Information and Communication Technologies

Developing the Framework for an Epidemic Forecast Infrastructure

Work Package 1.

Deliverable 1.3

Models of disease transmission under seasonality and other external drivers

Annual Progress Report
2011.02.01 to 2012.01.31

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Introduction

The project objectives for the third period for WP1 were concerning the modelling of population contact networks, the structure of interacting populations and the effect of seasonality. In particular, WP1 was expected to provide insights on how seasonality and other external drivers affect the transmission and propagation of diseased. The work carried in this third period produced many major publications that represent the state-of-the-art in the field. WP1 activities have produced a wealth of scientific results that are reaching toward future deliverables and bridging the activities of other Work Packages. Results on the non linear dynamics of recurrent flu epidemics are providing inputs to the computational modelling platform in WP4 and at the same time are triggered by the data collected in WP3.

In this deliverable, the several contributions of partners involved in the WP1 are reported: Gulbenkian Institute (FGC-IGC), London School of Hygiene and Tropical Medicine (LSHTM), Tel Aviv University (TAU), University of Lisbon (CMAF).

London School of Hygiene and Tropical Medicine

Influenza is a seasonal disease, with epidemics occurring in the winter. It is a matter of some controversy, however, whether this is due to environmental changes (such as temperature, rainfall and humidity) or whether it is due to changes in human behaviour (more intimate contacts, as individuals spend more time indoors or with other individuals). As part of WP5 a contact questionnaire was developed and launched (Deliverable 5.2) by the team at LSHTM, and linked with the Influenza Monitoring System. This was done ahead of schedule to catch changes in contact patterns that may have occurred during the 2009 H1N1 ("swine flu") pandemic. Data on contact patterns collected during this period was analysed by Eames et al. [1], and fitted to data on the estimated number of weekly cases over the course of the epidemic. The UK experienced a summer wave in June and July, and a second wave in the autumn of that year. The period of low incidence (August) coincided with the school summer holidays. The contact survey is the first large-scale longitudinal survey of its kind, and clearly demonstrated a drop in contacts between school-aged children during the school holidays (Fig 1.). This change in contact was able to explain the epidemiological pattern in the UK, resulting in a termination of the summer wave (as the reproduction number was driven below one), and the reactivation of the epidemic in September, when contact patterns reverted to their normal levels. The relatively simple age-structured transmission model giving a remarkably good fit to the epidemic data (Fig 2). The paper therefore clearly demonstrates, for the first time, the importance of changes in contact patterns as a driver of influenza seasonality. It also integrates information collected from WP5 with a mathematical model developed as part of WP1 in order to further our understanding of the transmission and control of influenza. This work was wholly funded by EPIWORK.

Fig 1. The mean number of conversational contacts per day reported by each age group.

