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Estimating influenza latency and infectious period durations using viral excretion data

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ABSTRACT

Influenza infection natural history is often described as a progression through four successive stages: Susceptible–Exposed/Latent–Infectious–Removed (SEIR). The duration of each stage determines the average generation time, the time between infection of a case and infection of his/her infector.

Recently, several authors have justified somewhat arbitrary choices in stage durations by how close the resulting generation time distribution was to viral excretion over time after infection. Taking this reasoning one step further, we propose that the viral excretion profile over time can be used directly to estimate the required parameters in an SEIR model. In our approach, the latency and infectious period distributions are estimated by minimizing the Kullback–Leibler divergence between the model-based generation time probability density function and the normalized average viral excretion profile.

Following this approach, we estimated that the latency and infectious period last respectively 1.6 and 1.0 days on average using excretion profiles from experimental infections. Interestingly, we find that only 5% of cases are infectious for more than 2.9 days. We also discuss the consequences of these estimates for the evaluation of the efficacy of control measures such as isolation or treatment. We estimate that, under a best-case scenario where symptoms appear at the end of the latency period, index cases must be isolated or treated at most within 16 h after symptoms onset to avoid 50% of secondary cases.

This study provides the first estimates of latency and infectious period for influenza based directly on viral excretion data. It provides additional evidence that isolation or treatment of cases would be effective only if adopted shortly after symptoms onset, and shows that four days of isolation may be enough to avoid most transmissions.

Introduction

Influenza transmission is often studied using the standard Susceptible–Exposed–Infectious–Removed (SEIR) model, where an infected individual is first latent (or exposed: infected but not infectious), then infectious, before being removed. The latent period and infectious period distributions, as well as the contact rate in the population, must be specified to obtain quantitative outputs from the model. However, somewhat discrepant values have been used for the durations of the latent and infectious periods, as illustrated in many studies on the 2009 influenza pandemic (Fraser et al., 2009; Balcan et al., 2009; Colizza et al., 2009; Elveback et al., 1976; Flahault et al., 2009; Germann et al., 2006; Longini et al., 2004, 2005; Mills et al., 2004; Tuite et al., 2010; Pedroni et al., 2010; Baguelin et al., 2010; Yang et al., 2009a; Pourbohloul et al., 2009; Boni et al., 2009). For example, recent publications used a range of mean latency period from 0.64 (Fraser et al., 2009) to 3.0 (Pourbohloul et al., 2009) days and from 1.27 (Fraser et al., 2009) to 8.0 (Pourbohloul et al., 2009) days for the mean infectious period (see Fig. 1). For most studies (7 out of 9), these values were however not based on direct estimation from data. Indeed, detailed studies of influenza transmission are scarce; direct observation of the duration of latency or infectious period is impossible and nontrivial statistical analyses are necessary to estimate the time course of infectivity from observed chains of transmission. Some examples include the analysis of transmission within households or using epidemic curves (Fraser et al., 2009; Cauchemez et al., 2004; Boelle et al., 2011).

In view of these issues, alternative sources of information regarding the required parameters would be of interest. A

Abbreviations: GT, generation time; pdf, probability density function; SEIR, Susceptible–Exposed–Infectious–Removed; sd, standard deviation.

