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Cost analysis of a vaccination strategy for respiratory syncytial virus (RSV) in a network model

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Abstract

In this paper an age-structured mathematical model for respiratory syncytial virus (RSV) is proposed where children younger than one year old, that are the most affected by this illness, are specially considered. Real data of hospitalized children in the Spanish region of Valencia are used in order to determine some seasonal parameters of the model.

Then, we propose a complete stochastic network model to study the seasonal evolution of the respiratory syncytial virus (RSV) epidemics. In this model every susceptible individual can acquire the

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disease after a random encounter with any infected individual in the social network. The edges of a complete graph connecting every pair of individuals in the network simulate these encounters and a season dependent probability $\beta(t)$ determines whether the healthy susceptible individual becomes infected or not. We show that the prediction of this model is compatible with that of an ordinary continuous model, based upon differential equations, but sharper peaks are obtained in the case of the network. The results of both models are compared with hospitalization data of RSV infected children in the region of Valencia, Spain.

Weekly predictions about the number of children younger than one year old that will be hospitalized in the following years, in the Spanish region of Valencia are presented using previous model. Results are applied to estimate the regional cost of pediatric hospitalizations and to perform a cost-effectiveness analysis of possible vaccination strategies.

Keywords: Respiratory syncitial virus, Network mathematical model, Vaccination strategy, Cost estimation.

1 Introduction

The spread of epidemic diseases has been traditionally simulated by means of systems of differential equations [1, 2, 3]. Typically in these models we consider the fraction infected (I), susceptible (S) and recovered (R) individuals and propose a compartmental model for the transitions among these states. The resulting SIR model has been widely studied [3, 4] but, albeit it is a good approximation in some cases, it is clear it cannot be the final word in the epidemiology of any real disease.

However, the continuous approach cannot, by its own nature, distinguish among individuals and, consequently, the effect of age, sex, previous illnesses and any other parameters influencing the propagation of the epidemic under study are difficult to implement. In the differential equations approach we only consider continuous functions, I(t), S(t) and R(t) and insurmountable difficulties are faced out when the interest is upon the evolution of single individuals instead of an average over the full population. The vaccination programs are an example of a situation in which the network approach shows its advantages. In the network we can easily monitor the age of any individual

and implement vaccination doses at a given age for children or catch-up policies. In continuous models we use a vaccination probability but, this way, we cannot avoid counting the same inviduals two or more times and to obtain reliable costs of the diseases is difficult. Moreover, taking into account the local and discrete character of epidemic spread also allows to include variable susceptibility or recovery rates of individuals, mobility and long-range infections. For instance, the debate about targeted or mass vaccination in the control of smallpox has also been addressed within the context of network models [5, 6].

In this paper, we consider a complete network model for the propagation of the respiratory syncytial virus seasonal epidemic. This pandemic is the direct cause of around 1300 pediatric hospitalizations in the Spanish region of Valencia and 15000-20000 visits to primary care every year [7]. The cost to the Valencian Health System is estimated in 3.5 million euros per year. We have retrieved hospitalization data for children less than one year old in the region of Valencia as a consequence of bronquiolitis or pneumonia developed by RSV infection. Unfortunately, prevalence data is still not available but we will be able to compare with the models by an adequate scaling of the predicted infected children. On the other hand, most of the hospitalizations correspond to children less than one year old and, consequently, we have to single out this age group both in the continuous differential equation model and the network model.

Modelling of the RSV epidemic has also been carried out within the framework of the standard SIR differential model. For example, Weber et al. [9] developed SIRS (susceptible-infected-recovered-susceptible) mathematical model with four possible reinfections and applied it to explain the data curves for Gambia, Singapore, Florida and Finland. They found that the seasonal component depends on the local climate of the country under study and even the period of the epidemic can be different. This paper leads us to conclude that the propagation of RSV is still not understood properly because the sharp peaks at the outbreaks are not adequately fitted by continuous models. Similar approach has also been adopted by White et al. [8] in a nested RSV model.

On the other hand, continuous models are more reliable concerning the application of optimizing techniques as shown below. Consequently, it is our objective in this paper to propose a two-age group generalization of Weber's model [9] and use it to fit the seasonal parameters. Seasonality of the infection probability is modelled by a single harmonic as follows: $\beta(t) =$

$b_0 + b_1 \cos(2\pi t + \varphi)$. Once the seasonal parameters are fitted we apply it to the evolution of a complete network model, with a Forster-Mckendrick population model, for the Valencian region. The network includes a node for every person in the region of Valencia: an average of 4252386 inhabitants during the four year period from January 2001 to December 2004 where data was harvested.

