

## Modeling epidemics caused by respiratory syncytial virus (RSV)

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### Abstract

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection in children. In this paper we use models of RSV transmission to interpret the pattern of seasonal epidemics of RSV disease observed in different countries, and to estimate epidemic and eradication thresholds for RSV infection. We compare the standard SIRS model with a more realistic model of RSV transmission in which individuals acquire immunity gradually after repeated exposure to infection. The models are fitted to series of monthly hospital case reports of RSV disease from developed and developing countries. The models can explain many of the observed patterns: regular yearly outbreaks in some countries, and in other countries cycles of alternating larger and smaller annual epidemics, with shifted maxima in alternate years. Previously these patterns have been attributed to the transmission of different strains of RSV. In some countries the timing of epidemics is not consistent with increased social contact among school children during term time being the major driving mechanism. Climatic factors appear to be more important. Qualitatively different models gave equally good fits to the data series, but estimates of the transmission parameter were different by a factor of 4. Estimates of the basic reproduction number ( $R_0$ ) ranged from 1.2 to 2.1 with the SIRS model, and from 5.4 to 7.1 with the model with gradual acquisition of partial immunity. © 2001 Elsevier Science Inc. All rights reserved.

**Keywords:** Respiratory syncytial virus (RSV); SIRS model; SEIRS model; Parameter estimates; Threshold conditions; Transmission

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## 1. Introduction

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection in children. Clinical features of RSV infection range from those of a common cold to bronchiolitis and severe pneumonia. Cases of RSV disease occur in seasonal epidemics. The majority of hospitalized cases are aged under 6 months, but the infection can also be a cause of mortality in the elderly. In this paper we develop a model of RSV transmission, and apply it to the interpretation of series of monthly case reports of RSV disease from developed and developing countries. The mechanisms underlying the different patterns of seasonal epidemics observed in different countries are not well understood; our aim in this paper is to examine the effect of population dynamics of transmission on the interpretation of the role of climatic and social factors in driving these epidemics. Furthermore, RSV vaccines are under development; if suitable models can be developed they can be used to evaluate the likely impact of vaccination programmes.

In Section 2 we outline the properties of RSV. In Section 3 we describe extensions to the SIRS model which includes features specific to RSV transmission. Suitable values for some of the model parameters could be obtained from results given in the medical literature, but some parameters, especially the mean  $b_0$  of the transmission parameter  $\beta$  and its seasonal amplitude, had to be estimated by fitting the models to monthly case reports of RSV disease (Section 4). Separately we investigated the effects of different assumptions about the duration of immunity on model behavior (Section 5), and the influence of stochastic variation in some parameter values. In Section 6 we give the results of several simulations when the seasonal variation of the weather is correlated to the annual variation of the transmission parameter. Threshold conditions for our models are given in Section 7. Some final discussions are given in Section 8.

## 2. Properties of RSV

RSV is the most common cause of acute lower respiratory tract infection in children worldwide [1–3]. A striking feature of RSV infection is its seasonality: in temperate climates, most of the RSV-associated disease episodes occur in the cold season, whereas in the tropics, most appears to occur in the wet season [3]. RSV appears to be a predominantly human pathogen: it has been found in some animals, but these are not believed to play a role in the transmission to humans [4]. The incubation period is between 2 and 8 days (average 5 days) [5,6]. In infected persons, the mean duration of shedding is reported 6.7 days with a range of 1–21 days [7]. Neonates are relatively protected; the infection is rare in the first month of life. Earlier infection happens in infants with low concentrations of maternal antibody [8]. The mean titre of maternal IgG antibody to RSV was significantly higher in mothers whose babies remained uninfected than in those whose babies had proven RSV infection before 6 months of age [9]. After the neonatal period, virtually all non-immunes who encounter the virus become infected. Immunity to reinfection is acquired gradually. In one longitudinal study during an epidemic, the attack rate for first infection was 98% [10]. The rate for second infections was lower (75%,  $P < 0.001$ ); and for third infections, 65% [10]. Older children and adults become re-infected frequently: the annual re-infection rate for children 5–9 yr of age is reported to be 20%, for those 10–14 yr of age 17%, for those 15–19 yr 10%, and for adults 3–6% [11].

In another study [12], 15 adults with previous natural RSV infection were challenged with RSV of the same strain group (A) at 2, 4, 8, 14, 20, and 26 months after natural infection. By 2 months about one-half and by 8 months two-thirds of the subjects became re-infected. Within 26 months 73% had two or more and 47% had three or more infections. The interval between infections tended to increase after two closely spaced infections [12]. In infected families, 46% of members became infected, including 10 of 16 infants. Secondary attack rate for all ages was 27%, and that for infants 45% [13]. An infant's older sibling appeared most likely to introduce the virus into the family. Most infections are mild, even in infancy: only 1.6–3.3% of infants need admission to hospital [14,15]. Further characteristics of the virus and infection are shown in Table 1.

### 3. Models

In our models the population is divided into distinct groups (of susceptible, infected, or immune individuals) and we use deterministic continuous transitions between the states. So the overall setting is the one treated in-depth in the literature, see, e.g., [27]. We assume homogeneous mixing in the population and do not model spatial spread of epidemics. For RSV almost simultaneous outbreaks of RSV epidemics with different strains of the virus have been reported throughout a whole area (see, e.g., [28]) so that spatial effects do not seem to be of central importance for RSV epidemics. Thus our models are systems of ordinary differential equations (ODEs) (see, e.g., [27,29–32]).

#### 3.1. General remarks

The ODEs in the following models are non-linear, but most of the transitions in the systems are given by linear laws. In many cases estimates of mean residence times are available in the medical literature, from which we have obtained the value of the corresponding transition parameter assuming an exponential distribution of residence times.

To simplify analysis, we have assumed birth and mortality rates are equal, so that the total population is constant. This simplification is justified when the annual infection rate is much bigger than the population growth. We use unit scaled models, i.e. we set the total population to be 1 and use fractions for the state variables.

#### 3.2. SIRS model

As a first approximation we consider a simple model consisting of susceptible ( $S$ ), infected and infectious ( $I$ ), and recovered ( $R$ ) individuals. Recovered individuals are immune to re-infection. A characteristic feature of RSV is that immunity after infection is temporary, so that the recovered individuals become susceptible again, cf. Section 2.

