission in children

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Abstract

Respiratory syncytial virus (RSV) is the main cause of lower respiratory tract infections in children. Whilst highly seasonal, RSV dynamics can have either one-year (annual) or two-year (biennial) cycles. Further, some countries show a ‘delayed biennial’ pattern, where the epidemic peak in low incidence years is delayed. We develop a compartmental model for RSV infection, driven by a seasonal forcing function, and conduct parameter space and bifurcation analyses to document parameter ranges that give rise to these different seasonal patterns. The model is sensitive to the birth rate, transmission rate, and seasonality parameters, and can replicate RSV dynamics observed in different countries. The seasonality parameter must exceed a threshold for the model to produce biennial cycles. Intermediate values of the birth rate produce the greatest delay in these biennial cycles, while the model reverts to annual cycles if the duration of immunity is too short. Finally, the existence of period doubling and period halving bifurcations suggests robust model dynamics, in agreement with the known regularity of RSV outbreaks. These findings help explain observed RSV data, such as regular biennial dynamics in Western Australia, and delayed biennial dynamics in Finland. From a public health perspective, our findings provide insight into the drivers of RSV transmission, and a foundation for exploring RSV interventions.

Keywords: respiratory syncytial virus, infectious disease, mathematical modelling, bifurcation analysis, seasonality

14 1. Introduction

15 Respiratory syncytial virus (RSV) is one of the predominant causes of
16 respiratory tract infections in young children and seasonal epidemics are ob-
17 served globally. RSV detections are known to be age-dependent, with an
18 estimated 60% of children infected with RSV in their first year of life [1] and
19 almost all children infected by the time they turn two years of age [2, 3].
20 Fewer infections are detected in older children and adults. Immunity to RSV
21 following recovery from infection is partial and limited in duration, and re-
22 infection throughout early childhood is common [4, 5]. However, the specific
23 mechanisms of the immune response to RSV following recovery from an in-
24 fection are not well documented [4, 6] and the average duration of immunity
25 is not accurately known.

26 Winter RSV epidemics occur in many temperate countries, with few in-
27 fections in the summer months [7, 8, 9, 10]. However, the underlying drivers
28 of these seasonal patterns are not well understood. Weather-related factors
29 such as lower temperatures, higher rainfall and reduced sunlight, as well as
30 social factors such as indoor crowding in the colder and wetter months, are
31 all possible causes [11, 12].

32 Observed seasonality in the incidence of infectious diseases has implica-
33 tions for interventions. For RSV, prophylaxis with the monoclonal antibody
34 palivizumab has been found to be safe and effective for high-risk children
35 [13], although it is expensive and the timing of the RSV season must be
36 understood for effective implementation. There is currently no licensed vac-
37 cine for RSV, although several vaccines are being evaluated [14]. Phase two
38 clinical trials of an RSV vaccine have commenced by GlaxoSmithKline in
39 healthy women (NCT02360475) [15]. Phase three clinical trials of RSV F
40 nanoparticle vaccines for pregnant women (NCT02624947) and for the el-
41 derly (NCT02608502) have been commenced by Novavax [16, 17]. Rollout
42 of a future vaccination strategy will need to be based on a comprehensive
43 understanding of seasonality in order to optimise the timing of delivery.

44 Mathematical models play a key role in identifying the drivers of observed
45 patterns of infectious diseases, as well as informing the planning of poten-
46 tial health interventions [18]. Previous models of RSV have concentrated
47 on modelling the data from specific geographic regions [19, 20, 21], with
48 several studies suggesting that climatic factors drive seasonal transmission

49 [19, 22, 23]. The current literature, however, does not explain why seasonal
 50 dynamics differ between temperate locations. Recent work has identified
 51 that the interaction between demography and imperfect immunity can affect
 52 the dynamics of infectious diseases [24, 25]. Here, using a SEIRS model, we
 53 explore how the birth rate, waning immunity and seasonality might inter-
 54 act to yield different dynamics of RSV. We classify the numerical solutions
 55 produced by this model and identify the main parameters that contribute
 56 to different qualitative outputs. Finally, we link these findings to RSV data
 57 from different countries.

58 2. Model and parameter values

Figure 1: The schematic diagram for the SEIRS model for two age classes, where A refers to children under 12 months of age, and B refers to children between 12 and 24 months. The boxes represent disease states, and the arrows illustrate the progression of states of infection. The line representing the flow from recovered to susceptible individuals is dashed for visual clarity. Further details of the model formulation and terminology can be found in [26].