Moreover a PIV-vectored vaccine is already under development and clinical studies have been carried out since past year [17]. This vaccine could be available in the near future and, consequently, it is an urgent task to anticipate vaccination strategies. To the best of our knowledge, vaccination strategies for RSV have not been studied and the imminence of the application of PIV-vectored vaccines demands such an study. A previous work on the cost-effectiveness of immunoprophylaxis with palivizumab has been recently reviewed [18].

The layout of this paper is as follows. In Section 2 the underlying classical compartmental mathematical model with two age groups is introduced. Section 3 is devoted to the details of the stochastic network model. Optimization techniques and simulation results for both models compared with real data for hospitalization in the region of Valencia is presented in Section 4. A cost-effectiveness analysis is carried out in Section 5 for a vaccine scenario in this region. The paper ends with some discussions and conclusions.

2 Two-age group differential model for RSV transmission

In this section we introduce a generalization of the standard SIRS model for RSV [9] which includes two age groups. The reason for this extension relies upon the fact that most hospitalizations in the region of Valencia and surely all over the world correspond to children younger than one year old. Therefore, in order to fit the data from hospitalizations derived from RSV infections we must, at least, consider two age groups: G_1 corresponding to children less than one year old and G_2 which includes the rest of the population. Denoting by $S_i(t)$, $I_i(t)$ and $R_i(t)$, $i = 1, 2$ the fraction of susceptible, infectious and recovered people on each group the resulting system of evolution equations

can be written as follows:

$$\begin{aligned} S_1'(t) &= \mu - [\beta(t)(I_1(t)+I_2(t)) + c_1 + d_1] S_1(t) + \gamma_1 R_1(t), \quad (1) \\ S_2'(t) &= c_1 S_1(t) - [\beta(t)(I_1(t)+I_2(t)) + d_2] S_2(t) + \gamma_2 R_2(t), \quad (2) \end{aligned}$$

$$\begin{aligned} I_1'(t) &= \beta(t)(I_1(t)+I_2(t)) S_1(t) - [\nu_1 + c_1 + d_1] I_1(t), \quad (3) \\ I_2'(t) &= c_1 I_1(t) + \beta(t)(I_1(t)+I_2(t)) S_2(t) - [\nu_2 + d_2] I_2(t), \quad (4) \end{aligned}$$

$$\begin{aligned} R_1'(t) &= \nu_1 I_1(t) - [\gamma_1 + c_1 + d_1] R_1(t), \quad (5) \\ R_2'(t) &= c_1 R_1(t) + \nu_2 I_2(t) - [\gamma_2 + d_2] R_2(t), \quad (6) \end{aligned}$$

with the initial condition

$$\begin{aligned} S_1(0) &= S_1^0, \quad I_1(0) = I_1^0, \quad R_1(0) = R_1^0, \quad (7) \\ S_2(0) &= S_2^0, \quad I_2(0) = I_2^0, \quad R_2(0) = R_2^0, \quad (8) \end{aligned}$$

where μ is the birth rate, c_1 is the transition rate from age group G_1 to G_2, d_1 and d_2 are death rates for each age group, γ is the transition rate from recovered to susceptible and ν is the transition rate from infectious to recovered. The infection rate $\beta(t)$ is usually modelled as a harmonic:

$$\beta(t) = b_0 + b_1 \cos(2\pi t + \varphi), \quad (9)$$

where b_0, b_1 and φ are parameters to be obtained by fitting the data for the region under consideration. This kind of functions have been considered not only for RSV [9] but also for other seasonal epidemics such as measles [10].

The average time a person remains infected is 10 days [11] and the average recovering time is 200 days [9]. Then, $\gamma_i = 365/200$ and $\nu_i = 365/10$ are the transition rates between the compartments R and S, I and R, respectively.

In order to fit the population parameters of the continuous model we have resorted to the Valencian Institute for Statistics [12]. Processing this database we find that the average population in the Valencian region is 4252386 inhabitants during the period of interest from year 2001 to year 2004. The mean fraction of both subpopulations are $N_1 = 0.01037$ and $N_2 = 0.98963$. The mean birth rate, $\mu = 0.01075$ and the mean death rate of age group G_1 is given by $d_1 = 0.0006796$.

