



# Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence



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## ABSTRACT

Dynamic transmission models are essential to design and evaluate control strategies for airborne infections. Our objective was to develop a dynamic transmission model for seasonal influenza allowing to evaluate the impact of vaccinating specific age groups on the incidence of infection, disease and mortality. Projections based on such models heavily rely on assumed ‘input’ parameter values. In previous seasonal influenza models, these parameter values were commonly chosen ad hoc, ignoring between-season variability and without formal model validation or sensitivity analyses. We propose to directly estimate the parameters by fitting the model to age-specific influenza-like illness (ILI) incidence data over multiple influenza seasons. We used a weighted least squares (WLS) criterion to assess model fit and applied our method to Belgian ILI data over six influenza seasons. After exploring parameter importance using symbolic regression, we evaluated a set of candidate models of differing complexity according to the number of season-specific parameters. The transmission parameters (average  $R_0$ , seasonal amplitude and timing of the seasonal peak), waning rates and the scale factor used for WLS optimization, influenced the fit to the observed ILI incidence the most. Our results demonstrate the importance of between-season variability in influenza transmission and our estimates are in line with the classification of influenza seasons according to intensity and vaccine matching.

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## 1. Introduction

Influenza presents as a mild disease in most healthy adults but is responsible for significant morbidity and mortality among vulnerable groups such as the elderly, patients with underlying health conditions and children. Recently, several countries have introduced routine vaccination of children for two main reasons. The first is that the rate of influenza hospitalizations in young children is as high as in elderly. The second is that children play an important role in influenza virus transmission, so that childhood

vaccination would provide indirect protective effects for the community.

We developed a dynamic transmission model for seasonal influenza with the aim to enable projecting the effectiveness and cost-effectiveness of mass vaccination strategies (Beutels et al., 2013). In this paper, we focus on the dynamic transmission model and estimate key parameters by fitting the model to an age-specific time series of influenza-like illness (ILI) incidence. The model relies on data from Belgium, such as ILI incidence, vaccination coverage and demographic data, though the concepts and methods are generally applicable. In Belgium, influenza vaccines are currently recommended for people over 50 years (with priority for those over 65 years), people with underlying chronic illness, pregnant women and health care workers (Beutels et al., 2013). In order to gain insights into the existing modelling approaches, we conducted a thorough literature review (details in Supplementary material), which yielded 25 articles presenting dynamic transmission

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models for seasonal influenza. We classified these articles in four main groups based on the modelling approach used.

First, there are standard mathematical models such as SIR (susceptible–infectious–recovered) and compartmental extensions thereof that are mainly designed to capture single epidemics (e.g. Glasser et al., 2010). Second, another group of models extends the previous class by including adaptive parameters for seasonality such as seasonally forced transmission rates (e.g. Finkenstadt et al., 2005; Vynnycky et al., 2008). Influenza occurs in annual epidemics during the winter period, which has been related to many factors e.g. temperature and humidity, viral production, and contact patterns (Fuhrmann, 2010; Shaman and Kohn, 2009; Willem et al., 2012). Third, some narrative reviews focused on the comparison of various dynamic models (e.g. Ballesteros et al., 2009). Fourth, a final group focused on multi-strain models to evaluate the impact of cross-immunity between different influenza strains by means of theoretical derivations or simulations (e.g. Andreasen, 2003; Prosper et al., 2011).

We used the dynamic model of Vynnycky et al. (2008) as a basis for our model because it is an age-stratified model with seasonally forced transmission rates, including annual vaccination. As influenza is mainly spread from person to person through respiratory droplets, transmission depends directly on age-specific rates of making social contact. Over the last decade, important advances were made in the collection of social contact data to parameterize infectious disease transmission models, such as the large population-based survey conducted in eight European countries as part of the POLYMOD project (Mossong et al., 2008). The use of empirical observations to inform the ‘who acquires infection from whom’ matrix has been successfully applied to model the transmission of different airborne infections (Goeyvaerts et al., 2010; Kretzschmar et al., 2010; Ogunjimi et al., 2009; Wallinga et al., 2006). Vynnycky et al. (2008) were the first to use POLYMOD contact data to parameterize transmission rates for seasonal influenza.