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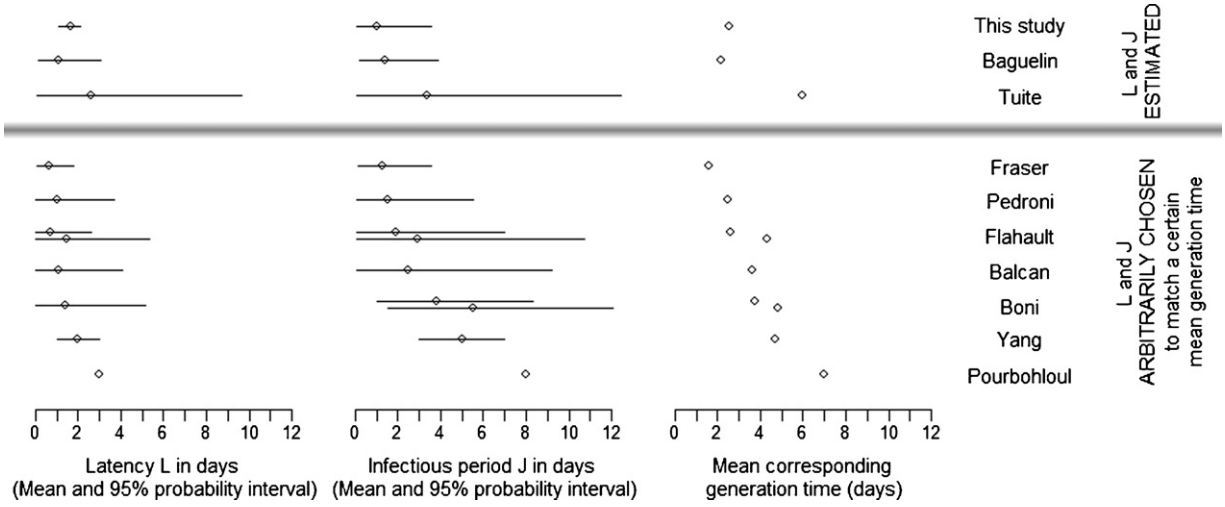

Fig. 1. Comparison of several latencies and infectious periods found in the literature (Fraser et al., 2009; Balcan et al., 2009; Flahault et al., 2009; Tuite et al., 2010; Pedroni et al., 2010; Baguelin et al., 2010; Yang et al., 2009a; Pourbohloul et al., 2009; Boni et al., 2009), and the corresponding generation time. The dots show the mean and the lines show, when available, the symmetric 95% probability interval. The studies above the gray line estimate the mean latency and the mean infectious period, whereas those below the gray line posit the values, in general to match a certain mean generation time.

natural candidate is the profile of viral excretion following infection, measured in experimental infections with known time of infection (Carrat et al., 2008). Indeed, viral excretion forms the biological basis of transmission. Importantly, profiles of viral excretion have been put forward in several recent models to support particular model parameterizations. For example, Mills et al. (2004) reported that their choice of parameters made the probability of being infectious "comparable with the relative amount of viral shedding from human volunteer studies"; Ferguson et al. (2005) estimated a profile of infectiousness over time "remarkably consistent with viral shedding data from experimental infection studies", and Chao et al. (2010), assumed that "the individual's infectiousness (was) proportional to the log of the daily viral titers".

Taking this reasoning one step further, it is natural to propose that viral titers could be used as a primary source for SEIR parameter estimation. This was already suggested in a review of human experimental influenza infections (Carrat et al., 2008), where an average generation time was calculated from viral titers profiles over time. However, as of today, no method has been described to estimate the latent and infectious periods of the standard SEIR model based on viral excretion data. Therefore, in this article, we first show how these two components of the standard SEIR model may be related to viral excretion profiles. We show that this relationship can be expressed in terms of the generation time distribution (GT, time between infection of a case and infection of his/her infector), which is a key parameter in epidemic models. The latency and infectious period for influenza are then estimated by equating the SEIR distribution of the generation time to the viral excretion profile using experimental data. Using these estimates, and considering the best case scenario where the appearance of symptoms coincides with the end of the latent period, we compute the proportion of secondary infections avoided by isolation or effective treatment at a certain time after symptoms onset. We finally discuss our results with respect to other published values of latency and infectious period.

Linking the generation time distribution in the standard SEIR model to viral excretion

Outline

We first describe two models of influenza transmission: the first one is the standard SEIR model; the second one is a new formulation proposed to link viral excretion with transmission. The natural history of influenza described by these two models will be different at the individual level, as the first assumes a constant hazard of transmission during a defined infectious period, while the other proposes time dependent hazard of transmission related to viral excretion. However, we will show that both models can lead to the same description at the population level, as illustrated in Fig. 2: in other words, the force of infection exerted at each time on a susceptible individual can be made equal in both models, therefore leading to the same transmission dynamics.