Under the assumption of constant population in both age groups the following relations must be fulfilled:

$$\mu = N_1 c_1 + N_1 d_1, \tag{10}$$

$$\mu = d_1 N_1 + d_2 N_2. \tag{11}$$

From Eq. (10) we get $c_1 = 1.03596$ and Eq. (11) yields the second mortality rate, $d_2 = 0.01085$.

3 The Social Network model for RSV

In this section we discuss the implementation of a social network model for the propagation of the RSV. We consider that every person in the region under consideration occupies a node of a network of relations among individuals. These individuals could be in any of the three states: susceptible, infective or recovered with respect to the virus. Despite random networks have already been proposed as an optimal model for epidemics our approach relies upon the complete graph, i. e., every person is potentially connected with any other person in the region. From another point of view, this model is a cellular automata [13] with N nodes and three possible states for each node. The network starts in a state in which every individual is susceptible save for an small group of infectives which play the role of the source of the epidemic.

Evolution rules are as follows:

- Every time step (set to one day) we draw a pseudorandom number for every infective individual, if this number is smaller than the transition rate per day, $\nu = 0.1$ days^{-1} we change the state of the individual to recovered.

- Similarly for every recovered individual we perform the stochastic transition to susceptible with a probability $\gamma = 0.005$ every time step of one day.

- The infection process is simulated by a mean-field procedure. The probability for a susceptible individual to become infected at a given day is:

$$P(S \to I) = 1 - (1 - \beta^\star)^{I(t)}, \tag{12}$$

where β is the probability for a susceptible individual to become in social contact with a infective individual times the probability for the disease to be transmitted in this contact. $I(t)$ is the number of infected persons at time step t. The correspondence with the rate in the continuous model is as follows:

$$\beta^\star = \frac{\beta}{N}, \tag{13}$$

being N the total constant population.

The mean-field approach has been successfully applied in other network models [14] and it yields good results in comparison with the correct, but very computational intensive, procedure of visiting every pair of infectious and susceptible sites to determine the propagation of the infection at the next time step. The required condition to this simplifying procedure to be valid is that $\beta^\star$ must be sufficiently small, $\beta^\star \ll 1$.

The transitions from infectious to recovered and then to susceptible are controlled by the biology of the virus and the human host. In this case we have simulated the process by a constant probability of transition from a state to the next independent of the time that the individual has remained in the initial state. This is equivalent to the standard exponential distribution of remaining times which plays a main role in the traditional classical continuous mathematical epidemics models [15].

One of the advantages of the network is the possibility of implementing easily more realistic demographic models. In the case of the social network for the region of Valencia we have chosen a discrete Forster-McKendrick model with constant population [4].

The evolution rules for the population pyramid (the number of individuals as a function of their age, $N(t)$) are as follows:

(a) Every time step, τ, people with age t years increase their age to $t+1$,

(b) A fraction $d(t)N(t)$, corresponding to the individuals which die with age t, is removed from the age group of t years,

(c) In order to fulfill the condition of constant population a number

$$\text{Newborns}(\tau) = \sum_{t=0}^{\text{tmax}} d(t)N(t) \tag{14}$$

of newborns are included into the model.

In order to obtain a plausible population model for Valencia we have evolved the population accordint to these rules from an initial uniform age state to get the stationary population pyramid used in the simulations of RSV propagation. The results are discussed in the next section.

4 Simulation and fitting of models

As mentioned above the continuous model is more suitable to the application of a fitting procedure because the numerical integration is far faster than the simulation of the social network. Our data correspond to children less than one year old than were hospitalized as a consequence of RSV infection. In order to fit this data we have to select values for the seasonal parameters: b_0, b_1 and φ, and also for the parameter s which gives us the fraction of children, from the total population of infected children in the age group G_1, that become hospitalized.

For a given set of parameters numerical integration of Eqs. (1)-(5) is performed starting from an initial condition in which a one percent of the children in age group G_1 are infected at January 1st, 1999. The transient is sufficiently short to achieve the stationary state for the RSV dynamics by January 2001. So, we can use this integration to fit the real data. The fitting is carried out by means of the downhill simplex method due to Nelder and Mead [16].

