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A deterministic model for highly contagious diseases: The case of varicella

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Abstract

The classic nonlinear Kermack-McKendrick model based upon a system of differential equations has been widely applied to model the rise and fall of global pandemic and also seasonal epidemic by introducing a forced harmonic infectivity which would change throughout the year. These methods work well in their respective domains of applicability, and for certain diseases, but they fail when both seasonality and high infectivity are combined. In this paper we consider a Susceptible-Infected-Recovered, or SIR, model with two latent states to model the propagation and evolutionary history of varicella in humans. We show that infectivity can be calculated from real data and we find a nonstandard seasonal variation that cannot be fitted with a single harmonic. Moreover, we show that infectivity for the present strains of the virus has raised following a sigmoid function in a period of several centuries. This could allow the design of vaccination strategies and the study of the epidemiology of varicella and herpes zoster.

Key words: Compartmental models; Highly contagious diseases; Infectivity evolution; varicella

1 Introduction

In their pioneering work of 1927, Kermack and McKendrick proposed a mathematical model for the evolution of infectious diseases based upon a system

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of differential equations [1,2]. In the original model three populations where considered: Susceptibles, S, which are healthy but can be infected, Infected, I, which have been communicated the bacteria or virus by contact with another infected individual, and Recovered, R, i.e., those infected individuals who have cleared the disease. The recovered individuals may become susceptible again after a period of immunity, in such a case the model is known with the acronym SIRS. Other combinations: SI, SIS or SIR have been considered. In some cases a state of latency is also introduced. Latent individuals are already infected by they have not developed the symptoms of the disease and they are usually not infectious or their infectiveness is reduced.

A characteristic of many infectious diseases is that they show seasonal patterns. Some examples are: Influenza [3], Respiratory Syncytial Virus or RSV [4,5], Rotavirus disease [6] or varicella [7]. The factors of this seasonal behaviour are still unknown in many cases [8] and it is believed that several concurrent agents may be acting. Seasonality of infections by RSV have been associated to meteorological factors [9] such as temperature or humidity but also to ultraviolet radiation [10]. Dushoff et al. proposed a dynamical resonance mechanism for the amplification of oscillations in influenza pandemic [11], later on Acedo et al. discussed the emergence of seasonal behaviour in network models without external forcing [12]. Production of Vitamin D has also been studied as a possible immunity factor in the seasonal variations of influenza [13]. In any case, it is still unclear what of these factors are direct causes of seasonality instead of mere correlates.

Concerning models based upon coupled differential equations and for the purpose of capturing the seasonal behavior, it is usual to introduce a forcing term in the transmission [4,5]. This term takes the form:

$$b = b_0 + b_1 \cos\left(\frac{2\pi t}{T} + \phi\right) \ , \tag{1}$$

where $T = 1$ year, t is the time passed since the beginning of the year, usually measured in weeks, and ϕ is an offset phase to be deduced by fitting the real data. This oscillatory forcing of the infectivity allows very reasonable fitting for the epidemiological data of RSV [4,5] but it do not work for other highly contagious diseases as we will see in this paper and, in particular, for varicella, where b must be deduced from the incidence of the disease if any reliable fitting is to be found.

varicella is a highly contagious disease caused by the varicella Zoster Virus (VZV) [7,14,15]. This virus is the responsible for both varicella and Herpes Zoster and it has a very high prevalence in populations all around the world. varicella affects mostly children and, in most cases, it is a benign infection. Occasionally may complicate but it has a low death rate. However, it is more

severe in adults [14].

The experiment we are going to perform will start retrieving and preparing data of varicella cases, then a simple model will be built. Furthermore, we will develop a procedure to calculate the values of the weekly transmission rate b_t. Thus, on the one hand we will see that the growing of the transmission rates of any year can be written as the transmission rates in the year 1 (base case) by a sigmoid function. On the other hand, we will prove that the approximation of the transmission rates b_t by a cosine seasonal forcing term as $b_0 + b_1 \cos(\frac{2\pi t+\phi}{52})$ will lead to a good approximation at the beginning but deteriorating soon as the time goes on.