59 A deterministic, ordinary differential equation SEIRS model for RSV
 60 transmission is shown in Equation (1). A schematic diagram identifying the
 61 progression between disease states is provided in Figure 1, where S , E , I and
 62 R represent, respectively, the susceptible, exposed, infectious and recovered
 63 proportions of each age group. In order to capture the known epidemiology
 64 of RSV with respect to age, the model is compartmentalised for two age

65 classes: children 12 months of age and younger are denoted by A , and those
 66 between 12 and 24 months of age are denoted by B . This model was first
 67 presented in [27].

$$\begin{aligned}
 \frac{dS_A}{dt} &= \mu - \beta_A S_A (I_A + I_B) + \nu R_A - \eta S_A \\
 \frac{dE_A}{dt} &= \beta_A S_A (I_A + I_B) - \delta E_A - \eta E_A \\
 \frac{dI_A}{dt} &= \delta E_A - \gamma I_A - \eta I_A \\
 \frac{dR_A}{dt} &= \gamma I_A - \nu R_A - \eta R_A \\
 \frac{dS_B}{dt} &= \eta S_A - \beta_B S_B (I_A + I_B) + \nu R_B - \eta S_B \\
 \frac{dE_B}{dt} &= \eta E_A + \beta_B S_B (I_A + I_B) - \delta E_B - \eta E_B \\
 \frac{dI_B}{dt} &= \eta I_A + \delta E_B - \gamma I_B - \eta I_B \\
 \frac{dR_B}{dt} &= \eta R_A + \gamma I_B - \nu R_B - \eta R_B.
 \end{aligned} \tag{1}$$

68 This age structure was chosen as severe RSV infections are typically de-
 69 tected in children under 24 months of age and the majority of children hos-
 70 pitalised with RSV are under 12 months of age [28]. Although RSV has
 71 more recently been identified as an important pathogen in adults [29], the
 72 transmission mechanism between different age groups is not well understood.
 73 Further, it is thought that RSV is typically introduced into a households by
 74 a school-aged child [30], suggesting that adults are not the main drivers of
 75 transmission. In recent work, we showed that this model produces qualita-
 76 tively similar dynamics regardless of whether adults were incorporated [26],
 77 hence adults were not included in the present model.

78 The seasonal nature of the transmission dynamics is modelled using a
 79 sinusoidal forcing function (such as in [18, 19, 31]) given in Equation (2). For
 80 the older age class (the 12 to 24 month old children), reduced susceptibility
 81 to infection is modelled by scaling the seasonal forcing function by a factor
 82 α .

$$\begin{aligned}
 \beta_A(t) &= b_0[1 + b_1 \sin(2\pi t + \phi)] \\
 \beta_B(t) &= \alpha \beta_A(t).
 \end{aligned} \tag{2}$$

83 The default parameter values, listed in Table 1, have been chosen from
84 the literature or have been obtained by fitting the model to RSV data from
85 Perth in Western Australia. To fit these parameters, the model was solved
86 numerically using the `MATLAB ode45` routine, and the parameters ν , b_0 , b_1 ,
87 α and ϕ were varied, while the other parameters remained fixed. We used
88 the `MATLAB fminsearch` function to perform the fitting with a modified least
89 squares statistic to fit the model to the two infectious age classes simultane-
90 ously, such as in [21]. Note that our estimate of the immunity period ($1/\nu$) is
91 slightly longer than the 200 days assumed by other models [19, 20, 21]. The
92 phase shift parameter ϕ allows the model to be fitted to data from different
93 regions, where RSV epidemics peak at different times. Our present analysis
94 is not directly linked to data from one region, and hence the parameter ϕ
95 was set to zero. A summary of default parameter values and analysis ranges
96 are listed at Table 1.

Table 1: Table of default parameter values, where rates are given in years. Fitted values were obtained by fitting the model to laboratory confirmed RSV cases from Perth, Western Australia [21].