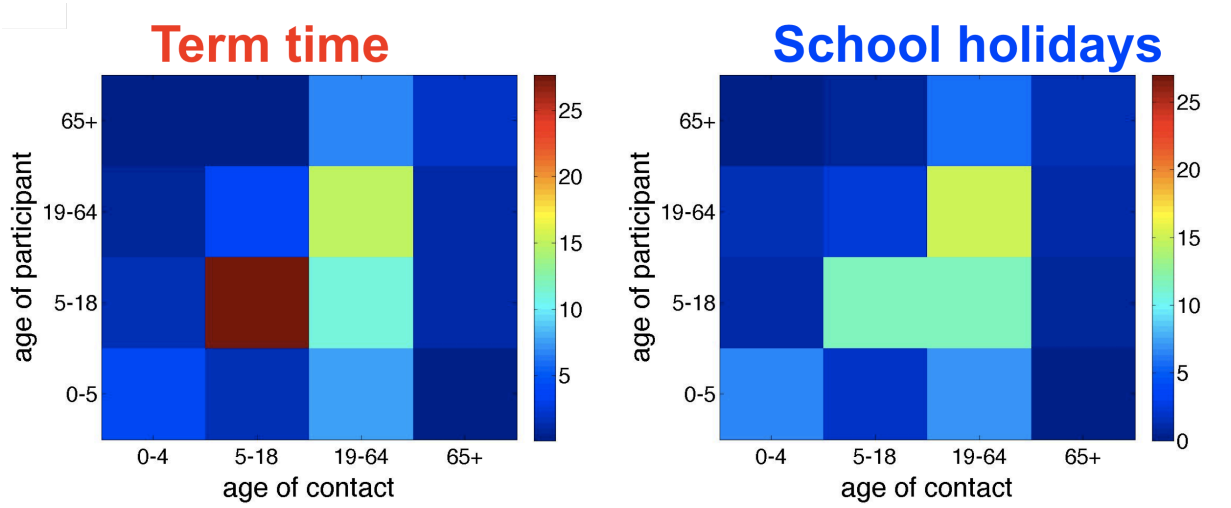
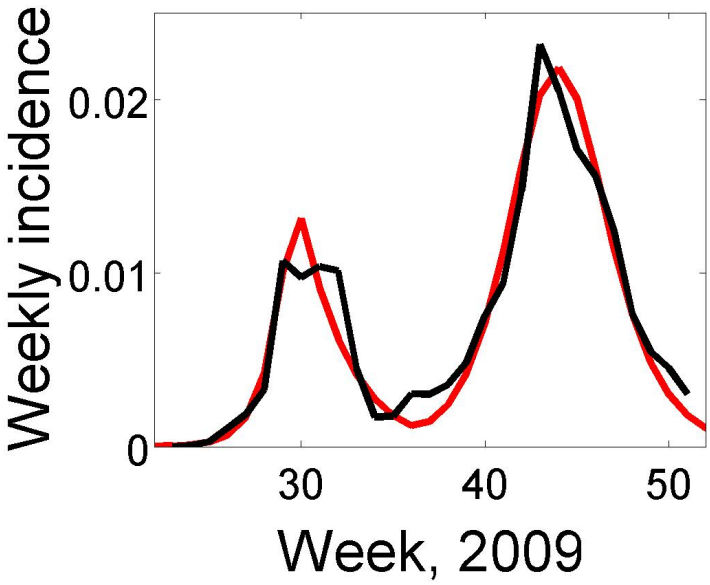


Fig 2. A comparison of the per-capita weekly incidence (black) and the best-fitting model output (red).



[1] Eames KTD, Tilston NL, Brooks-Pollock E, Edmunds WJ Measured Dynamic Social Contact Patterns Explain the Spread of H1N1v Influenza PLoS Computational Biology (in press)

[2] Funk S, Nishiura H, Heesterbeek H, Edmunds WJ and Checchi F. Independent transmission cycles in animal reservoits of gambiense Human African Trypanosomiasis. *Science* (in review).

