Contents

Chapter 1

Introduction

1.1 Bronchiolitis and the Respiratory Syncytial Virus

Bronchiolitis, meaning inflammation of the bronchioles, is a clinical complex usually affecting children less than two years old. It is characterised by wheezing, dyspnoea, tachypnoea and poor feeding. The clinical characteristics, originally termed congestive catarrhal fever, have been recognised for over 150 years. It was not until the late 1950s that the epidemiology and viral aetiology of the illness were first described [21, 22, 72].

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and is among the most important pathogens causing respiratory infection in infants worldwide. Epidemics occur during winter months, in temperate climates, and during the rainy season, in tropical climates [18].

RSV is the prototype of the Pneumovirus genus, which also includes the closely related bovine, ovine and caprine and a more distantly related virus, the pneumonia virus of mice.

1.1.1 Respiratory syncytial virus structure

From a structural point of view we can say that virus are particles surrounded by a lipid bilayer with the attachment (G) glycoproteins and the fusion (F) glycoproteins that form the characteristic spikes of virus as seen in the scheme of the RSV-virion in Figure 1.1.

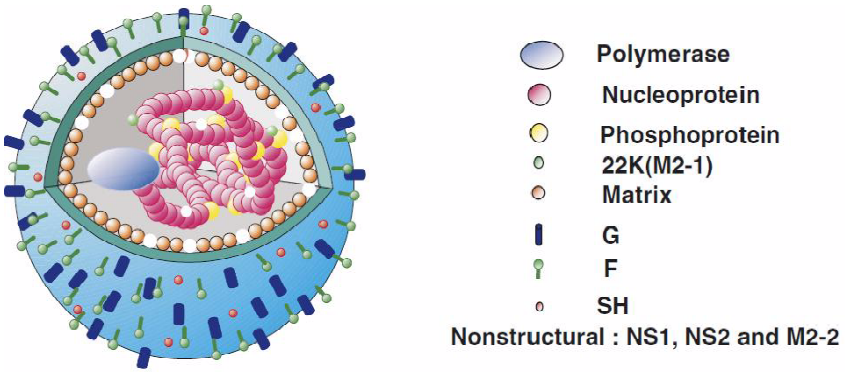

Figure 1.1. *Scheme of the RSV-virion* [72].

By electron microscopy, the RSV-virions have sizes and shapes heterogeneous as we can see in Figure 1.2. There are two types of viral particles: round- or kidney-shaped and diameter from 150 to 250 nm and filaments and up to 10 μm in length [12].

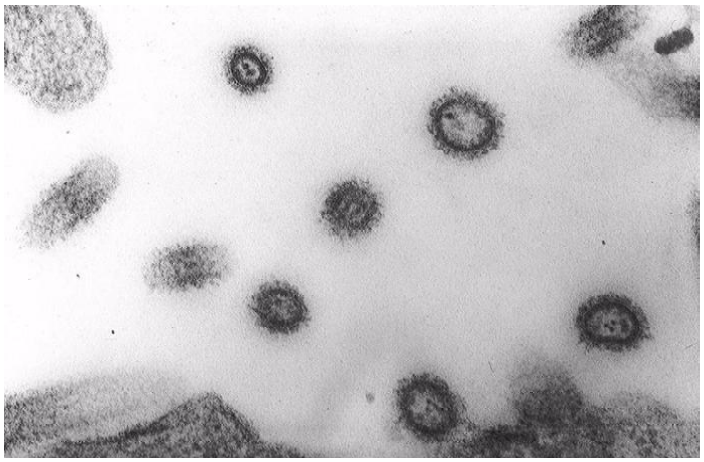

Figure 1.2. *RSV-virions by an electron microscopy. Heterogeneus sizes ans shapes can be observed* [12, 72].

On another hand RSV can be divided into two groups or strains, A and B, which can be distinguished antigenically with polyclonal animal sera [25] and monoclonal antibodies [39]. There are conflicting reports concerning the relative severity of disease caused by the two groups of the viruses [19]. Initial studies using monoclonal antibodies showed that both groups of RSV co-circulate in epidemics, although their relative incidence may vary. In general, throughout the world, group A isolates are more often detected than group B isolates [19].

1.1.2 Spread

RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious material contacts the mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough.

First, RSV infects the cells of the upper respiratory tract. The incubation period is estimated to be between two and eight days [31]. Viral load in the upper airways peaks early, 1 to 2 days after onset of symptoms, and continues to decline even if lower respiratory tract symptoms subsequently develop [28]. Infection will spread to the lower respiratory tract in $30-50\%$ of infants, $1-3$ days after the onset of the illness [50]. Transition to the lower respiratory tract is thought to be by both direct spread along the respiratory epithelium and by aspiration of nasopharyngeal secretions [84, 18].

Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. During the first RSV infection, between 25% and

40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and between 0.5% to 2% require hospitalization, although these limits are not a completely closed case. Most children recover from illness in 8 to 15 days and the majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems [20].

The majority will have mild symptoms such as a runny nose with or without a dry cough. A small percentage, $1 - 3\%$, develops acute bronchiolitis, caused by inflammation and narrowing of the small airways of the lung. The affected babies become breathless and need hospital care for oxygen therapy and assistance with feeding [58].

The severity of illness ranging from a mild upper respiratory tract illness to severe lower respiratory tract disease [19]. The ability of individuals to deal successfully with infectious diseases is influenced by several variables, including the nature of the pathogen, environmental factors, preexisting illness and even heritable genetic variations [58].

In elderly adults, RSV infection can cause a variety of signs and symptoms. In this people, clinical manifestations of RSV may range from a mild common cold syndrome to severe respiratory distress and failure. Rhinorrhea, nasal congestion, and cough are frequently reported in RSV infections, while sore throat has been noted in approximately 25% of cases. Gastrointestinal symptoms are quite uncommon and fever is 38^oC or less in about half of the reported RSV infections in elderly adults [75].

As regard to the incidence there is a large literature that testifies to the importance of RSV as a cause of both community and hospitalised childhood with lower respiratory tract infection (LRTI) in resource-poor settings. In the review [102], the estimated proportion of community-

acquired LRTI in children due to RSV was 10% (range $1 - 22\%$) from community-based studies and 18% ($6 - 40\%$) from hospital out-patient or in-patient studies. These estimates and others appearing in the literature are useful starting points but are clearly crude, with compounding imprecision due to uncertainty of each component of the calculation.

A generic protocol was developed by WHO setting out a clear case for denominator-based studies to estimate the incidence of LRTI due to RSV in children under 5 years of age in developing countries [111]. Some key limitations as poorly defined population denominator for incidence, estimation, inadequate information on the severity of disease by age, absence of rural studies with potentially differing risk factors for transmission than urban poor and other, make it difficult to study the incidence [78].

Hospital-based studies in developing countries show similar age distribution as in industrialised countries: on average 39% of cases are under 6 months, and 63% under 1 year [102]. Studies clearly illustrate the importance of incidence in the first year of life over incidence in older age groups [78].

In other studies [88] have found that RSV-associated mortality is statistically higher in the developing than the developed countries [78].

1.1.3 Reinfections

It has been known for many years that RSV can repeatedly reinfect individuals, although overall it appears that second and subsequent infections are generally less severe than the primary infection, namely, there is an accumulation of resistance to LRTI disease with successive infections [55, 41, 108].

Observations at the community level, the epidemics often show re-

placement of predominant genotype while at the same time there also appears to be positive selection on the G protein, what would favour the concept of viral variation playing a role in susceptibility to reinfection. Thus, the molecular epidemiological evidence suggests that group or genotype infection prevalence influences future transmission of the homologous and heterologous variants within a population, a notion supported by a recent mathematical model, [106].

In a study of adult volunteers who were repeatedly challenged with the same strain of virus, found that reinfection could readily be achieved [48]. The duration of immunity tended to increase after two closely spaced infections. Higher neutralising antibody levels before challenge correlated significantly with protection against infection. However, even in subjects with the highest antibody levels, the risk of reinfection was 25%. They suggested that humoral neutralising, F, and G antibodies correlate with resistance to reinfection, but protection is far from complete and is of short duration [19].

The risk of re-infection in children and adults is inversely correlated with the levels of neutralizing serum antibodies [41, 98, 75].

1.1.4 Treatment

The standard treatments of RSV-bronchiolitis by means of adrenaline, bronchodilators, steroids or the anti-viral rivabirin have also been criticized as conferring no real benefit for the patients [54]. Last one is effective in reducing viral load, but does not affect disease outcome [58].

At the present moment only Palivizumab, (humanised murine monoclonal IgG_1 antibody) targeted against the surface F protein which induces the fusion of the syncytial cells [72], is effective as an immunoprophylactic measure which reduces the risk of serious LRTIs on high-risk children. Nevertheless, in a recent study [99] cost-effectiveness is only

found for the prevention of acute RSV-infections in children with chronic lung disease or congenital heart disease. This treatment is generally supportive until the infection runs its natural course [18].

1.1.5 Seasonality

It has been known for many years that RSV causes annual epidemics during the winter in temperate climates. In the UK the annual epidemic usually peaks around December [19]. Similar annual epidemics occur in many temperate countries, though there are exceptions such as Finland where every two years there is a minor peak of RSV activity in April followed by a major peak in December [100]. In the USA, RSV activity often peaks slightly later, around February, but the cause of these variations is unknown [38]. In Valencian Community, as can be seen in Figure 1.3., the peaks occur in December or January.

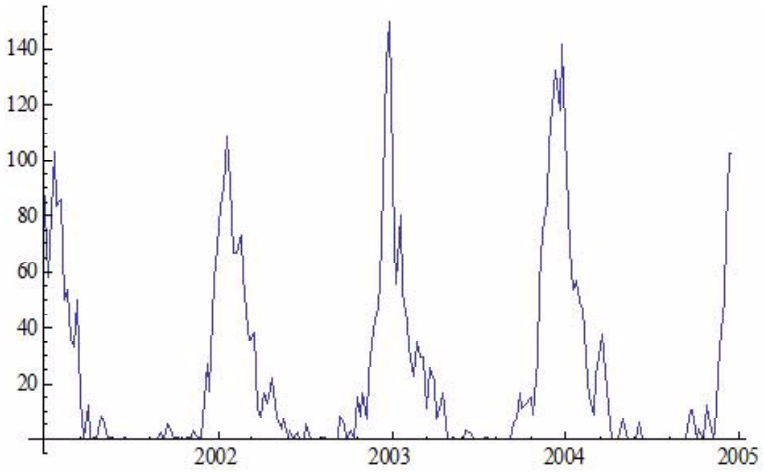

Figure 1.3. *Data of weekly hospitalizations of children younger than one year old since January 2001 to December 2004.*

In the tropics, RSV outbreaks are often associated with the rainy season in those countries with seasonal rainfall and have also been associated with religious festivals [103]. In South Africa, RSV epidemics also occur in the autumn and winter in HIV-negative children. However, there is not seasonality in HIV-positive infants [68].

The cause of the strict seasonality of RSV epidemics is not known but it seems likely that social conditions such as the return to school after the long summer break in developed countries or indoor crowding during the rainy seasons in the tropics are contributing factors [19].

Almost invariably epidemics begin in coastal (low altitude) locations or areas surrounded by water then moving inland [88] but locations sharing the same weather patterns and separated by small distances can experience epidemics completely out of phase [85].

Seasonal infections of humans range from childhood diseases as measles, diphtheria and chickenpox, to faecal-oral infections, such as cholera and rotavirus as Respiratory syncytial virus (RSV), vector-borne diseases including malaria and even sexually transmitted gonorrhoea, see [42].

In modeling transmission of seasonal diseases, nonlinear systems of ordinary differential equations have been used with a coefficient given by a periodic continuous functions $\beta(t)$ (called sometimes seasonally-forced function) that incorporates the seasonality of the spread in the environment, see [29, 11, 61, 107, 106, 104, 74, 43]. Many authors take, as an example of seasonally-forced function, the expression

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

where $b_0 > 0$ is the baseline transmission parameter, $b_1 > 0$ measures the amplitude of the seasonal variation in transmission and $0 \leq \varphi \leq 2\pi$ is the normalized phase angle. For other examples of this type of functions see [61, 33, 104].

1.1.6 Risk factors for RSV infection

The classical risk factors for RSV disease in developing countries are chronic lung disease, congenital heart disease, immunosuppression and prematurity, although there is an issue as to whether such factors are also prominent in the developed countries. However, 60% of serious RSV disease occurs in infants who are without known risk factors [26]. RSV is also an important cause of morbidity and mortality in elderly people [37]. On another hand, other factors are of interest given their high or increasing prevalence in much of the developing world:

- Malnutrition. Poor nutritional status is identified as a risk factor for increased incidence [87, 95, 97, 13] and severity [14] of LRTI in less-developed countries.
- Malaria. In endemic locations malaria is an influence on estimates of RSV prevalence among LRTI cases or incidence of RSV associated LRTI. As well, it is also a potential risk factor for RSV infection [79].
- HIV. Prolonged shedding of RSV in HIV−positive children has epidemiological implications in relation to persitence of the virus within communities and seasonal dynamics of infection [88].
- Nosocomial RSV infections. Past studies in developed countries clearly demonstrate RSV to be highly efficient at transmission within the hospital environment [45]. Estimates of this risk vary in the literature from $6 - 21\%$ [79].