Parameter	Definition	Value	Range	Reference
μ	Birth rate for Perth in 2009	$\frac{22,394}{1,658,992} = 0.0135$	$0.01 \leq \mu \leq 0.02$	[32]
η	Ageing rate	1		
b_0	Overall transmission rate	3,215	$2,900 \leq b_0 \leq 3,500$	Fitted value
b_1	Amplitude of seasonal forcing	0.522	$0 \leq b_1 \leq 1$	Fitted value
α	Scaling factor for reduced susceptibility in older children	0.228	$0 \leq \alpha \leq 1$	Fitted value
$1/\delta$	Latent period	4 days		[19]
$1/\gamma$	Infectious period	9 days		[19, 20, 33]
$1/\nu$	Immunity period	230 days	182 to 304 days	Fitted value
ϕ	Phase shift	0		

97 For the sensitivity and bifurcation analyses, biologically realistic ranges
98 were chosen for the parameters that were allowed to vary. The birth rate
99 μ was allowed to vary in the range $[0.01, 0.02]$, which corresponds to a life
100 expectancy of between 50 and 100 years, such as in [24]. The rate of waning
101 immunity ν was allowed to vary in the range $[1.2, 2]$, which corresponds
102 to an immunity period of between 182 and 304 days. The value for the
103 transmission rate b_0 varied in the range 2,900 to 3,500 and the amplitude of
104 seasonal forcing varied in the range $[0, 1]$.

105 The basic reproduction number $\mathcal{R}_0$ was calculated using the Next Gen-
106 eration Matrix method [34]. Seasonal forcing was not included, but rather
107 the average transmission rate was used, which provides a basic reproduction

number in the absence of seasonal fluctuations in transmission (see Supplementary Material). Substituting the default parameter values from Table 1, we found that $\mathcal{R}_0 = 1.32$. This is in the range $[1.2, 2.1]$ suggested by Weber *et. al.* [19] for another compartmental RSV transmission model, although we acknowledge it does not fully capture seasonality in the reproduction number [35].

3. Sensitivity analysis

A sensitivity analysis was used to identify which parameters contribute most to variation in model output. For the RSV model, the key parameters explored were: the immunity parameter ν , the birth rate μ , the scaling parameter α , the transmission parameter b_0 and the seasonality parameter b_1 . In the case of the immunity parameter, there is relatively little epidemiological evidence to quantify the duration of immunity following infection. A similar situation holds for the scaling parameter α that accounts for reduced susceptibility in older children, which is reported but not generally quantified in the literature. Finally, parameter values for the birth rate, transmission rate, and strength of seasonal forcing are likely to vary with population, and no one fixed value is appropriate for all populations.

The sensitivity analysis was performed using the method of Partial Rank Correlation Coefficient (PRCC), using Latin Hypercube Sampling (LHS) to efficiently sample the parameter space. The PRCC gives a value for each parameter between -1 and $+1$, with an absolute value close to 1 indicating that the parameter strongly influences the model outcome. The outcome chosen for our sensitivity analysis was the cumulative number of infectious individuals for both age classes over time. We found that, after allowing for a burn in period, the correlation coefficient remained constant over time. As such, the outcome is shown for a single time point in Figure 2.

The parameters most strongly correlated with the cumulative number of infectious individuals were the recovery rate γ , the birth rate μ and the transmission rate b_0 . The PRCC for the recovery rate γ (the inverse of the duration of infectiousness) was close to -1 , indicating that increasing the rate of recovery (or decreasing the duration of infectiousness) contributes to a lower number of infectious individuals. The PRCC for the birth rate μ was close to $+1$, indicating that increasing the inflow of susceptibles substantially contributes to a higher cumulative number of infective individuals. Similarly,

143 increasing the transmission parameter b_0 greatly contributed to the number
 144 of infectives over time.

Figure 2: Output of the Partial Rank Correlation Coefficient (PRCC) sensitivity analysis, where Latin Hypercube Sampling (LHS) was used to sample the parameter space. PRCC values indicate the strength of association between model parameters and the cumulative number of infective individuals. As the correlation for each parameter remained constant over time, the output is shown at a single time point.

145 Based on this analysis, several parameters were selected to be explored in
 146 more detail. While the recovery rate γ was highly inversely correlated with
 147 RSV infections, the duration of infectiousness has been well documented
 148 compared to the other parameters. The birth rate μ was further examined,
 149 as demographic factors vary between countries. The waning immunity pa-
 150 rameter ν was also explored, given that less is known about the duration of
 151 immunity for RSV compared to other clinical factors. Finally, the parame-
 152 ters b_0 and b_1 in the seasonal forcing functions β_A and β_B were investigated.
 153 Although b_1 was not highly correlated with the outcome, differences in RSV
 154 dynamics for different countries and climates are well documented, and we
 155 expect the seasonality parameter to play an important role in capturing cli-
 156 matic factors.

