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Structural differences in mixing behavior informing the role of asymptomatic infection and testing symptom heritability

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ABSTRACT

Most infectious disease data is obtained from disease surveillance which is based on observations of symptomatic cases only. However, many infectious diseases are transmitted before the onset of symptoms or without developing symptoms at all throughout the entire disease course, referred to as asymptomatic transmission. Fraser and colleagues [1] showed that this type of transmission plays a key role in assessing the feasibility of intervention measures in controlling an epidemic outbreak. To account for asymptomatic transmission in epidemic models, methods often rely on assumptions that cannot be verified given the data at hand.

The present study aims at assessing the contribution of social contact data from asymptomatic and symptomatic individuals in quantifying the contribution of (a)symptomatic infections. We use a mathematical model based on ordinary differential equations (ODE) and a likelihood-based approach followed by Markov Chain Monte Carlo (MCMC) to estimate the model parameters and their uncertainty.

Incidence data on influenza-like illness in the initial phase of the 2009 A/H1N1pdm epidemic is used to illustrate that it is possible to estimate either the proportion of asymptomatic infections or the relative infectiousness of symptomatic versus asymptomatic infectives. Further, we introduce a model in which the chance of developing symptoms depends on the disease state of the person that transmitted the infection.

In conclusion, incorporating social contact data from both asymptomatic and symptomatic individuals allows inferring on parameters associated with asymptomatic infection based on disease data from symptomatic cases only.

1. Introduction

In the absence of effective vaccines or treatment, controlling the spread of an infectious disease during the early stages of an outbreak, relies on (i) isolation of symptomatic cases and (ii) tracing and quarantining the contacts of these cases. Hence, the timing of onset of symptoms relative to the start of infectiousness is a crucial factor in the success of these public health interventions. It has been shown that the proportion of asymptomatic infections (i.e. transmission that occurs before symptom onset or without showing symptoms at all) is a key parameter to predict whether or not isolation and contact tracing will lead to containment [1]. It is therefore important to use an epidemic model that explicitly takes into account asymptomatic transmission. However, in many cases the available data is based on observations of symptomatic individuals only. To overcome this limitation, models often rely on untestable assumptions, e.g. assuming a fixed proportion of asymptomatic individuals [2] or ignoring pre-symptomatic transmission [3].

Data on social contacts of individuals in a population have already proven to be a valuable additional source of information when estimating the Who Acquires Infection From Whom (WAIFW) matrix and the basic reproduction number R_0 (see e.g. [4,5]). More recently, social contact data have also been used to gain insight in the impact of illness on social contact patterns [6]. It was found that individuals symptomatic with influenza-like illness (ILI) have less social contacts than asymptomatic individu-

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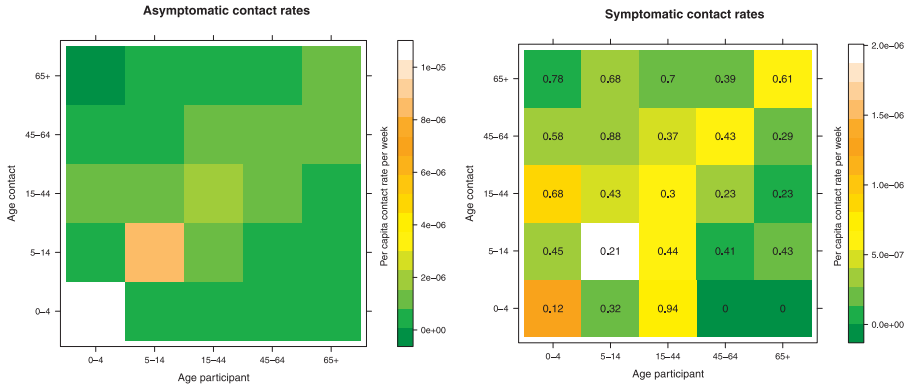

Fig. 1. Age-specific contact rates for asymptomatic individuals (left) and symptomatic individuals (right) based on the age classes of the incidence data. The right plots displays the percentage reduction in contact rates between symptomatic versus asymptomatic individuals.

als. Furthermore, the age distribution of contacts differs between symptomatic and asymptomatic cases. These differences in mixing behavior affect the expected distribution of infection during the early stages of an outbreak, which allowed Van Kerckhove and colleagues [7] to estimate the proportion of ILI infections caused by asymptomatic cases (34%; CI: 0%–77%) from ILI incidence data.