As, e.g., in [31,33,34] the seasonal influence on the transmission parameter  $\beta$  is modeled by the cosine function. Using the simple linear mass action law as, e.g., used in [27,31,33,34], we obtain the following system of ODEs:

$$\frac{d}{dt}S = \mu - \mu S - \beta(t)SI + \gamma R,$$

Table 1

Factors associated with transmission of and protection against RSV

Factor	Findings and comment	Reference
Viability of the virus	RSV in freshly obtained infant secretions was recovered from countertops for up to 6 h, from rubber gloves for up to 1 1/2 h, from cloth gowns and paper tissue for 30–45 min, and from skin for up to 20 min.	[16]
Transmission distance of virus	No infection in volunteers more than 6 ft away from infected infants.	[17]
Cross-protection between subtypes	Infection with subgroup A strains of RSV provided some protection from a second infection with the homologous, but not the heterologous, subgroup of the virus.	[18]
	Primary group A infection elicited antibodies cross-reactive with group B virus in the PRNB and the ELISAS for GB and FB. In contrast, primary group B infection induced significant increases in mean concentrations of antibody cross-reactive with group A virus only in the FA ELISA. Second RSV infections caused by group B viruses in children with histories of primary group A infection induced heterologous rises in the PRNA and GA assays, suggesting that prior group A infection had primed for a more extensive cross-reacting antibody response at the time of second RSV infections with group B viruses.	[19]
Circulation of subtypes	Three patterns of yearly outbreaks existed in 15 sequential years: (1) strong predominance of group A strains (9 yr with 83–100% A strains), (2) relatively equal proportions of group A and B strains (4 yr), and (3) strong predominance of group B strains (78–85%) in 2 yr, separated by a decade. The first pattern of highly dominant A strains occurred in cycles of 1 or 2 consecutive years with a single intervening year in which B strains were greater than or equal to 40% of the isolates.	[20]
Severity of disease	Although lower respiratory tract disease (LRD) was common (22.4% during year 1 and 13.0% during year 2), most children had only one LRD illness. Reinfection illnesses were generally mild, and risk of reinfection decreased to only 33.3% during year 4. Hospitalization rate 1.6%.	[14]
	West Virginia: 3.3% hospitalized.	[15]
	Immunity induced by a single infection had no demonstrable effect on illness associated with reinfection 1 yr later; however, a considerable reduction in severity occurred with the third infection.	[10]
	First year of life: 40% ALRI, 1% hospitalized.	[21]
	The maximum yearly admission rate occurred among infants aged 1–3 months: 24.5 per 1000 of that age group were admitted to hospital (industrial areas double the rate of rural).	[2]
Sex distribution	North East England: 2% of under 1 yr olds admitted.	[22]
	1.8:1 male:female for LRI.	[1,23]
	1.5:1 male:female for LRI.	[24]
	Equal for mild infection.	[1,23]
Risk factors: crowding	Between 1 and 3 months of age, in multivariate analysis, only sex and the number of others sharing the room remained as significant direct risk factors. Being in day care was a significant risk factor in the 7–9 month age range.	[25]
Socio-economic class	Children living in electoral wards in the two more deprived groups were more than 1.5 times as likely to be admitted (OR 1.67, 95% CI 1.25–2.24).	[26]

$$\begin{aligned}\frac{d}{dt}I &= \beta(t)SI - \nu I - \mu I, \\ \frac{d}{dt}R &= \nu I - \mu R - \gamma R,\end{aligned}$$

where  $\beta(t) = b_0(1 + b_1 \cos(2\pi t + \phi))$ . Here we have used:

- $S$ : susceptibles;
- $I$ : infecteds;
- $R$ : recovered;
- $\mu$ : birth rate = mortality rate;
- $\gamma$ : rate of loss of immunity;
- $\nu$ : rate of loss of infectiousness;
- $b_0$ : average of transmission parameter  $\beta$ ;
- $b_1$ : amplitude of the seasonal fluctuation in the transmission parameter  $\beta$ .

### 3.3. Model with gradual reduction in susceptibility to reinfection, maternally derived immunity, and a latent period

To incorporate more of the characteristic features of RSV, we extended the model in the following ways.

Firstly, we include a latency period by introducing a group  $E$  of individuals who have been infected but are not yet infectious. These individuals become infectious at a rate  $\sigma$ . For RSV we can assume the latency period being equal to the time between infection and onset of symptoms, as the symptom (runny nose and sneezing) is the way of shedding and dispersing the virus.

Newborn infants of immune mothers are protected by maternal antibodies. We therefore introduce a group  $M$  of children born completely protected. We assume the fraction of newborns that are protected is equal to the fraction of the general population that have temporary immunity after recovering from infection. Protection wanes, and so protected children become susceptible; the transition parameter from  $M$  to  $S$  will be denoted by  $\xi$ .

The risk of an exposed person developing an infection decreases after the first experience of infection. Interpreting the results given in Section 2 the following specification seems to be in accordance with the known data. At least four reinfections should be distinguished. We will assume that the reduced risk is 50% after one infection, 35% after two, and 25% after three. After three infections the assumption of a constant reinfection risk is made. Thus for the corresponding transmission parameters we have the relations  $0.5\beta_1 = \beta_2$ ,  $0.35\beta_1 = \beta_3$ , and  $0.25\beta_1 = \beta_4$ . The susceptible individuals of any group can be infected by the infectious individuals of any group, because our model does not distinguish between different strains of the virus but only between the number of previous infections. For all groups we assume the same average durations of the latency period, the period of infectiousness and of immunity. Current knowledge about RSV indicates that there are only slight changes in these parameters after reinfection so that these simplifications are justified. Moreover, when we allowed the duration of immunity to depend on the number of previous infections the models gave poorer fits to the data than the simpler model, cf. Section 5.2.

The model is described by a system of ODEs of dimension  $1 + 4 \times 4 = 17$ , which we refer to as MSEIRS4 in the following.

The equations are given in Appendix A.

#### 4. Parameter estimates

For the simulations and parameter estimation we used Matlab. The functions describing the vector fields and their Jacobians were generated from a representation of the dynamical system in the computer algebra system Maple by a tool written by Goller [35] under the supervision of the first author. The integrators used were the standard Matlab functions `ode23t` and `ode15s`.

