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The dynamical consequences of seasonal forcing, immune boosting and demographic change in a model of disease transmission

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HIGHLIGHTS

- Immune boosting induces cyclical behaviour in a model of infectious disease dynamics.
- Seasonal forcing of transmission also induces cyclical behaviour in this system.
- The birth rate, waning rate and forcing interact to generate complex dynamics.
- Periodic cycles in the forced system are related to unforced limit cycle dynamics.
- The "demographic transition" may lead to new dynamical regimes for certain diseases.

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ABSTRACT

The impact of seasonal effects on the time course of an infectious disease can be dramatic. Seasonal fluctuations in the transmission rate for an infectious disease are known mathematically to induce cyclical behaviour and drive the onset of multistable and chaotic dynamics. These properties of forced dynamical systems have previously been used to explain observed changes in the period of outbreaks of infections such as measles, varicella (chickenpox), rubella and pertussis (whooping cough). Here, we examine in detail the dynamical properties of a seasonally forced extension of a model of infection previously used to study pertussis. The model is novel in that it includes a non-linear feedback term capturing the interaction between exposure and the duration of protection against re-infection. We show that the presence of limit cycles and multistability in the *unforced system* give rise to complex and intricate behaviour as seasonal forcing is introduced. Through a mixture of numerical simulation and bifurcation analysis, we identify and explain the origins of chaotic regions of parameter space. Furthermore, we identify regions where saddle node lines and period-doubling cascades of different orbital periods overlap, suggesting that the system is particularly sensitive to small perturbations in its parameters and prone to multistable behaviour. From a public health point of view — framed through the 'demographic transition' whereby a population's birth rate drops over time (and life-expectancy commensurately increases) — we argue that even weak levels of seasonal-forcing and immune boosting may contribute to the myriad of complex and unexpected epidemiological behaviours observed for diseases such as pertussis. Our approach helps to contextualise these epidemiological observations and provides guidance on how to consider the potential impact of vaccination programs.

1. Introduction

The impact of seasonal effects on the time course of an infectious disease can be dramatic. Two well-known examples are the observed winter-onset of influenza in temperate climates (Lipsitch and Viboud, 2009), and the seasonal fluctuation in incidence of mosquito-borne diseases such as dengue (Aguiar

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et al., 2011). While the latter is well understood as a direct consequence of the role of climatic factors in driving annual fluctuations in the mosquito population size, the underlying causes for the former are imperfectly understood. Influenza seasonality may involve a range of climatic variables such as temperature and humidity that interact with biological (e.g. virus survival) and sociological (e.g. human contact and mixing behaviour) factors (Altizer et al., 2006; Lipsitch and Viboud, 2009). Many other diseases, such as measles, varicella (chickenpox), rubella and pertussis (whooping cough) also display seasonal characteristics which, importantly, have changed over the course of the 20th century (Bauch and Earn, 2003).

From the mathematical point of view, the effects of seasonal forcing in an epidemiological context can be studied in a number of ways. The first and foremost is the bifurcation approach, through which variations in model solutions due to changes in system parameters are analyzed using bifurcation diagrams (Kuznetsov, 2004). As the intensity and frequency of seasonal forcing are varied, the appearance of forced oscillations in the population can be studied systematically. Many studies of such systems exist in the literature, see for example Bolzoni et al. (2008), Kuznetsov and Piccardi (1994), Kuznetsov et al. (1993), Rinaldi and Muratori (1993), Doveri et al. (1993), Scheffer et al. (1997), Rinaldi et al. (1993) and Tanaka and Aihara (2013). Related examples include an analysis of seasonal forcing for a predator–prey model (Taylor et al., 2012) and the study of a model for immune priming (Best, 2013).

Other approaches to analysing such models include resonance theory (Greenman et al., 2004) or perturbation methods (King and Schaffer, 1999, 2001) which have been used elsewhere successfully in models relevant for epidemiology, ecology and demography (Schaffer et al., 2001; Greenman and Norman, 2007; Greenman and Pasour, 2011; Upadhyay and Iyengar, 2005; Choisy et al., 2006; He and Earn, 2007). In the context of infectious diseases, Earn et al. (2000) demonstrated that transitions from predictable to unpredictable, and potentially chaotic, behaviour for childhood diseases such as measles may arise naturally from changes in birth rates and/or vaccination schedules once seasonal fluctuations in the rate of infection were accounted for. In all these works, parameters that regulate the strength and periodicity of seasonal variations are shown to be responsible for the birth of complex phenomena of interest from both the biological and mathematical point of view, including multi-year cycles, chaotic dynamics, intermittent and catastrophic behaviors and multistable states.