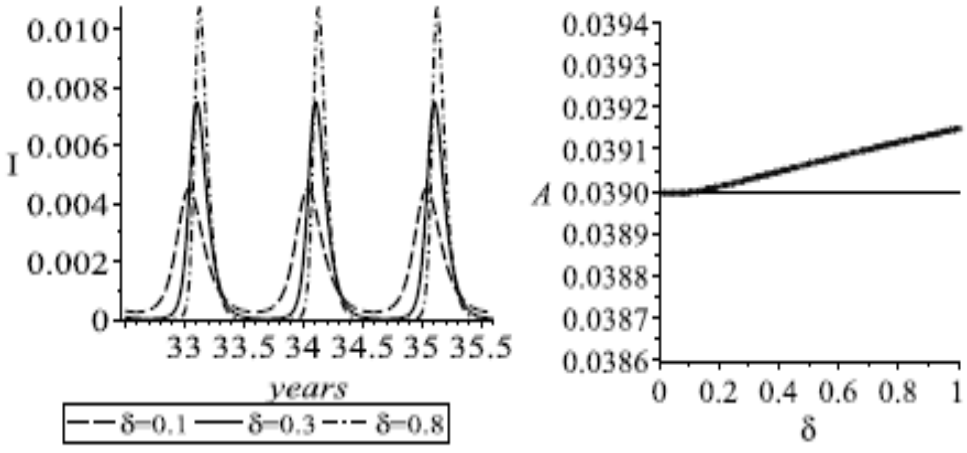
The attack rate A of seasonal models

When a new infectious agent invades a population without prior immunity, the size of the resulting epidemic is determined by the reproductive number R0, which is itself dependent on the duration of infection and on its transmissibility. Once the infectious agent has been circulating for a while, the size of recurrent epidemics depends crucially also on the degree of immunity which has developed in the population due to previous exposures, or in other words on the fraction of susceptibles in the population. This fraction is itself governed by the size of previous epidemics, as well as by the rate of replenishment of susceptibles, either through demographic processes (births or immigration) or through the loss of previously acquired immunity. In this work we consider the former, in which case the simplest model for describing the process is the well-known SIR model. Moreover, since a constant coefficient SIR model leads to damped oscillations converging to an endemic equilibrium, explanation of recurrent epidemics which occur during specific months of the year requires the positing of a seasonally- dependent transmission coefficient. The seasonality in the transmission can be due to climatic factors influencing pathogen survival outside the host, or to seasonal changes in host immune function or host behavior.

$$\dot{S} = \mu(1-S) - \beta(t)SI$$
$$\dot{I} = \beta(t)SI - (\gamma+\mu)I$$
$$\dot{R} = \gamma I - \mu R$$

$$\beta(t) = \bar{\beta} \qquad Attack\ rate = A^* = \mu(1 - 1/R_0)$$

$$Eg., \quad \beta(t) = \bar{\beta}[1 + \delta \sin(2\pi\omega t)]$$



We observe that the shape of the epidemic curve changes considerably as the strength of seasonality d varies (see left part of Fig. 1). However, when we compute the attack rate for different values of d (see right part of Fig. 1), we observe that the change in the attack rate is very small – and the attack rate remains close to its value for the unforced case (A = 0.039) even when the seasonality parameter d is close to 1. For the three epidemic curves in the left part of the figure the attack rates are A = 3.9002% for d = 0.1, A = 3.9034% for d = 0.3, A = 3.9121% for d = 0.8. This surprising phenomenon

of near independence of the attack rate on the strength of seasonal forcing is quite general and appears, in our numerical experiments, for all values of the parameters for which the steady state is periodic. Attempting to explain this phenomenon mathematically is the main motivation and aim of our work.

With some work we find bounds for A and show that it lies very close to

$$A^* = T\mu(1-1/R_0), \qquad (*)$$

that is, the Attack rate in the absence of seasonality (d=0). Here T is the period of the epidemic.

The fact that seasonality has only a minor effect on attack rates means that some simple epidemiological considerations derived from the non-seasonal model through formula (*) carry over without
change to the case of seasonal forcing. For example:
(1) Consider the dependence of the attack rate on the birth rate μ. Since, the dependence of R0 on u is nearly negligible, so (*) shows that the attack rate depends linearly on the birth rate l. In view of our results, this will hold, to a good approximation, also in the seasonal case.
(2) We can use the fact that (*) gives an excellent approximation to the average attack rate in the seasonally forced case to study the effect of vaccination. If a fraction / of the population ϕ is vaccinated at birth, the attack rate changes to $A^* = T\mu(1-\phi-1/R_0)$. This is an interesting result given the otherwise intractability of the seasonal model.

A detailed investigation of these phenomena are given in our paper Katriel and Stone 2012.

Modelling seasonal influenza

We are interested in testing the fit of various models to seasonal Influenza data. Each model represents different assumptions about Influenza transmission and evolution. Our aim is to examine to what extent each model can explain both the typical characteristics of seasonal Influenza epidemics and the variability in characteristics of epidemics across space and time. By finding the best fitting parameter values for each model and comparing the models to select the best fitting model we hope to learn what are the factors and parameter values that shape seasonal Influenza epidemics.