The optimal parameter fits were obtained in most cases by non-linear least squares using functions provided in the ‘Matlab non-linear toolbox’. Fitting ‘by hand’ was used if the Matlab functions did not converge within several hours of computation time.

During model fitting, the values of the parameters  $\mu, \sigma, \nu$  and  $\xi$  were held constant at the values given in Table 2. For the birth rates  $\mu$  we used the values given in [36] for the particular countries. (Since RSV infections are mainly a childhood disease, we use the actual birth rates and not the mortality rates in our models, in which we have set these to equal values in order to obtain constant population.)

Values of four parameters were determined by fitting the model: the mean of the transmission parameter  $b_0$ , its relative seasonal amplitude  $b_1$ , the phase angle  $\phi$  (in years,  $0 \leq \phi < 1$ ) and a scaling factor  $s$ , which scales the number of infectious individuals in our unit scaled model to the empirical case reports. The phase angle  $\phi$  was normalized in the following way: for a value of 0, a maximum of the cosine function used in  $\beta(t)$  coincides with the first maximum of the empirical cases. For the MSEIRS4 model the estimated values for  $b_0$  apply to the transmission rate for the first infection (Appendix A). The values for the other groups are the corresponding multiples according to the discussion given in Section 3.3.

The models were fitted to data on the reported number of hospital cases of RSV disease. We assumed the ratio of the number of cases to the number of infectious individuals in the population

Table 2  
Results of model fits

Location	model	$\mu$	$\nu$	$\gamma$	$\sigma$	$\xi$	$b_0$	$b_1$	$s$	$\phi$	$e$	$\bar{n}$	$l$	$R_0$
Gambia	SIRS	0.041	36	1.8			60	0.16	736	0.15	53.6	14	36	1.7
Gambia	MSEIRS4	0.041	36	1.8	91	13	256	0.20	913	0.26	61.4	14	36	7.1
Florida	SIRS	0.016	36	1.8			62	0.10	1678	0.14	112.1	32	44	1.7
Florida	MSEIRS4	0.016	36	1.8	91	13	268	0.13	2009	0.03	113.5	32	44	7.4
Finland	SIRS	0.013	36	1.8			44	0.36	2420	0.60	453.9	27	111	1.2
Finland	MSEIRS4	0.013	36	1.8	91	13	192	0.39	2600	0.19	378.2	27	111	5.3
Singapore	SIRS	0.016	36	1.8			77	0.14	2554	0.28	276.2	58	82	2.1
Singapore	MSEIRS4	0.016	36	1.8	91	13	260	0.12	4082	0.0	307.1	58	82	7.2

The values of  $\mu, \nu, \gamma, \sigma, \xi$  are expressed as rates per year. The phase angle in years is denoted by  $\phi$ . We use  $e = \sqrt{\sum(\text{res. norm})^2}$ ,  $\bar{n}$  denotes the average number of monthly case reports, and  $l$  gives the length of the data series in months. For the computation of the basic reproduction number  $R_0$ , see Section 7.

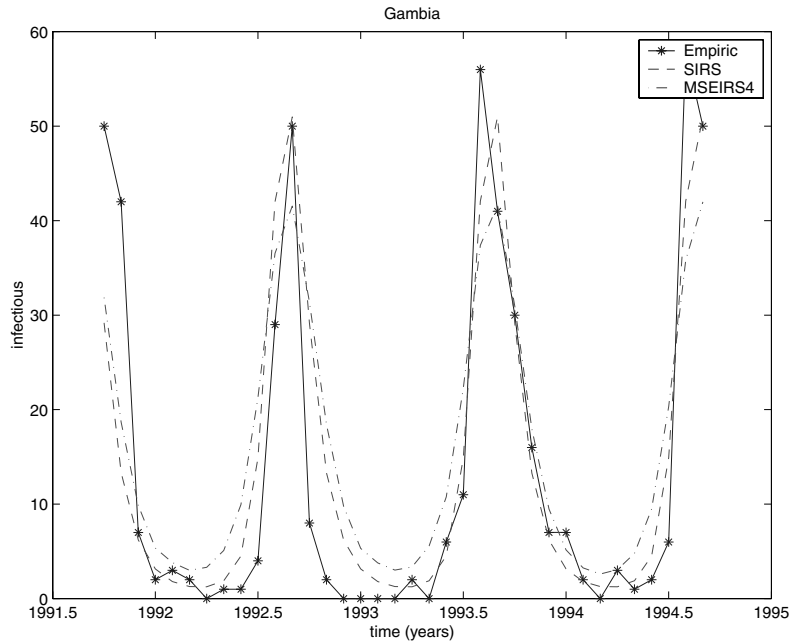


Fig. 1. Results of parameter estimates: Gambia.

was a constant. This constant can be calculated from the scale factor  $s$  when the size of the entire population is known and could be compared to values given in the literature, cf. Section 2.

The quality of the fit is determined by the sum of squared 2-norm of the residual between the empirical data and the model predictions. This value is also returned by the Matlab function `lsqcurvefit`, which we have used for parameter estimation.

For tropical countries we have relatively long series of monthly case reports from Gambia [37] and from Singapore [38].<sup>2</sup> As a relatively typical data set for developed countries we use the one for Florida given in [39]. Another pattern in the case reports can be found in the data published in [40] for Turku, Finland.

Parameter estimates are summarized in Table 2. Plots of the fitted curves and the data are given in Figs. 1–4.

#### 4.1. Discussion

Both models fit the case reports data almost equally well. Using appropriate values for the mean value  $b_0$  of the transmission parameter  $\beta$  modest values for its relative annual variation  $b_1$  are sufficient to give an amplitude of highs which is more than ten times that of the lows. So a small amplitude in the driving force is amplified several fold in the outcome, which is in good

<sup>2</sup> For the parameter estimates, we use only a restricted time series of the data available for Singapore. The full time series of empirical data will be used in Section 5.3.