In recent work, we used a combination of bifurcation analysis and numerical simulation to study the dynamics of a previously published model of pertussis infection (Lavine et al., 2011) in which protection following infection is not lifelong and immunity may be 'boosted' due to continual circulation of disease (Dafilis et al., 2012). Where Lavine et al. (2011) focussed on the role of vaccination in inducing undamped oscillatory dynamics, we demonstrated that a declining in the birth-rate, as observed in Western populations over the past century, was capable of transitioning the system from one characterised by endemic steady-state dynamics to one in which sustained (undamped) oscillations in disease prevalence characterised the system. Our and Lavine et al. (2011)'s results were derived in the absence of any seasonal fluctuations in the transmissibility of the pathogen.

In this paper we extend the model to include seasonal forcing and investigate the model's behaviour using bifurcation analysis and numerical simulation. Particular attention is devoted to understanding how changes in the strength of immune boosting and the intensity of seasonal forcing elicit different behaviour, and how such behaviour varies with the assumed birth-rate for the population.

The paper is organized as follows. In Section 2 we introduce the model of transmission. A discussion of the analytic and computational techniques used for our analysis is provided in Section 3. Section 4 presents the main findings. We discuss the epidemiological consequences of our study in Section 5.

2. The SIRWS model with demography and immune boosting

Extending the classic *S*usceptible–*I*nfectious–*R*emoved mode of disease dynamics, Lavine et al. (2011) introduced the 'SIRWS' model in which the population is separated into those who are susceptible to infection (S), those infected and infectious (I), those recovered, no longer infectious and immune to re-infection (R) and those whose immunity has waned sufficiently such that exposure, while not leading to productive infection, provides a 'boost' to immunity (W). Fig. 1 shows the population compartments and associated flows. Assuming mass action dynamics, the corresponding equations for the model are

$$\frac{dS}{dt} = -\beta(t)IS + 2\kappa W + \xi(1-S) \tag{1a}$$

$$\frac{dI}{dt} = \beta(t)IS - \gamma I - \xi I \tag{1b}$$

$$\frac{dR}{dt} = \gamma I - 2\kappa R + \nu\beta(t)IW - \xi R \tag{1c}$$

$$\frac{dW}{dt} = 2\kappa R - 2\kappa W - \nu\beta(t)IW - \xi W \tag{1d}$$

where $\beta(t) = \beta_0(1+\eta\cos(2\pi t))$ is the annually forced transmission coefficient, parameterised by a baseline value β_0 and a seasonal strength η, $1/\gamma$ is the average duration of infectiousness (in the absence of death), $1/\kappa$ is the average duration of protection (in the absence of immune boosting and death), ν is the factor describing the relevant strength of immune boosting ($W \to R$) compared to infection ($S \to I$) and ξ is the birth rate for the population. We assume a constant population size and no infection-induced mortality, and so the death-rate is also ξ.

The key feature of the model is the second non-linear term for the transition from $W \to R$. This term is directly proportional to the force-of-infection βI and allows for the overall effective duration of immunity (the expected time to transition from R to S) to reduce as the prevalence of infection (and so disease, I) drops. Critically, the constant of proportionality, ν, may be greater than or less than one. As in earlier works (Lavine et al., 2011; Dafilis et al., 2012), $\nu > 1$ implies that an exposure *insufficient to initiate productive infection in a susceptible individual may nonetheless be sufficient to boost immunity*. A more detailed description of the basic mathematical properties of the model may be found in Dafilis et al. (2012).

To undertake the present study on the role of seasonal-forcing (η) and its interaction with the strength of immune boosting (ν) and the population birth-rate (ξ), we must choose a set of biologically realistic parameters with which to simulate the model.

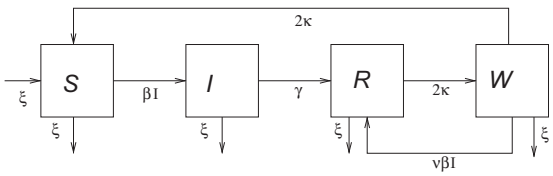

Fig. 1. A schematic diagram of the SIRWS model with demography and immune boosting. In the absence of immune boosting ($\nu = 0$), the system reduces to the classic SIR(S) model, but with the return flow from R to S split into two stages. The strength of immune boosting may be less than ($\nu < 1$) or greater than ($\nu > 1$) the force of infection βI. The inclusion of this extra feedback loop in the model has fundamental consequences for the dynamical properties of the system (Dafilis et al., 2012).