157 4. Parameter space analysis

158 In earlier work [27, 21, 26], we described the basic dynamics of the nu-
 159 merical solutions to the model. We characterise the solutions as either ‘an-

160 nual' (period one) solutions or 'biennial' (period two) solutions, shown at
 161 (i) and (ii), respectively, in Figure 3. Biennial patterns in RSV disease lev-
 162 els have been observed a number of regions including Chile [36], Germany
 163 [10], Switzerland [7] and northern U.S.A. states such as Wyoming and South
 164 Dakota [37]. We can further classify the biennial dynamics to describe where
 165 the timing of the minor peak (the year of fewer infections in a biennial cy-
 166 cle) occurs markedly later than the major peak, shown in Figure 3(iii). We
 167 refer to this type of pattern as 'delayed biennial'. Such dynamics have been
 168 observed in Finland [38] and Croatia [39]. Finally, reducing the amplitude
 169 of seasonal forcing b_1 such as in Figure 3(iv) replicates the RSV dynamics
 170 typically observed in tropical climates, with less pronounced annual peaks
 171 [11] and disease occurring at a low level throughout the year. Setting the
 172 amplitude of seasonality to $b_1 = 0$ (so that no seasonal forcing occurs) results
 173 in damped oscillations, with no long-term seasonality in disease incidence,
 174 thus the periodicity seen here is a result of seasonal forcing.

175 We examined the dynamics of the numerical solutions with respect to the
 176 birth rate μ and the rate of waning immunity ν by solving the equations for
 177 a range of parameter values and then identifying the amplitude and location
 178 of the annual peaks (Figure 4). In each case, we compared the timing of
 179 the epidemic peak in a given year with the timing of the peak in the follow-
 180 ing year. Annual or regular biennial cycles showed no difference in timing,
 181 whereas delayed biennial dynamics showed a difference (the 'delay') of up
 182 to 50 days. Varying the birth rate μ showed a region of delayed biennial
 183 dynamics, outside of which regular annual dynamics were present. Varying
 184 the immunity parameter ν showed that, for shorter durations of immunity,
 185 the model produces annual solutions only, whereas increasing this parameter
 186 within a biologically plausible range produces biennial patterns. Figure 4 (i)
 187 and (ii) show separately the results of the parameter space analysis for μ and
 188 ν . Figure 4(iii) shows a two parameter map demonstrating the regions of
 189 annual and biennial output, and the extent of the minor peak delay in days.

190 **5. Bifurcation analysis**

191 The sinusoidal forcing term in Equation (2) reflects changes in transmis-
 192 sion caused by climatic variation throughout the year, and drives the seasonal
 193 dynamics produced by the model. A bifurcation analysis allows us to quan-
 194 tify the different types of dynamics produced by the model, for different
 195 values of these two parameters, within plausible ranges. We are interested in

Figure 3: Four plots demonstrating the qualitative types of model output: annual, biennial, delayed biennial and tropical. Plot (ii) shows the model output with the parameters fixed at the baseline values listed in Table 1. For the other plots, one parameter was varied while the others were fixed at the baseline values, in order to produce different dynamics: (i) $b_0 = 3401$, (iii) $\nu = 1.15$, and (iv) $b_1 = 0.1$. They illustrate the key role played by the forcing function in determining the observed differences in the dynamics.

196 examining the stable periodic solutions of our model and how the dynamics
 197 of these solutions change for different parameter choices.

198 For this part of the analysis, the differential equations were solved and the
 199 bifurcation analysis was performed using the continuation package AUTO
 200 within XPPAUT [40]. AUTO tracks the bifurcation curves of periodic
 201 systems by linearising about fixed points and finding the eigenvalues of the
 202 resulting system matrix [41, 42]. Plots were produced using MATLAB.
 203 XPPAUT requires the system of differential equations to be autonomous.
 204 Consequently, we transformed our non-autonomous periodic forcing term
 205 using the Hopf oscillator, as in [43, 44, 24]. This oscillator is driven by the
 206 following coupled system