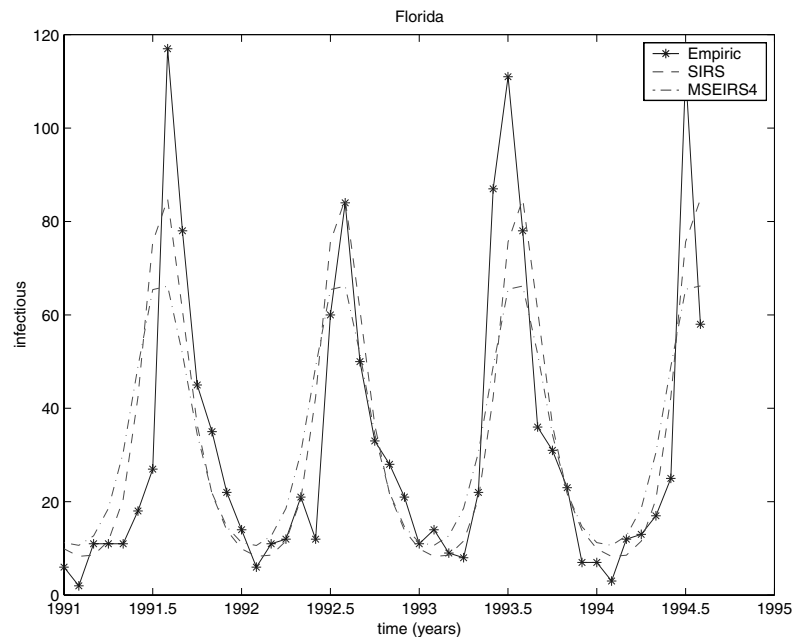


Fig. 2. Results of parameter estimates: Florida.

accordance with observation. The reported annual outbreaks of epidemics in many places can be fitted quite well with both models, and the cycles of alternating larger and smaller annual epidemics that are reported from other places can also be generated by these models by changing the relative amplitude of seasonal variation of the transmission parameter. The larger amplitude in the transmission parameter for places with alternating higher and lower outbreaks such as Turku, Finland, seems to be quite reasonable in comparison with tropical countries, in which annual outbreaks are predominant. Even the observed shift in the maxima of the monthly case reports in alternate years from 12 to 15 months, is reproduced in the model fits.

The estimated values for  $\beta$  in the SIRS model are in the same range for all four countries; for the MSEIRS4 model the estimated values of  $\beta = \beta_1$  are also in the same range for all countries but is about a factor of 4 higher than the value of  $\beta$  for the SIRS model. As can be seen from the further simulations given in Section 5 (and the threshold estimates given in Section 7) values of  $\beta$  much smaller or larger would yield results that could not fit the empirical data well, even if much higher values for  $b_1$  were used.

## 5. Results of further simulations

In fitting the models we held the parameters  $\mu$ ,  $\nu$ ,  $\sigma$ ,  $\gamma$ , and  $\xi$  at fixed values. For some of the parameters, especially  $\gamma$ , present knowledge is only sufficient to determine a certain interval for its values, so we performed additional simulations in order to estimate the sensitivity of the simulations to changes in this parameter (Fig. 5) and to changes in  $b_0$  and  $b_1$  (Figs. 6 and 7).



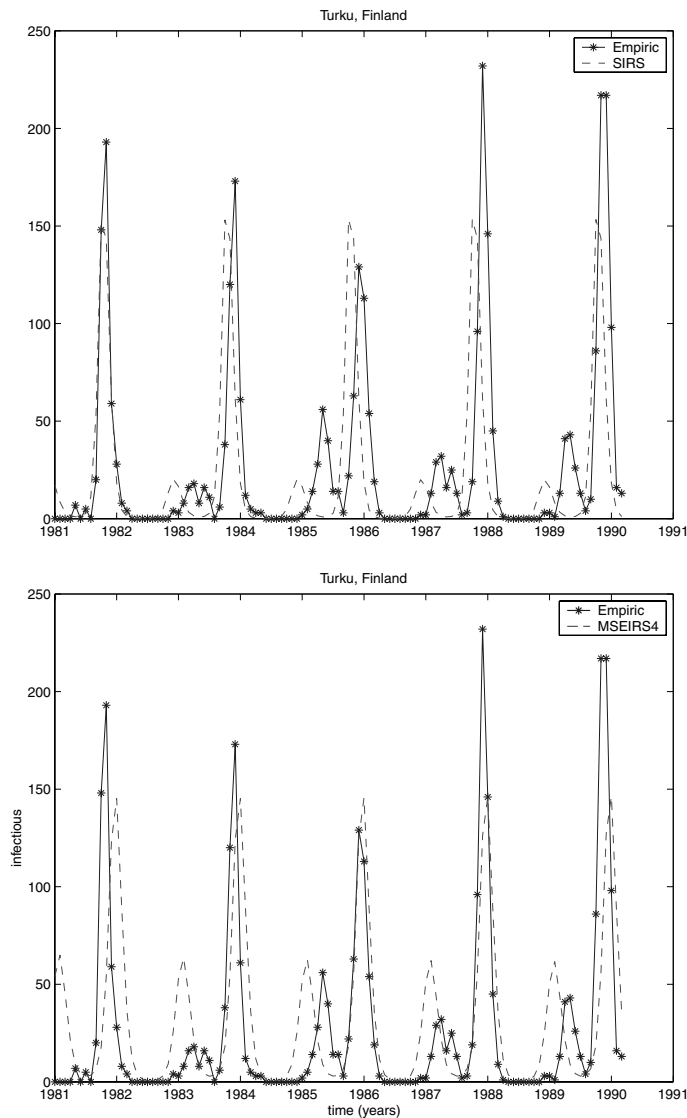


Fig. 3. Results of parameter estimates: Finland.

As initial values for the simulations each group was given the same size and we used 100 years of simulated time as a run-in period.

As can be seen in simulations A and B, varying  $\gamma$  within the realistic range for RSV does not have a major influence on the outcome of the simulations.