We will show that the transmission rate follows the same pattern over the years and that the scale increases following a sigmoid behavior. Also, we show that, sometimes, it is not possible to capture the seasonal behavior using seasonal forcing terms in the transmission term and other strategies should be used. We will illustrate this using data of varicella incidence.

The problem we are discussing is known in the literature as the inverse problem in epidemiology, i. e., to find the forcing term from epidemiological data [16]. In a recent work, Marinov et al. have proposed a generalized least square method to find optimum values for the infectivity and recovery rates. However, these values are assumed to be constant over the whole interval as they apply their method to a short outbreak of influenza instead of considering the long term evolution of a pandemic. A similar method was used by Leecaster et al. [17] to study the variations from one year to another of the incidence of respiratory syncytial virus (RSV) infections. The problem of the seasonal variations of RSV have motivated many studies in which a relation to social factors, such as school terms, or weather data is considered [4]. But none of these factors is clearly statistically significant in the oscillations of the incidence of the disease. For these reasons, Novotni and Weber proposed a stochastic optimization method to deduce the infectivity function, $\beta(t)$, from the incidence data. They find that the dynamics of RSV can be modelled as "noisy limit cycles". A similar idea was proposed by Keeling et al. [19] to achieve an explanation of the seasonality in measles and whooping cough as a consequence of a contact rate governed by school terms.

The case of the inverse problem for highly contagious diseases, such as varicella, is marked by a particular difficulty because every year a large proportion of the cohort of children is infected. As a consequence the transmission rate becomes very large and, apart from the seasonal variations, we must also study the increase of the transmission rate year after year in such a way that a stationary state is finally achieved. Starting from an initial state with no recovered individuals we deduce the transmission rate from a deterministic recursive method. The process is repeated for the following years until a sta-

tionary seasonal infection rate is obtained. The results could then be used in the simulation of vaccination strategies for which a systematic modelling is still lacking.

To achieve these objectives we propose a new compartmental model with two latent states of one week duration. By using this model to fit the incidence data of varicella we estimate a non-sinusoidal temporal forcing term. We show that the infectivity rate must rescale year after year keeping its seasonal variations to allow the survival of the varicella strains. Moreover, it is found that the global prefactor for the infectivity is a sigmoid function and that the evolution to the stationary state takes four centuries, at least. This is compatible with the known large history of the varicella-zoster virus (VZV) [20].

The paper is organized as follows. In Section 2 we describe the retrieval and preparation of the data for varicella. In Section 3, we describe the model building. In this section we also state a procedure to calculate the variable transmission rates b_t and study the patterns they follow. In Section 4, we show that a seasonal forcing term does not perform as well as the variable transmission rates. Finally, in Section 5, we present the conclusions.

2 Epidemiological data for varicella

The data on the number of infected individuals per week was obtained from a report from Royal College of General Practitioners entitled: *New RSC Communicable and Respiratory Disease Report for England & Wales, 36/2014* [21]. They averaged over a period of 10 years prior to the introduction of the vaccine to get the data in Figure 1.

These data are very similar to the ones that appear in the varicella report bulletin of the Community of Valencia 2012 [22].

We are going to use the data from UK because they are more regular (10 years average) with the demographic data of the Community of Valencia. The total population of Valencia is 5129266 with 47574 newborns in 2012. Note that the incidence in Figure 1 correspond to reported cases, but the doctors assume that around 95% of the cohort is infected by varicella every year. For future

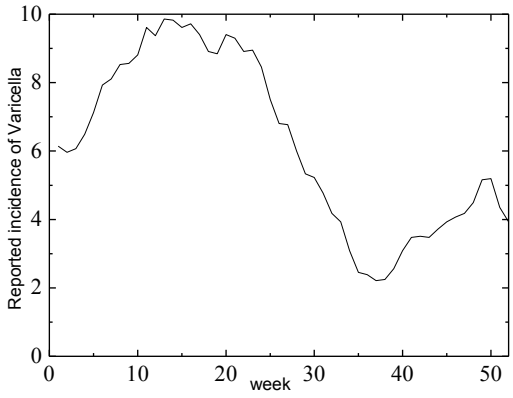

Fig. 1. Reported individuals infected with varicella per 10^5 as a function of the week averaged over a period of ten years in UK. The epidemiological behavior of the disease is markedly seasonal.