Figure 4: Variations in the timing of seasonal peaks as a function of the birth rate μ and the immunity rate ν . Figures (i) and (ii) show the delay in days of the ‘minor’ peak for a range of μ and ν values respectively, with all other parameters fixed. Figure (iii) shows the timing delays on a colour scale as a function of both μ and ν . Figures (i) and (ii) were created using a log-transformed version of the model for improved numerical accuracy. Parameters not stated have the values listed in Table 1.

$$\begin{aligned}\frac{du}{dt} &= u(1 - u^2 - v^2) - 2\pi v, \\ \frac{dv}{dt} &= v(1 - u^2 - v^2) + 2\pi u,\end{aligned}$$

and has the solution

$$u(t) = \cos(2\pi t), \quad v(t) = \sin(2\pi t).$$

207 The differential equations were first integrated for 400 years to allow
 208 the system to stabilise. The final solution point was then used as initial
 209 conditions to integrate the model for one period (one year) in order to perform
 210 the bifurcation analysis in **AUTO**. The bifurcation analysis was conducted for
 211 the transmission parameter b_0 and the amplitude of seasonal forcing b_1 . The
 212 outputs of the bifurcation analysis are shown at (i) and (ii) in Figure 5. For

each figure, the y-axis shows the peak number of infectives. For the region of period-doubling solutions, the stable solution (the green line) is depicted as the maximum proportion of infectious individuals in the year with the higher number of cases. The blue line is used to highlight the unstable solution. The younger age class is used to show the bifurcation dynamics, however, the older age class produces similar results.

The bifurcation diagrams for b_0 and b_1 show similar qualitative characteristics. Both feature a central region of biennial dynamics, contained within a single period doubling bifurcation and a single period halving bifurcation. Parameter values outside this central region therefore produce regular annual dynamics. A range of initial conditions were sampled for the bifurcation analysis in order to identify other potential basins of attraction, however the annual and biennial cycles seem to be a robust feature of this model.

It is of interest to observe the system dynamics when the two key parameters are varied simultaneously, as the bifurcation analysis of b_0 may depend on that of b_1 . The bifurcation analysis for b_0 was carried out using a range of different values for the seasonal forcing parameter b_1 . The period doubling and halving bifurcations were recorded, and the results of this analysis are shown in Figure 5(iii). This plot shows the region of parameter combinations of b_0 and b_1 that will produce biennial dynamics (within the region captured by the two curves) and annual dynamics (outside the region). Panel (iv) shows the delay on a colour map for the same two parameters, in a similar fashion to Figure 4(iii).

6. Discussion

In this study, we showed that our age structured mathematical model for RSV transmission (1) was able to produce four qualitatively distinct types of dynamics: annual, biennial, delayed biennial and tropical. We identified the key parameters in the model (birth rate, rate of waning immunity, transmission rate, and seasonality) that explain these different dynamics, and documented the parameter ranges for which these dynamics occur.

Our parameter space analysis allowed us to examine the ranges of the birth and immunity rates that produced annual, biennial and delayed biennial dynamics. Both the immunity rate and the birth rate effectively moderate the flow of susceptibles into the population. However, the parameter space analysis showed that there is an intermediate range of birth rates that

Figure 5: The bifurcation structure of the model. The first two plots show (i) a bifurcation diagram for the transmission parameter b_0 and (ii) a bifurcation diagram for the amplitude of seasonal forcing b_1 . For the b_0 bifurcation, all other parameters are fixed, with $b_1 = 0.522$. For the b_1 bifurcation, all other parameters are fixed, with $b_0 = 3,215$. Both diagrams show similar qualitative dynamics, with a central region of period two dynamics contained within a single period doubling (PD) and single period halving (PH) bifurcation. Plots (iii) and (iv) show, respectively, a two-parameter bifurcation diagram and the timing delay on a colour scale for b_0 and b_1 .

correspond to delayed biennial dynamics, outside of which the dynamics revert to regular annual. This output is consistent with the birth rate analysis in [45]. In addition, the work by Pitzer *et. al.* indicates that the transition from biennial to annual RSV dynamics in California between the 1990s and 2000s may be due to changes in the birth rate [37].

The analysis of the immunity parameter alone produced a different picture from that of other parameters, with a one-way transition from regular annual to delayed biennial dynamics as the duration of immunity increases. Although birth rates vary between countries, we expect that the typical duration of immunity would be consistent across different regions, being a clinical

feature of RSV. As RSV immunity is not well understood, this analysis adds insight into values that might be reasonable. The two parameter analysis in Figure 4 suggests that the duration of immunity must be at least 220 days for annual, biennial and delayed biennial dynamics to occur for different birth rates, although we acknowledge that this value may change with different demographic model structures. In a similar model where one 0-24 month age class was fitted to data, the fitted duration of immunity was 160 days [21]. These results complement the existing literature on the contribution of birth rate and waning immunity to infectious disease dynamics [24, 25, 46].