1.1.7 Disease sequelae

Serious RSV disease frequently is followed by pulmonary abnormality such as a propensity for wheezing that can persist to adolescence. Whether

RSV contributes to the development of asthma remains controversial, but it certainly can exacerbate it [70]. Otitis media is another common complication of infection by RSV and other respiratory viruses [26].

1.2 Impact on health system

As mentioned before, during the first RSV infection, young children have signs or symptoms of bronchiolitis or pneumonia, and a percentage of them require hospitalization. In fact, RSV is the most important respiratory virus of young children, and the major cause of hospitalizations specially for bronchiolitis and pneumonia in infants [51].

In the USA, more than 120.000 infants are hospitalised annually with RSV infection, with more than 200 deaths attributed to RSV lower respiratory tract disease [90]. Total hospital charges for RSV-coded primary diagnoses during four years, from 1997 to 2000, were estimated to have been $2.6 billion [66].

In Spain, there are $15.000 - 20.000$ attentions in medical primary services due to RSV each year. As a particular case, in the Spanish region of Valencia, around 1.280 children younger than five years old are hospitalized each year as a consequence of bronchiolitis caused by RSV. This is an incidence of 400 cases each 100.000 children younger than a year, with 6 hospitalization days as the average [30]. In particular, the cost of pediatric hospitalization for the Valencian Health System has been estimated in 3.5 million euros per year [30] without taking into account indirect costs [1], with a cohort of newborns of 45.000 children.

RSV is the cause of annual seasonal epidemics with minor variations each year and its coincident incidence with other widespread viral infections, such as influenza or rotavirus, produces a high number of hospitalizations saturating the Health System. Moreover, as we mentioned

before, its transmission is very easy and the nosocomial infections are frequent [49].

Therefore, the research on RSV and other virus and the developing of strategies to control epidemics are important from both the sanitary and economic point of view. Another problem is the study of vaccines to protect individuals at early ages, when the immune system is not completely developed. In this context it is important to notice that the most seriously ill cases are not due to the RSV infection but they are related to an anomalous immune response of the child [27].

1.3 Vaccines

In the 1960*s* trials of formalin inactivated whole virus (FI−RSV) was used as a vaccine and given via the intramuscular route. Vaccinees produced antibodies to the virus, but these were non-neutralising. On exposure to natural infection, vaccinees developed more severe disease than controls, resulting in 80% requiring hospital admission compared to 5% of controls and 2 children died [63]. This outcome indicates that an inappropriate host response to the virus could lead to enhanced disease [58].

Nowadays, there is no licensed vaccine against RSV. High-risk infants can be substantially protected by monthly intramuscular injections of a commercially available RSV-neutralizing antibody (palivizumab) administered during the RSV epidemic season [10]. However, this treatment is too expensive and inconvenient for broader use at the present time. There is also no clinically effective antiviral therapy against RSV. The nucleoside analog ribavirin is effective in cell culture and in experimental animals, but has been disappointing clinically [9]. In the future, it may be possible to control infection and disease by a combination of antiviral and anti-inflammatory agents [15], but this remains experimental.

Thus, there is a worldwide need for an RSV vaccine, and probably for two different vaccines [26]. The primary need is for a pediatric vaccine, preferably to be administered in the first weeks of life. There also is a need for a vaccine which likely will be different from the pediatric one for RSV-experienced individuals at increased risk for serious RSV disease, including the elderly as well as individuals with chronic lung disease or congenital heart disease. Also, it will be necessary to demonstrate the absence of any association between intranasal RSV vaccination and apnea/sudden infant death syndrome.

The only vaccines under clinical evaluation for pediatric use at the present time are live intranasal vaccines [26] based on:

(i) attenuated RSV or

(ii) attenuated PIV3 expressing the RSV F protein as a bivalent RSV/HPIV3 vaccine.

On another hand, a PIV-vectored vaccine is already under development and clinical studies have been carried out since past year [91, 92]. This vaccine could be available in the near future and, consequently, it is an urgent task to anticipate vaccination strategies. In Chapters 2 and 3 we consider a newborn vaccination strategy for Valencia in terms of an estimated cost of the vaccine, the average cost of the hospitalization of RSV children which develop acute symptoms and taking into account the cost from parent work loss. 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 a study. A previous work on the cost-effectiveness of immunoprophylaxis with palivizumab has been recently reviewed [99]. If the PIV-vectored vaccine is finally released onto the market, the societal impact may be extraordinary and could be a cost-effective public health intervention [1].

The aim must be to develop a vaccine that provides protection against severe disease since the evidence indicates that it may not be possible to provide complete protection against infection. In the meantime, the use of prophylactic measures such as antibody preparations together with antiviral drugs and immune modulators will provide some defence against the severe disease [19].

1.4 Mathematical Models

Mathematical models have been revealed as a powerful tool to analyze the epidemiology of the infectious illnesses, to understand their behavior, to predict their social impact and to find out how external factors change the impact. In the case of RSV, the building of a reliable model is a priority objective to predict the medical care requirements needed in each season.

1.4.1 Continuous models

The spread of epidemic diseases has been traditionally simulated by means of systems of differential equations [62, 34, 76]. Typically in these models we consider the fraction of infected (I), susceptible (S) and recovered (R) individuals and propose a compartmental model for the transitions between these states.

Some mathematical models for RSV have been developed previously. For instance, in [104], a SIRS (susceptible - infectious - recovered - susceptible) and a MSEIRS4 (maternally derived immunity - susceptible - latent - infectious - recovered - susceptible) mathematical model with four possible re-infections. These models were studied and applied with data from Gambia, Singapore, Florida and Finland. In [107] a nested RSV model, stochastic simulations and fitting with data from several countries are presented. In another work [106], authors consider the two

types of the RSV, A and B, and develop a SIRS model where re-infection by any of both types of RSV virus is possible, fitting the model with data of England & Wales and Finland. This last paper interprets the pattern of seasonal epidemics of RSV disease observed in different countries and estimates the epidemic and eradication thresholds for the RSV infection. The presented models are fitted to clinical data to estimate some parameters.

We have constructed and analyzed a continuous SIRS model with two age groups to study the spread of RSV in Valencia and have performed a cost analysis of potential vaccination strategies. In Chapter 2 and in [1] are exposed the results of this study.

The SIRS model has been widely studied [76, 57] but, albeit it is a good approximation in a lot of cases, it is clear that this cannot be the last word in the epidemiology of a real disease. These continuous approaches cannot, by its own nature, distinguish among individuals and, consequently, the effect of age, sex, previous illnesses and some other parameters influencing in 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 can show its advantages.

1.4.2 Network models

In a network model 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 [53, 64].

Recently, an outburst of interest in cellular automata models [110] for epidemic spread has been generalised among researchers in epidemiology. Among many others, we have seen in the literature some applications to hepatitis B transmission [7], the immune system [32], plagues which devastate some crops [71] and the HIV pandemic [56]. Most cellular automata models are defined in euclidean lattice substrates with the individuals occupying the sites of the lattice. Nevertheless, in many situations only the topology of the network is relevant for the spreading of the epidemic. More refined models using random networks as the basic substrate have also been considered [109].

A network is a set of nodes representing individuals. Labels or properties may be assigned to each node, such as, age, sex, state respect to disease (susceptibility, infection, recovery and so on). Nodes are connected by ties that represent disease transmission paths. Once the network model and the disease evolution rules are stated, it is possible to simulate the evolution of the network over time and study the effect of disease on the population. When the ties are assigned randomly, we are in a random network. There are a lot of ways to assign ties to nodes randomly, depending on the probability distribution chosen: Poisson, Exponential distribution, Power-law distribution (also known as scale-free networks), etc. Papers studying the transmission dynamics of certain diseases using scale-free networks have recently been published [80, 81, 86, 67]. Scale-free networks allow the dynamics analysis of infectious diseases in a similar way to the continuous models, which is an interesting advantage. However, only diseases with specific transmission structures, for exam-

ple, sexually transmitted diseases, may be approached using scale-free networks.

Considering this aspect we have generated a network model based on the SIRS structure to study the spread of RSV in Valencia and their possible vaccination strategies. In Chapter 3 and in [2] are exposed the results of this study.

Some drawbacks of the previous models are the homogenous mixing of individuals or the fact that seasonal behavior is forced by imposing a cosine variation of the infection rate. All these limitations are solved by the social random network model proposed in the Chapter 4 of the present thesis.

Unfortunately, this modelling does not have the same advantages as the scale-free networks because it cannot be approached by differential equations, hence parameter estimation should be done carrying out simulations using the network structures with a large set of parameters in an intensive computing environment. In this work, we have used a computational system following the paradigm of distributed computing. This system will allow us to estimate the parameters in random network epidemic models. This system consists of a client/server structure where the server delivers tasks to be carried out by client computers, and when the task is finished, the client sends the obtained results to the server to be stored until all tasks are finished and ready to be analysed.

1.5 A brief Outline of this Dissertation

This thesis dissertation is as follows:

In Chapter 2, we propose an age-structured SIRS continuous mathematical model for RSV 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. 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 this model. Results are applied to estimate the regional cost of pediatric hospitalizations and to perform a cost-effectiveness analysis of possible vaccination strategies. This chapter is based on paper [1].

In Chapter 3, the age-structured mathematical model for RSV is used to determine the seasonal parameters. After that, we propose a complete stochastic network model to study the seasonal evolution of the RSV epidemics. In this model every susceptible individual can acquire the 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 the above mentioned age-structured model based upon differential equations, but sharper peaks are obtained in the case of the network. Then, on the network model, we propose the vaccination of children at 2 months, 4 months and 1 year old, and we study the cost of this vaccination strategy, which is emerging as the most plausible to be applied when the vaccine hits the market. It is worth to note that this vaccination strategy is simulated in the network model because to implement it in the continuous model is very difficult and increases its complexity. This chapter is based on paper [2].

However, the explanation of the seasonal outbreaks of this disease remains poorly understood. Hence, in Chapter 4, we study the propagation of RSV in the Spanish region of Valencia by simulating a random social network of contacts among one million of individuals to elucidate

the problem. We implement a SIRS model for the RSV epidemic in a random network of contacts among the individuals. The average degree of each node ranges from 15 to 124 and a client-server software ($Sisifo$) was developed in order to perform a distributed computer calculation in a cluster to estimate the disease infection probability. More than three years of equivalent computing time were required to explore the relevant combinations of average degree and infection probability. The standard SIRS model for RSV propagation incorporates a seasonal forcing function in the infection parameter. However, the statistical relation among RSV outbreaks and weather conditions remains unclear. We show that, in a random social network, seasonal epidemic emerge as a self-organization process modulated by the infection probability and the immunity period after recovering from the infection. We have obtained the best fit with the hospitalisation data for the region of Valencia and a probability of infection in a social contact per day, and an average of 200 days of immunity after recovery from the infection. Only parameters in a narrow band are shown to be capable of sustaining seasonal RSV epidemic in the population. This implies that simple prophylactic measures could reduce dramatically the incidence of seasonal pandemics.

We show in this chapter that random social networks are a more realistic model than traditional continuous approaches to epidemic propagation. We prove the possibility of self-sustained seasonal epidemic modulated by the loss of immunity of recovered individuals.

Finally, in Chapter 5, there are some conclusions and future research.

Chapter 2

Mathematical modeling of respiratory syncytial virus (RSV): Vaccination strategies and budget applications

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

2.1 Introduction

Of those respiratory viruses that affect young children Respiratory syncytial virus (RSV) is the most important, and the major cause of hospitalizations specially for bronchiolitis and pneumonia in infants [51]. Its impact on the Health Systems is increasing as the incidence of hospitalization in children for bronchiolitis increases [65].

Besides, the impact of RSV on adults has been recently studied, as up to 18% of the pneumonia hospitalizations in patients older than 65 are due to RSV [52].

Taking into account that RSV is an illness for which the most affected individuals (the most hospitalizations) in the Spanish region of Valencia are children younger than one year old we must develop an adequate demographic model.

We will use a model with two age groups: G_1, corresponding to children younger than one year old and G_2, for the rest of the population. Birth and mortality rates as well as the transition rate from G_1 to G_2 are obtained from real statistical data.

The evolution of infected individuals is predicted by means of Weber's SIRS model [104] generalized to take into account the two age-groups and numerically integrated by standard numerical methods.

This chapter is organized as follows. In next Section we discuss the age-structured SIRS model estimating some demographic parameters from data of the Instituto Valenciano de Estadística (Valencia's Statistical Service [59]). In the following Section, data corresponding to hospitalizations of children younger than one year old are presented and a Nelder-Mead procedure for model fitting is developed. A cost-effectiveness analysis is carried out in section Results for a vaccination scenario in the same region. Conclusions are given in the last section of

this chapter.

2.2 Methods

The Spanish region of Valencia [96] is located in eastern Mediterranean Spain, with an extension of 23.255 km^2 and a population of 4.202.607 inhabitants (2001), composed by three provinces, Castellón (north), Alicante (south) and Valencia (middle).

Following Section 6.1, p. $634 - 635$ in [57], we can introduce an age-structured SIRS model with two age groups: $i = 1$ corresponds to children from 0 to 1 year old and $i = 2$ corresponds to the rest of the population. This is justified because the disease is more acute in children younger than 1 year old as hospitalizations' data confirm.