reference we list the number of cases in the 52 weeks of the year:

$$
\begin{aligned}
D = (&862.036, 837.406, 852.185, 911.295, 999.962, 1113.26, 1137.89, 1197, \\
&1201.92, 1236.41, 1349.7, 1315.22, 1384.18, 1379.26, 1349.7, 1364.48, \\
&1320.15, 1251.18, 1241.33, 1320.15, 1305.37, 1251.18, 1256.11, 1187.15, \\
&1054.15, 955.629, 950.702, 842.332, 748.739, 733.962, 669.925, 586.184, \\
&551.702, 433.481, 344.814, 334.962, 310.333, 315.258, 359.592, 433.481, \\
&487.665, 492.592, 487.665, 522.148, 551.702, 571.407, 586.184, 630.518, \\
&724.109, 729.036, 610.814, 551.702).
\end{aligned} \tag{2}
$$

If we call I the weekly incidence vector given in Fig. 1 and we define $s = 5129266 = \left(\sum_{j=1}^{52} I_j\right)/10^5$ and $e = 0.95 \times 47574/s$, then the vector D is given by $D = 5129266 \times e \times I/10^5$.

3 Mathematical modelling

In order to build the model to study the dynamics of varicella, we consider the following 5 states in the week t: susceptible (S_t), latent of 1st week (L_t^1), latent of 2nd week (L_t^2), infectious (I_t) and recovered (R_t).

A susceptible (healthy) individual gets infected by a successful contact with an infected individual and becomes latent of the 1st week. After a week the

individual becomes latent of the 2nd week. During the latency states the individual is infected but not infectious. Then, after another week, the individual becomes infectious and can infect susceptible individuals. This state lasts a week and after this week, the individual recovers and has a permanent immunity [14].

Even though reinfection of recovered individuals are possible, in this model we assume that it does not occur. Second cases of varicella have been reported after natural infection but they are uncommon [23]. Then, the dynamics of the varicella spread can be modeled with the following system of difference equations, t in weeks,

$$\begin{aligned} S_{t+1} &= S_t + \mu - dS_t - b_t \tfrac{S_t I_t}{P_T}, \\ L^1_{t+1} &= L^1_t - dL^1_t - L^1_t + b_t \tfrac{S_t I_t}{P_T} = b_t \tfrac{S_t I_t}{P_T} - dL^1_t, \\ L^2_{t+1} &= L^2_t + L^1_t - dL^2_t - L^2_t = L^1_t - dL^2_t, \\ I_{t+1} &= I_t + L^2_t - dI_t - I_t = L^2_t - dI_t, \\ R_{t+1} &= R_t + I_t - dR_t, \end{aligned} \tag{3}$$

where b_t is the transmission rate for week t, $\mu = \frac{47574}{52} = 914.885$ is the weekly number of newborns, $P_T = 5129266$ is the total population in the Community of Valencia (2012) and d the weekly death rate. In order to preserve the population (constant population) $d = \frac{\mu}{P_T} = 0.000178366$. The model graphic flow can be seen in Figure 2.

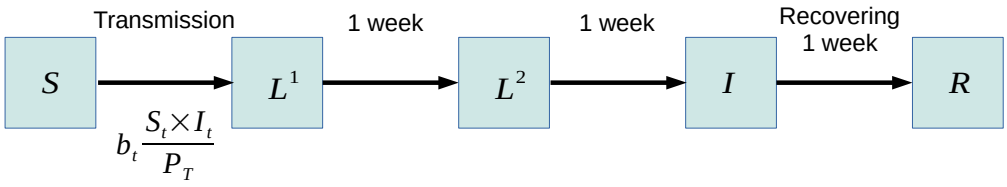

Fig. 2. Model graphic flow.

3.1 Determining the transmission rate per week b_t, $t \geq 1$

All the model parameters are known except for the transmission term, b_t. Our objective in this section is to find the values of the transmission rate which allows the model to fit the real epidemiological data in Fig. 1.

In order to establish a feasible initial condition, taking D the vector of data defined in (2), we are going to consider the following initial conditions:

- $R_0 = 0$, that is, initially there are not recovered individuals.