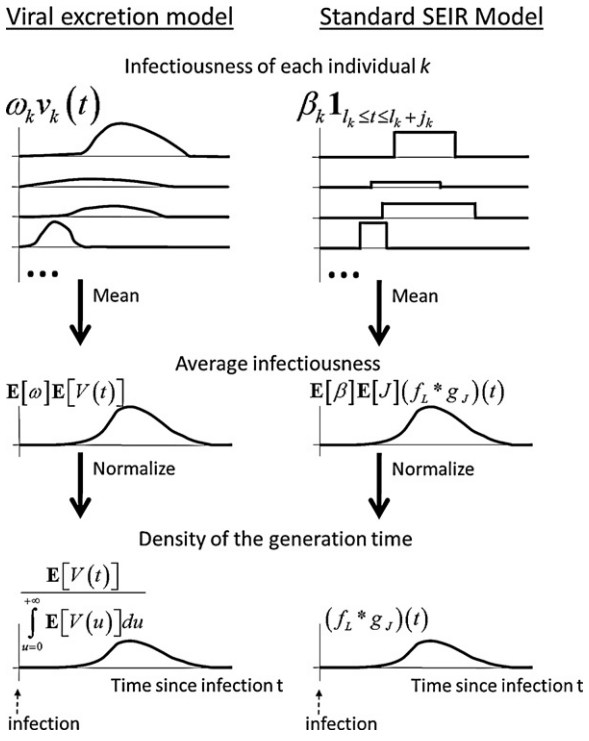

Fig. 2. Schematic parallel between infectiousness after infection in the Standard SEIR model and the viral excretion model, at the individual and population levels. See main text for explanations on notations. x_k designates the realization of a random variable x in individual k.

Matching these two models thus allows estimating parameters of the standard SEIR model from viral excretion data. The resulting SEIR model will be equivalent, at the population level, to the viral excretion model (Fig. 2).

Generation time in the standard SEIR model

In the standard SEIR model, susceptible individuals become infected through contact with an infectious case. After infection, a case is latent (i.e. in the E stage) for a random duration L then infectious for a random period J and is eventually removed. The probability density functions (pdf) of L and J are denoted f_L and f_J. For each case, his/her rate of contact leading to disease transmission is assumed to be non-zero and constant during the infectious period, with random value β. Following Svensson (2007), we assume that L, J, and β are independent. In this description, secondary infections caused by a case occur according to a time inhomogeneous Poisson process with intensity $\beta \mathbf{1}_{\{L \le t \le L+J\}}$, where $\mathbf{1}_A$ denotes the indicator function defined by $\mathbf{1}_A = 1$ if A is true and $\mathbf{1}_A = 0$ otherwise.

The probability density function of the generation time is (Svensson, 2007)

$$\Psi_{SEIR}(t) = (f_L * g_J)(t) \quad (1)$$

where $*$ stands for the convolution operator, $g_J(t) = (1 - F_J(t))/E[J]$, with F_J the cumulative density function of J and $E[J]$ the expectation of J. In this model, $\Psi_{SEIR}(t)E[J]$ equals the percentage of cases who are still infectious at time t after infection, thereby linking the "infectious profile" to the generation time distribution. We assume that the distributions of L and J are fully characterized by a vector of parameters θ, so that the generation time pdf is $\Psi_{SEIR}(t, \theta)$.

Generation time in the viral excretion model

We describe here a transmission model based on individual viral excretion where the generation time distribution would match the (suitably normalized) average viral excretion profile over time. A common description of transmission models is that infected individuals make infectious contacts in time according to a time inhomogeneous Poisson process with intensity $\lambda k(t)$, where λ is a random amount of infectivity, and $k(t)$ the probability density of a (random) positive measure (Svensson, 2007). We let this intensity be proportional to $V(t)$, the (random) viral excretion at time t after infection (i.e. $\lambda k(t) = \omega V(t)$, where ω is a positive random number). This particular formulation would arise, for example, if contacts occurred according to a homogeneous Poisson process in time, with transmissibility per contact proportional to viral excretion at that time.