Our model variations are achieved not only by the design of the model and the choice of parameters to be used but also by deciding which parameters to constrain or not constrain across seasons and locations. For example, we could choose to constrain the initial susceptible levels at the beginning of each season to the levels at the end of the previous season so that the susceptible levels are always changing gradually in time (a regular SIRS model). If we don't constrain the initial susceptible levels at the beginning of each season we can get susceptible levels that are changing gradually within a season but can have sudden jumps between seasons. These jumps in susceptible levels could be related to a new strain of Influenza that is antigenically different from the strain of the previous season. Another example is choosing whether to constrain the seasonal forcing to be the same forcing in all Influenza seasons or allow different forcing in different seasons. Any conclusion drawn as to which of these options is more likely could attest to the nature of the factor governing seasonal forcing of Influenza. Of course, in both of the examples above, the second option uses more model parameters then the first option, so it is expected that the second option would always fit the data better. For a fair comparison of the likelihood of different models with different number of parameters we need to use a statistical test that compensates for the number of parameters used in the model such as AIC or similar tests.
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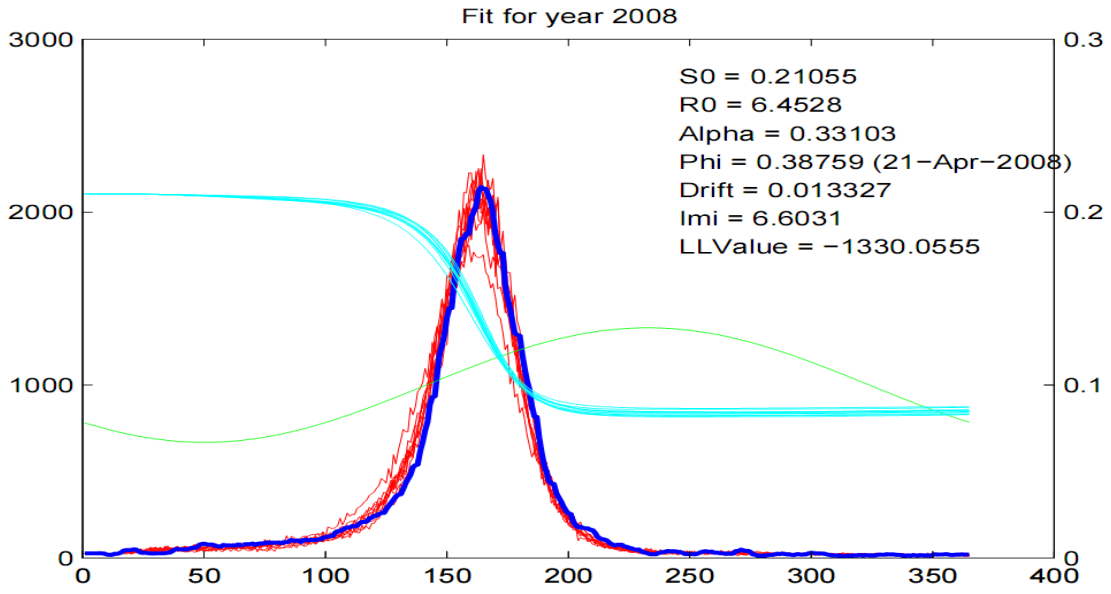


The plot above shows a typical model of real Israeli flu data fit where we estimate the initial susceptible S0, the reproductive number Ro, the likelihood and various other parameters.

Katriel G & Stone L. Attack rates of seasonal epidemics. ***Mathematical Biosciences*** 235: 56-65 (2012).

Gulbenkian Institute

We first studied an SIR system of differential equations with periodic coefficients describing an epidemic in a seasonal environment. Unlike in a constant environment, the final epidemic size may not be an increasing function of the basic reproduction number R_0 or of the initial fraction of infected people. Moreover, large epidemics can happen even if $R_0 < 1$. But like in a constant environment, the final epidemic size tends to 0 when $R_0 < 1$ and the initial fraction of infected people tends to 0. When $R_0 > 1$, the final epidemic size is bigger than the fraction $1-1/R_0$ of the initially non-immune population. In summary, the basic reproduction number R_0 keeps its classical threshold property but many other properties are no longer true in a seasonal environment. In light of these theoretical results we have proceeded to model influenza epidemics.