- $I_0 = D_{52} = 551.702$, because, in order to obtain the first transmission rate value b_1 we need to start with the number of infected individuals corresponding to the last week of December.
- Taking into account that $I_1 = D_1 = 862.036$ and from the model (3) $I_1 = L_0^2 - dI_0$, we obtain that $L_0^2 = 862.134$.
- Now, taking into account that $I_2 = D_2 = 837.406$ and from the model (3) $I_2 = L_1^2 - dI_1$ and $L_1^2 = L_0^1 - dL_0^2$, we have that $L_0^1 = 837.713$.
- Finally, $S_1 = P_T - L_1^1 - L_1^2 - I_1 = 5127014.45$.

With these initial conditions we guarantee that I_0, I_1 and I_2, the three first values of infected returned by the model, match the infected data D_{52}, D_1 and D_2.

Now, if we define the model output vector

$$M_t = (S_t, L_t^1, L_t^2, I_t, R_t), \quad t \geq 0, \tag{4}$$

substituting the values of

$$M_0 = (5127014.45, 837.713, 862.134, 551.702, 0),$$

into the model given by Eq. (3), we can obtain M_1, and substituting M_1 into the model again, we obtain M_2, and recursively, we can obtain M_t for $t \geq 0$. Using this recursion, we have that $I_3 = -0.448175 + 551.46b_1 = D_3$, and $b_1 = 1.54614$. Also, using the value b_1 and the recursion, $I_4 = -0.456081 + 861.514b_2 = D_4$ and $b_2 = 1.05831$. We can continue calculating the transmission rates b_t using the values of the previously calculated b_j, $j < t$, and the recursion process. If we assume that the vector of infected D is the same for every year, we can calculate 52 transmission rates (one peer week) for every year. The transmission rates b_t for the first year and for the year 1000 can be seen in Figures 3 and 4.

It is noteworthy the similitude between transmission rates in Figures 3 and 4. The same scaled behaviour is found in the intermediate years. Let us name Y_k the vector of 52 values of the calculated transmission rates in the year k.

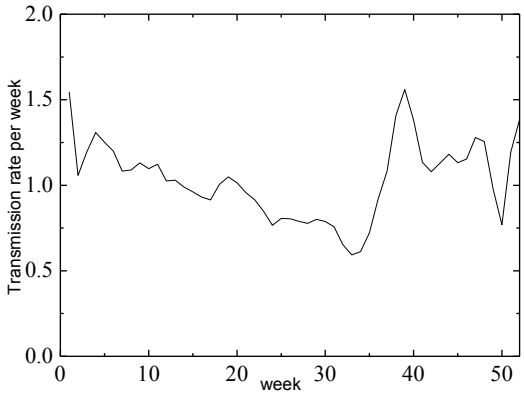

Fig. 3. Transmission rates per week for the first year. Observe that the only difference between this figure and Fig. 4 is the scale (y-axis). In the intermediate years the shape is the same with different scales.

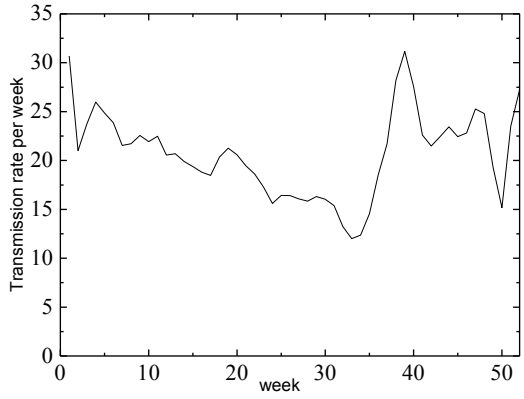

Fig. 4. The same as Fig. 3 but for the year 1000.