Importantly, and irrespective of interpretation, the (backwards) generation time distribution associated with this transmission process is the normalized average viral excretion profile

$$\Psi_V(t) = \frac{E[V(t)]}{\int_{u=0}^{+\infty} E[V(u)]du},$$

in exact agreement with the empirically derived result by Carrat et al. (2008).

This review of experimental influenza infection studies provided the average profiles of viral excretion after infection measured in 12 studies where human volunteers were experimentally challenged with seasonal AH1N1 or AH3N2 influenza virus. We used the weighted mean of these curves, summarizing viral excretion in 157 individuals.

The discrete (daily) estimate of the generation time probability density function obtained using this average viral excretion profile is denoted $\widehat{\Psi}_V$.

Identical dynamics in SEIR and viral excretion model with identical generation time distribution and R_0

Consider an epidemic model in which individuals are classified as susceptible or infected. Susceptible individuals can be infected through contact with infected cases. The probability of transmission given a contact depends on the infectivity of the infected case at time of contact. The dynamics of the deterministic model in a population of size N, in terms of the incidence H and the number of susceptibles S, is governed by the following renewal equations (see for example Fraser, 2007):

$$\frac{dS}{dt} = -H(t)$$

$$H(t) = \frac{S(t)}{N} \int_{\tau=0}^{+\infty} R_0 \psi(\tau) H(t-\tau) d\tau$$

where R_0 is the basic reproduction number (average number of secondary cases that an infected individual introduced in a fully susceptible population would infect) and ψ is the probability density function of the generation time (average time between infection of a case and infection of his/her infector).

From those equations, it is clear that two epidemics in the same population, with the same reproduction number, the same generation time distribution, and the same initial conditions, will have exactly the same dynamics of incidence and number of susceptibles.

Therefore, this provides a formal link between the two models presented above. If the standard SEIR model is calibrated so that its generation time distribution matches that of the viral excretion model, then the dynamics of both models will be exactly the same, starting from the same initial conditions.

Estimating the influenza latency and infectious period distributions from viral excretion data

Parametric deconvolution of the generation time distribution

The vector θ of parameters specifying the distributions of the latent and infectious period in the standard SEIR model was estimated by minimizing the Kullback–Leibler (KL) divergence $D(\theta)$ between $\widehat{\Psi}_V$ and Ψ_{SEIR}, where $D(\theta) = \sum_{d=0}^{T} \widehat{\Psi}_V(d) \log(\widehat{\Psi}_V(d)/\phi(d, \theta))$ (Kullback, 1959). In this expression, T is the number of days with detectable excretion and $\varphi(d, \theta) = \int_{d-1/2}^{d+1/2} \Psi_{SEIR}(u, \theta) du$ is the discretized SEIR model-based generation time pdf, integrated over a time step of one day.

Both the latency L and infectious period J are assumed to follow shifted Weibull distributions, with parameters $\theta = (s_L, a_L, b_L, s_J, a_J, b_J)$ and respective pdf:

$$f_X(t) = \left(\frac{a_X}{b_X}\right) \left(\frac{t - s_X}{b_X}\right)^{a_X - 1} e^{-(t - s_X/b_X)^{a_X}} 1_{\{t \ge s_X\}} \quad (2)$$

for $X = L$ or J. In that formulation, s_X, a_X, b_X are respectively the shift, shape and scale parameters of the Weibull distribution.

The integrals were numerically estimated using the Gauss–Kronrod quadrature with 61 Kronrod points (Kronrod, 1965) and D minimized using a conjugate gradient algorithm (Bonnans et al., 2003). For all numeric aspects, custom routines were coded using the C language and the GNU Scientific Library.

Confidence intervals

To estimate the variability of parameter estimates, we used a leave one out (jackknife) approach (Shao, 2003): we obtained 12 different average viral excretion profiles by systematically omitting

one of the 12 studies (and thereby removing one of the 12 average profiles of viral excretion) considered by Carrat et al. (2008). Jackknife estimates of the standard deviations of estimated parameters were then obtained from the repeated estimations.

Validation

We numerically checked the identifiability of model parameters.