Influenza viruses are highly infectious and cases can show a variety of symptoms such as fever, runny nose and sore throat. A substantial number of cases also show little to no apparent symptoms. Several challenge studies have looked at the dynamics of viral shedding and symptoms following influenza virus infections; for a review see [8]. Symptomatic cases are considered to be more infectious than asymptomatic cases, since it was found that clinical cases have a higher quantity of virus in nasal wash fluids compared to individuals who did not develop symptoms. In addition, a positive correlation was found between severity of illness and the mean quantity of virus. The link between administered dose and development or degree of symptoms is less clear. Carrat and colleagues [8] reported a negative correlation between inoculated dose and fever, whereas Huang et al. [9] did not find a dependency between inoculated dose and disease outcome. Their findings point to host factors leading to asymptomatic infections. Hence, it is clear that more research is needed to find the precise link between the amount and duration of viral shedding, the development and the degree of symptoms and the transmission of the virus.

In the current study we will extend the work of Van Kerckhove et al. [7] by incorporating social contact data from asymptomatic and symptomatic individuals to inform mixing patterns in a compartmental model described by a system of ordinary differential equations. We will illustrate inference on parameters related to asymptomatic infection using incidence data on influenza-like illness. Furthermore, we will also investigate the possibility that the chance of developing ILI symptoms depends on whether infection came from a symptomatic or an asymptomatic case. The paper is organized as follows. In Section 2, we introduce the model structure, data and estimation procedure. In Section 3, the ILI data are analyzed, and, lastly, Section 4 summarizes our main results, conclusions, and avenues for further research.

2. Material and methods

2.1. Data

2.1.1. ILI data

Weekly incidence data were obtained from general practitioners' weekly consultation data on influenza-like-illness (ILI) from England and Wales during the early part of the A/H1N1pdm influenza epidemic in 2009 (weeks 23–29) [10]. Pre-existing immunity to the pandemic strain was obtained from a serological study in England the year before the pandemic [11].

2.1.2. Social contact data

We use data from a social contact survey that was carried out during the A/H1N1pdm influenza epidemic in England. This survey is described in detail in [6]. Briefly, participants were recruited into the study through packs with antiviral medication distributed at thirty-one antiviral distribution centers throughout England during the epidemic. The packs contained a social contact diary to be filled in on one day during the time they were symptomatic with ILI. Two weeks later (by which time participants were expected to have recovered), participants were sent a similar, follow-up questionnaire. Thus, the study aimed to obtain two contact diaries from each participant: one completed when the participant was showing symptoms and one completed after he or she had recovered. In these contact diaries participants were asked to record details about each person they met during the course of a day: gender and (estimated) age of the contact, social setting and duration of the encounter, frequency with which that person was met, and whether the encounter involved any skin-to-skin contact (e.g., hand-shake, kiss, or contact sport). A total of 140 participants returned two completed contact diaries. Based on this information social contact matrices C^a and C^s for both recovered (assumed to be the same as asymptomatic) and symptomatic individuals were calculated, respectively [7]. These matrices are presented in Fig. 1.

2.2. Transmission models

2.2.1. Non-preferential model

We use a compartmental model which describes the disease dynamics for influenza and infections with similar disease progress. In this model, individuals either develop symptoms or not after a pre-symptomatic stage. We will refer to this model as the non-preferential transmission model, since the development of symptoms is independent of the status of the infector. It is depicted as a flow diagram in Fig. 2. Note that superscripts indicate clinical status of the infected individual: symptomatic 's' or asymptomatic 'a'.

Hence, we assume that susceptible individuals are infected at rate $\lambda(t)$. Following infection, individuals enter the exposed compartment (E) in which they are infected but not yet infectious. After a mean latent period $1/\gamma$ individuals become asymptomatic infectious, entering the compartment I_1^a. We define ϕ; $0 \leq \phi \leq$