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Indirect transmission and the effect of seasonal pathogen inactivation on infectious disease periodicity

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ABSTRACT

The annual occurrence of many infectious diseases remains a constant burden to public health systems. The seasonal patterns in respiratory disease incidence observed in temperate regions have been attributed to the impact of environmental conditions on pathogen survival. A model describing the transmission of an infectious disease by means of a pathogenic state capable of surviving in an environmental reservoir outside of its host organism is presented in this paper. The ratio of pathogen lifespan to the duration of the infectious disease state is found to be a critical parameter in determining disease dynamics. The introduction of a seasonally forced pathogen inactivation rate identifies a time delay between peak pathogen survival and peak disease incidence. The delay is dependent on specific disease parameters and, for influenza, decreases with increasing reproduction number. The observed seasonal oscillations are found to have a period identical to that of the seasonally forced inactivation rate and which is independent of the duration of infection acquired immunity.

Introduction

Many diseases exhibit seasonal cycles in incidence data, most notably childhood diseases such as measles and rubella (Anderson and May, 1991; Dowell, 2001). For such diseases, it is widely accepted that the observed cycles are linked to the timing of school terms and the subsequent increase in contact rates among the immunologically naive child population (Keeling et al., 2001; Stone et al., 2007). The mechanism driving the seasonal occurrence of influenza and other respiratory infections is less well understood. While increased contact rates due to indoor crowding during winter undoubtedly facilitate greater disease transmission, it is more likely a contributing factor and not the driving mechanism (Lofgren et al., 2007). Seasonal influenza places a considerable burden on public health systems with annual global incidence in the range 5–15% of the population, resulting in up to 500,000 deaths (Stohr, 2002). Targeted interventions to reduce this burden could be significantly improved if the seasonal stimulus was better understood.

The cause of seasonality must be attributed to annual changes associated with either the host or the infectious disease pathogen (Grassly and Fraser, 2006). In addition to increased contact rates during winter, higher transmission rates have been linked to changes in the human immune system. Possible variations in human immune function have been attributed to fluctuations in melatonin secretion regulated by the annual light-dark cycles and to deficiencies in vitamin D during the winter months (Cannell et al., 2008; Lofgren et al., 2007; Nelson and Demas, 1996). Experiments on mice in an environmentally controlled environment found that mice were more susceptible to infection during the winter months (Schulman and Kilbourne, 1963). For diseases transmitted through indirect pathways (e.g. respiratory droplets, fomites, fungal spores, waterborne pathogens) the ability of the pathogen to survive outside of its host must play a vital role in the transmission process (Grassly and Fraser, 2006). This survival potential would be greatly influenced by environmental factors. Early studies on the survival of the influenza virus in air indicated that pathogen survival peaks at low relative humidity and low temperatures resulting in increased viral transmission (Harper, 1961; Hemmes et al., 1960). Experiments to study the airborne transmission of influenza among Guinea pigs further supported this theory indicating that transmission among subjects peaked in cold dry air (Lowen et al., 2007). However, while indoor relative humidity is minimized in winter, outdoor humidity peaks. More recent studies identify absolute humidity as a more likely seasonal driver, as both indoor and outdoor absolute humidity display cyclic behaviour in temperate regions that minimizes in winter (Shaman and Kohn, 2009). Influenza virus survival increases with low absolute humidity leading to increased transmission in winter (Shaman et al., 2010). Other

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theories for increased viral inactivation in summer consider ultraviolet radiation and air toxicity, however, little work has been undertaken to support such theories (Weber and Stilianakis, 2008).

A crucial factor to consider when assessing the impact of environmental factors on seasonal transmission is the mode of disease transmission. For respiratory diseases three modes of pathogen transmission have been identified: droplet, contact and airborne transmission (Weber and Stilianakis, 2008). Droplet transmission occurs when, following an expiratory event by an infected individual, large pathogen-carrying droplets (diameter $\gtrsim 10\,\mu$m) are deposited directly onto the mucous membranes of a susceptible person. The direct nature of such a transmission pathway precludes a significant impact by environmental factors on either the droplet itself or its pathogen load. Conversely, the contact (through fomites or direct human-to-human contact) and airborne (small aerosol droplets with diameter $\lesssim 10\,\mu$m) modes of transmission render the pathogen vulnerable to environmental conditions during prolonged periods spent external to its host organism. For the specific case of the influenza virus, the efficiency of contact transmission is determined by the survival rate of the pathogen on solid surfaces and human skin. The high inactivation rates observed on hands can limit the occurrence of transmission via the contact route, however, a continuous supply of fomites from infected individuals could possibly counteract this (Weber and Stilianakis, 2008). This mode of transmission is greatly influenced by human behaviour (e.g. cough etiquette, hand washing) and thus a seasonal variation in its impact would be difficult to quantify. Airborne droplets remain exposed to the ambient environmental conditions for prolonged periods of time and could act as an important agent driving seasonal disease incidence. For respiratory diseases mediated by airborne droplets and for a spatially homogeneous distribution of susceptibles, pathogen removal is the result of three distinct processes: gravitational settling, pathogen inactivation and inhalation (Stilianakis and Drossinos, 2010). Environmental factors are capable of influencing the first two of these processes (Shaman and Kohn, 2009). The gravitational settling rate of a droplet is determined from its diameter, which is influenced by evaporation effects determined by the ambient air properties. However, a review of experimental studies by Shaman and Kohn (2009) found that there is insufficient evidence to support such a hypothesis. They concluded that seasonal variations in environmental conditions are most likely incorporated through the pathogen inactivation term.