Influenza epidemics, enabled by viral antigenic drift, occur invariably each winter in temperate climates. We fitted influenza transmission models (1,2) to time series of influenza-like illness as monitored from 2003 to 2010 by two independent symptomatic surveillance systems (Influenzanet and EISN) in three European countries (The Netherlands, Belgium, Portugal). By assuming that seasonality only acts upon the manifestation of symptoms, the model shows a significant correlation between the absolute humidity and temperature at the time of infection, and the proportion of influenza infections fulfilling the clinical ILI case definition, the so-called ILI factor. When a weather-dependent ILI factor is included in the model, the epidemic size of influenza-like illness becomes dependent not only on the susceptibility of the population at the beginning of the epidemic season but also on the weather conditions during which the epidemic unfolds (Figure 1). The combination reduces season-to-season variation in epidemic size and, interestingly, leads to a non-monotonic trend whereby the largest ILI epidemic occur for moderate initial susceptibility (Figure 2).

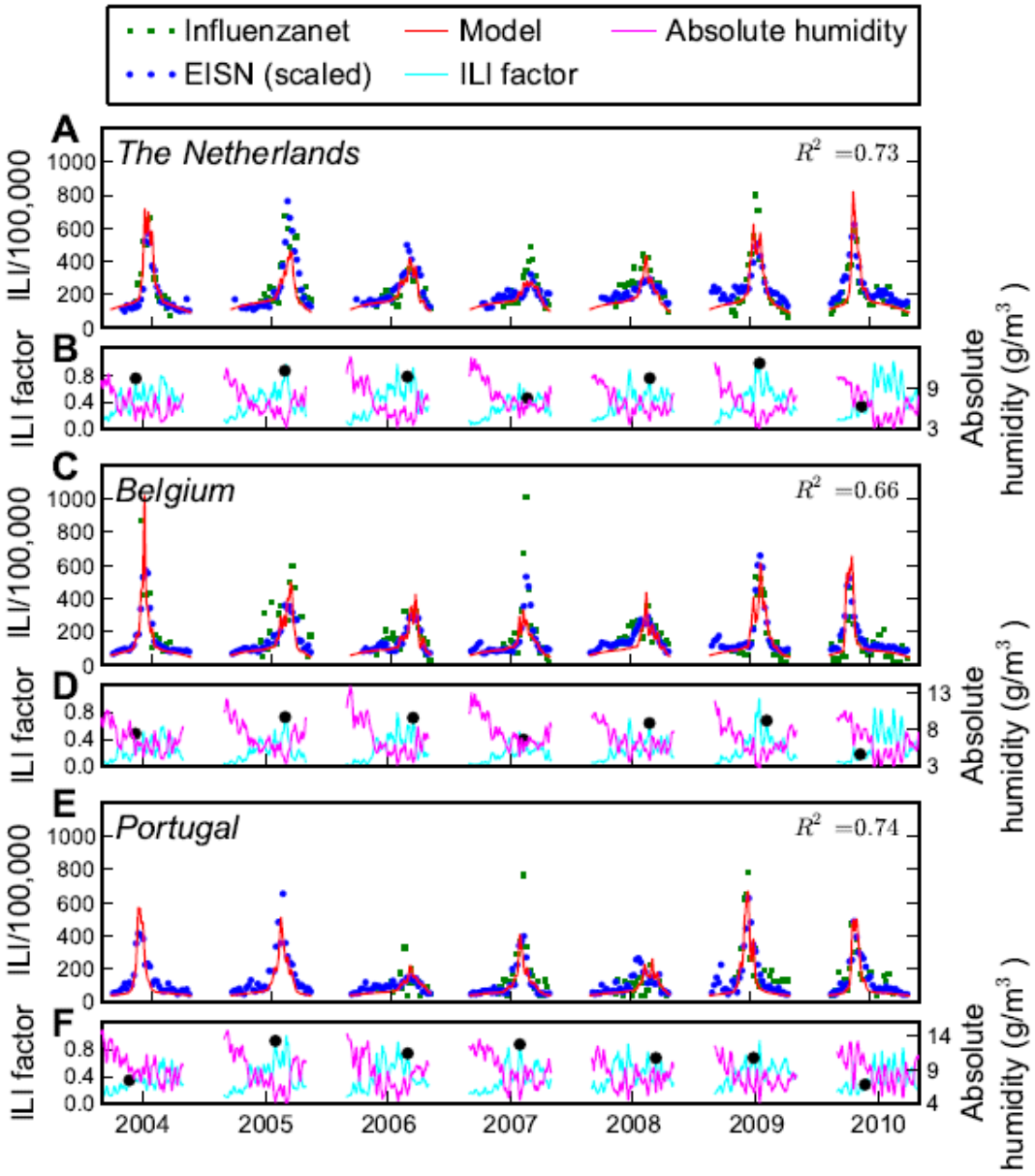


Figure 1: The best fit of the model to sequential influenza epidemics, between 2003 and 2010, in three countries: A) The Netherlands, C) Belgium, and E) Portugal (2003-2010). The typical absolute humidity and the corresponding ILI factor *p* are shown for B) The Netherlands, D) Belgium, and F) Portugal. The black dots on the ILI factor curve indicate the time of the epidemic peaks.

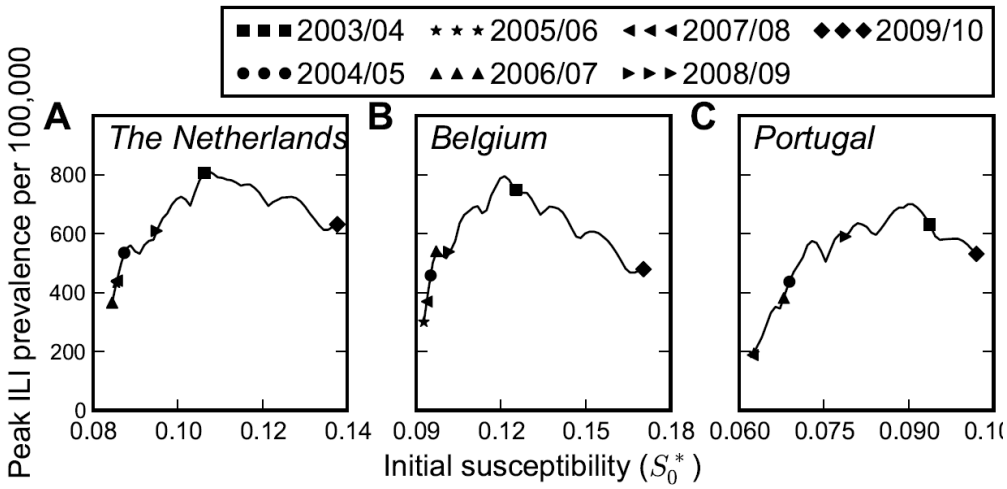


Figure 2: The peak ILI prevalence as a function of the initial susceptibility of the population for The Netherlands, Belgium, and Portugal. The lines are obtained by running the model with estimated parameters for a range of initial susceptible proportions. Then the ILI value is extracted. Values corresponding to epidemic seasons included in this study are specifically marked.