In this paper, we propose to directly estimate the dynamic model parameters by fitting the model to multi-season ILI incidence. In many countries, ILI incidence is monitored via surveillance systems such as sentinel networks or online surveys (Vandendijck et al., 2013). We capture between-season heterogeneity by allowing for season-specific parameters, such that the associated uncertainty can be propagated in predictions for future epidemics and the evaluation of vaccination strategies. By contrasting model predictions against relevant incidence data, our approach improves upon the practice of imputing pre-specified values to uncertain parameters, such as transmission or waning rates, without formal model validation or sensitivity analyses. Parameter values for dynamic models of seasonal influenza were commonly chosen ad hoc or based on inadequate data, e.g. related to historical observations or pandemic influenza.

There are few examples of dynamic transmission models for seasonal influenza that were actually fitted to incidence data. Hsieh (2010) estimated age-specific transmission probabilities by fitting to cumulative pneumonia and influenza mortality data from a single low-intensity season, however, the fit to the crude mortality data seems dubious. Finkenstadt et al. (2005) developed a stochastic model to estimate the rate of antigenic drift from multi-season ILI incidence data. Their results supported the presence of immunity loss, which we will account for by assuming continuous waning after infection or vaccination. Their dynamic model as such was less relevant to our setting as it ignored annual vaccination and age-dependent transmission. The same was true for the deterministic model by Poletti et al. (2011), which was fitted to ILI incidence data from a single season using a least-squares approach and designed to estimate the impact of behavioural changes during the 2009 H1N1 pandemic. We elaborate on their least-squares method when fitting

our model to multi-season ILI incidence data, including age-specific post-stratification weights.

Pitman et al. (2013, 2012) used a model similar to Vynnycky et al. (2008) to evaluate childhood vaccination in England and Wales. In both studies (Vynnycky et al., 2008; Pitman et al., 2012), parameter values were imputed rather than estimated by fitting the model to epidemiological data. However, during preparation of the current paper, Baguelin et al. (2013) presented another model with the same purpose, using an MCMC-based method to estimate model parameters from ILI incidence data. We briefly discuss the main differences between our approaches at the end of this paper.

## 2. Materials and methods

In this section, we first describe the ILI incidence data after which the dynamic transmission model is introduced, outlining its general structure, the interpretation of the parameters and the model assumptions. At the end of this section, we introduce the statistical methods used to estimate the parameters in the dynamic transmission model.

### 2.1. ILI incidence data

The ILI incidence data were collected from a sentinel network of general practitioners (GPs) in Belgium coordinated by the Scientific Institute of Public health. Each week, the GPs report the total number of ILI consultations by four age groups, 0–4, 5–14, 15–64 and  $\geq 65$  years, using the following case definition: sudden onset of symptoms, high fever, respiratory (i.e. cough, sore throat) and systemic symptoms (i.e. headache and muscular pain). Weekly estimates for the denominators are available as well, reflecting the population covered by the sentinel network. We analyze data from the last six pre-pandemic influenza seasons, from October 2003 to August 2009, as displayed in Fig. 3. The ILI incidence data are described in more detail by Hanquet et al. (2011) and Bollaerts et al. (2013).

Additionally, a fraction of ILI patients were swabbed by the GPs in the sentinel network during the influenza activity period and tested for influenza A and B. The swabbing of ILI cases was carried out ‘ad hoc’ using quota for each sentinel GP, but without any objective or consistent criteria, and was therefore likely age biased. Due to the non-systematic nature of the swabbing, the weekly laboratory-confirmed influenza case data were incomplete, especially in young children and individuals over 65 years of age. Further, there were few cases of influenza B in Belgium during the study period. We therefore fitted the dynamic model to ILI incidence data rather than to influenza-confirmed ILI incidence data, and calibrated model-based outcomes for the economic evaluation (Beutels et al., 2013).

We thus assume one generic influenza virus, which should be interpreted as an average of past influenza A and B strains. Therefore in our model, waning of immunity may capture actual waning of acquired immunity as well as lack of cross protection. The model partly captures season dominance of A and B strains and transmission heterogeneity by incorporating season-specific parameters.

### 2.2. Dynamic transmission model

#### 2.2.1. General structure of the model

We elaborate on the model Vynnycky et al. (2008) and use the same notation. This is an age-stratified SEIRS model with vaccination, classifying the population into compartments of susceptible ( $S_a(t)$ ), exposed ( $E_a(t)$ ); infected but not yet infectious), infectious ( $I_a(t)$ ), recovered ( $R_a(t)$ ) and vaccinated ( $V_a(t)$ ) individuals, as displayed in Fig. 1. Both recovered and vaccinated individuals are

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