First, the criterion $D(\theta)$ was calculated over a grid of plausible parameter values to investigate the uniqueness of the minimum. We considered values of the average infectious period between 0.25 and 5.75 days (step 0.25) and values of the average latency period between 0.25 and 3.25 days (step 0.25). For both distributions we investigated coefficients of variation (ratio of the standard deviation over the mean) between 0.25 and 5 (step 0.25)

Then, the shifted-Weibull distributions for L and J (see formula (2)) were replaced with shifted-Gamma distributions, and the estimates obtained under both assumptions were compared.

Finally, we applied our estimation procedure to generation time distributions obtained from known latency and infectious periods. Two sets of distributions for L and J were taken from the literature: those proposed by Elveback et al. (1976) and Longini et al. (2005) respectively. In each case, the GT distribution was first calculated using formula (1); then the deconvolution procedure was applied, and the relative error of estimation in the mean and standard deviation of L and J was computed.

Predicting the effectiveness of isolation or treatment

Isolation and treatment of symptomatic cases are often considered in order to bring an epidemic under control. Such control measures can only be introduced once cases have been detected, thus after symptoms onset. Their effectiveness can be assessed by quantifying, for each case, the proportion of the overall infectivity that is avoided thanks to the control measures.

Assuming that infectivity is proportional to viral excretion, this requires the knowledge of individual viral excretion profiles and times of symptoms onset, data which are scarce, and which we did not have access to.

However, studies using a SEIR formulation commonly assume that for influenza, latency and incubation period coincide (Fraser et al., 2009; Balcan et al., 2009; Yang et al., 2009a; Boni et al., 2009; Ferguson et al., 2005; Carrat et al., 2006), so that symptoms onset corresponds to the beginning of the infectious period. Making such an assumption allows linking the dynamics of infections predicted by the model with the observed dynamics of symptomatic cases.

Other studies (Pourbohloul et al., 2009) assume that symptoms appear sometime after the beginning of the infectious period.

From a control measure perspective, this second scenario is worse as it allows an infectious asymptomatic stage, where individuals are infectious but cannot be detected. Here, we consider the best-case scenario where symptoms appear at the end of the latency period. Assessing the effectiveness of isolation or treatment of cases under this scenario is quite straightforward within the SEIR framework.

Using the estimated infectious period distribution, we computed the proportion of secondary infections which could be avoided if all symptomatic cases were isolated (or treated with a treatment reducing infectivity by 100%) at time σ after onset of symptoms (assumed equal to the start of infectious period), and for a duration τ.

We assumed that an infected case effectively isolated or treated at time σ after symptoms onset and for a duration τ would cause $\beta \times (J\mathbf{1}_{J\leq\sigma} + \max(\sigma, J-\tau)\mathbf{1}_{J>\sigma})$ secondary cases, leading to a proportion $\varepsilon(\sigma,\tau) = \int_{j=\sigma}^{+\infty} \min(j-\sigma,\tau) f_J(j)dj \,/\, \int_{j=0}^{+\infty} j f_J(j)dj$ of avoided secondary infections. In the case of treatment, the parameter σ can be seen as incorporating both the time between symptoms onset and treatment and a possible delay after treatment before reduction of infectivity.

Numerical results

The best fit between the discretized SEIR generation time pdf and the normalized average daily viral excretion profile is shown in Fig. 3A. The corresponding latency distribution has average 1.63 ± 0.06 days and standard deviation (sd) 0.26 ± 0.08 days and the infectious period distribution average 0.99 ± 0.25 days and sd 0.96 ± 0.15 days, as shown in Fig. 3B and C. The infectious period is typically short, with 95% (respectively 99%) of cases having an infectious period shorter than 2.90 ± 0.55 days (respectively 4.41 ± 0.63 days).

Numerical explorations did not reveal identifiability problems. A thorough exploration of the parameter space showed a unique minimum (see Fig. 4 for the mean values). Using shifted Gamma distributions for L and J led to very similar results: the average latency was 1.7 days (sd 0.3 day) and the average infectious period was 1.0 days (sd 0.9 day).

Last, the relative errors between the original and reestimated parameters means in the Elveback (Elveback et al., 1976) and in the Longini (Longini et al., 2005) distributions were less than 2%.