Thus, for the corresponding years in Figures 3 and 4, we have

$$
\begin{aligned}
Y_1 = (&1.54614, 1.05831, 1.19564, 1.30826, 1.2508, 1.19935, 1.08201, 1.0892,\\
&1.13053, 1.09748, 1.12306, 1.02543, 1.03006, 0.989696, 0.961239, 0.931224,\\
&0.914087, 1.00498, 1.04881, 1.01353, 0.956981, 0.914934, 0.847843, 0.76574,\\
&0.806154, 0.80458, 0.78904, 0.777545, 0.801159, 0.788765, 0.757366, 0.652099,\\
&0.592862, 0.611884, 0.721567, 0.921517, 1.08203, 1.40794, 1.55937, 1.38113,\\
&1.13437, 1.07969, 1.12951, 1.18181, 1.13244, 1.15294, 1.27853, 1.25504,\\
&0.977829, 0.769101, 1.19343, 1.38424),\\
Y_{1000} = (&30.7048, 21.0123, 23.7385, 25.9828, 24.8597, 23.8569, 21.5452,\\
&21.7114, 22.5621, 21.9381, 22.4828, 20.5643, 20.6929, 19.9145, 19.3745,\\
&18.7982, 18.4756, 20.3378, 21.2573, 20.5726, 19.4496, 18.6192, 17.2717,\\
&15.6075, 16.4338, 16.404, 16.0827, 15.8384, 16.3083, 16.0411, 15.3833,\\
&13.227, 12.0036, 12.3621, 14.5462, 18.5349, 21.7144, 28.1964, 31.1729,\\
&27.5659, 22.6053, 21.4815, 22.4401, 23.4476, 22.4395, 22.818, 25.2771,\\
&24.7952, 19.3053, 15.1674, 23.5041, 27.2568).
\end{aligned}
\tag{5}
$$

Now, our goal is to study how the weekly transmission rates grow year by year. To do that, we run the recursion 1500 years and with the transmission rates obtained, we build the matrix $G = (Y_k/Y_1)_{k=2}^{1500}$ of size 1499×52, where the division Y_k/Y_1 is componentwise. We have drawn the vector columns of length 1499 of the matrix G for the first and the last week of the year in Fig. 5. We see that the growth of the weekly transmission rates follows a sigmoid.

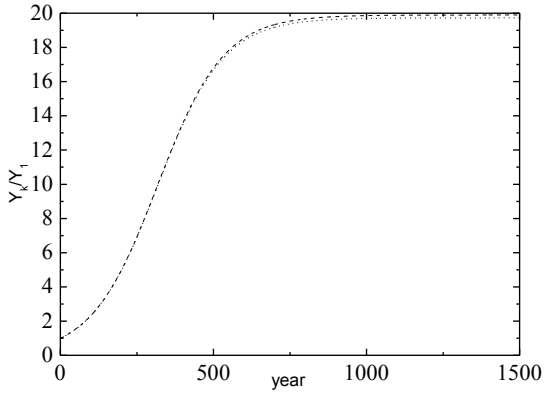

Fig. 5. Growth of the transmission rates for the first (dotted line) and the last week (dashed line) of the year. Notice the sigmoid shape of the graphs and the small differences among them.

Then, if we consider the general sigmoid function $f_t = \frac{a}{e^{-bt}+c}$, we are going to find the a, b and c that make f_t to fit the best with the weekly data of each column of G. The resulting 52 values of a, b and c obtained are drawn in Figures 6-8.

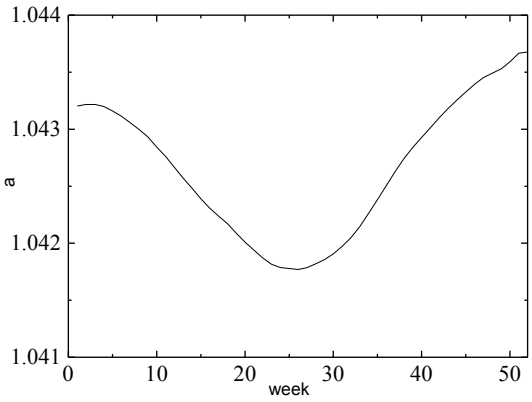

Fig. 6. Weekly values of a that make f_t to fit the best with the weekly data of each column of G.

