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Species interactions may help explain the erratic periodicity of whooping cough dynamics

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ABSTRACT

Incidence of whooping cough exhibits variable dynamics across time and space. The periodicity of this disease varies from annual to five years in different geographic regions in both developing and developed countries. Many hypotheses have been put forward to explain this variability such as nonlinearity and seasonality, stochasticity, variable recruitment of susceptible individuals via birth, immunization, and immune boosting. We propose an alternative hypothesis to describe the variability in periodicity – the intricate dynamical variability of whooping cough may arise from interactions between its dominant etiological agents of *Bordetella pertussis* and *Bordetella parapertussis*. We develop a two-species age-structured model, where two pathogens are allowed to interact by age-dependent convalescence of individuals with severe illness from infections. With moderate strength of interactions, the model exhibits multi-annual coexisting attractors that depend on the $\mathscr{R}_0$ of the two pathogens. We also examine how perturbation from case importation and noise in transmission may push the system from one dynamical regime to another. The coexistence of multi-annual cycles and the behavior of switching between attractors suggest that variable dynamics of whopping cough could be an emergent property of its multi-agent etiology.

1. Introduction

Historical records of childhood diseases exhibit complex patterns in dynamics. Dating back to the early twentieth century, case notifications of childhood diseases show a variety of temporal patterns, including regular cycles of variable period and apparently aperiodic dynamics (Anderson and May, 1991; Earn et al., 1998, 2000; London and Yorke, 1973; Rohani et al., 1999; Bhattacharyya et al., 2015). Moreover, the temporal epidemic pattern in a given location sometimes switches from one dynamical regime to another over long time-scales (Earn et al., 2000; Bolker and Grenfell, 1993; Rohani et al., 2002; Bauch and Earn, 2003). Historical surveillance often relies on clinical diagnosis, i.e., symptoms such as fever and rash, diarrhea, or ILI (influenza-like illness). Thus the dynamics observed may be due to the dynamics of the focal pathogen or interactions among the multiple pathogens that result in clinical syndrome. Complex temporal dynamics have been frequently documented in time series of whooping cough, which is a disease that can be caused by several strains of bacteria in the genus *Bordetella*. The two dominant species are *pertussis* and *parapertussis*. Changes in temporal patterns of whooping cough incidence are frequently seen even within single populations governed by otherwise stable demographics (Broutin et al., 2005a). The dominant periodicity of whooping cough is annual or ranges from 3–5 years as documented in many settings: Portugal (Gomes et al., 1999), the United States (Hethcote, 1998; Tanaka et al., 2003), the United Kingdom (England and Wales) (Rohani et al., 1999; Anderson et al., 1984), and rural Senegal (Broutin et al., 2005b). A long time series of whooping cough reports from Copenhagen in the early 20th century provides an excellent illustration of variable periodicity; the time series of case notifications switches back and forth between long periods of annual cycles and periods of 3-year cycles, displaying distinct shifts between low-amplitude, noisy oscillations to high-amplitude well-defined cycles (Fig. 1).

Many hypotheses have been put forward to explain this erratic periodicity of whooping cough dynamics including noise in transmission (Rohani et al., 1999, 2002), slow changes in susceptible recruitment by birth and immunization (Earn et al., 2000; Broutin et al., 2010), and stochasticity in other epidemiological parameters such as latent and infectious periods (Nguyen and Rohani, 2008). Keeling et al. showed how seasonal forcing due to the binary nature of contact patterns during school closures introduces perturbations and switching

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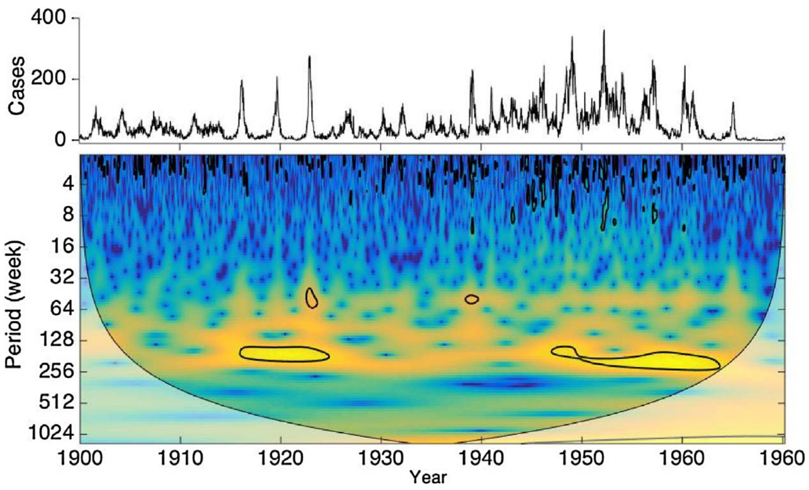