Fig. 5 shows the proportion of secondary infections which could be avoided by isolating or treating cases after symptoms onset, depending on the duration of isolation or treatment. To reduce by

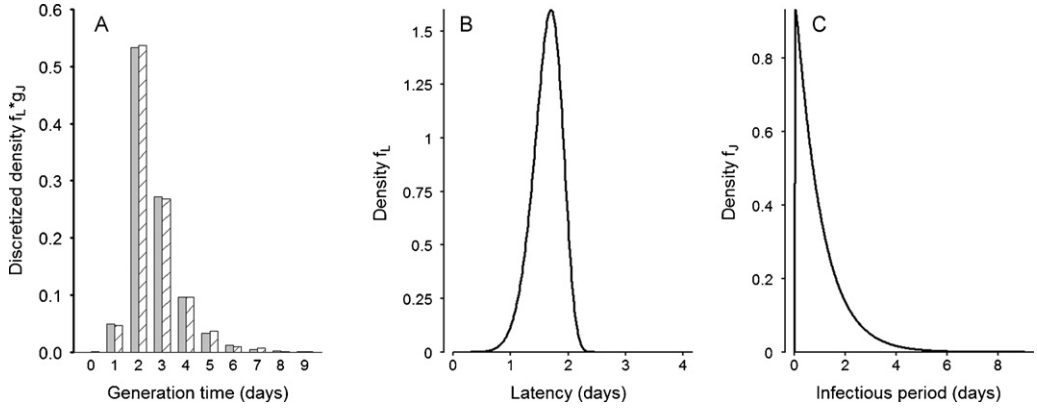

Fig. 3. (A) Normalized average daily viral excretion after experimental influenza infection (hatched bars, data from Carrat et al., 2008), and fitted discretized generation time probability density function using a standard SEIR model (gray bars). (B) Estimated distribution for the latency L. (C) Estimated distribution for the infectious period J.

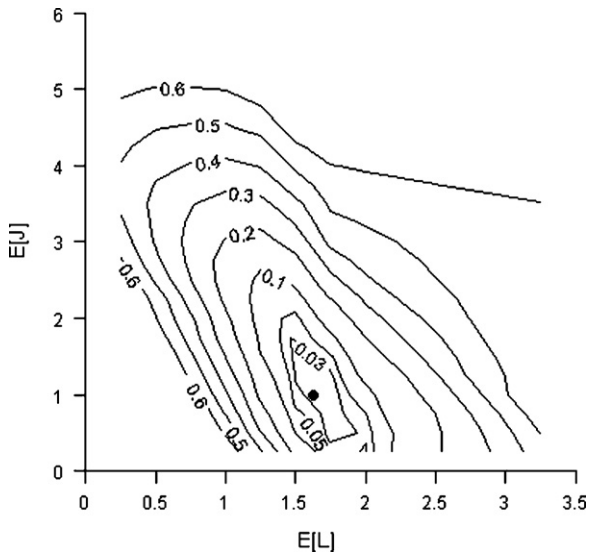

Fig. 4. Minimum value of the Kullback–Leibler (KL) divergence according to the average latency (*x* axis) and infectious period (*y* axis). The dot indicates the estimated minimum. The KL divergence at this point has a value of 0.0037.

50% the number of secondary cases, a case should be isolated or treated at most within 16 h after symptoms onset. If cases were isolated or treated 2 days after symptoms onset, the proportion of secondary cases avoided would be only 12%.

Discussion

Viral excretion has been put forward to qualitatively support the choice of parameter values in transmission models in several recent major publications regarding influenza. However, as of now, viral excretion has not been used for obtaining more quantitative estimates. Here, we proposed that viral excretion profile can be linked to the generation time distribution in the standard SEIR model, and we estimated parameters under this assumption.

Using time profiles of viral excretion in subjects experimentally infected with influenza, we have estimated that the mean latency and infectious period for influenza are 1.6 (95%CI 1.5–1.7) and 1.0 days (95%CI 0.5–1.7). In particular, we found that 95% of cases were infectious for less than 2.9 days. This is remarkably consistent with recent results obtained by Donnelly et al. (2011) who estimated, with independent data and a totally different approach, that only 5% of transmission events took place >3 days after the onset of clinical symptoms with H1N1 2009 infection. The short infectious period makes interventions aiming at reducing transmission highly dependent on the time of initiation after symptoms onset.