Looking at the Figs. 6-8, we can see that the shape of the values of a and c are the same. In fact, the componentwise difference between the values of a

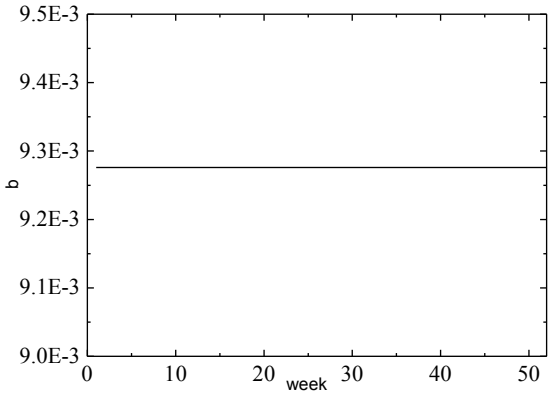

Fig. 7. The same as Fig. 6 but for b.

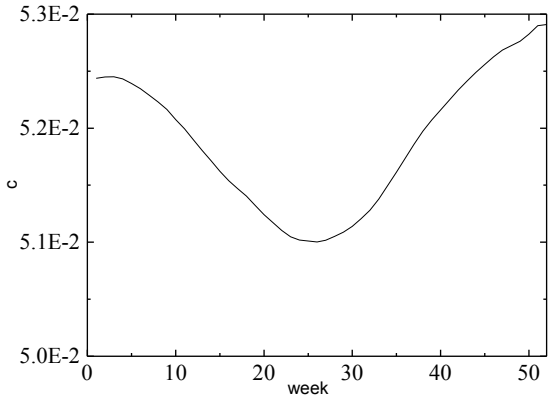

Fig. 8. The same as Fig. 6 but for c.

and c are all constant equal to 0.990767. Also, the graph of b is constant equal to 0.00927584.

Consequently, the values of a, b and c are very similar for each week. If we take the mean of the 52 values of a, b and c we get: $A_m = 1.04266$, $\gamma = 0.00927584$ and $\zeta = 0.0518882$, respectively. Then, an accurate approximation to the 52 weekly values of the transmission rate for year $k > 1$ will be

$$\widehat{Y}_k = \frac{A_m}{e^{-\gamma k} + \zeta} Y_1, \;\; k > 1. \tag{6}$$

The forced transmission rate for varicella given by Eq. (6) in terms of the infectivity deduced from the first year in Eq. (5) provides a very precise fitting of the seasonal pandemic obtained by replicating the incidence in Fig. 1 and Eq. (2). However, the functional form of this seasonal infectivity as shown in Figs. 3 and 4 is rather complicated. In the next section, we study the varicella

model with a simplified transmission rate (seasonal forcing term) where the infectivity is approximated by a single harmonic with a sigmoidal prefactor.

4 Simplified seasonal forcing term

Let us consider the seasonal forcing term

$$\beta_t = b_0 + b_1 \cos(\frac{2\pi t + \phi}{52}),\ t \geq 1. \tag{7}$$

We have calculated b_0, b_1 and ϕ such that β_t provides a least-squares fit of the data for Y_1 in Eq. (2). The obtained results are $b_0 = 1.03095$, $b_1 = 0.216799$ and $\phi = 0.200717$. In Fig. 9 we compare the fitting harmonic function in Eq. (7) with the transmission rates derived for the model during the first year.

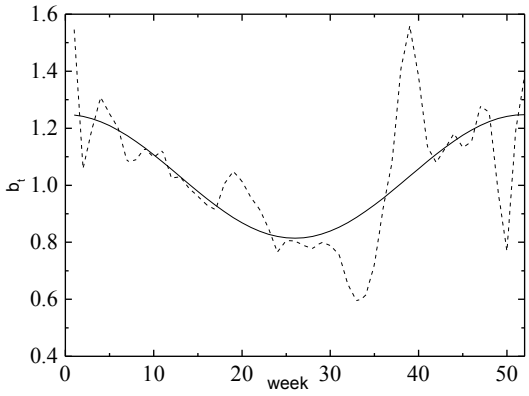

Fig. 9. Best fitting of the seasonal forcing term β_t, $1 \leq t \leq 52$ (solid line) to the vector data Y_1 (dashed line).