Applying Nelder-Mead method we find the following set of parameters:

$$b_0 = 69.52, \tag{15}$$
$$b_1 = 14.31, \tag{16}$$
$$\varphi = 5.997, \tag{17}$$
$$s = 0.0219\ . \tag{18}$$

The results are plotted in Fig. 1. In this figure we also compare with the simulation results for the social networks, with $N = 4252386$ individuals and 4 runs, taking into account only the children less than one year old at a given week. We consider that a fraction s of these children become hospitalized as fitted by the Nelder-Mead method. In the case of the network the peaks corresponding to the outbreaks are sharper and fit better the trend shown in the data, specially the major outbreak ocurred at the winter of 2004.

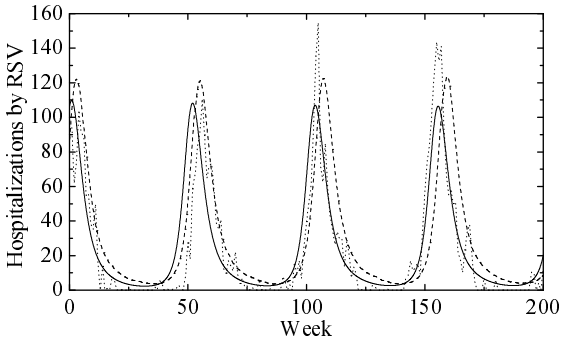

Figure 1: Model fitting since January 2001 to December 2004. The points are data of weekly hospitalizations of children younger than one year old, the continuous line the scaled solution of the system of differential equations for infected children younger than one year old, $s \times I_1(t)$ and the dashed line is the prediction of the social network model.

5 Vaccination strategy and costs

In this section we develop a cost-effectiveness analysis for a vaccination strategy for RSV. The strategy consists of the vaccination of non-infected children at 2 and 6 months and at 1 year old. A fraction $p = 85\%, 90\%$ and 95% of non-infected are vaccinated. In the fraction p we consider those children that have been vaccinated the three times and, therefore, the vaccine protection is complete. Under this point of view, our predictions and estimations are conservative beacause the children with only one or two vaccines may have a partial protection that the model does not consider. Then, taking the next 5 years, costs are taken as the mean cost of these 5 years. Hence, the total cost of RSV healthcare is calculated as follows:

- Hospitalization cost: Taking into account an average of 6.28 hospitalization days for every acutely infected child [7] and 500 euro per day and child hospitalized.
- Vaccination cost: We calculate the number of children vaccinated during a year and an estimated cost of 100 euro per dose. Three doses are programmed during the first year of life, at 2, 4 months and a year old.
- Parent work loss: We take into account that for every hospitalized children parents lose $d = 6.28$ days of work (average hospitalization of RSV infected children). In the case of infected children we assume that they develop milder symptoms but, nevertheless, a parent loses d days of work. This is a social parameter difficult to be determined. We will simulate cost-effectiveness for $d = 2, 3, 4$. The labor cost in Spain is 75.21 euro per day [17].

The results for the costs of hospitalization, vaccination, parent work loss and global cost for a vaccination of 85%, 90% and 95% of the non-infected children, for $d = 2, 3$ or 4 days of parent work loss in the case of children that do not develop sufficiently acute symptoms to become hospitalized, are the following:

- Estimated cost per year (in euros) without vaccination strategies.

	$d = 2$	$d = 3$	$d = 4$
Hospitalization costs	3,574,904	3,574,904	3,574,904
Vaccination costs	0	0	0
Parent work loss cost	8,186,293	12,010,570	15,834,848
TOTAL	11,761,196	15,585,474	19,409,752

- Estimated cost per year (in euros) when a fraction of 85% of non-infected are vaccinated at 2, 4 months and a year.

	$d = 2$	$d = 3$	$d = 4$
Hospitalization costs	1,190,934	1,190,934	1,190,934
Vaccination costs	10,851,915	10,851,915	10,851,915
Parent work loss cost	2,727,161	4,001,171	5,275,181
TOTAL	14,770,010	16,044,020	17,318,030

- Estimated cost per year (in euros) when a fraction of 90% of non-infected are vaccinated at 2, 4 months and a year.

	$d = 2$	$d = 3$	$d = 4$
Hospitalization costs	1,059,320	1,059,320	1,059,320
Vaccination costs	11,486,715	11,486,715	11,486,715
Parent work loss cost	2,425,772	3,558,986	4,692,201
TOTAL	14,971,806	16,105,021	17,238,235

- Estimated cost per year (in euros) when a fraction of 95% of non-infected are vaccinated at 2, 4 months and a year.