For each age group we have also three subpopulations according to the state of the individuals with respect to the disease:

- Susceptibles, $S_i(t), i = 1, 2$ the proportion of those at risk of contracting the disease,
- Infectives, $I_i(t), i = 1, 2$ the proportion of those infected and capable to transmit the disease, and
- Recovered, $R_i(t), i = 1, 2$ the proportion of those who are recovered of the disease and are temporary immune to re-infection.

Notice that $S_i(t)$, $I_i(t)$ and $R_i(t)$, respectively, correspond to the fraction of susceptible, infected and recovered of age group $G_i, i = 1, 2$ and

$$0 \leq S_i(t), I_i(t), R_i(t) \leq 1.$$

Then the age-structured model can be represented by a compartmental diagram as we can see in Figure 2.1.

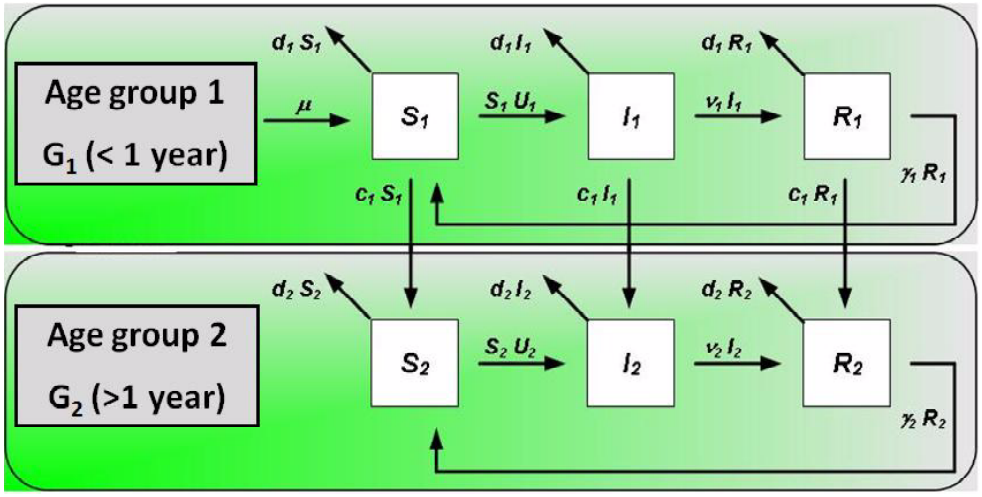

Figure 2.1. *A two-age group differential model SIRS to fit data from hospitalizations: G_1, children less than one year old and G_2, rest of the population. The seasonality appears in the contacts* $U_1(t) = U_2(t) = \beta(t) \cdot (I_1(t) + I_2(t))$, *with* $\beta(t) = b_0 + b_1 cos(2\pi t + \varphi)$.

This model is defined by the following system of differential equations

$$\begin{aligned} S_1'(t) &= \mu - [\beta(t)\,(I_1(t) + I_2(t)) + c_1 + d_1]\,S_1(t) + \gamma_1 R_1(t), \quad (2.1)\\ S_2'(t) &= c_1 S_1(t) - [\beta(t)\,(I_1(t) + I_2(t)) + d_2]\,S_2(t) + \gamma_2 R_2(t), \quad (2.2) \end{aligned}$$

$$\begin{aligned} I_1'(t) &= \beta(t)\,(I_1(t) + I_2(t))\,S_1(t) - [\nu_1 + c_1 + d_1]\,I_1(t), \quad (2.3)\\ I_2'(t) &= c_1 I_1(t) + \beta(t)\,(I_1(t) + I_2(t))\,S_2(t) - [\nu_2 + d_2]\,I_2(t), \quad (2.4) \end{aligned}$$

$$\begin{aligned} R_1'(t) &= \nu_1 I_1(t) - [\gamma_1 + c_1 + d_1]\,R_1(t), \quad (2.5)\\ R_2'(t) &= c_1 R_1(t) + \nu_2 I_2(t) - [\gamma_2 + d_2]\,R_2(t), \quad (2.6) \end{aligned}$$

with the initial condition

$$\begin{aligned} S_1(0) &= S_1^0, I_1(0) = I_1^0, R_1(0) = R_1^0, \quad (2.7)\\ S_2(0) &= S_2^0, I_2(0) = I_2^0, R_2(0) = R_2^0, \quad (2.8) \end{aligned}$$

where

- μ is the birth rate,
- $\beta(t) = b_0 + b_1 \cos(2\pi t + \varphi)$, is the disease transmission rate, expressed in this way to represent the seasonality of this disease. This type of functions are also considered in other studies where seasonality is relevant [104], [44],
- c_1, is the growth rate from age group G_1 to G_2,
- $d_i, i = 1, 2$, are the death rates for each age group,
- γ_i, where $\frac{1}{\gamma_i}, i = 1, 2$, is the average time an individual of age group G_i remains immune against the re-infection,
- ν_i, where $\frac{1}{\nu_i}, i = 1, 2$, is the average time to recover from the illness for an individual of age group G_i.

We must notice that this model assumes some simplifying hypotheses:

(i) Primary and secondary infections have the same rate of recovery and infectivity but this is not the case in real clinical situations [49].

(ii) The mixing between the different age groups is homogeneous.

(iii) There is no maternal antibody protection.

It would be possible to generalize further the model in Eqs. (2.1)-(2.6) to take into account that the strength of successive reinfections is smaller and smaller. However, there is no reliable data of these clinical parameters for the different age groups. Heterogeneity could also be included by modulating the transmission rate, $\beta(t)$, with a contact matrix $C_{ij}, i, j = 1, 2$. But this will increase the number of parameters to fit and therefore, an additional difficulty to obtain reliable fitted parameters in an acceptable time. For these reasons, we will study in this chapter

the simpler model taking into account that the cost-effectiveness of the vaccination program could be slightly different in a more general model.

Maternal antibody protection has been already studied in the context of RSV models by Weber et al. [104] but there are no noticeable changes respect to the simpler SIRS model without early antibody protection. On the other hand, we have performed CHAID (chi-squared automatic interaction detection) analysis with data of hospitalized children in the Spanish region of Valencia obtaining an average duration of 23 days for the maternal antibody protection period, and this can be considered as a perturbation of the simpler SIRS model.

2.2.1 Estimating parameters

Numerical values can be assigned to most of the above parameters. For instance, γ_i, and $\nu_i, i = 1, 2$ can be obtained from [51], [104], the average time to recover from RSV is 10 days and the average time to lose the immunity is 200 days, both with independence of the age group. Then,

$$\gamma_1 = \gamma_2 = \frac{365}{200}, \tag{2.9}$$

$$\nu_1 = \nu_2 = \frac{365}{10}, \tag{2.10}$$

If we denote by N_i the fraction of persons in age group $G_i, i = 1, 2$ (with respect to the total population) the evolution equations for the fraction of individuals in each group is given by:

$$N_1' = \mu\,(N_1 + N_2) - d_1 N_1 - c_1 N_1, \tag{2.11}$$

$$N_2' = c_1 N_1 - d_2 N_2, \tag{2.12}$$

$$N_1 + N_2 = 1. \tag{2.13}$$

Using demographic data of the Spanish region of Valencia in the period from years 2001 to year 2004 [59], where hospitalizations data are available, we obtain:

- The mean population, 4.252.386 inhabitants.
- The mean fraction of both subpopulations, $N_1 = 0.01038$ and $N_2 = 0.98962$.
- The mean birth rate, $\mu = 0.0107497$.
- The mean death rate for each age group, $d_1 = 0.0006796$ and $d_2 = 0.00912862$.

Under the assumption of constant population for each age group ($N_1' = N_2' = 0$) and Eq. (2.11), we find a simple relation for the transition rate from age group G_1 to age group G_2:

$$c_1 = \frac{\mu}{N_1} - d_1 = 1.03495. \tag{2.14}$$

By adding the Eqs. (2.11)-(2.13), we also find the following relation:

$$\mu = d_1 N_1 + d_2 N_2. \tag{2.15}$$

Finally we choose a new d_2 to satisfy Eq. (2.15), i. e., $d_2^* = 0.0108554$, which it is different from the real value of $d_2 = 0.00912862$ because the population is not really constant in the four years interval considered. Nevertheless, the difference is sufficiently small (about 7.200 dead persons) to be ignored in our study.

Hence, as it can be seen, only parameters b_0, b_1 and φ remain unknown, that is, parameters dependent on the seasonality.

2.2.2 Source RSV data

From $CMBD$ (Basic Minimum Data Set) database of the Spanish region of Valencia we obtained data of hospitalizations by illnesses related to RSV (bronchiolitis, infection, pneumonia, etc.) of children younger than 1 year old during the period January 2001 to December 2004. After processing the data we obtain the weekly hospitalizations of children in the group G_1 caused by a RSV related infection as shown in Figure 2.2.

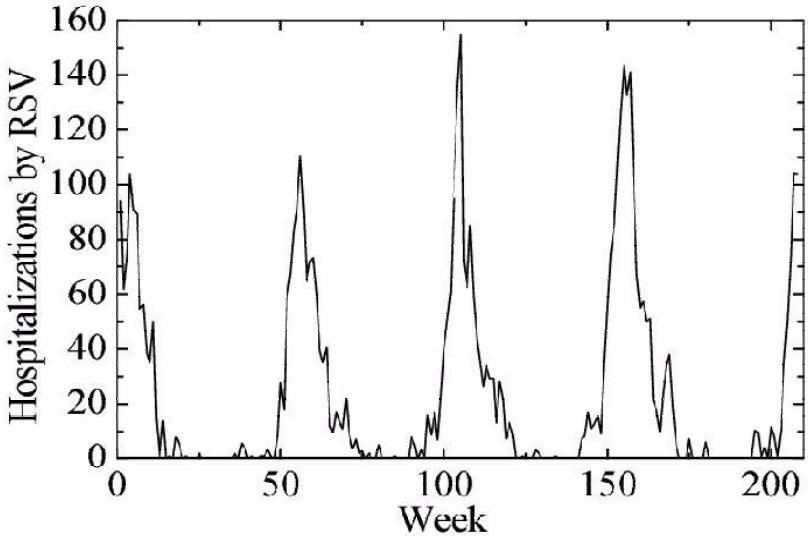

Figure 2.2. *Weekly hospitalizations by RSV infections since January 2001 to December 2004 of children younger than 1 year old in the region of Valencia.*

We must mention that data are referred to hospitalizations, not to infected people. This means that only a proportion of infected are hospitalized and this proportion or scale, called s, should be estimated in the model data fitting.

2.3 Results

2.3.1 Model fitting

In order to fit the data for hospitalized children younger than one year old we have numerically integrated the system of differential equations in Eqs. (2.1)-(2.5) for different sets of unknown parameters: b_0, b_1, φ and the scale parameter s of the proportion of the infected in G_1 that are hospitalized.

Additionally, the initial condition data is also unknown. We have considered throughout all the simulations that a fraction of a one per cent of the children in the age group G_1 are infected at January 1st, 1999 and the rest of individuals are susceptible.

The procedure for fitting the model is as follows: we solve numerically the system of differential equations in Eqs. (2.1)-(2.5) with the aforementioned initial values. After a period of 2 years of transient evolution the solution becomes periodic. This numerical solution is optimized by mean of the Nelder-Mead algorithm [77, 83], that does not need the computation of any derivative or gradient, impossible to know in this case.

The values of b_0, b_1, φ and s that minimize the function for the region of Valencia are:

$$b_0 = 69.52 \tag{2.16}$$
$$b_1 = 14.31 \tag{2.17}$$
$$\varphi = 5.997 \tag{2.18}$$
$$s = 0.0219. \tag{2.19}$$

For the different health districts where the fitting procedure has been carried out we obtain very similar values. This supports the reliability of

the fitting procedure because the parameters b_0, b_1 and φ are known to depend on the climatological conditions of the countries where the RSV epidemic has been studied [106, 107].

The parameter s is specially interesting because it give us information about the proportion of infected children which have to be hospitalized as a consequence of the infection. According to the data in (2.19) we have found that 2.19% of the infected children are hospitalized by a disease derived from RSV infection.

The graphical representations of this model fitting can be seen in Figure 2.3.

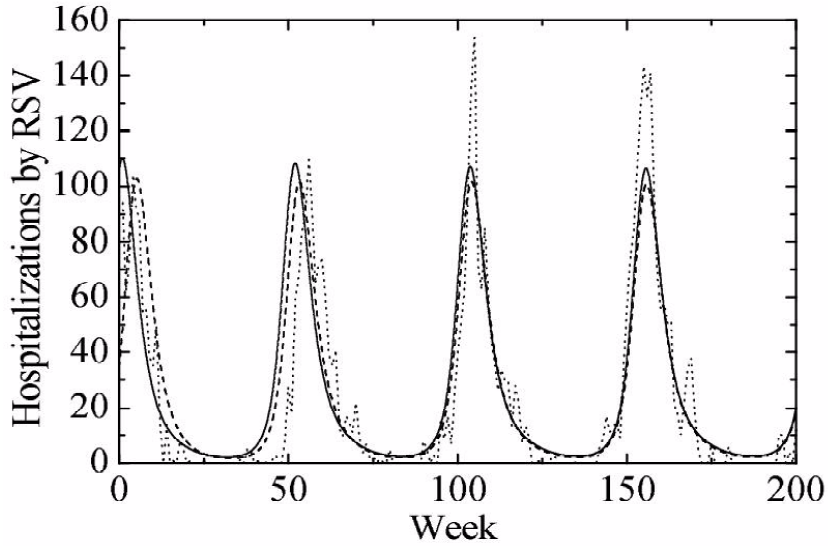

Figure 2.3. *Model fitting since January* 2001 *to December* 2004. *The points are data of weekly hospitalizations of children younger than one year old and the continuous line the scaled solution of the system of differential equations for infected children younger than one year old,* $s * I_1(t)$. *Dashed line corresponds to the fitting with* $\gamma_1 = \gamma_2 = 1.59$.

