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Additional Information

Random networks to study the dynamics of respiratory syncytial virus (RSV) in the Spanish region of Valencia

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Abstract

Seasonal fluctuations in the incidence of several respiratory infections are a feature of epidemiological surveys all around the world. This phenomenon is characteristic of the influenza and respiratory syncytial virus pandemics. However, the explanation of the seasonal outbreaks of these diseases remains poorly understood. Many statistical studies have been carried out in order to provide a correlation of the outbreaks with climatic or social factors without achieving a definitive conclusion. Here we show that, in a random social network, self-sustained seasonal epidemics emerge as a process modulated by the infection probability and the immunity period after recovering from the infection. This is a purely endogenous phenomenon that does not require any exogenous forcing. Assuming that this is the dominant mechanism for seasonal epidemics, many implications for public health policies in infectious respiratory diseases could be drawn.

Key words: RSV epidemic, Social networks, Random networks

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1 Introduction

Respiratory Syncytial virus is a single-stranded RNA virus discovered more than fifty years ago in a child with bronchiolitis [1]. This virus is the cause of a seasonal epidemic in many countries all around the world. Only in Spain, there are around 15,000-20,000 visits to primary care due to RSV every year. Also, up to 18 % of the pneumonia hospitalisations in older than 65 are due to RSV [1]. This epidemic is also a major concern in immunocompromised patients at any age [2].

Its coincidence with other seasonal epidemics, such as influenza and rotavirus produces a large number of hospitalisations year after year, and saturates the National Health System. In particular, the cost of pediatric hospitalisation for the Valencian Health System has been estimated in 3.5 million euro per year [3] without taking into account indirect costs [4], with a cohort of newborns of 45,000 children.

The main characteristic of RSV and influenza pandemics is its seasonality, i.e., its incidence on the human population fluctuates broadly and regularly year after year with large peaks of infections occurring at the same time of the year in the same country. However, depending on the country, the time at which the largest peak is reached varies from midwinter to early spring [5]. Seasonality is also found in climatic conditions as different as those of Gambia, Singapore, Florida or Finland [6]. In the case of tropical countries a connection with the rainy season has been suggested. Following the idea of the influence of climatic conditions, whatever they should be, on the infection probability the seasonal behavior is forced into standard models by proposing a cosine variation in the form $b = b_0 + b_1 \cos(2\pi t)$, where t is measured in years.

Despite the many studies performed throughout the last decades there is not a conclusive proof on the underlying mechanism giving rise to these oscillations [7]. It has been suggested that the changes in the transmission rate could be provoked or correlated with humidity, temperature, or even ultraviolet radiation [8,9]. Social factors are also a possibility: school terms or more time spent indoors in the winter season. Nevertheless, a connection with school terms in the region of Valencia (Spain) is difficult to establish because there is a delay of several months between the beginning of the school period (beginning of September) and the maximum peak of activity of RSV (December or January).

Dushoff et al. have suggested that the intrinsic fluctuations of the SIRS model could be amplified by dynamical resonance [10]. In this model the variations of the infection probability are too small to be detected in any practical study and this should explain why laboratory experiments and epidemiological studies

have failed to establish the connection with climatic or social seasonal patterns and the seasonality of influenza or RSV pandemic.

In this paper, we follow a different approach by considering the propagation of the disease in a random network of connections among the individuals. We find that the intrinsic fluctuations of the SIRS model are amplified by the network and a seasonal pattern arises even on the absence of seasonal forcing. This casts a doubt on the relevance of exogenous forcing to drive the seasonality behaviour. The paper is organized as follows: The random network model for the propagation of RSV is proposed in Section 2. In Section 3 we discuss the phase diagram of behaviour in terms of the infection probability, b , and the average number of contacts for the network nodes, k . The fitting of hospitalization data for the Spanish region of Valencia is presented in Section 4. The paper ends with some concluding remarks in Section 5.

2 The Random Network Model

Social networks has been ascertained from real data and used to study the social pandemic of smoking [11] and obesity [12].

In contrast with social networks 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 the air and also by direct contact with infected secretions [13]. RSV, as other respiratory viruses, induces coughing and sneezing in infected subjects, which also favors the transmission of the disease.

For these reasons, we have chosen the random network model as the most appropriate to the modeling of the transmission of RSV and infectious diseases in general. The detailed monitoring of peoples activities in order to ascertain possible contagion contacts is too complicated to be considered, although it has been attempted for the city of Portland [14].

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 this node). Consequently, the number of links in the network is given by Nk . These links are randomly assigned to pairs of individuals with the obvious rule that at most only a link can connect two individuals.

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 [14]. 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 has been 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 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 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 [1] but γ must be derived from the evolution of the disease because there is no clinical information about it. Fitting of hospitalization data in continuous models is optimal for an average of 200 days of immunity after the infection [4,6]. 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 computer program must check the evolution of the state of every susceptible individual on a very large set 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 two 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. [6]) is used.