	$d = 2$	$d = 3$	$d = 4$
Hospitalization costs	918,047	918,047	918,047
Vaccination costs	12,135,225	12,135,225	12,135,225
Parent work loss cost	2,102,266	3,084,353 ,	4,066,440
TOTAL	15,155,538	16,137,625	17,119,712

A reduction of more than 2 million euros of total cost is predicted for an estimation of 4 days of parent work loss on average for infected children. In the case of 3 days of parent work loss, the increasing of the cost is around 600,000 euros, but however, the hospitalization and parent loss work costs decrease dramatically at expense of vaccination cost. These decreasing avoid the saturation in the hospital casualty departments (what allows a more reasonable distribution of human and material resources) and the companies are not so indirectly affected in productivity by the disease.

Moreover, we have not taken into account the long-term effects of RSV infections. In particular, there is an agreement among pediatrics about a connection among RSV at early ages and asthma episodes of children and adolescents. This has been confirmed by recent studies in mice [18]. Therefore, even of the assumption that parents only lose three working days for caring children which develop mild symptoms of RSV a positive balance for the implementation of the vaccine is obtained.

6 Conclusions

Continuous differential models have been very popular among mathematical epidemiologists for a long time. However, the availability of computers with large amount of memory and processing power allows us to use networks as an alternative and more realistic approach to the disease dynamics. In the networks we can isolate individuals and follow their evolution as they become infected, recover and become susceptible again. Taking into account different characteristics of the individuals: variable susceptibility, sex, age as labels to the node. This fact only shows that networks are a more flexible tool than traditional models based upon differential equations.

In this paper we have compared a SIRS compartmental model for the respiratory syncytial virus epidemic with a homogenous social network in which the nodes, representing the individuals, are labelled as susceptible, infected or recovered and evolve from one state to another by random rules. We have applied these models to the fitting of the hospitalization data for children in the region of Valencia as a consequence of RSV infection. A clear advantange of the continuous models is that differential equations can be integrated faster than simulating the propagation of the disease in the network. As an alternative approach to the continuous model versus network model dilemma [6] we have adopted the following perspective: (i) The continuous model is used as a guide to fit the seasonal parameters and the scale s relating the prevalence with the hospitalizations, a derivative free Nelder-Mead method is suitable for this task, (ii) these parameters are used as input in the network models. By this procedure we have obtained a reasonable fit of the data in both cases but the sharp peaks observed in the data are obtained only in the case of the social network. This is not a consequence of the particular set of parameters the Nelder-Mead method converge to but a feature that distinguished both methods generally.

Mean-field-like approach is also applied in order to reduce large computation time required when dealing with the large complete contact network. In the mean-field approach susceptible individuals get infected with a probability that depends on the number of infected individuals at a given time. This approach allows us to perform computations involving the total population of the region of Valencia in a reasonable amount of time.

We have developed a model for newborn vaccinations with two remainders during the first year of life. Assuming a cost of 300 euro per vaccination a positive balance for the implementation of the proposed vaccination strategy

is obtained even with the cautious assumption that parents only lose 3 days in the case of infected children which do not become hospitalized. We must take into account that these results are obtained with a simple extension of a recently proposed SIRS model [9] and should be considered as a first order approximation. However, we have also checked that a mean-field network approach replicates the result discussed in this paper even with a continuous Forster-Mckendrick population model [4] which it is more realistic than the two age groups proposed in this paper.

A more general model including heterogeneity of contacts among individuals, variable strength of re-infection and maternal antibody protection is currently under study and will be published elsewhere.

Network models for RSV also provide several possibilities for future research: vaccination strategies such as a catch-up before the outbreak or planned vaccinations of newborns with remainders during the first year of age can be implemented and follow the individual evolution of vaccinated children. The extinction of the epidemic after implementing the vaccination program can also be studied as a consequence of the reduction of the susceptible population. For sufficiently small populations the virus cannot percolate through the network but in the case of continuous models epidemics can also bounce off even for unrealistically small prevalences. Moreover, in networks it is easier to know how many individuals satisfy certain intensity conditions from the epidemic point of view and evaluate yearly costs to be faced by the the health system due to the disease and the child vaccination strategies. Work along these lines is in progress and will be published elsewhere.

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