The average time of recovery from the RSV illness $\left(\nu_1 = \nu_2 = \frac{365}{10}\right)$ is a well-known value [51, 104]. It can also be obtained and compared with the statistical analysis of hospitalization data.

On the other hand, a larger uncertainty is found on the average time of immunity following RSV infection, $\frac{1}{\gamma}$. Weber et al. [104] reported the value $\gamma = 1.8$ corresponding to an average of 200 days of immunity. This value was contrasted by a sensibility analysis. Similar values have been proposed by White et al. [107]. In order to verify that the fitting of the RSV hospitalization data to a SIRS model requires and immunity period compatible with the values suggested in the literature we have performed a more detailed sensibility analysis. We have considered that the value of γ is in the range $1.0 < \gamma < 2.5$. A Nelder-Mead optimization algorithm was applied to obtain the best values of γ, the seasonal parameters b_0, b_1, φ and the scale factor s. The best fit is obtained with the values:

$$b_0 = 71.99 \tag{2.20}$$
$$b_1 = 13.11 \tag{2.21}$$
$$\varphi = 6.065 \tag{2.22}$$
$$s = 0.0233 \tag{2.23}$$
$$\gamma = 1.59. \tag{2.24}$$

These values are very similar to those obtained in Eqs. (2.16)-(2.19) with the assumption $\gamma = 1.8$ and confirms that a SIRS model approach to the spread of RSV disease implies an immunity time after infection of 200 days, approximately. In Figure 2.3 we also compare with this second fitting but the difference is minimal.

2.3.2 A Vaccination Strategy

In this section we develop a cost-effectiveness analysis for a newborn vaccination strategy for RSV. The effect of the vaccine is to remove a fraction p of newborns from the S_1 state and place them on a new vaccinated V state until they grow up to the next age-group. The box diagram for the

model is plotted in Figure 2.4.

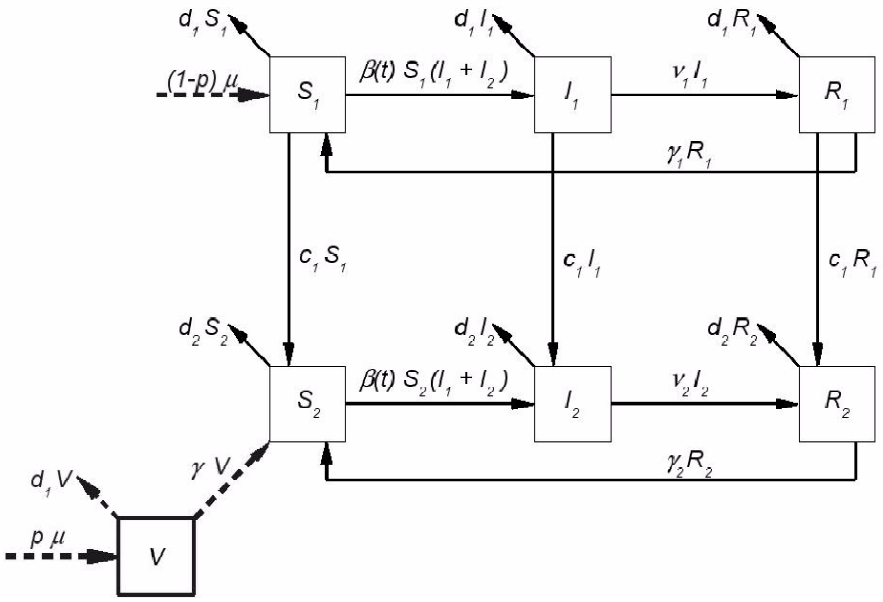

Figure 2.4. *Box diagram of a RSV model with two age groups and newborn vaccination.*

The reason for the V state individuals to evolve to the S_2 state instead of S_1 is the large immunization period, at least equal to the immunization of the children recovered from the disease, $\gamma = \frac{365}{200}$ days. Moreover, the children should receive additional reminding doses during the first year of life and, consequently, their immunization is prolonged.

In Figure 2.5 we have plotted the evolution of the total number of infected children younger than one year old in the region of Valencia after the vaccination program implemented right after the beginning of the fifth year. A fraction of the 85% is vaccinated. We see that the number of infected children decays to less than 1.000 just two years after the vaccination begins.

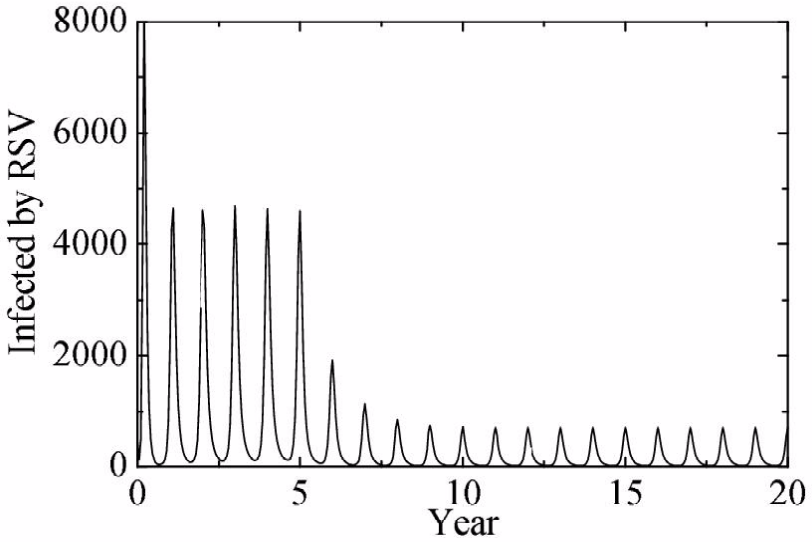

Figure 2.5. *Prediction of the model for the total number of infected children in the region of Valencia. Vaccination of 85% of newborn children begins after the fifth year.*

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 and 500 euro per day and child hospitalized [30].
- 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.
- Parent work loss: We take into account that for every hospitalized children parents lose 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, parent lose d days of work. This is a social parameter difficult to determine. We will simulate cost-effectiveness for $d = 2, 3, 4$. The mean labour cost in Spain is 75.21 euro per day [35].

The results for the costs of hospitalization, vaccination and parent work loss are plotted in Figures 2.6 and 2.7.

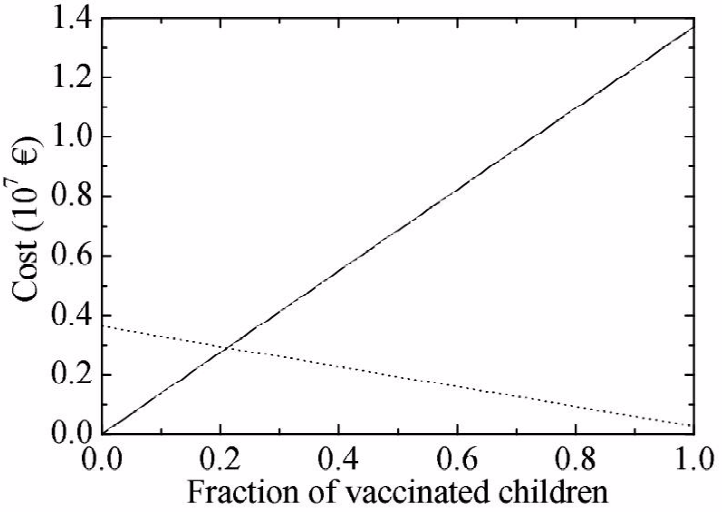

Figure 2.6. *Vaccination cost (solid line) and hospitalization cost (dotted line) vs. the fraction of vaccinated newborn children.*

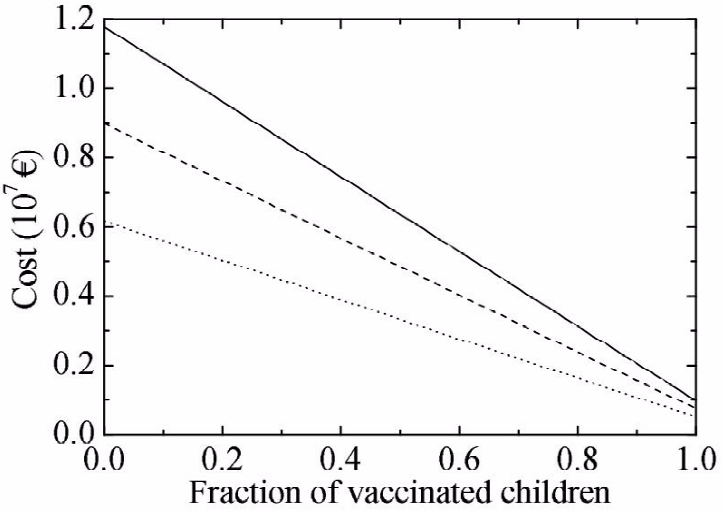

Figure 2.7. *The same as Figure 2.6 but for the parent work loss. We take into account* $d = 6.28$ *days of work loss on average for hospitalized children and* $d = 4, 3$ *and* 2 *days of work loss for infected children which do not need hospitalization (solid, dashed and dotted lines, respectively).*

The global result for the cost-effectiveness analysis is plotted in Figure 2.8 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.

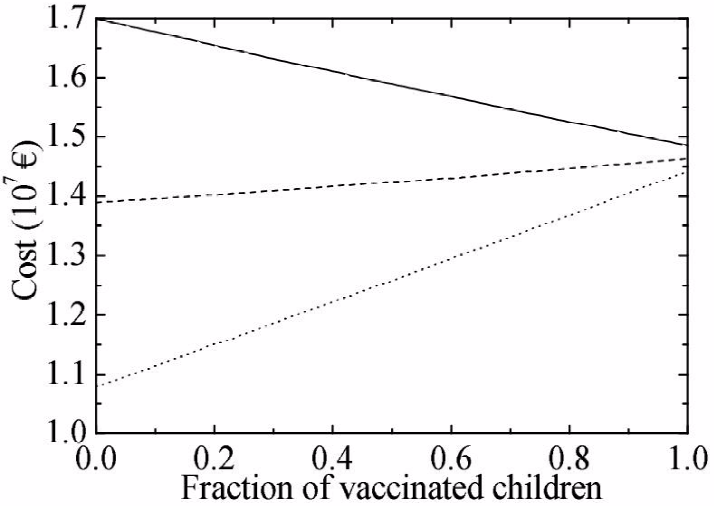

Figure 2.8. *Hospitalization + Parent Work Loss + Vaccination, Total cost, related to RSV infections as a function of the fraction of vaccinated newborn children. Solid line correspond to $d = 4$ days of Parent Work Loss, dashed line to $d = 3$ days and dotted line to $d = 2$ days.*

A reduction of 2 million euro of total cost is predicted for an estimation of 4 days or parent work loss on average for infected children. Moreover, we have not taken into account the long-term effects of RSV infections. In particular, there is an agreement among some pediatricians about a connection between RSV at early ages and asthma episodes of children and adolescents [70]. This has been confirmed by recent studies in mice [60]. Therefore, even of the assumption that parents only lose four working days for caring children who develop mild symptoms of RSV a positive balance for the implementation of the vaccine is obtained.

2.4 Discussion

In this chapter we present an age-structured model for RSV that fits well with the data of hospitalized children younger than one year old in the region of Valencia (Spain). A Nelder-Mead method [77] has been implemented in order to estimate the parameters which determine the seasonality and also the fraction of infected children that become hospitalized as a consequence of the RSV infection.

We have used the data of hospitalized children younger than a year old as a consequence of RSV infection in the period from years 2001 to 2004.

Independently of the health district considered, we have obtained very similar parameters for the variation of the infection rate with time in the SIRS model: $\beta(t) = b_0 + b_1 \cos(2\pi t + \varphi)$. This is not surprising because it is expected that this parameters depend only on the climatological conditions of the country [106, 107]. Climate in Valencia is Mediterranean with an average temperature around $18°C$ and minimum temperatures in January (the month in which the highest number of children hospitalizations due to RSV is observed). Moreover, the absence of mountain chains, except for the Iberian Mountains in the Northwest where population density is small, implies no significant climatic changes between the coast and the interior of the region. The study of these correlations is an interesting problem in itself and it must be treated by means of statistical analysis. Socio-demographic factors, as the opening and closening of schools, could be a secondary source for the outburst of the RSV. However, this is, apparently, not so important as climate because in Valencia schools open in September and the seasonal outbreak normally happens at the end of November.

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 4 days in the case of infected children that do not become hospitalized. We must take into account that these results are obtained with a simple extension of a recently proposed SIRS model [104] and should be considered as a first order approximation.

Another possible alternative is the MSEIRS4 model with reinfections [104] but taking into account that the vaccine is expected to avoid infections during the first year of life similar results to the model proposed in this chapter are expected.