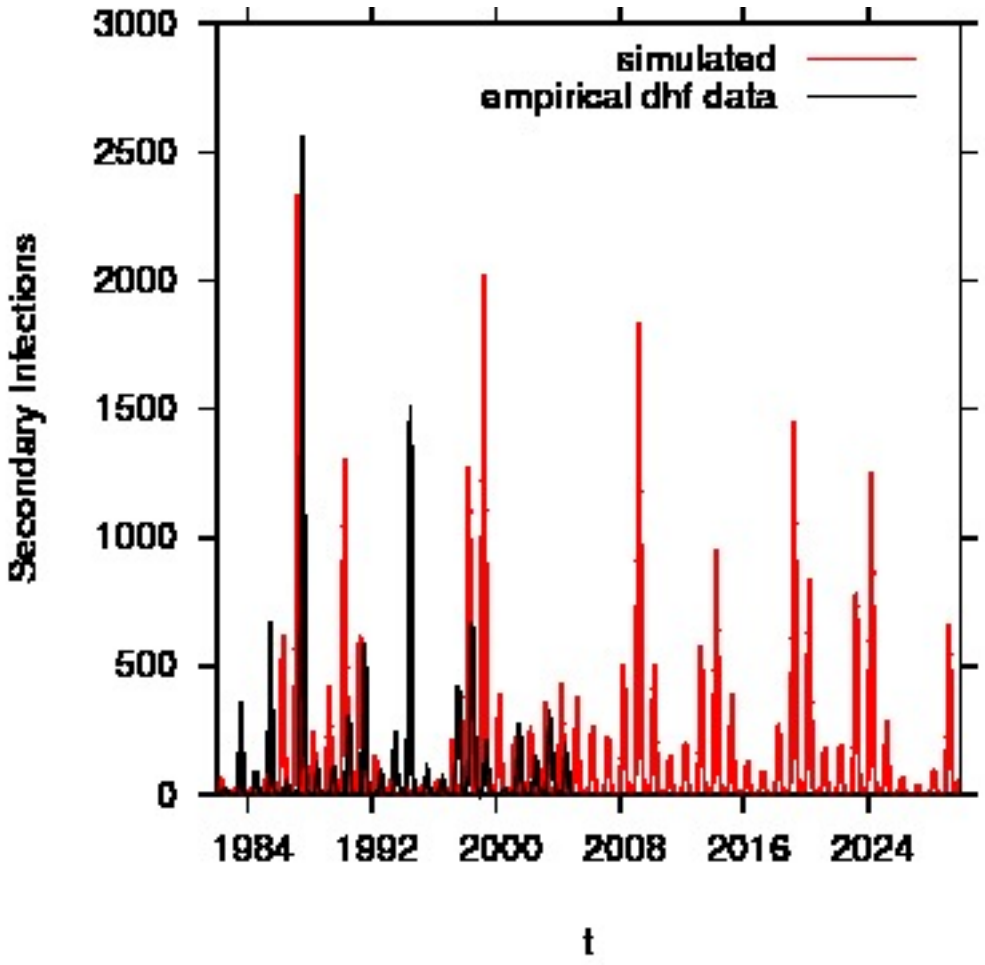
This work has been supported by the Epiwork project for the 50% of the effort.

Publications:

1. Coelho FC, Codeço CT, Gomes MGM (2011) A Bayesian framework for parameter estimation in dynamical models. *PLoS ONE* **6**(5):e19616.
2. van Noort SP, Aguas R, Ballesteros S, Gomes MGM (2012) The role of weather on the relation between influenza and influenza-like illness. *J Theor Biol* 298C:131-137.