On the occasion of the 2009 A/H1N1 pandemic, estimates of the generation time from field data were very consistent, with a mean value of 3 days (Boelle et al., 2011). However, in models of influenza transmission using a standard SEIR formulation for the natural history, the average generation time was not always in accordance with this value (see Fig. 1). Moreover, in most models, the mean latency and infectious period durations were somewhat arbitrarily chosen to match a certain average generation time rather than estimated. Therefore, to compare our results with other studies, it is fair to distinguish between the studies where the parameters were estimated from data and those where "guesstimates" were used, and to gauge how realistic the corresponding generation times were.

Fig. 1 shows that the average duration of the latency period found in our study compares with that generally used for modeling influenza, although our distribution of the latency period is narrower than most distributions used in the literature. This might be an effect of not using an exponential distribution, unlike most other studies. On the other hand, our estimate of the average duration of the infectious period is lower than most values used in models. However, our distribution of the infectious period compares with that in Baguelin et al. (2010), the only other study where a realistic generation time distribution was used and latency and infectious period were estimated: their estimated average latency period was 1.40 days (versus 0.99 in our study), with a 95% probability interval of [0.19–3.90] (versus [0.04–3.55] in our study).

It is difficult to assess to what extent the viral excretion profile after experimental infection is similar to that after natural infection, since measuring viral excretion early after natural infection is challenging. However, it is reassuring that several studies, which analyzed transmission chains in closed settings such as households, have estimated generation time distributions which are consistent with the average viral excretion profile after experimental infection (Fraser et al., 2009; Yang et al., 2009a; Ferguson et al., 2005; Cauchemez et al., 2009; Ghani et al., 2009; White et al., 2009; Lessler et al., 2009; Hahne et al., 2009; McBryde et al., 2009; France et al., 2010; Suess et al., 2010; Leung et al., 2010).

One may also object that our results depend on the scale over which viral excretion is expressed. For example, in Mills et al. (2004) and Chao et al. (2010), the viral excretion data is on the log-scale to match the GT distribution used; on the contrary, Ferguson et al. (2005) compared infectivity profiles with viral excretion on the natural scale. Quantitatively, we found that the difference was not negligible: the mean GT was 3.5 days (Jackknife 95% CI 3.2–3.9

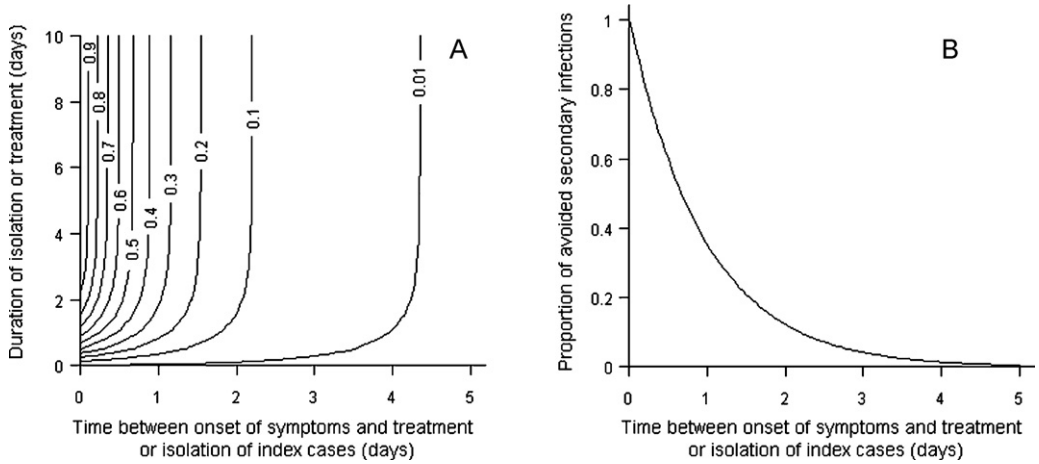

Fig. 5. (A) Proportion of avoided secondary infections according to time and duration of isolation. (B) Proportion of avoided secondary infections according to time of isolation, assuming permanent isolation.