On the other hand, although the cosine function to simulate the seasonal strength of the infection rate, $\beta(t)$, is the most widely used other alternatives inspired in the relation with climatological factors are probably more realistic. Nevertheless, there is no general agreement on which factors are relevant to unleash the most acute episodes of the epidemic during the winter season: humidity, temperature or even ultraviolet B radiation has been related to the propagation of the RSV virus [105]. Further research on these factors on the region of Valencia could also provide better information on the epidemic propagation and the outcome of vaccination programs.

Chapter 3

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

In this chapter the same age-structured mathematical model for RSV where children younger than one year old are specially considered is revised. In the previous chapter we have already obtained some seasonal parameters of the model from real data of hospitalized children in the Spanish Region of Valencia.

By using these parameters we propose a complete stochastic network model to study the seasonal evolution of the RSV epidemics. In this model every susceptible individual can acquire the 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 in-

fected or not. We show that the prediction of this model is compatible with the above mentioned age-structured model based upon differential equations, but sharper peaks are obtained in the case of the network.

Then, on the network model, we propose the vaccination of children at 2 months, 4 months and 1 year old, and we study the cost of this vaccination strategy, which is emerging as the most plausible to be applied when the vaccine hits the market. It is worth to note that this vaccination strategy is simulated in the network model because to implement it in the continuous model is very difficult and increases its complexity.

3.1 Introduction

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, in order to take into account the local and discrete character of epidemic spread, network 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 [53, 64].

In this chapter, we consider a complete network model for the propagation of the respiratory syncytial virus seasonal epidemic. We have retrieved hospitalization data for children less than one year old in the region of Valencia as a consequence of bronchiolitis 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.

As discussed in Section 1.4.1 several epidemic RSV models has also been carried out as for example in [104]. 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 chapter 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. [107] in a nested RSV model.

On the other hand, continuous models are more reliable concerning the application of optimizing techniques as shown below. Consequently, we use in this chapter the seasonal parameters fitted in Section 2.3 in a two-age group model to make 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 4.252.386 inhabitants during the four year period from January 2001 to December 2004 where data was harvested.

Also introduced in Section 1.3 that a PIV-vectored vaccine is under development and that their clinical studies have been carried out since past year [92, 91]. The imminence of the application of these PIV-vectored vaccines demands to make studies on the cost-effectiveness of possible vaccination strategies. Remember that a previous work on the cost-effectiveness of immunoprophylaxis with palivizumab has been recently published [99].

The layout of this chapter is as follows. In Section 3.2 is devoted to the details of the stochastic network model. Simulation results obtained from both models, continuous an social network, are presented and compared

in Section 3.3 with real data for hospitalization in the region of Valencia. A cost analysis is carried out in Section 3.4 for a vaccine scenario in this region. The chapter ends with some discussions and conclusions about results.

3.2 The Social Network model for RSV

In this section we discuss the implementation of a social network model for the propagation of the RSV. This model is based on the two-age group continuous model developed in Chapter 2. In the network model 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 [110] with N nodes and three possible states for each node. The network starts in a state in which every individual is susceptible except for a 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:

$$P(S \to I) = 1 - (1 - \beta^\star)^{I(t)}, \tag{3.1}$$

where $\beta^\star$ is the probability for a susceptible individual to become in social contact with an 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:

$$\beta^\star = \frac{\beta}{N}, \tag{3.2}$$

being N the total constant population.

The mean-field approach has been successfully applied in other network models [4] 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 [17].

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 [57].

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 $t + \tau$,

(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

$$\text{Newborns}(\tau) = \sum_{t=0}^{\text{tmax}} d(t)N(t) \tag{3.3}$$

of newborns are included into the model.

In order to obtain a plausible population model for Valencia we have performed a simulation from a uniform population distribution and evolving the system in time to achieve the stationary age pyramid. This simulation program allows us to obtain a reasonable population model. In the next section the results of the network and continuous models for epidemic propagation are discussed.

3.3 Simulation and model fitting

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.

As we saw in Section 2.2, numerical integration of Eqs. (2.1)-(2.6) to fit the real data by means of Nelder and Mead we found the following set of parameters:

$$b_0 = 69.52, \tag{3.4}$$

$$b_1 = 14.31, \tag{3.5}$$

$$\varphi = 5.997, \tag{3.6}$$

$$s = 0.0219. \tag{3.7}$$

The results are plotted in Figure 3.1.

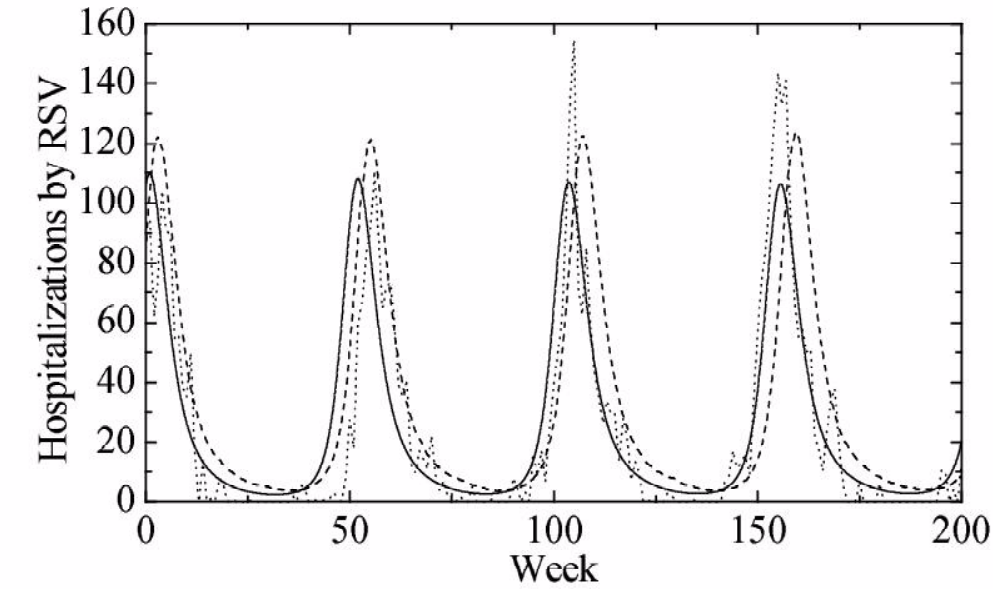

Figure 3.1. *Model fitting since January* 2001 *to December* 2004. *The points are data of weekly hospitalizations of children younger than one year old, the continuous line the scaled solution of the system of differential equations for infected children younger than one year old,* $s \times I_1(t)$*, and the dashed line is the prediction of the social network model.*

In this Figure 3.1 we also compare with the simulation results for the social networks, with $N = 4.252.386$ 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.

3.4 Vaccination strategy and cost

In this section we develop a cost analysis for a vaccination strategy for RSV. The main purpose of vaccination is to avoid the first RSV infection which is the most acute, affects children younger than a year old, and sometimes, the overreaction of the child immune system leads to very severe situations that require hospitalization. Newborns are too young to be vaccinated and the emerging strategy to be considered by the doctors, is the vaccination of non-infected children in three doses: at 2 months, 4 months and 1 year old.

Although the network model allows to know the state of each individual at any time, in the reality the doctors cannot check the state of children younger than a year old respect to the disease because the test is very expensive and not practical. Hence, the doctors only allow vaccination of healthy children. Thus, in order to simulate a close-to-real situation, let us consider the vaccination of two months old susceptible or recovered children. The recovered children are not suitable for vaccination, but doctors cannot check their state, however, the number of recovered children of two months old is very small. The reason for this comes from the fact that during the first month, approximately, the child benefits from the maternal antibody protection. Moreover, if we take into account that the disease last around a week there is a very narrow time interval of three weeks for the child to become infected and recover before the vaccination.

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 because the children with only one or two doses 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 [30] 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 euros per dose. Three doses are programmed during the first year of life, at 2, 4 months and 1 year old.

- Parent work loss: We take into account that for every hospitalized children parents lose 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 the costs for $d = 2, 3, 4$. The labor cost in Spain is 75.21 euro per day [35].

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 1 year old.

	$d = 2$	$d = 3$	$d = 4$
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 1 year old.

	$d = 2$	$d = 3$	$d = 4$
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 1 year old.

	$d = 2$	$d = 3$	$d = 4$
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 2 or 3 days of parent work loss, the increasing of the total cost is around 3.400.000 and 550.000 euros, respectively, but however, the hospitalization and parent loss work costs decrease dramatically at the expense of vaccination cost. These reductions 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 due to the disease. Moreover, we have not taken into account the long-term effects of RSV infections.

Therefore, even on the assumption that parents only lose two or three working days taking care of children which develop mild symptoms of RSV, a positive balance for the implementation of the vaccine is obtained.

3.5 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, recovered and become susceptible again, taking into account different characteristics of the individuals: variable susceptibility, sex and 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 chapter 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 [64] 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.

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 must take into account that these results are obtained with a simple extension of a recently proposed SIRS model [104] 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 chapter even with a continuous Forster-Mckendrick population model which is more realistic than the two age groups proposed previously.

We have considered a vaccination strategy with a first dose for children aged 2 months and two booster doses at the age of 4 months and a year. Assuming a cost of 300 euro per vaccination we obtain that this vaccination strategy is cost-effective because the total cost without vaccination is larger than the total cost with vaccination for typical fractions of vaccinated children.

A more realistic model, in which a random network with a Poisson distribution of the number of bonds for a given individual is implemented, will be considered in the next chapter.

Chapter 4

Seasonal RSV epidemic in a Random Social Network

The explanation of the seasonal outbreaks of this disease remains poorly understood. In this chapter we study the propagation of RSV in the Spanish region of Valencia by simulating a random social network of contacts among one million of individuals to elucidate the problem.

We have implemented a SIRS model for the RSV epidemic in a random network of contacts among the individuals. The average degree of each node ranges from 15 to 124. A client-server software was developed in order to perform a distributed computer calculation in a cluster to estimate the disease infection probability. More than three years of equivalent computing time were required to explore the relevant combinations of average degree and infection probability.

Traditional models of epidemic propagation are based upon continuous differential equations. The standard SIRS model for RSV propagation incorporates a seasonal forcing in the infection parameter. However, the statistical relation among RSV outbreaks and weather conditions remains unclear. We show that, in a random social network, seasonal epidemic emerge as a self-organization process modulated by the infection

probability and the immunity period after recovering from the infection.

The best fit with the hospitalisation data for the region of Valencia is obtained for an average number of contacts, k, a probability of infection in a social contact per day, b, and an average of immunity after recovery from the infection. The fraction of children aged < 1 year that become hospitalized constitutes a 5.56% of the total of infected children at a given week of the year. Only parameters in a narrow band are shown to be capable of sustaining seasonal RSV epidemic in the population. This implies that simple prophylactic measures could reduce dramatically the incidence of seasonal pandemics.

4.1 Introduction

Respiratory Syncytial Virus is the cause of a seasonal epidemic in many countries all around the world. Weber et al. recently developed several models for the propagation of RSV: a SIRS model and a MSEIRS4, more general model in which maternal derived immunity and a latent state previous to the infectious state are considered. In the latter case, up to four possible re-infections were considered. These models were successfully applied to fit seasonal data for the RSV epidemic in Gambia, Singapore, Florida and Finland [104]. A similar stochastic model and a model with two strains of RSV was proposed by White et al. and used to fit data from England & Wales and Finland [107].

Some drawbacks of these models are the homogenous mixings of individuals, high-risk group such as children under 1 year of age are not considered separately or the fact that seasonal behavior is forced by imposing a cosine variation of the infection rate. All these limitations are solved by the social network model proposed in this chapter.

In most countries, RSV occurs yearly but the time of the largest peak of infections varies from midwinter to early spring [40]. Despite ongoing efforts relating the most acute episodes of the epidemic to meteorological

factors such as humidity, temperature or even ultraviolet radiation, there is no general agreement on this subject [73], [105]. For these reasons, we performed a study of the propagation of the disease in a random network of contacts among individuals of a typical society with a sufficiently large amount of persons to sustain the epidemic. An important parameter in controlling the evolution of the epidemic appears to be the average time of immunity, the period that a person remains immune to reinfections after suffering the disease. If this period is very large the virus disappears before the appearance of another pool of susceptible individuals to allow the viruses to replicate. This is a polemic parameter for RSV: Weber et al. [104] found that this average time was approximately 200 days. This was achieved by fitting the loss of immunity rate, $\gamma = 1.8$, corresponding to 360 $days/1.8 = 200$ $days$, in the SIRS and MSEIRS4 models for the epidemiologic RSV data from Gambia, Florida, Finland and Singapore. This is also consistent with the sensitivity analysis presented in [1], in Chapter 2 and with results obtained with the random network in this chapter.

4.2 Methods

4.2.1 Hospitalization Data

Hospitalisation data for bronchiolitis, pneumonia and pathologies related to RSV was retrieved from the hospitals' discharge databases ($CMBD$) of the region of Valencia from years 2001 to 2004. This database includes age of the patient, date of admission and date of discharge. We have performed a filtering of this database to calculate a histogram of the number of patients as a function of the week of the year. An average of 6.28 days of hospitalisation was found in this period, which is consistent with the average time of recovery from the infection [99, 104]. On the other hand, we have also found that most hospitalisations (97%)

correspond to children under one year of age, which appears to be a widespread characteristic of this respiratory disease [20]. This data is plotted in Figure 4.1.