Model findings show good agreement with data from around the world. Times series data for RSV in Finland shows a markedly delayed biennial pattern [38]. The average birth rate for Finland between 1981 and 1990 (the time period of the data) [47] corresponded with the rates that produced a delayed pattern in our analysis. RSV detections for Switzerland between 1988 and 1999 show a regular biennial pattern [7], and the birth rate of up to 0.0127 during this time period [48] corresponds with the non-delayed dynamics indicated by our analysis. Another interesting comparison is Colorado and Maryland, U.S.A. Both states have a similar latitude, and hence similar expected seasonal fluctuations. However, biennial dynamics have been observed in Colorado [49] and annual dynamics in Maryland [50], where the birth rate has historically been lower.

There are two distinct serotypes of RSV: RSV-A and RSV-B. This model does not model the dynamics of the two different RSV strains, due to limited data. Strain diversity has been suggested as a possible driver of biennial dynamics [51], however other studies have shown that the biennial dynamics cannot be explained only by circulation of the two subtypes [52, 53, 37].

We established the existence of period doubling and period halving bifurcations when the transmission and seasonality parameters were changed. Stone [54] showed that such patterns are an alternative to the period-doubling route to chaos that is often present in these types of population models. The existence of period doubling and period halving bifurcations suggests robust dynamics, which is consistent with the known regularity of RSV outbreaks worldwide. Our bifurcation analysis also indicated that the seasonality parameter must exceed a threshold in order for the model to produce biennial dynamics. This corresponds to the known epidemiology of RSV, where biennial patterns are typically observed in temperate regions only, where there is a marked difference in climate between the summer and winter months. In tropical regions, where the climate may be more consistent year-round,

296 winter peaks of RSV are less pronounced.

297 The sinusoidal forcing function applied in this paper is commonly used in
298 models for seasonal epidemics. A drawback of this approach is that this func-
299 tion is a proxy for any number of seasonal (such as climatic, weather-related
300 or social) variables. There is scope to include a more realistic transmission
301 function that incorporates such factors and this will be considered in future
302 work.

303 The model simulates RSV infection in two child age groups and does
304 not include adults. RSV infections are mainly observed in young children,
305 however it is not clear whether the low numbers of infections recorded in
306 adults are due to fewer infections in older age groups, or less severe symptoms
307 that result in fewer detections. In recent work [26], we showed that our model
308 produces qualitatively similar dynamics irrespective of whether or not adults
309 are included, and so only two age groups were modelled for this study. In
310 future work, we will consider a more extensive age-structured model that
311 incorporates both adult and child age structures, as well as an appropriate
312 contact matrix. Further, a drawback of the compartmental approach to age
313 structuring, rather than continuous ageing, is that the time spent in each age
314 class is exponentially distributed [18]. However, the compartmental ageing
315 approach is more mathematically tractable than a continuous approach and
316 is widely used in the literature.

317 Knowledge of the seasonal trends of RSV infections, and a better un-
318 derstanding of what is driving these seasonal patterns in different parts of
319 the world, provides many benefits, including health system preparedness [55].
320 The sensitivity and parameter space analysis in our study shows that demog-
321 raphy plays an important role in RSV dynamics. While RSV epidemics are
322 remarkably consistent in many regions, a shift in the birth rate could have
323 implications for the timing and magnitude of RSV, which may necessitate
324 a change in prophylaxis administration for high risk children. Prophylaxis
325 for RSV is costly and as such schedules need to be based around times that
326 produce the maximum effectiveness during the peak of the RSV season. An
327 understanding of the drivers of RSV seasonality and predicting peak activity
328 would aid in planning the most cost effective RSV prophylaxis programs.
329 Further, RSV vaccine development is proceeding rapidly. Our analysis pro-
330 vides insight into the most important parameters to consider when developing
331 models for vaccine administration, such as immunity and transmission, and
332 the differences that might be expected in these parameters in different re-
333 gions. In future work, we will consider how to adapt this model to help plan

334 for the rollout of a RSV vaccine.

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