### 5.1. Change of transmission parameter $\beta$

Simulation C shows that when the value of  $b_0$  is much higher than we have estimated, there is only a slight variation in the proportion of infectious individuals, but no ‘epidemic outbursts’

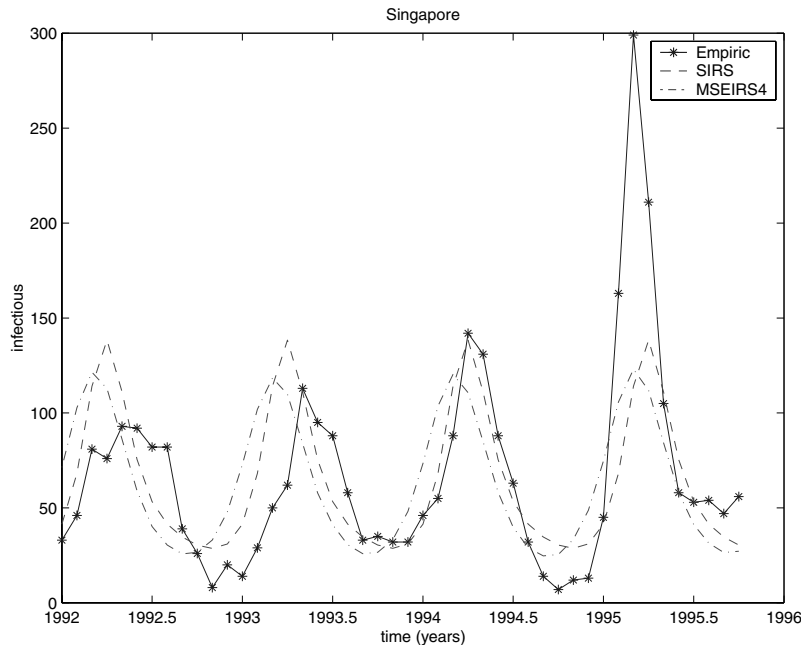


Fig. 4. Results of parameter estimates: Singapore.

occur. So even if one considers that there may be uncertainty in our estimates, the estimates for  $b_0$  made in the previous section appear to be of the right order of magnitude.

In general, the group of at least four times infected  $I_4$  is much larger than  $I_1$ ,  $I_2$ , and  $I_3$ . However, in simulation D, in which  $\beta$  is much smaller than in the previous simulations, this group is only about three times larger than the other groups of infected. If we have a value of  $\beta$  that is even smaller, the groups of first and second infected do not change too much, but the group of multiply infected is even smaller than these groups, cf. simulation E. Using a community wide study, in which the entire population is being tested for RSV infections, these different outcomes of simulations could be tested against empirical data. Unfortunately, no such empirical data are available up to now.

## 5.2. Different immunity periods for different groups

In addition to the variation of the transmission parameter  $\beta$  among the various groups after reinfections it seems to be a plausible possibility to vary the duration of immunity, i.e. not to use the same parameter  $\gamma$  for all groups but different parameters  $\gamma_1, \dots, \gamma_4$ . However, in the simulations for Finland, we noticed the following: extending the duration of the average immunity for the group of multiply infected by only 20% in comparison to the groups of up to two times infected forces an annual cycle of infections with identical highs. Thus having such different parameters gives worse fits to the empirical data than the simpler possibility of having the same duration of immunity for all groups.

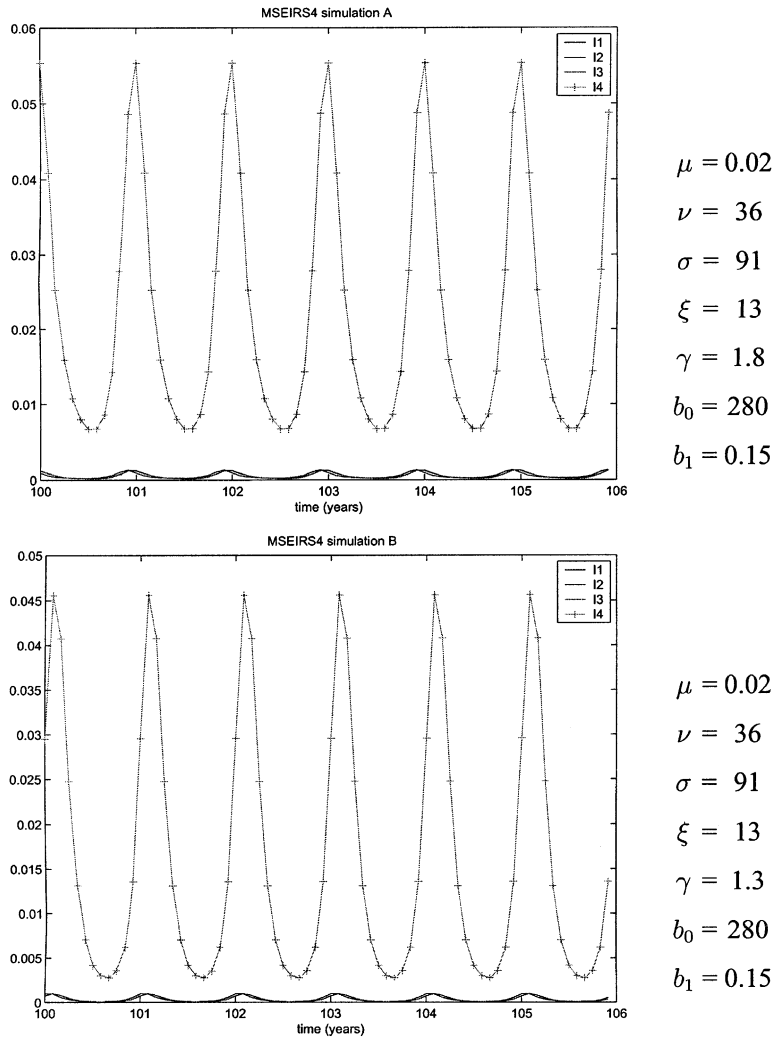


Fig. 5. Simulations for MSEIRS4 model: standard values and smaller value for  $\gamma$ .

### 5.3. Change of parameters within simulation

In the data series for Singapore, the case reports for the year 1989–1992 show a similar pattern to the ones in Turku, i.e. with alternating highs and lows and the lows being phase shifted for about 3 months.

In Fig. 8 we show the case reports with the outcome of the SIRS models (with parameters fitted for 1992–1995) and a ‘combined SIRS’ model: we use  $b_0 = 50$  and  $b_1 = 0.32$  for the years 1989–1992 and then we use the values obtained above for the other years, i.e.  $b_0 = 77$  and  $b_1 = 0.14$ .