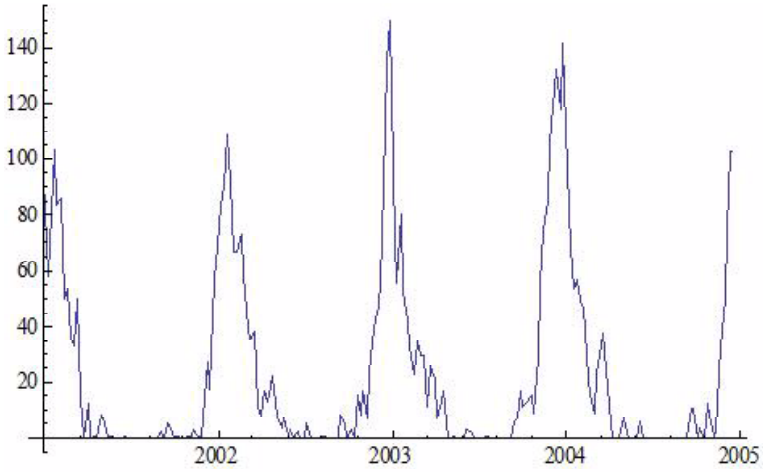

Figure 4.1. *Data of weekly hospitalizations of children younger than one year old since January 2001 to December 2004.*

4.2.2 Population Model

For a realistic simulation of a disease which affects, with different degrees of severity, to the several age groups of the society, we need to incorporate a reasonable population model. We have retrieved mortality rates for Valencia from the Valencian Institute of Statistics [59] and simulated a Forster-McKendrick dynamical model with constant population [57]. This is implemented in the random network by the following algorithm:

(*i*) Every subject in the network has an age assigned to him/her. The age is increased in every time-step (our unit of time is 1 day).

(*ii*) Every time step we check whether the subject dies or survives until the next time- step. This is calculated by generating a pseudo-random number and comparing it with the mortality rate per day corresponding to the age of the subject.

(*iii*) If a subject dies, he or her is replaced by a susceptible newborn. This way the population remains constant by definition.

A warming-up period is allowed for the population pyramid to stabilize and the epidemic propagation is simulated afterwards.

4.2.3 Random Network SIRS Model

The emergent science of networks provides several standard alternatives of implementation of the network substrate. The most traditional is based upon the pioneer work of Erdös and Rényi [16], the so-called "random graphs", where connections among the pairs of subjects are created with the same probability. Alternative models are the scale-free networks [8] or the small-world networks of Watts and Strogatz [101]. The small-world phenomenon (i. e., every pair of nodes are connected through a path which crosses a small amount of neighbours) is found in many social networks linked by friendship, collaboration or other social binds. These social networks have been ascertained from real data and used to study the social pandemic of smoking [24] and obesity [23].

In contrast with social networks binds, the spread of infectious diseases is determined by random encounters among people who live in the same geographical area: meeting at the bus stops, crossing in the streets, gathering at shop centers, etc. RSV is known to be transmitted by large-particle aerosols through air and also by direct contact with infected secretions [46]. RSV, as other respiratory viruses, induces coughing and sneezing in infected subjects, which favors the transmission of the disease.

For these reasons, we have chosen the random network model as the most appropriate modeling of the transmission of RSV and infectious diseases in general. The detailed monitoring of people's activities in order to ascertain possible contagion contacts is too complicated to be considered, although it has been attempted for the city of Portland [36].

Random networks are characterized by the number of individuals or nodes ($N = 1.000.000$ in our simulations) and the average number of contacts of every individual, k (called the degree of the node). Consequently, the number of links in the network is given by $N \cdot k$. These links are randomly assigned to pairs of individuals with the obvious rule that at most only a link can connect two individuals. The degrees of the nodes in the resulting random network follow a Poisson distribution with mean k. For every individual in the network an age is assigned according to the stationary age pyramid of Valencia, estimated according to the procedure discussed above.

We must point out that, in the detailed ascertainment of the social contact network obtained by Eubank et al. for the city of Portland, a Poisson-like distribution is also found for the degree of locations and people [36]. This emphasizes random networks as a realistic model for epidemic propagation in urban areas.

An initial state in which a small fraction of the individuals is infected is chosen as the starting point for the evolution algorithm of the SIRS model as follows:

(i) Infected individuals recover with probability ν, where $1/\nu$ is the average time to recover from the illness for an individual of a given age group.

(ii) Recovered individuals become susceptible again with probability γ per time step, where $1/\gamma$ is the average time an individual remains immune against re-infection.

(iii) The main difference with the standard continuous model is found in the infection procedure: every susceptible individual can only be infected by already infected individuals connected through existing links with him or her. This occurs with a probability b per time step in each contact.

The average time of recovery from the RSV illness (approximately 10 days) is a well-known value reported in the literature [51] but γ must be derived from the evolution of the disease because there is no clinical information about it. Fitting with hospitalisation data in continuous models is optimal for an average of 200 days of immunity after the infection [1], [104]. This will be confirmed for the random network.

The third step of the algorithm, corresponding to the propagation of the infection, is extremely time-consuming: the evolution of the state of every susceptible individual on a very large set must be done by analyzing the propagation of the infection through the links with every infected individual in its neighbourhood.

In order to obtain results for this model in a reasonable time, distributed computing is necessary. A client-server application was developed in order to coordinate many computers in the calculation of the epidemic propagation. Results were stored in the server for later processing. We have obtained more than 60.000 tests for different combinations of the average number of contacts, k, and the propagation probability, b. This would have needed more than three years of computation in a single computer dedicated to the task. Note that k and b are constants to be determined and that no periodic forcing (as in the continuous model of Weber et al. [104] or a recent proposal to assess vaccination strategies [1]) is used.

A similar approach has been taken by other large-scale epidemiology projects involving the control of malaria in which the $BOINC$ platform for distributed computing through the Internet is used [69]. The advantage of distributed computing in intranets, as we are using, is a greater control on the hardware and the management of problems that may arise during computation. Moreover, this is a procedure easy to implement in Universities and research centers where computer rooms are usually idle on weekends.

4.3 Results

4.3.1 Phase diagram and epidemic behaviours

An unexpected result for the propagation of epidemics in the random network is that a sustained seasonal behavior is obtained even for constant infection probabilities, i.e., by assuming that the virus is transmitted with the same efficacy with independence of the season. Consequently, meteorological parameters (or social ones as the beginning of the academic year and the gathering of children in schools and nurseries) are not determinant factors in the formation of the seasonal peaks of hospitalisations according to the model presented in this chapter.

This is in sharp contrast with standard continuous models for RSV where the seasonality must be forced into the model by considering an annual variation of the transmission probability usually represented by a cosine function [1, 104, 107].

To obtain a global perspective of the propagation behavior in the random network we tested 60.000 combinations of k (in the range $5-124$) and the transmission probability in a person-to-person contact ($0 \leq b \leq 0.005$ with 0.00001 jumps). For most of these combinations the epidemic disappears after the first outbreak. This happens for two reasons:

– for low probabilities of contagion the epidemic cannot spread to a sufficient number of individuals and the virus disappears when the small number of individuals affected by the disease recover from it;

– for large probabilities of contagion a very high outbreak peak develops but the epidemic fades away afterwards because most of the population becomes recovered and there is no reservoir of susceptibles to maintain the virus waiting for the loss of immunity of the rest of the population.

For intermediate values of the infection probability b there are endemic situations and, for some of them, a seasonal epidemic appears. The corresponding region is plotted in Figure 4.2.

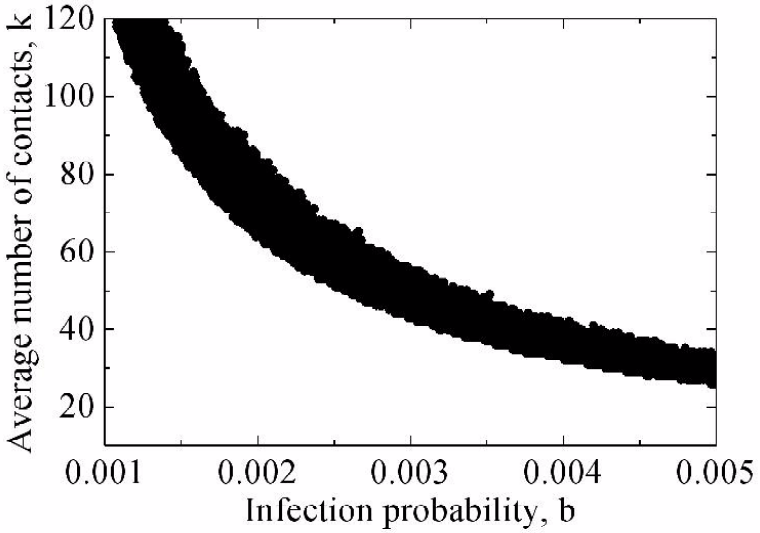

Figure 4.2. *Phase diagram for the epidemic behaviours of the random network model. The region in which the epidemic does not fade away (endemic behaviour) is plotted in black.*

An important consequence of this behavior is that a small variation in the parameters (infection probability, b or average degree of connectivity, k) could lead to the disappearing or emergence of an endemic situation or a seasonal epidemic if the initial situation is close to the border between the black and white regions. In this situation a campaign to make the population conscious of taking prophylactic measures, as those spoiled by the recent Influenza $H1N1$ menace, could be highly effective [94].

4.3.2 Fitting with Hospitalization Data

By exploring the 60.000 tests performed in the region displayed in *Figure* 1, we have selected the best fit of hospitalization data for children under 1 year of age in the region of Valencia (Spain). This was done by calculating the smallest mean-square deviation from the real data. In the process we

have taken into account that the population of Valencia was an average 4.252.386 inhabitants in the three provinces: Castellón (North), Valencia (Middle) and Alicante (South) according to the $2001 - 2004$ censuses. We also must calculate (as a parameter to fit) the fraction of infected children, s, that become hospitalized because there are no prevalence data for RSV in the region.

The best fit was obtained for the following values: $b = 0.00338$, a mean of 338 per 100.000 successful contacts per day, $k = 48$, a mean of 48 contacts, successful or not, per individual per day and $s = 5.565$, 5.565% of the weekly infected children younger than a year are hospitalized.

The mean quadratic error obtained, $MSE = 13.78$, is even better than the one obtained by fitting the continuous models [1]. Results are plotted in Figure 4.3.

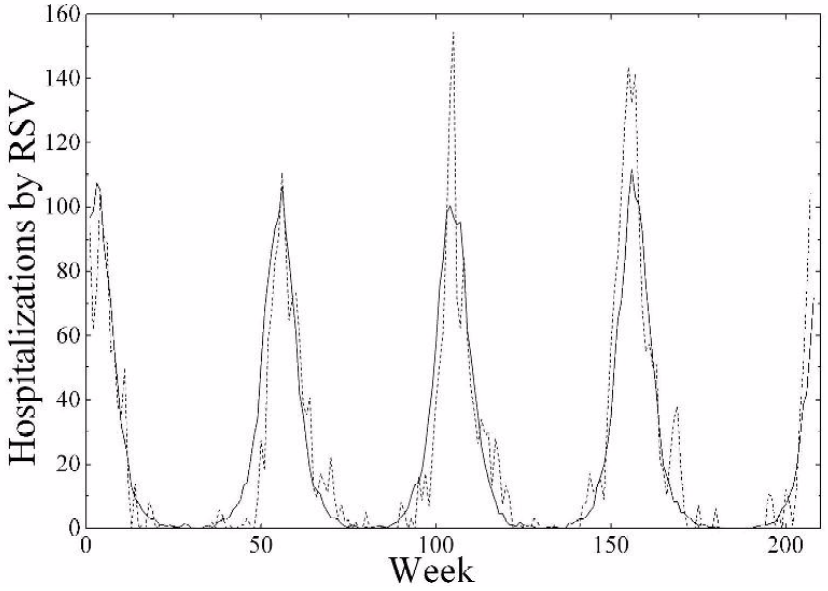

Figure 4.3. *The number of hospitalisations of children under* 1 *year of age in the Spanish region of Valencia: real data (dotted line) and fitting corresponding to the random network model (solid line). The period of time goes from January* 2001 *to December* 2004.

Adults aged 65 and older are also at risk as a consequence of RSV infections. An annual mean of 11.321 deaths related to RSV infections were estimated for the United States during the period $1976-1999$ [93]. We have no data of RSV mortality for Valencia but we have calculated the number of infected elders according to the model. The result is plotted in Figure 4.4.