The seasonality of infectious diseases is usually incorporated in deterministic models through a time dependent transmission rate. Outbreaks are typically simulated using a sinusoidal function or, in the case of childhood diseases such as measles, a step function is employed to represent school terms (Grassly and Fraser, 2006; Keeling et al., 2001). Models incorporating natural birth and death processes display damped oscillations towards an endemic disease state (Fisman, 2007). However, if the period of the applied seasonal forcing is close to the intrinsic period of the damped oscillations then the two effects can resonate to produce large amplitude seasonal oscillations (Dushoff et al., 2004). An important consideration in any analysis of seasonal influenza is the process of antigenic drift, whereby continuous small changes in the virus requires the production of a new vaccine each year. This phenomenon can be integrated into the standard deterministic models by allowing recovered individuals to lose their acquired immunity after a specified period of time (Dushoff et al., 2004). An important factor neglected in the standard deterministic models is the mechanism driving the seasonal variation. If the theory that the impact of annual variations in environmental conditions on pathogen survival/inactivation is indeed valid then models should incorporate this phenomenon. In this paper, we present such a model.

In section "A model for indirect transmission of an infectious disease" we analyze a model for the spread of an infectious disease by means of an intermediate free-living pathogenic state, which is exposed to the ambient environmental conditions. This general model, applicable to a variety of free-living organisms (e.g. viruses, bacteria, fungi, protozoa), was introduced by Anderson and May (1981) to describe indirect disease transmission between free-living microparasites and their invertebrate hosts. Variations of the basic model have been employed to describe the spread of a pathogen through a generalized environmental state (Li et al., 2009), the spread of a waterborne bacteria (Tien and Earn, 2010), bacterial and prion disease in livestock and wildlife (Nieuwhof et al., 2009; Miller et al., 2006), and the transmission of respiratory diseases by airborne droplets (Stilianakis and Drossinos, 2010). The model has even been adapted to describe the spread of fungal spores in a vineyard (Burie et al., 2006) and the point release of an infectious agent (Reluga, 2004). With such a wide range of applications and descriptive abilities the intrinsic characteristics of the infectious agent are a vital model component and can radically impact the dynamics. A pathogen characteristic of primary importance is its ability to survive for prolonged periods outside of its host, which is directly influenced by environmental conditions and, thus, cannot be ignored in the quest to identify seasonal disease drivers. Therefore, we first analyze the general model and consider its behaviour for both short-lived and long-lived pathogenic states. An important outcome of this analysis is that, in the case of short-lived pathogens, a quasi-steady state exists whereby the pathogen dynamics can be described in terms of the infected population alone. This quasi-steady approximation can also be applied to an non-autonomous model describing seasonal outbreaks. This model is analyzed in section "Seasonal variation in pathogen inactivation", where we consider the consequences of a seasonal variation in the pathogen inactivation rate and how it impacts disease incidence.

A model for indirect transmission of an infectious disease

Many infectious diseases are primarily transmitted by means of an intermediate environmental reservoir, in which free-living pathogens are capable of surviving outside of the host organism. For example, waterborne outbreaks can persist through the shedding of pathogens by an infected individual into a water source which is then ingested by a susceptible individual. Similarly, respiratory diseases can be transmitted from person to person via pathogen loaded airborne droplets or fomites expelled into the environment by infected individuals during expiratory events (e.g. coughing or sneezing). The efficiency of such transmission pathways will depend on the ability of the pathogen to survive in the intermediate reservoir (e.g. air, water). In this section we present a generalized model for the transmission of an infection by means of such a pathogen reservoir.

Consider a closed population of N individuals, of which $S(t)$ are susceptible, $I(t)$ are infected and $R(t)$ are recovered. Infected individuals shed pathogens into an intermediate reservoir, which are free-living (outside of the host organism) and can transmit infection through contact with the susceptible population, Fig. 1. The total number of pathogens in the reservoir is $P(t)$. A deterministic model for the disease dynamics is

$$\frac{dS}{dt} = d(N-S) + \sigma(N-S-I) - \frac{\beta}{N}PS,$$

$$\frac{dI}{dt} = \frac{\beta}{N}PS - (\mu + d)I,$$

$$\frac{dP}{dt} = \kappa I - \alpha P,$$

where the total human population $N = S + I + R$ is constant. The duration of time spent in the infected state is $T_I = 1/(\mu + d)$, where $1/\mu$