The ‘phase shift’ of about one month, which occurs in the empirical cases between the values from 1989 to 1992 and the ones for the years from 1993 to 1995 can be reproduced in the SIRS model with this single change of parameters.

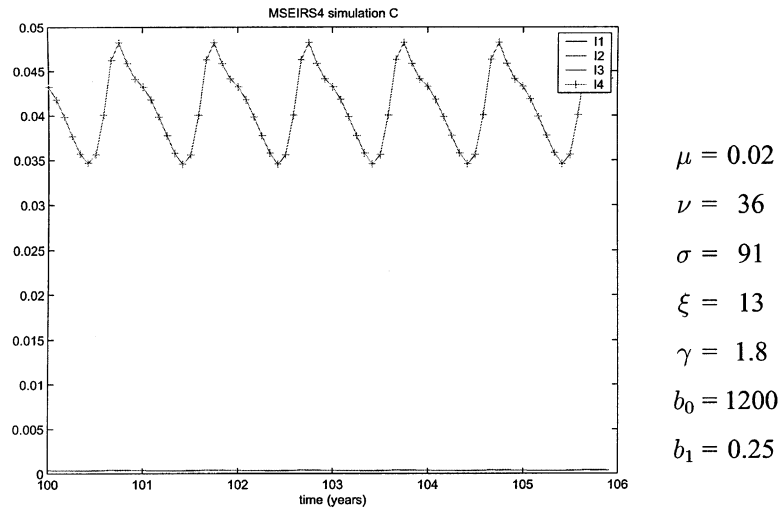


Fig. 6. Simulations for MSEIRS4 model: higher values for  $b_0$  and  $b_1$ .

## 6. Correlating the transmission parameter with weather data

In the work of several authors, e.g., [3,38], attempts to correlate weather conditions with the epidemics of RSV have been made. This work is motivated by the fact that cyclic changes in the social behavior of school children (the beginning of school terms) do not seem to be linked to RSV epidemics [22]. For example, in Gambia, outbreaks occurred before the beginning of the school year [37]. It is possible that other social factors such as indoor crowding during the rainy season might play a role, but little is known about this. This is in contrast to other childhood diseases like measles, for which the beginning of school terms seems to be a main triggering mechanism in some settings.

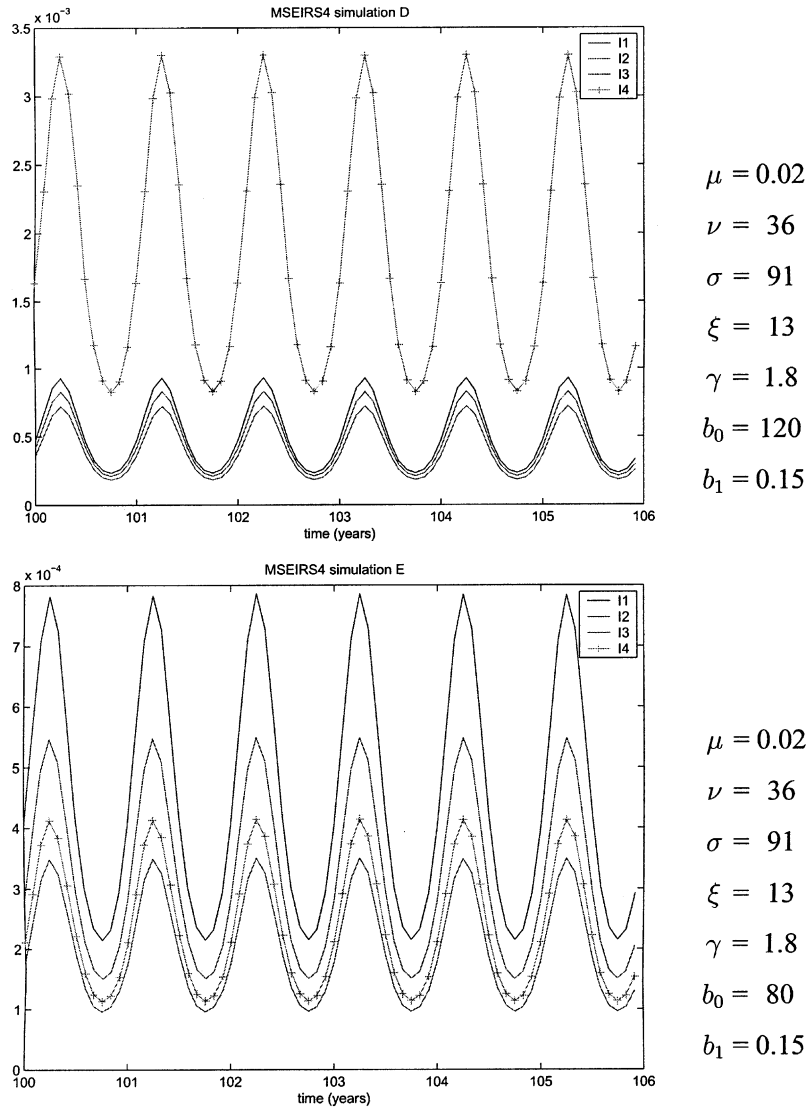
In order to test the influence of weather conditions we modified our models in the following way. Instead of using the cosine function to simulate seasonal variations of  $\beta$ , we used the following. For some measurement data  $m(t)$  with mean value  $\bar{m}$ , minimum value  $m_{\min}$  and maximum value  $m_{\max}$  we set

$$\beta(t) = \begin{cases} b_0 \left( 1 + b_1 \frac{m(t) - \bar{m}}{m_{\max} - \bar{m}} \right) & \text{if } m(t) > \bar{m}, \\ b_0 \left( 1 + b_1 \frac{m(t) - \bar{m}}{\bar{m} - m_{\min}} \right) & \text{otherwise.} \end{cases}$$

Using the average daily rainfall as the driving force we obtain the results shown in Fig. 9 for Gambia. For the parameters we have used the same values as in Section 4.

Using the precipitation as the driving force, the predicted maxima of the epidemics are about 1–2 months later than observed in the data. (Although the precise timing of epidemic maxima is uncertain because the time resolution of the observations is one month.)