In a realistic simulation of a disease which affects with different degrees of severity to the different age groups of the society we also need to incorporate in our model a reasonable population distribution. We have retrieved mortality rates for Valencia from the local Institute of Statistics [15] and simulated a Forster-McKendrick dynamical model with constant population [16]. This is

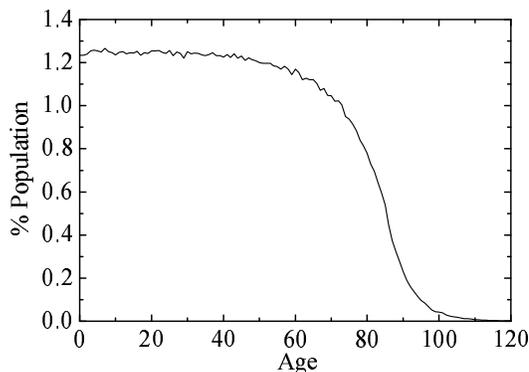


Figure 1. Population pyramid for Valencia in the period of our study. The percentage of population is shown for every age (in years).

implemented in the random network by the following algorithm:

- (i) Every subject in the network has an age assigned to it. The age is increased in 1 day 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 pseudorandom number and comparing it with the mortality rate per day for a subject of the age under consideration.
- (iii) If a subject dies it 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. The resulting population distribution, consistent with the averaged data for the years 2001-2004, is shown in Fig. 1.

3 Phase Diagram and Epidemic Behaviour

An unexpected result for the propagation of epidemics in the random network is that a sustained seasonal behaviour 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 hospitalizations according to the model presented in this paper.

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 [4,6].

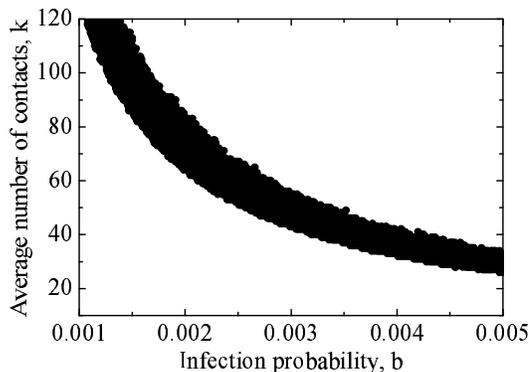


Figure 2. Phase diagram for the epidemic behaviour of the random network model. The region in which the epidemic does not fade away is plotted in black.

In order 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.

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 Fig. 2.

4 Fitting of Hospitalization Data

Hospitalization data for bronchiolitis, pneumonia and pathologies related to RSV was retrieved from databases in the hospitals of the region of Valencia from years 2001 to 2004. This database includes data about the 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 hospitalization was found in this period which is consistent with the average time of recovery from the infection [17]. On the other hand, we have also found that most hospitalizations correspond to children under one year of age which appears to be a widespread characteristic of this respiratory disease [18].

By exploring the 60,000 tests performed in the region displayed in Fig. 2, 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 calcu-

late (as a parameter to fit) the fraction of infected children, s , that become hospitalized because there are not prevalence data for RSV in the region.

The best fit was obtained for the following values: $b = 0.00338$ (338 of each 100.000 contacts between an infected and a susceptible are successful and the virus is transmitted), $k = 48$ (every day, each inhabitant in the Valencian Community has a mean of 48 contacts) and $s = 0.05565$. Results are plotted in Fig. 3.

The sensitivity to the social conditions and the contagion probability is manifested in the fact that endemic or seasonal behaviour are found only for $0.00267 \leq b \leq 0.00348$ for a social network with 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, but stable, equilibrium achieved for the social network of hosts and the pathogen.

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.

In order to assess the effect of exogenous factors, such as humidity, low winter temperatures or annual changes in social patterns we have considered a cosine forcing term on the infection probability with an amplitude of a 1 % compared with the constant term b_0 , i. e., we substitute b_0 by $b_0(1 + 1/100 \cos(2\pi t))$ in the simulations. This is the amplitude considered by other authors [10] to explain the amplification of intrinsic SIRS fluctuations. The result is also plotted in Fig. 3. We observe that this provokes only a small perturbation on the seasonal pattern. We can conclude that the effect of the social network on the amplification of the natural SIRS fluctuations is far more important than the seasonal forcing.

5 Discussion and conclusions

In this paper we propose 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.

According to our model, external factors which have been proposed in order to explain the seasonality: humidity, low winter temperatures, even ultraviolet B radiation [8,9] can provide a secondary reinforcement or a role in the first outbreak of the disease but the structure of social network seems to be a more important factor. Generation after generation, the host-pathogen system

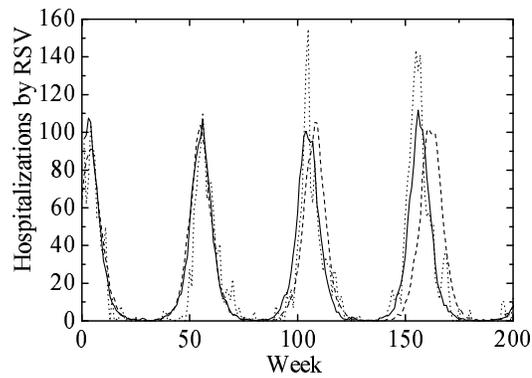


Figure 3. The number of hospitalizations of children under 1 year of age in Spanish region of Valencia: real data (dotted line) and fitting corresponding to the random network model (solid line). The dashed line corresponds to the forced system with a cosine amplitude $b_1 = b_0/100$. The period of time goes from January 2001 to December 2004.

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 [3]. 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. With a vaccine closer in the horizon, Public Health policies for controlling RSV are going to be designed with anticipation. Further work along this line will be published elsewhere.

Acknowledgements

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