Fig. 1. Time series of the weekly reported cases in Copenhagen (upper panel), and wavelet decomposition of the square-root transformed reports (lower panel). Yellow areas of the wavelet plot indicate stronger support for cycles of the period identified on the left axis. The 5% significance level against red noise (indicated by yellow lighter shed) is shown as a thick contour. The other black line denotes the cone of influence (COI), where edge effects might distort the picture is shown as a lighter shade. Here, the dataset shows several lighter regions around the band of 1–3 year period, indicating stronger support for cycles of these respective periods. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between different attractors (Keeling et al., 2001). Bauch and Earn performed perturbation analysis to show that non-resonant peaks in childhood disease, like measles, can arise due to transient dynamics in response to vaccination and slow changes in birth rate (Bauch and Earn, 2003). Recently, Lavine et al. proposed that models combining impermanent immunity with sensitive immune boosting can capture the change in age-incidence following vaccination and predict, under some circumstances, coexistence of cyclic and annual attractors (Lavine et al., 2013, 2011). Here, we explore a different mechanism based on an endogenous factor – species interactions via short-term isolation of host individuals – which gives an alternative explanation for the erratic dynamics of whooping cough.

Ecological interference through quarantine or convalescence has been shown to give rise to multi-annual outbreaks of diseases with distinct phase differences (Rohani et al., 1998, 2003). Here, we study the consequence of any such effects on the dynamics of two dominant etiological agents of whooping cough: *pertussis* and *parapertussis*. Though both bacteria can result in whooping cough, parapertussis generally results in less severe disease than pertussis. In the pre-vaccination era, *Bordetella parapertussis* accounted for between 0.1% and 10% of reported whooping cough cases (Lautrop, 1971; Miller et al., 1941). In Copenhagen between 1945 and 1970, parapertussis accounted for only (~0.049%, Fig. 2) of whooping cough cases (Lautrop, 1971). In this rare study that separated whooping cough incidence by etiological agents pertussis and parapertussis exhibit cycles of distinct 4-year periodicity, with a 2-year phase lag, suggesting a potential dynamical interaction despite the low absolute incidence of parapertussis. Parapertussis is starting to receives more attention because of better diagnostic tools (like PCR (polymerase chain reaction)), improved surveillance methods, and increased awareness (He and Mertsola, 2008; Pittet et al., 2014; Rodgers et al., 2013). Recent observational studies have documented laboratory confirmed cases and outbreaks of parapertussis in a vaccinated population in Finland in 1985 (Mertsola, 1985) and from 1994–1997 (He et al., 1998), several states of United States from 2008–2011 (Cherry, 2005), China in 2011 (Zhang et al., 2014), and Canada in 2011(Fisman et al., 2011).

Whooping cough disease can be caused by either species of bacterium; the time series that have been classically studied reflect infections with either and may reflect the dynamics of interactions between them. Infections by either of these two species can lead to severe disease, though the rate of severe illness due to parapertussis is much lower (Lautrop, 1971). Moreover, the severity of illness varies over age; children develop more severe disease than adults (British Society for the study of infection, 1997; Miller and Fletcher, 1976). Individuals with severe illness may self-quarantine at home or in hospital, thus limiting their interactions and potential for transmission. Thus, *interference* between these two pathogens may result when those with severe disease have lower exposure to the other species (e.g. during a period of convalescence) even though they may still be technically susceptible. Here, we develop a two-pathogen model where the strength of interaction between species arises from the age specific proportion of individuals with severe disease that will be temporarily removed due to a period of convalescence. We show that complex time series dynamics and multiple coexisting attractors in aggregate time series can arise from ecological interactions between pathogens. Further we show that random perturbations can cause jumps between those attractors. Thus our

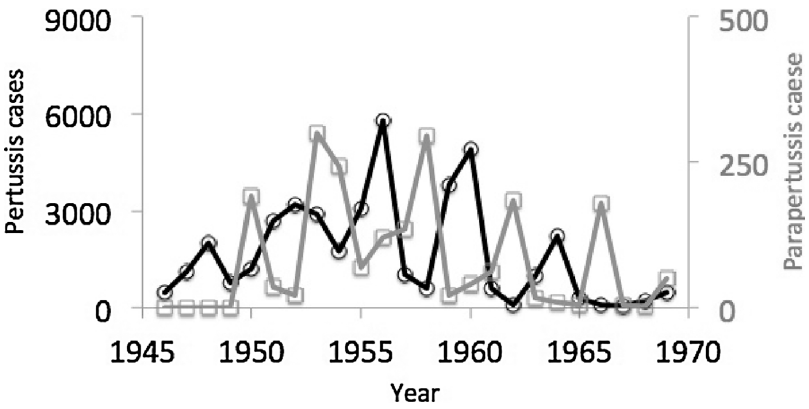

Fig. 2. Annual reported cases of *B. pertussis* and *B. parapertussis* in the city of Copenhegan and surrounding suburban counties from 1945 to 1969 (Lautrop, 1971). Both strains exhibit out-of-phase dynamics with 4 year periodicity, though *B. parapertussis* has much lower frequency than *B. pertussis*.