The average daily rainfall does not give an explanation for the seasonal variation of the transmission parameter for other tropical countries. For Singapore, a phase shift of almost half a year occurs between actual and predicted maxima of RSV infections. This has also been observed in [38]. Using the average monthly minimum temperature as a driving force gives slightly better

Fig. 7. Simulations for MSEIRS4 model: smaller values of  $b_0$ .

fits. However, in this tropical environment these changes are small and do not appear to be biologically plausible.

Different social and climatic factors seem to cause the seasonal change of the transmission parameter in various countries. Identifying these factors is a topic for further research.

## 7. Thresholds for the models

The SIRS model with simple vital dynamics (as in Section 3.2, but with the transmission parameter  $\beta(t)$  assumed to be a constant,  $\beta$ ) has a unique equilibrium if the basic reproduction rate

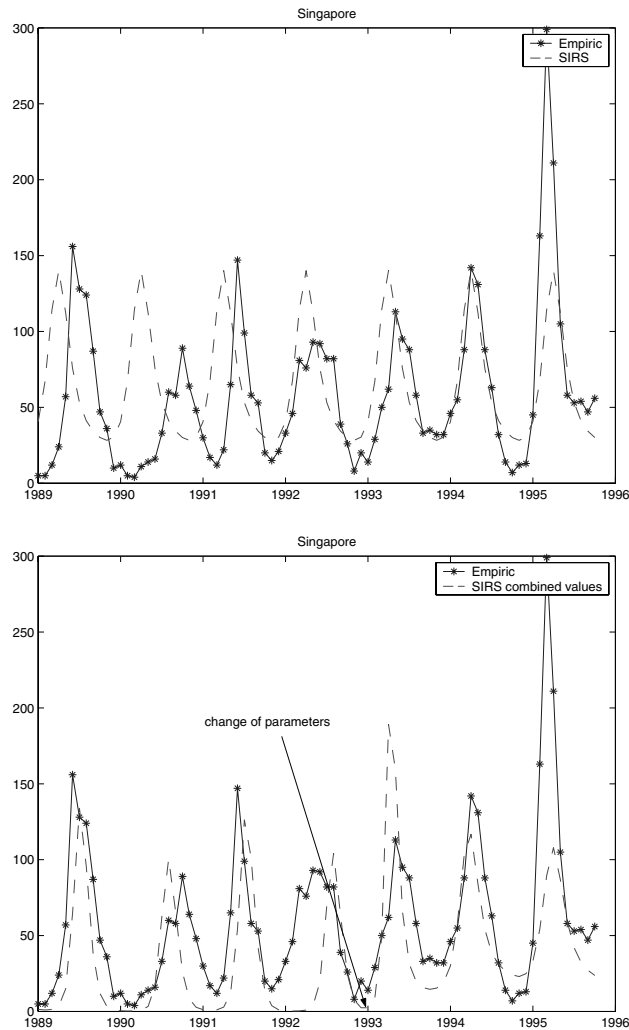


Fig. 8. Simulations for Singapore without and with change of parameters.

$\beta/(\mu + \nu)$  exceeds one [41]. If the birth and recovery rates  $\mu$  and  $\nu$  take the values given in Table 2, then  $\beta$  must exceed 36 for the infection to persist in the community. This value is about half the value estimated from fitting the model to the case reports series (Table 2).

It can be shown (by solving the equations (Appendix A) at equilibrium for the total infectious fraction  $I_1 + I_2 + I_3 + I_4$  and examining the nature of the roots of the resulting quartic equation) that the MSEIRS4 model has a unique stable equilibrium with  $0 < I \leq 1$  if

$$\frac{\beta_1 \sigma}{(\nu + \mu)(\sigma + \mu)}$$

exceeds 1. We were also able to derive this expression for the basic reproduction rate symbolically using the Maple computer algebra system, by computing the eigenvalues of the Jacobian of the

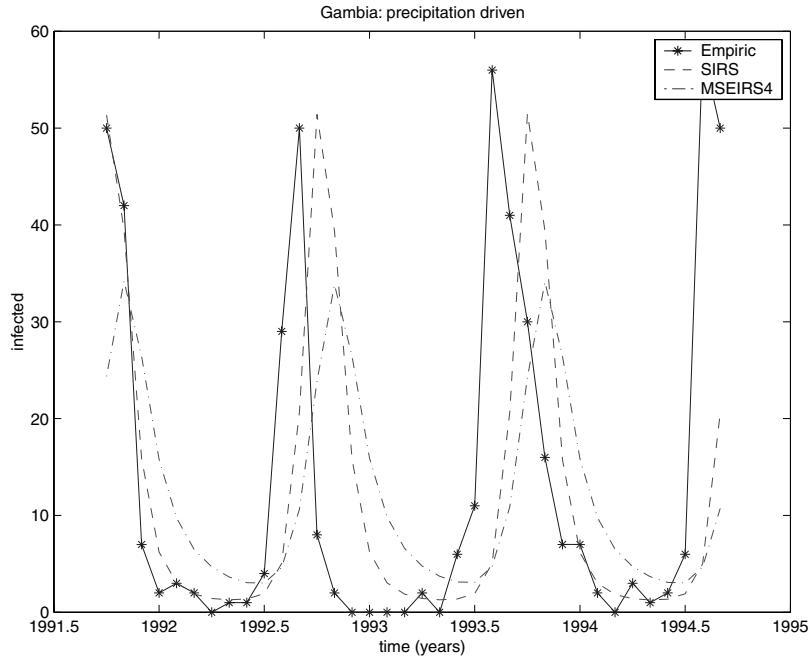


Fig. 9. Gambia: results of simulations using precipitation as driving force.

system at the disease-free equilibrium and determining the conditions for the dominant eigenvalue to have negative real part. The resulting expression for  $R_0$  differs from that for the SIRS model only in the factor  $\sigma/(\sigma + \mu)$ , the probability (numerically very close to unity) of surviving the latent period. Fixing  $\sigma, \mu$  and  $\nu$  at the values given in Table 2, we calculate that  $\beta_1$  must exceed 36 for disease persistence. Although the two models give almost equally good fits to the data series, estimates of the transmission parameter, and of the magnitude of the basic reproduction rate (last column of Table 2) differ between the two models by a factor of about 4.