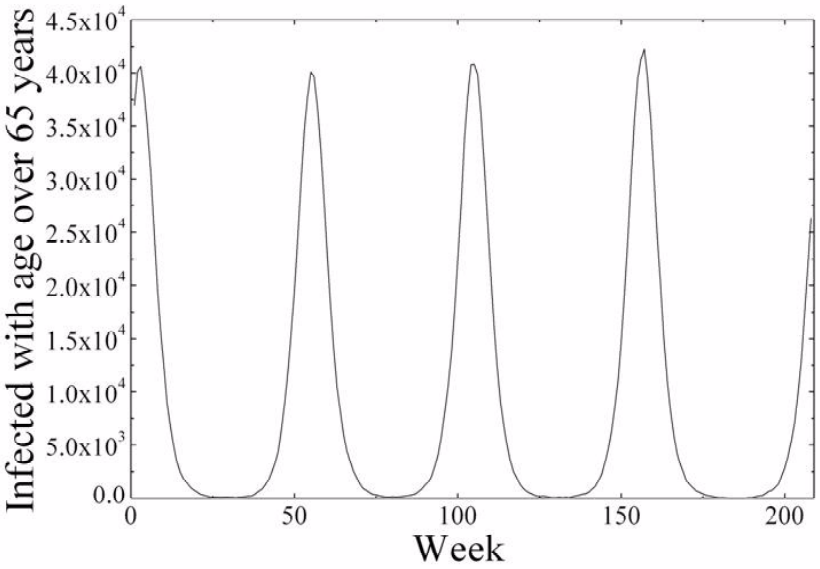

Figure 4.4. *The number of infected adults aged* 65 *and older according to the random network model for Valencia during the* $2001-2004$ *period of time. Values are from a total of* 1.000.000 *inhabitants.*

The sensitivity to the social conditions and the contagion probability is manifested in the fact that endemic or seasonal behaviours are found only for $0.00267 \leq b \leq 0.00348$ for a social network with a degree $k = 48$. Similarly, if b is kept fixed to the fitting value $b = 0.00338$, the values of k are in the range $40 \leq k \leq 49$. This gives a clear idea of the delicate equilibrium achieved for the social network of hosts and the pathogen.

An endemic equilibrium is attained for example for $b = 0.003$ and $k = 48$ as shown in Figure 4.5. In this case we retrieve a typical behavior of continuous SIRS models [3].

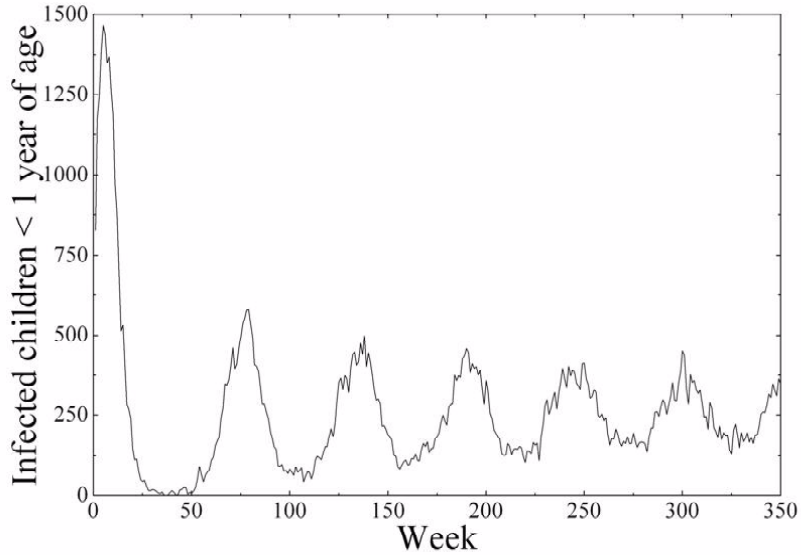

Figure 4.5. *The number of infected children under* 1 *year of age for a population of* 1.000.000 *individuals. The average degree of the random network is also* $k = 48$ *but the infection probability is now* $b = 0.003$.

For the same $k = 48$ and a value of b just outside the narrow band in Figure 4.2 such as $b = 0.00349$ the epidemic disappears after an initial strong outbreak as shown in Figure 4.6.

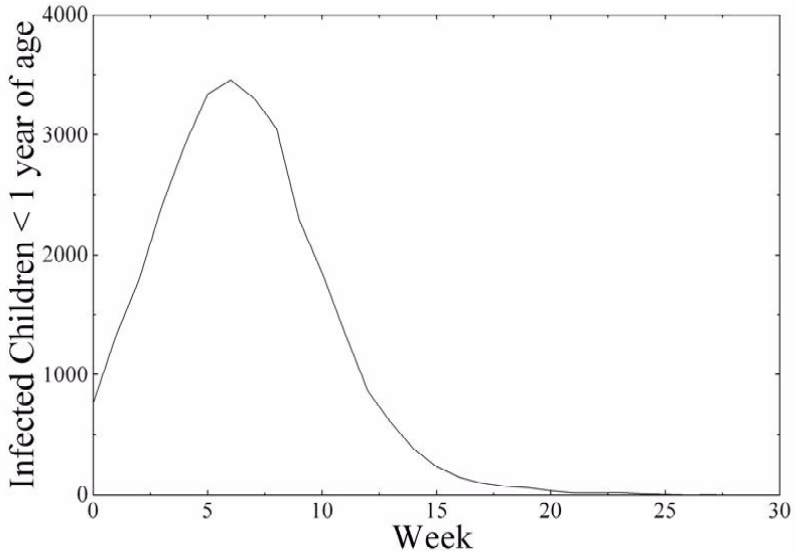

Figure 4.6. *The same as Figure 4.4 but for* $k = 48$ *and* $b = 0.00349$.

4.4 Discussion

In this chapter we have proposed a random network model for the propagation of RSV and other respiratory epidemics that challenges current views on the more relevant factors for RSV spreading and stability of the seasonal patterns. RSV propagation has been studied according to the standard SIRS models [1], [104], [107] which are descendants of the classical Kermack-Mckendrick differential model proposed more than 80 years ago [62]. The continuous models exhibit many unrealistic features: the disease can prevail even if prevalence decays towards negligible values, population is not considered as distinguishable individuals with specific characteristics: age, sex, clinic history, etc., but as a mass and, moreover, the spread of the disease does not take into account geographic and social distribution of the population because contagion takes place as a global phenomenon.

Networks are emerging as a more realistic paradigm in epidemiology: Halloran et al. proposed recently a model to assess vaccination strategies for smallpox in a social network of 2.000 individuals [53], [64]. However, this work was artificially restricted to a very small community to keep computations manageable. In this spirit we have proposed a random network SIRS model for the propagation of RSV in large communities of individuals encompassing regions or nations. To perform simulations for one million of individuals in the random network a client-server application was developed to distribute the computation in the University's Intranet. Epidemiological modeling for networks is a very computing-intensive task and parallelization software (including Internet based solutions such as $BOINC$) is necessary to obtain results in a reasonable amount of time that must be shorter than the scale of time of the epidemiological menace in order to implement policies in advance. Performance achieved the equivalent of 3 years of computing time in a single week with a hundred computers.

This computing power allowed us to disclose the phase diagram of the model and identify the regions of the parameter space where seasonal epidemics or endemic behaviours are stable. The most remarkable novelty over traditional models is that seasonality emerges naturally as a consequence of the random structure of the social network and the mean immunization time for individuals, which is a parameter that depends only on the pathogen and the human immune system. External factors which have been proposed in order to explain the seasonality: humidity, low winter temperatures, even ultraviolet B radiation [105] can only provide a secondary reinforcement or a role in the first outbreak of the disease. Generation after generation, the host-pathogen system finally settles in the stationary seasonal state. Viruses whose infectivity in a given population network or interaction with the human immune system is not adequate become finally extinct. Darwinian natural selection plays the key role here.

In Valencia, Spain an increase in the hospitalization by RSV has been observed in recent years [30]. In the context of the random network model this could be explained as the consequence of the increasing number of children in nursery schools and, consequently, the larger degree of connectivity, k, of the network.

This result has important consequences for policymakers because an adequate social strategy involving campaigns for making the population become aware of the epidemiological problems and take simple prophylactic measures in the periods before and during the seasonal peaks, could displace the equilibrium and reduce the incidence of the disease more efficiently than usually expected.

Chapter 5

Conclusions

Mathematical models have been revealed as a powerful tool to analyze the epidemiology of the infectious illnesses, to understand their behavior, to predict their social impact and to find out how external factors change the impact.

In the case of RSV, the building of a reliable model is a priority objective to predict the medical care requirements needed in each season.

In this dissertation we have provided, via mathematical models, additional understanding of the transmission dynamics of RSV.

Furthemore, we have introduced and studied vaccination strategies, that never have been studied so far.

Also we have performed a cost analysis of these strategies.

Finally, we have also introduced the use of random networks in the study of the spread of RSV which is a promising technique for understanding the transmission dynamics of this and other diseases.

Bibliography

[1] Acedo L, Díez-Domingo J, Moraño JA and Villanueva RJ. Mathematical Modelling of Respiratory Syncytial Virus (RSV): vaccination strategies and budget applications. Epidemiol Infect, 2010; 138: 853.

[2] Acedo L, Moraño JA and Díez-Domingo J. Cost Analysis of a Vaccination Strategy for Respiratory Syncytial Virus (RSV) in a network model. Mathematical and Computer Modelling, accepted 2009, doi: 10.1016/j.mcm.2010.02.041.

[3] Acedo L, González-Parra G and Arenas AJ. Modal series solution for an epidemic model. Physica A 2010; 389: 1151-1157.

[4] Acedo L, A second-order phase transition in the complete graph stochastic epidemic model, Physica A 370. 2006; 613.

[5] Arenas AJ, Moraño JA and Cortés JC. Non-standard numerical method for a mathematical model of RSV epidemiological transmission. Computers & Mathematics with Applications, 2008; 56: 670-678.

[6] Arenas AJ, González-Parra G and Moraño JA. Stochastic modeling of the transmission of Respiratory Syncytial Virus (RSV) in the region of Valencia, Spain. Biosystems, 2009; 96: 206-212.

[7] Ahmed H and Agiza N, On modelling epidemics Including latency, incubation and variable susceptibility, 253. 1998; 347.

[8] Albert R and Barabási AL. Emergence of scaling in random networks. Science 1999; 286: 509-512.

[9] American Academy of Pediatrics, C. O. I. D. A. C. O. F. A. N. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics 1996; 97: 137.

[10] American Academy of Pediatrics, C. O. I. D. A. C. O. F. A. N. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003; 112: 1442.

[11] Anderson R and May R. Infectious Diseases of Humans. Oxford Univ. Press, London/NewYork. 1991.

[12] Bächi T and Howe C. Morphogenesis and ultrastructure of respiratory syncytial virus. J Virol 1973; 12: 1173-1180.

[13] Ballard T and Neumann MD. The effects of malnutrition, parental literacy and household crowding on acute lower respiratory infections in young Kenyan children. J Trop Pediatr 1995; 41: 813.

[14] Berman S. Epidemiology of acute respiratory infections in children of developing countries. Rev Infect Dis 1991; 13 Suppl 6: S454-462.

[15] Blanco JC, Boukhvalova MS, Hemming P, Ottolini MG and Prince GA. Prospects of antiviral and anti-inflammatory therapy for respiratory syncytial virus infection. Expert Rev Anti Infect Ther 2005; 3: 945.

[16] Bollobás B, Random Graphs, 2^o Ed, Cambridge University Press, 2001.

[17] Brauer F and Castillo-Chavez C, Mathematical Models in Population Biology and Epidemiology, Springer Verlag, 2001.

[18] Brearey SP and Smyth RL, Pathogenesis of RSV in Children, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007. 141-162.

[19] Cane P, Molecular Epidemiology and Evolution of RSV, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007. 89-114.

[20] Center for Disease Control, Respiratory Syncytial Virus. Respiratory and Enteric Viruses Branch. Reviewed on October 17, 2008. Retrieved February 2, 2009 at http://www.cdc.gov/rsv/index.html.

[21] Chanock RM, Roizman B and Myers M. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent. I. Isolation, properties and characterization. Am J Hyg 1957; 66: 281-290.

[22] Chanock RM and Finberg L. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA) Epidemiological aspects of infection in infants and young children. Am J Hyg 1957; 66: 291-300.

[23] Christakis NA and Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med 2007;357:370-9.

[24] Christakis NA and Fowler JH. The Collective Dynamics of Smoking in a Large Social Network. N Engl J Med 2008; 358:2249-58.

[25] Coates HV, Alling DW and Chanock RM. An antigenic analysis of respiratory syncytial virus isolates by a plaque reduction neutralisation test. Am J Epidemiol 1966; 83:299-313.

[26] Collins PL and Murphy BR, Vaccines against Human Respiratory Syncytial Virus, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007. 233-278.

[27] Crowe JE, Respiratory syncytial virus vaccine development, Vaccine 2002: 20: 532-537.

[28] DeVincenzo JP, El Saleeby CM and Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. J Infect Dis 2005; 191(11): 1861-1868.

[29] Diallo O and Koné Y. Melnikov analysis of chaos in a general epidemiological model. Nonlinear Analysis: Real World Applications, 8. 2007; 20-26.

[30] Díez-Domingo J, Ridao-López M, Úbeda-Sansano I, et al., Incidencia y costes de la hospitalización por broquiolitis de las infecciones por virus respiratorio sincitial en la Comunidad Valenciana. Años 2001 y 2002, Anales de Pediatría 2006; 65-4. 325.

[31] Domachowske JB and Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. Clin Microbiol Rev 1999; 12(2): 298-309.

[32] dos Santos RMZ, Immune responses: getting close to experimental results with cellular automata models, Ann. Rev. of Comp. Physics VI, D. Stauffer (Ed.), 1999, World Scientific Publ. Co., pp. 159-202.

[33] Earn DJD, Rohani P, Bolker BM, Earn J and Grenfell BT. A simple model for complex dynamical transitions in epidemics. Science, 2000; 287: 667-670.

[34] Edelstein-Keshet L, Mathematical Models in Biology, Random House, New York, 1988.