days) using the normalized viral excretion on the log scale, but only 2.6 days (Jackknife 95% CI 2.4–2.8 days) using the natural scale. Although the former option leads to a generation interval in agreement with data reported in a recent study where the average GT was 3.6 days (95% CI 2.9–4.3 days) (Cowling et al., 2009), most estimates reported during the A/H1N1 (2009) pandemic (Fraser et al., 2009; Yang et al., 2009a; Cauchemez et al., 2009; Ghani et al., 2009; White et al., 2009; Lessler et al., 2009; Hahne et al., 2009; McBryde et al., 2009; France et al., 2010; Suess et al., 2010; Leung et al., 2010) and seasonal influenza (Cauchemez et al., 2004; Ferguson et al., 2005) support a shorter generation time, so that the choice of the natural scale for viral excretion appears to better match epidemiological evidence.

The infectious period distribution provides crucial information on the effectiveness of control measures depending on their timing and duration. Based on our new estimate of the infectious period distribution, and under the optimistic but commonly adopted scenario where symptoms onset coincides with the beginning of the infectious period, in order to achieve a 50% reduction in the number of secondary cases, it is necessary to isolate or treat index cases at most within 16 h after symptoms onset. If cases are isolated or treated as late as 2 days after symptoms onset, only 12% of secondary cases can be avoided. These results were obtained by assuming that all cases became symptomatic at the start of their infectious period.

A more realistic assumption is that the infectious period starts before the onset of symptoms. For instance, Lessler et al. (2009) found a median incubation period of 1.4 days, which is shorter than our median latency period of 1.63 days. If the infectious period indeed starts before the onset of symptoms, isolation or treatment of index cases would be even less effective than what we found. Accounting for asymptomatic infections would also lead to more dramatic results. Our results are in line with those of other studies (Yang et al., 2009b; Halloran et al., 2007), which found no effectiveness of treating index cases with antivirals within the two days following symptoms onset. As a comparison, assuming an infectious period distributed as in Yang et al. (2009a) with a higher average (5 days versus 1 day for us), 60% of secondary cases would be avoided by isolating or treating cases within 2 days after symptoms onset.

Our study provides the first estimates of influenza natural history parameters based on viral excretion data, which supports a short infectious period lasting one day on average. This result is additional evidence that isolation or treatment of cases would be efficient only if initiated within the few hours after symptoms onset. Therefore, it is very unlikely that an infected individual can be isolated or treated early enough after his symptoms. A more efficient control strategy would consist in isolating or treating close contacts of symptomatic individuals. Those contacts, although they are likely to have already been infected, might not be infectious yet. Hence isolating or treating them might effectively prevent further transmission.

Our method could be applied to estimate the durations of latency and infectious period in standard SEIR models for any pathogen for which viral excretion profiles or, more generally, generation time distributions, are available. In particular, different estimates could be obtained for the latency and infectious period according to the influenza subtype. It would also be interesting to assess how the latency and infectious period are modified under antiviral treatment by applying our method to viral excretion profiles measured in infected individuals under antiviral treatment. Moreover, here, we assumed that the distribution of the generation time was given by the average profile of viral excretion after infection. We neglected behavioral and environmental components of the infectiousness (Grassly and Fraser, 2008), which could affect the generation time distribution if they vary over time. If reliable data on the dynamics of contacts after infection were available, these data could, together with data on viral excretion profiles, lead to a more accurate description of the generation time distribution. Our method could then be applied to estimate the corresponding durations of latency and infectious periods.

Finally, a natural continuation of this work, which would require individual data on viral excretion profiles after infection, would be to compare the stochastic SEIR model, calibrated using our method, to the stochastic model in which each individual is assumed infectious proportionally to his/her viral load. While, as we have shown, the dynamics of the deterministic models are the same, the dynamics of the stochastic versions should be different. In particular, it would be interesting to compare the effect of control measures in both frameworks.

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