An approximate expression for the infectivity in the week t of year k, $B_{k,t}$ can be given by:

$$\begin{aligned} B_{k,t} &= \tfrac{A_m}{e^{-\gamma k}+\zeta}\beta_t \\ &= \tfrac{A_m}{e^{-\gamma k}+\zeta}(b_0 + b_1 \cos(\tfrac{2\pi t+\phi}{52})),\ k > 1,\ 1 \leq t \leq 52, \end{aligned} \tag{8}$$

where we have replaced the Y_1 values by the approximation given by the harmonic function in Eq. (7). Now, we can iterate the discrete equations of the model in Eq. (3) to analyze the evolution of the epidemic according to the infectivities of Eq. (6) and the approximation of Eq. (8).

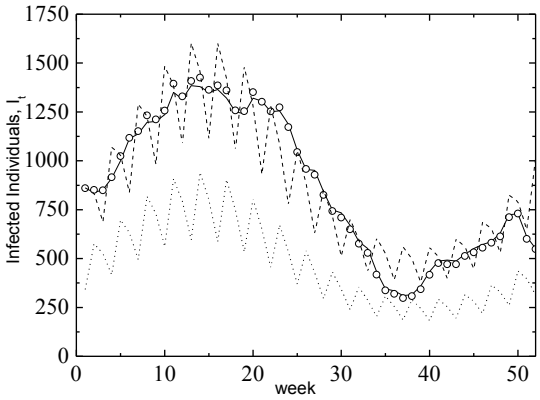

Fig. 10. Evolution of the seasonal incidence of the varicella epidemic using two models for the infectivity. The solid line is the real averaged data for UK as given in Eq. (2), the dots are the prediction obtaining by iterating the equations of the model with the infectivity given in Eq. (6) after 400 years, the dashed line (dotted line) corresponds to the simplified model with the approximate infectivity in Eq. (8) after one year (twelve years).

We have plotted the results in Fig. 10. The predictions of the original model with the sigmoidal modulation of the infectivity fitting in Eq. (6) are stable and very accurate even after 400 years of evolution. However, if we use the harmonic approximation with sigmoidal prefactor in Eq. (8) the predictions deteriorate very fast.

Consequently, we have shown that varicella, and probably other infectious diseases with high infectivity, cannot simply be modelled with harmonic seasonal forcing. The detailed calculation of the transmission rate deduced from the data is required for stable predictions in the long run. Moreover, in these diseases the infectivity should grow year after year in the initial stages of the pandemic in order to adapt to the diminishing proportion of susceptible individuals.

5 Conclusions

In this paper, we have shown that a SIR model with latency cannot fit some seasonal diseases with high infectivity if a cosine variation of the infectivity is assumed. A procedure to deduce the infectivity week after week from real data on the number of infectious individuals has been discussed. This procedure has been applied to the varicella epidemic to obtain a nonstandard seasonal infection rate. Using this rate it was possible to fit the seasonal pandemic and keep it stable in the predictions for several centuries (assuming constant

population).

Moreover, starting from an initial condition with few or no recovered individuals, we have shown that the envelope of the infectivity in different years is a sigmoidal function whose parameters were given explicitly for our case.

varicella is a very contagious disease caused by the varicella-Zoster Virus, whose closest relatives in the evolutionary tree are other alphaherpesviruses from which they evolved around 120 million years ago [24]. Although, it can infect other primates, it is only a pandemic in humans so its recent evolution is closely related to that of the hominid species. In our study we have suggested that the VZV virus should have changed in a period of several centuries before achieving a stationary state in its relation to the host. Taking into account the long history of the virus we should consider this numerical result with caution. Firstly, the population has grown exponentially in the last centuries implying larger cohorts of newborns every year susceptible to be infected by VZV. Recovery from varicella is not total because re-emergence in the form of shingles also happens in the adult population. It is known that a single individual with developed shingles could initiate an epidemic of varicella [24]. Consequently, this kind of latency could help to keep the virus circulating without, necessarily, a sigmoidal increase of its infectivity.

In a future work we will take into account these factors: non-constant population and infections of children caused by outbreaks of shingles in adults. This model could be applied to the impact of varicella vaccination programs in the control of the manifestations of shingles. The technique developed in this paper can also be applied to other seasonal infectious diseases: RSV, influenza and others which are, conventionally, studied using harmonic forcing.

The computations carried out in this paper and the figures can be obtained in a *Mathematica* [25] notebook, downloading it from `http://franchi.imm.upv.es/seasonal/Varicella_TR.nb`.

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