[35] Encuesta Trimestral de Coste Laboral, Instituto Nacional de Empleo, Spain [on-line]. Available from http://www.ine.es [Accessed April 21, 2009]

[36] Eubank S, Anil Kumar VS, Marathe MV, Srinivasan A, Nan W. Structure of Social Contact Networks and Their Impact on Epidemics. DIMACS Series in Discrete Mathematics and Theoretical Computer Science 2006;70:181-214.

[37] Falsey AR and Walsh EE, Respiratory syncytial virus infection in adults. Clin Microbiol Rev 2000;13:371-384.

[38] Felton KJ, Pandya-Smith I, Curns AG, Fry AM, Anderson LJ and Keeler NM. Respiratory syncytial virus activity-United States, 2003-2004. MMWR 2004; 53: 1159-1160.

[39] Gimenez HB, Hardman N, Keir HM and Cash P. Antigenic variation between human respiratory syncytial virus isolates. J Gen Virol 1986; 67: 863-870.

[40] Glezen P and Denny FW, Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973; 288: 498-505.

[41] Glezen WP, Taber LH, Frank AL and Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986; 140: 543-546.

[42] Grassly NC and Fraser C. Seasonal infectious disease epidemiology. Proceedings of the Royal Society B, 273. 2006; 2541-2550.

[43] Greenhalgh D and Moneim IA, SIRS epidemic model and simulations using different types of seasonal contact rate. Systems Analysis Modelling Simulation, 2003. 43(5): 573-600.

[44] Grenfell B, Bolker B and Kleczkowski A, Seasonality, demography and the dynamics of measles in developed countries, in: D. Mollison

(Ed.), Epidemic Models – Their Structure and Relation to Data, Cambridge University, 1995; 248-268.

[45] Hall CB, Douglas Jr. RG, Geiman JM and Messner MK. Nosocomial respiratory syncytial virus infections. N Engl J Med 1975; 293: 1343-1346.

[46] Hall CB and Douglas RG Jr. Modes of transmission of respiratory syncytial virus. J Pediatr 1981;99:100 -103.

[47] Hall CB, Powell KR, MacDonald NE, Gala CL, Menegus ME, Suffin SC and Cohen HJ. Respiratory syncytial viral infection in children with compromised immune function. N Engl J Med 1986; 3152: 77.

[48] Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 1991; 163: 693-698.

[49] Hall CB, Nosocomial respiratory syncytial virus infections: The "cold war" has not ended, Clinical Infectious Diseases 2000: 31: 590-596.

[50] Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344 (25): 1917-1928.

[51] Hall CB, Respiratory syncytial virus and human metapneumovirus, in: R. D. Feigin, J. D. Cherry, G. J. Demmler, S. L. Kaplan (Eds.)., Textbook of Pediatric Infectious Diseases, 5th Edition, Saunders, Philadelphia, PA, 2004; 2315-2341.

[52] Han L, Alexander J and Anderson L, Respiratory syncytial virus pneumonia among the elderly: An assessment of disease burden, The Journal of Infectious Diseases 1999: 179: 25-30.

[53] Halloran ME, Longini Jr. IM, Nizam A et al., Containing Bioterrorist Smallpox, Science, 298. 2002; 1428.

[54] Handforth J, Sharland M and Friedland JS. Ed.: Prevention of respiratory syncytial virus infection in infants. BMJ 2004; 328: 1026-1027.

[55] Henderson FW, Collier AM, Clyde WA and Denny FW. Respiratory syncytial virus infections, reinfections and immunity: a prospective, longitudinal study in young children. N Engl J Med 1979; 3000: 530.

[56] Hershberg U, Louzoun Y, Atlan H, et al., HIV time hierarchy: winning the war while, loosing all the battles, Physica A, 289 (1-2). 2001; 178.

[57] Hethcote HW, The mathematics of infectious diseases, $SIAM$ 2000; Review 42; 4. 599.

[58] Hull J, Genetic Susceptibility to RSV Disease, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007: 115-140.

[59] Instituto Valenciano de Estadística, [on-line]. Available from http://www.ive.es. [Accessed 3 August 2007]

[60] Jafri HS, Chavez-Bueno S, Mejías A, et al., Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction and chronic inflammatory infiltrates associated with long-term airway hyperresponsiveness in mice, Journal of Infectious Diseases 2004: 189: 1856-65.

[61] Keeling M, Rohani P and Grenfell B. Seasonally forced disease dynamics explored as switching between attractors. Physica D: Nonlinear Phenomena, 148(3-4): 2001; 317-335.

[62] Kermack WO and McKendrick AG. Contributions to the mathematical theory of epidemics-I. Proc. Roy. Soc. 1927; 115A: 700-721. Reprinted in Bull. Math. Biol. 1991; 53(1-2): 33-55.

[63] Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K and Parrott RH. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969; 89(4): 422-434.

[64] Koopman J, Controlling smallpox, Science, 2002; 298: 1342.

[65] Langley JM et al, Increasing incidence of hospitalization for bronchiolitis among Canadian children 1980-2000, The Journal of Infectious Diseases 2003: 188: 1764-1767.

[66] Leader S and Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003; 143(Suppl 5): S127-S132.

[67] Lou J and Ruggeri T, The dynamics of spreading and immune strategies of sexually transmitted diseases on scale-free network, Journal of Mathematical Analysis and Applications, Volume 365, Issue 1. 2010; p 210-219.

[68] Madhi SA, Schoub B, Simmank K, Blackburn N and Klugman KP. Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. J Pediatr 2000; 137: 78-84.

[69] malariacontrol.net [on-line]. Available from http://www.malariacontrol.net. [Accessed March 5, 2010].

[70] Martinez FD. Heterogeneity of the association between lower respiratory illness in infancy and subsequent asthma. Proc Am Thorac Soc 2005; 2: 157.

[71] Martins ML, Ceotto G, Alves SG, et al., A cellular automata model for citrus variegated chlorosis, Phys. Rev. E 62. 2000; 7024.

[72] Melero JA. Molecular Biology of Human Respiratory Syncytial Virus, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007; 1-42.

[73] Meerhoff TJ et al, Variation of the Respiratory Syncytial virus and the relation with meteorological factors in different winter seasons, The Pediatric Infectious Disease Journal 2009: 28: 860-866.

[74] Moneim I and Greenhalgh D, Use of a periodic vaccination strategy to control the spread of epidemics with seasonally varying contact rate. Mathematical Bioscience and Engineering, 2005; 13: 591-611.

[75] Murata Y and Falsey AR. RSV Infection in Elderly Adults, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007. 163-182.

[76] Murray JD, Mathematical Biology, Springer-Verlag, Heidelberg, 1993.

[77] Nelder JA and Mead R, A simplex method for function minimization, The Computer Journal, 1964: 7: 308-313.

[78] Nokes DJ, Respiratory Syncytial Virus Disease Burden in the Developing World, in Respiratory Syncytial Virus, Perspectives in Medical Virology, 14, Cane P (Editor), Elsevier BV, 2007. 183-232.

[79] Nokes DJ, Okiro EA, Ngama M, White LJ, Ochola R, Scott PD, Cane PA and Medley GF. Respiratory syncytial virus epidemiology in a birth cohort from Kilifi district, Kenya: infection during the first year of life. J Infect Dis 2004; 190: 1828-1832.

[80] Pastor-Satorras R and Vespignani A, Epidemic Spreading in Scale-Free Networks, Phys. Rev. Lett. 86. 2001; 3200-3203.

[81] Pastor-Satorras R and Vespignani A, Epidemic dynamics in finite size scale-free networks, Phys. Rev. E 65. 2002; p. 035108/1-4.

[82] Pérez-Yarza EG, Moreno A, Lázaro P, Mejías A, Octavio R. The Association Between Respiratory Syncytial Virus Infection and the Development of Childhood Asthma. The Pediatric Infectious Disease Journal 2007; 26(8): 733-739.

[83] Press WH, Flannery BP, Teukolsky SA, et al., Numerical Recipes: The Art of Scientic Computing, Cambridge Univ. Press, 1986.

[84] Richardson LS, Belshe RB, Sly DL, London WT, Prevar DA, Camargo E and Chanock RM. Experimental respiratory syncytial virus pneumonia in cebus monkeys. J Med Virol 1978; 2(1): 45-59.

[85] Robertson SE, Roca A, Alonso P, Simoes EA, Kartasasmita CB, Olaleye DO, Odaibo GN, Collinson M, Venter M, Zhu Y and Wright PF. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 2004; 82: 914-922.

[86] Schneeberger A, Mercer CH et al., Scale-free networks and sexually transmitted diseases: A description of observed patterns of sexual contacts in Britain and Zimbabwe, Sex. Transm. Dis. 31. 2004; p. 380-387.

[87] Selwyn B, C. D. G. o. B Researchers. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Rev Infecti Dis 1990; 12(Suppl 8): S870-S888.

[88] Stensballe LG, Devasundaram JK and Simoes EA. ,Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003; 22: S21-S32.

[89] Sethi S, Murphy TF. RSV Infection-Not for Kids Only. N Engl J Med 2005; 352: 1810-1812.

[90] Simoes EA, Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr 2003; 143(Suppl 5): S118-S126.

[91] Study to Evaluate the Safety, Tolerability, Immunogenicity and Vaccine-Like Viral Shedding of MEDI-534, Against Respiratory Syncytial Virus (RSV) and Parainfluenza Virus Type 3 (PIV3), in Healthy 6 to < 24 Month-Old Children an in 2 Month Old Infants, http://www.clinicaltrials.gov/ct2/show/NCT00686075?term=RSV+VACCINE&rank=3 [Accessed July 23, 2009].

[92] Tang RS, Spaete RR, Thompson MW, et al., Development of a PIV-vectored RSV vaccine: Preclinical evaluation of safety, toxicity, and enhanced disease and initial clinical testing in healthy adults, Vaccine 2008: 26: 6373-6382.

[93] Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289: 179-186.

[94] Towers S, Feng Z. Pandemic $H1N1$ influenza: Predicting the course of a pandemic and assessing the efficacy of the planned vaccination programme in the United States. Eurosurveillance 2009; 14-41.

[95] Tupasi TE, de Leon LE, Lupisan S, Torres CU, Leonor ZA, Sunico ES, Mangubat NV, Miguel CA, Medalla F, Tan ST, et al. Patterns of acute respiratory tract infection in children: a longitudinal study in a depressed community in Metro Manila. Rev Infect Dis 1990; 12(Suppl 8): S940-S949.

[96] Valencia (autonomous community) [on-line]. Available from: http://en.wikipedia.org/wiki/Valencian_Community [Accessed August 3, 2007]

[97] Vathanophas K, Sangchai R, Raktham S, Pariyanonda A, Thangsuvan J, Bunyaratabhandu P, Athipanyakom S, Suwanjutha S,

Jayanetra P, Wasi C, et al. A community-based study of acute respiratory tract infection in Thai children. Rev Infect Dis 1990; 12(Suppl 8): S957-S965.

[98] Walsh EE, McConnochie KM, Long CE and Hall CB. Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis 1997; 175: 814-820.

[99] Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus with palivizumab in children: a systematic review and economic evaluation. Health Technology Assesment 2008: 12: 36 (http://www.hta.ac.uk).

[100] Waris M. Pattern of respiratory syncytial virus epidemics in Finland: two-year cycles with alternating prevalence of groups A and B. J Infect Dis 1991; 163: 464-469.

[101] Watts DJ. Small Worlds: The Dynamics of Networks Between Order and Randomness, Princeton University Press, 1999.

[102] Weber M, Mulholland E, Greenwood B. Respiratory syncytial virus infection in tropical and developing countries. Trop Med Int Health 1998; 3: 268-280.

[103] Weber MW, Dackour R, Usen S, Schneider G, Adegbola RA, Cane P, Jaffar S, Milligan P, Greenwood BM, Whittle H and Mulholland EK. The clinical spectrum of respiratory syncytial virus disease in The Gambia. Pediatr Infect Dis J 1998; 17: 224-230.

[104] Weber A, Weber M and Milligan P, Modeling epidemics caused by respiratory syncytial virus (RSV). Math Biosc 2001; 172: 95-113.

[105] Welliver RC, Temperature, Humidity, and Ultraviolet B Radiation Predict Community Respiratory Syncytial virus activity, The Pediatric Infectious Disease Journal 2007: 26: S29-S35.

[106] White LJ, Waris M, Cane P, Nokes D and Medley G, The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: seasonality and cross-protection, Epidemiology and Infection 2005: 133: 279-289.

[107] White LJ, Mandl JN, Gomes MGM, Bodley-Tickell A, Cane P, Perez-Brena P, Aguilar J, Siqueira M, Portes S, Straliotto S, Waris M, Nokes D, and Medley G, Understanding the transmission dynamics of respiratory syncytial virus using multiple time series and nested models, Mathematical Biosciences 2007: 209: 222-239.

[108] Wilson SD, Roberts K, Hammond K, Ayres JG and Cane PA. Estimation of incidence of respiratory syncytial virus infection in school children using salivary antibodies. J Med Virol 2000; 61: 81-84.

[109] Witten G and Poulter G, Simulations of infectious diseases on networks, Computers in Biology and Medicine, 37-2. 2007; 195.

[110] Wolfram S, Cellular automata and complexity: Collected Papers,[on-line]. Available from http://www.stephenwolfram.com/publications/books/ca-reprint/.

[111] Wright P and Cutts F. Generic Protocol to Examine the Incidence of Lower Respiratory Infection (LRI) Due Respiratory Syncytial Virus (RSV) in Children Less than Five Years of Age. Geneva: World Health Organization; 2000.