## 8. Discussions

We found that RSV epidemics can be modeled surprisingly well by relatively simple ODE models. These models, which can reproduce the reported regular annual outbreaks of epidemics seen in many places, can also reproduce the alternating cycles of large and smaller annual epidemics observed in some countries, with a change in the value of a single parameter (the relative seasonal amplitude of the transmission parameter). Fitted values of the relative amplitude were greater in places with alternating large and small outbreaks (such as Turku, Finland), and were lower in tropical places, where regular annual outbreaks are predominant. The models also exhibit a shift in the maxima in alternate years, similar to that observed in the case reports. Grossman et al. [42] showed that the seasonally forced SIR model (as Section 3.2 but with lifelong immunity) exhibits a period-doubling bifurcation, and they derived a critical value of  $b_1$  above which the oscillations in the infectious fraction show a qualitatively different pattern, with a secondary maximum every second year. These values agree well with values determined for the

MSEIRS4 model using simulation. In tropical areas, the combination of high birth rate and high mean annual transmission rate ( $b_0$ ) makes biennial cycles unlikely.

These results have been obtained using a cosine function for the seasonal variation, in which a phase shift for optimal fit was allowed. For different places the possible underlying mechanisms for the variation of the transmission parameters seem to be different.

Using meteorological data as a driving force, significant differences between the simple SIRS model and the ones modeling a latency period were observed. If the driving force has several peaks within one year, the infectious fraction also shows several peaks, whereas the models with latency periods ‘smooth out’ such short term variations and show annual (or biennial) peaks, which concurs better with the observed behavior.

The models indicate that there is a phase shift between the maxima of the transmission parameter and the maxima of the infectious fraction. Thus attempts to find direct correlations between meteorological variables and the numbers of reported RSV cases – e.g., [38] – should be interpreted carefully.

Some apparent switches in the pattern of seasonal epidemics can be explained with the models by allowing changes (within a simulation) of about 30% of the transmission parameter and its relative seasonal variability. Such changes of the parameters are a very restricted form of noise. As the required ratio does not seem to be unduly high, the observed pattern of RSV epidemics can be explained by the noisy limit cycles of the models. This can be contrasted to [33], in which a chaotic dynamical system is proposed as a better explanation for measles epidemics than noisy limit cycles, but is in coincidence with the findings of [32]. Moreover, there is no sensitive dependency on the initial values in our models, which is another strong argument against deterministic chaos as an explanation of the variations.

Qualitatively different models gave equally good fits to the case reports data series, but the estimated values of the transmission parameter differed by a factor of 4. Thus estimates of the basic reproduction rate obtained in this way are sensitive to details of model structure and therefore may be unreliable if an important feature has been omitted. However, at present it is not feasible to estimate  $R_0$  from cross-sectional survey data because of the difficulty of determining whether a child has had an infection. Intensive longitudinal sampling would be required. In contrast to measles, where a good serological test exists which indicates whether a person has been infected, this is not the case in RSV. After proven infection, only a small proportion of young children show serological evidence of this infection. Therefore, to determine the proportion of the population who were infected, a longitudinal follow-up of a cohort is required.

The estimates of  $R_0$ , which we have obtained from our estimates of the transmission parameters and the computation of threshold values, ranged from 1.2 to 2.1 with the SIRS model, and 5.4 to 7.1 with the model with gradual acquisition of partial immunity. So in our models, in which the transmission parameter occurs in a linear mass action law with the number of susceptibles and the critical proportion to vaccinate is  $1 - 1/R_0$ , the disease will die out if about 50% (resp. 85%) of the susceptibles are immunized.

One of the open questions is where the main driving force for transmission of RSV is. We do not know whether it is older children or adults. Humidity affects the survival of RSV in experimental conditions, but whether this is biologically important for the transmission is not known. Interestingly, in Gambia, measles epidemics tend to occur in the dry season and do not coincide with RSV epidemics, although the two viruses are biologically related [43]. This suggests a



different forcing mechanism. It is unlikely that vaccination against measles, which is done after 9 months of age, influences the observed pattern, as a seasonality of measles in the dry season has been described already in the pre-vaccination era [44]. Unfortunately, studies which would settle these questions have not been done.

The contribution of different age groups to the dynamics has implications for vaccination policy. Due to the likely short duration of protection, vaccination of infants might not be very effective unless epidemics are primarily driven by transmission among children below school age.

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### Appendix A. Equations of MSEIRS4 model

$$\begin{aligned}
 \frac{d}{dt}M &= R\mu - (\xi + \mu)M, \\
 \frac{d}{dt}S_1 &= \mu(1 - R) + \xi M - \mu S_1 - \beta_1(t)IS_1, \\
 \frac{d}{dt}E_i &= \beta_i(t)IS_i - (\mu + \sigma)E_i, \quad i = 1, \dots, 4, \\
 \frac{d}{dt}I_i &= \sigma E_i - (v + \mu)I_i, \quad i = 1, \dots, 4, \\
 \frac{d}{dt}R_i &= vI_i - (\mu + \gamma)R_i, \quad i = 1, \dots, 4, \\
 \frac{d}{dt}S_j &= \gamma R_{j-1} - \mu S_j - \beta_j(t)IS_j, \quad j = 2, 3, \\
 \frac{d}{dt}S_4 &= \gamma(R_3 + R_4) - \mu S_4 - \beta_4(t)IS_4, \\
 I &= I_1 + I_2 + I_3 + I_4, \\
 R &= R_1 + R_2 + R_3 + R_4, \\
 \beta_1(t) &= b_0(1 + b_1 \cos(2\pi t + \phi)), \\
 \beta_2(t) &= 0.5\beta_1(t), \\
 \beta_3(t) &= 0.35\beta_1(t), \\
 \beta_4(t) &= 0.25\beta_1(t).
 \end{aligned}$$

Here

- $\mu$ : birth rate = mortality rate;
- $\xi$ : rate of loss of protection by maternal antibodies;
- $\gamma$ : rate of loss of immunity;
- $v$ : rate of loss of infectiousness;
- $b_0$ : average of transmission parameter  $\beta_1$ ;
- $b_1$ : relative variation of transmission parameter  $\beta_1$ .

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