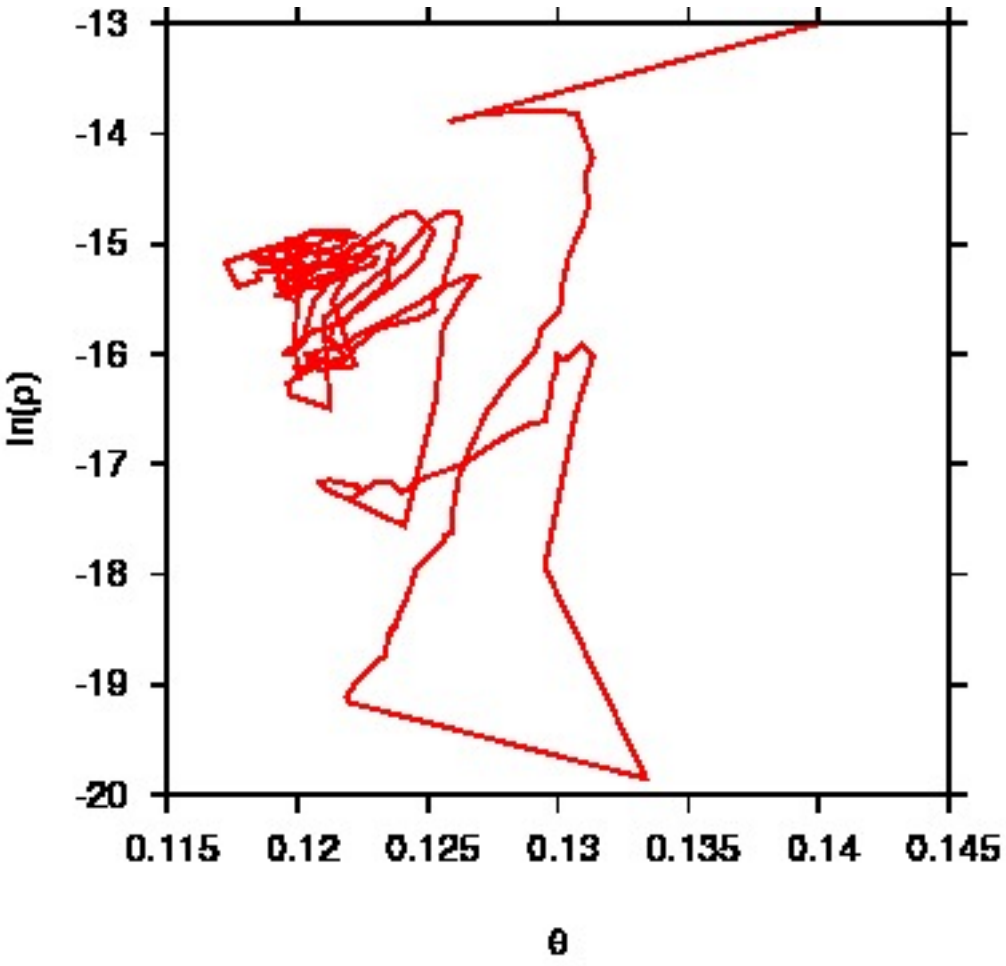
University of Lisbon

The influence of seasonality and import on multi-strain models, based on dengue fever as a test case, has been investigated. The dynamics of Northern Thailand shows good agreement with deterministic models, whereas the large area of the capital, Bangkok, has a much noisier dynamics, seasonality playing less of a role, but import is more important than in the North (Aguiar, Ballesteros, Kooi, Stollenwerk, JTB 2011). Since dengue hemorhagic fever (DHF) is a clear clinical picture, the present modelling and data analysis gives a better picture than for example influenza, for which notification data have turned out to be much less reliable.



In dynamically complex epidemiological models (SIR with seasonality as appropriate for influenza) as well the seasonality as the import can be estimated jointly with the initial conditions (no. of susceptibles and recovered at the beginning of the data set) and reliably (Stollenwerk, Aguiar, Ballesteros, Boto, Kooi, Mateus, In- terface Focus 2012). The currently best parameter estimation techniques for such population biological systems, iterated particle filtering (Ionides et al. 2006, Breto et al. 2009), had to be refined in order to capture the population noise in the likelihood function and not only observation noise. (This has future consequences for the parameter estimation of

influenza time series of Paris, Tel Aviv and Influenza Net, for which preliminary results have been obtained earlier during the Epiwork project).



Aguiar, M., Ballesteros, S., Kooi, B. W., Stollenwerk, N. (2011).
The role of seasonality and import in a minimalistic multi-strain dengue model capturing differences between primary and secondary infections: complex dynamics and its implications for data analysis. Journal of Theoretical Biology, 289, 181–196.

Stollenwerk, N., Aguiar, M., Ballesteros, S., Boto, J., Kooi, W. B., Mateus, L. (2012). Dynamic noise, chaos and parameter estimation in population biology, accepted for publication in Roy. Soc. Interface Focus.